Preface to the Second Edition

The first edition of *Family Practice Curriculum in Neurology* was published in 2001, and represented the realization of a dream that was shared by Ed Langston, MD, a family medicine educator, and Raymond A. Martin, MD, FAAN, a neurologist who is active in family medicine residency education. Drs. Langston and Martin set out to create a practical resource for family medicine residents to learn neurology. In my mind, three aspects of the publication set it apart — content, focus, and format.

Rather than create a comprehensive textbook of neurology, the editors identified topics that were relevant to family medicine residents during their training, as well as to practicing family physicians. The diseases, symptoms, and conditions are ones that we see regularly in our offices. In addition to a careful choice of topics, the publication includes a strong focus on family medicine. Each chapter was co-written by a neurologist and a family physician. So, not only are the topics relevant, but the reader will find an emphasis on the aspects of each condition that are particularly important from a family medicine perspective.

Finally, the publication benefits from the use of multimedia presentations. Not only can the reader review the details of a cranial nerve exam, but he or she can then watch a skilled examiner perform that testing. This serves to reinforce and clarify teaching points.

It was not long after publication of the first edition that it became clear that a second edition was needed. Several new topics have been added, and other existing chapters have been updated and refined. It is our hope that this Second Edition will be as well received as the first, and will serve as a valuable teaching tool for medical students, family medicine residents, and practicing family physicians.

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Chapter 1 – The Neurologic Examination

Section One

The Neurologic History

As family practitioners you will see patients with complaints that cover the full spectrum of medical practice. Many of these patients present with symptoms of pain, dizziness, forgetfulness, numbness, weakness and difficulty speaking or comprehending as their primary complaint, or as a portion of their history. In addition to a full medical evaluation, accurate assessment of these neurologic complaints will be of increasing importance to our current health care environment. Since up to 10 percent to 15 percent of a family practitioner's workload consists of neurologic problems, it is the goal of this program to provide an effective and efficient means of gaining this knowledge.

As a first step in evaluating the patient with a neurologic problem, the practitioner must obtain an accurate history. A good history alone will often suggest the correct diagnosis, and the examination can be tailored to specifically search for corroborating physical signs. Patients with neurologic disease may have impairments that make it difficult to elicit accurate information, and the diligent examiner may need to spend extra time questioning the patient or obtaining information from family or friends.

An important consideration in history-taking is to not only record the patient's complaint, e.g., dizziness, but to question exactly what the patient means by that complaint. The symptom "dizziness" often has different meanings to the lay public and the term could be used to connote lightheadedness, vertigo, tiredness, or malaise. If the examiner assumes it means vertigo then needless time and resources may be wasted in pursuing a non-existent complaint. Another example is "weakness" which to many patients may mean fatigability or lack of energy rather than loss of strength in specific muscle groups.

The temporal profile, i.e., whether it is acute, subacute, or chronic, is important in determining the diagnosis. For example, numbness and weakness of an extremity that is abrupt in onset suggests transient cerebral ischemia or stroke, while the same symptoms, if they develop over minutes, may be associated with the aura of migraine. Progression of the same symptoms over days may be due to a brain abscess and over weeks to months, a brain tumor.

One can develop a pattern of questioning for this portion of the history, which is facilitated by a predetermined outline. A partial, but useful list should include questions about the following symptoms:

- Visual defect
- Diplopia
- Hearing disturbance
- Involuntary movement
- Weakness
- Gait disturbance
- Incoordination
• Vertigo, lightheadedness
• Swallowing difficulty
• Speech disturbance
• Behavior/Mood change
• Aphasia
• Headache
• Bladder/bowel control

• Muscle atrophy
• Tremor
• Pain
• Numbness
• Paresthesia/anesthesia
• Memory
• Seizure/syncope

The Neurologic Examination
The neurologic examination should always be included as part of the general physical examination.

An adequate neurologic examination requires a few simple tools: a reflex hammer, disposable pin, cotton, tuning fork, tape measure, visual acuity card, aromatic substance to test smell, and printed copies of the Mini-Mental State Examination to include on the patients chart. These are small enough to carry in laboratory coat pockets or in a small travel case.

The following overview emphasizes points that a family practitioner should keep in mind; Examples will be used to point out the significance of each portion of the examination and how the findings relate to the patient's medical picture as a whole.

Basic neuroanatomy will be reviewed but it will be done in a way that is clinically useful and easy to remember. Note that the descriptions may differ slightly from precise anatomical pathways and neurophysiologic relationships, but will serve adequately for clinical localization and treatment application. In this fashion we hope to provide an educational tool that has utility and is user friendly.

A video is included that will demonstrate how to correctly perform and interpret the neurologic exam. It is to be used in conjunction with the text. Individual performance of the examination can be refined by repeated performance and evaluation by your clinical neurology faculty person.

Inspection and Observation
From the time the physician greets the patient he gets to observe him speaking, sitting, walking, making facial expressions and socially interacting. Examples are the hemiparetic or parkinsonian gait, facial asymmetry due to facial muscle weakness, presence of tremor, dysphasic or dysarthric speech and a whole host of other clinical signs. Patients may have pronounced muscle atrophy, the distribution of which can help provide important diagnostic clues. These signs are often missed solely because they are
not looked for and, once pointed out, are obvious. Obtaining and utilizing information such as this is what makes a good clinician.

The psychological state of the patient should also be noted. Patients may be depressed, hostile, apprehensive, preoccupied and even uncooperative. Recognizing such moods will help the examiner choose the approach best suited to maximize the information he obtains from the encounter. Reassurance and patience on the part of the examiner go a long way in gaining a patient's trust and cooperation.

The presence of pain may affect a patient's countenance, gait, and even ability to cooperate during the examination. It takes experience, gained by doing many of these examinations, to be able to recognize when patients are truly impaired or when symptoms and signs are exaggerated for secondary or other gain.

System Integration

When neurology is learned in the classic sense, the student studies individual functional neurological systems such as the motor, sensory, and cerebellar systems. This enables a greater depth of understanding, but in a one-month clinical rotation, time does not permit this luxury. If one is to gain clinically useful information in a limited time frame, it is best to provide understanding of broader functional concepts. These concepts must easily lend themselves to clinical application in patient care settings. In the spirit of this approach the following description will illustrate how the body moves by discussing the interactions of the extrapyramidal, pyramidal, sensory and cerebellar functional systems.

Figure 1-1: Initial state: Atonic

Figure 1-2: Extensor tone established.

Extrapyramidal System.

A useful concept is to imagine the human body as a marionette, all of whose controlling strings have no tension, and the puppet lies crumpled on the floor (Figure 1-1). For the puppeteer to create life-like movements, he must first stand the puppet up. To do this he puts tension on the strings that cause the trunk to become erect and the legs to extend (Figure 1-2). This provides the basic framework to initiate motion of the extremities. By analogy, a similar but lengthier process occurs in human infants as their nervous systems mature. The infant first lies supine on its trunk, with arms and legs flexed. Gradually, extensor tone straightens the legs and truncal erector tone.
enables it to sit up. Finally the baby is able to stand although it is wobbly and must grasp for support.

The portion of the nervous system responsible for this function is the **extrapyramidal system**. It consists of a number of reverberating circuits in the basal ganglia and brain stem that ultimately send impulses through spinal cord pathways that **tonically innervate** spinal interneurons controlling the tone of muscles which support the spine and keep the body **erect**. This is all done on an unconscious level. When something goes wrong with this system, as in Parkinson disease, the normal erect posture of the body becomes flexed, and more rigid. As the extrapyramidal system matures, fluid control of body posture provides the framework for initiation of individual extremity movements.

**Figure 1-2: Voluntary movement Pyramidal System.**

Voluntary movements, (Figure1-3), are largely initiated by the pyramidal system. Impulses go from premotor integrating areas in the frontal lobe to the upper motor neuron, which sends a crossed axon to the anterior horn cell in the spinal cord. Pyramidal tract initiated movements are crude and lack finesse. They are smoothed out and made more agile by the influence of other systems, such as the cerebellar, and via practice effect. There is also an inherent ability of the system to mature to certain degrees explaining the phenomenon of the "natural born athlete." Lesions of the pyramidal tract produce weakness, increased clumsiness, and alteration of motor tone. This will be discussed in greater detail later.

The development of erector tone, which has provided the supporting framework, and the initiation of voluntary movements are, however, still rudimentary and uncoordinated. What is needed is a system that monitors the motor activity and then smoothes out any irregularities in the desired action.

The cerebellum occupies a large portion of the posterior fossa, and is in a unique position to monitor impulses entering and leaving the brain. It's foreboding anatomical structure with its many lobes and folia often discourages students from getting a better understanding of how this elegant structure works. A most useful concept is to think of the cerebellum as a servomechanism. A good example of such a device is the automatic piloting system on an airplane. The pilot will set the autopilot to control speed at "x" knots, the course at a certain latitude-longitude, and the altitude at so many thousand feet. The servomechanism is basically a computer which compares the actual airplane speed, read from the speedometer; the altitude, read from the altimeter; and course (direction), read from a compass; to the settings that the pilot has entered as desired. Any **discrepancy** between the **desired** and **actual** readings will be corrected by output from
the computer. Altitude and position can be adjusted by moving the wing flaps, direction changed in similar manner, and speed by increasing or decreasing engine revs.

The cerebellum works in a manner similar to a servomechanism. It receives input from the sensory system and information about output from the pyramidal and extrapyramidal systems. When a person swings a tennis racquet, impulses travel down the pyramidal pathway to specific anterior horn cells in the spinal cord, which initiate movement. These same impulses are sent to the cerebellum, which receives them before the anterior horn cells, so that the cerebellum knows what movement is intended. As the arm begins to move, sensory proprioceptors send information back to the thalamus and sensory cortex so that the person is aware of his achieved arm movement. The cerebellum "knows" what was intended and what is actually being achieved. If there is any discrepancy, the cerebellum corrects this via inhibitory outflow pathways, which alter muscle tone and action.

One can thus visualize a dynamic and fluid interaction between these three systems, which enable the body to move in the most efficient manner. It is derangement of one or more of these systems that produce the pathologic states seen in symptomatic neurologic disease. Understanding how these systems work will enable the clinician to recognize and localize nervous system disorders.

An example from the preceding concept is illustrated by the clinical finding of ataxia. Ataxia is defined as motor incoordination but may be produced by lesions involving motor, sensory or cerebellar pathways. If a patient is noted to have arm clumsiness on finger to nose testing, this could be secondary to weakness of arm and hand muscles, to loss of proprioception in the upper extremity or due to a cerebellar lesion. If weakness is present, the clumsiness is defined as motor ataxia.

If strength is normal, and there is a marked proprioceptive deficit, such that the arm's position can only be determined by the patient looking at it, then we have sensory ataxia as the cause of arm clumsiness. Sensory ataxia of lower extremity and truncal muscles produces Romberg's sign whereby the patient can only maintain balance while standing if his eyes are open. This is because he has absent proprioceptive cues and must rely on vision to keep his balance.

Finally, if motor strength and sensation are normal and incoordination is still present, it is most likely of cerebellar origin. Localizing lesions to specific portions of the cerebellum will be covered later in this chapter.
Section Two

System Review
In this section the following systems will be reviewed in greater detail:

- Cranial Nerves
- Mental Status Examination
- Sensory System
- Extrapyramidal System
- Pyramidal System
- Cerebellum
- Peripheral Nervous System
- Individual Muscle Testing
- Evaluation of Speech and Language

Cranial Nerves
There are 12 cranial nerves; knowledge of the location and course of the cranial nerves is important in localizing lesions. (Figure 2.1)

Figure 2-1: Dorsal view of cranial nerve nuclei in the brainstem and upper cervical cord. Cranial nerve motor nuclei are on the left and sensory nuclei on the right.

Each of the cranial nerves will be reviewed individually for anatomy, tests of function, and potential pathology.

Cranial Nerve I–Olfactory Nerve Video
The olfactory nerve passes through the cribiform plate of the ethmoid bone and synapses onto the olfactory bulb, which traverse posteriorly and terminate in the ipsilateral hippocampal gyrus, with complex connections with multiple nuclei of the limbic system.

To examine the olfactory nerve, the patient is asked to close his/her eyes while compressing each nostril separately. A tube containing a common substance with a strong odor, such as coffee, cinnamon or peppermint, is then placed below the nostril. The patient is asked if he can smell the substance and, if so, recognize it. The patient's ability to simply smell the substance eliminates anosmia (absence of smell).

The most common causes of anosmia are the common cold and allergic rhinitis. Tumors of the frontal lobe, such as meningioma, may compress the olfactory nerve or bulb and produce anosmia. Smell, like other sensations, may diminish with age. In the setting of head trauma the olfactory nerve is the most commonly injured cranial nerve due to shearing injuries that may or may not be associated with fractures of the cribiform plate. If rhinorrhea occurs after head trauma, nasal drip should be checked for the presence of glucose with a Dextrostix? or urine test strip. A positive test for glucose suggests cribiform plate fracture with cerebrospinal fluid leak as discharge from nasal mucosa does not contain glucose.
Cranial Nerve II–Optic nerve (see Chapter on the Visual System for a separate discussion)

Cranial nerve II, the optic nerve, is composed of axons that originate in the ganglion cell layer of the retina. The optic disk of the fundus corresponds to the attachment of the optic nerve to the retina. The absence of rods and cones, the fundamental organs of sight, at the optic disk accounts for the blind spot in one's visual field. The optic nerve traverses posteriorly from the orbit through the optic foramen (which also contains the ophthalmic artery) and merges with the contralateral optic nerve to form the optic chiasm. A partial decussation of the optic nerves at the optic chiasm results in the formation of the optic tracts. Each tract contains axons from both retina, and project around the cerebral peduncles to synapse at the lateral geniculate body. Some fibers from the lateral geniculate body project to the midbrain to participate in the pupillary light reflex. From the lateral geniculate body arise the optic radiations which hug the lateral ventricles as they traverse posteriorly and then medially to the primary visual cortex in the occipital lobe.

The optic nerve is a special sensory nerve that can be assessed by testing for visual acuity, visual fields, and funduscopic examination of the retina. Visual acuity reflects central vision or vision subserved by the macula where cones are in highest concentration. Monocular vision is tested by having the patient cover one eye, hold a pocket-sized Snellen chart at arm's length, and read the smallest numbers on the chart that can be read. Visual acuity is graded from 20/20 to 20/800. Corrective lens, if available, should be worn during testing. In the event that visual acuity is so severely impaired that a miniature Snellen chart is not useful, ask the patient to count fingers placed about 14 inches in front. Failing this check for perception of movement, then light. Poor visual acuity may be associated with lesions involving the lens (cataracts), anterior optic chamber (glaucoma), retina (macular degeneration) or optic nerve (optic neuritis).
Figure 2-2: Examination of the patient's left eye visual fields by confrontation. The patient is asked to identify the number of fingers, which the examiner raises in each quadrant while centering his gaze on the examiner's right eye.

Visual field testing assesses the integrity of the optic pathways as it comes from the retina, optic nerves, optic chiasm, optic tracts, and optic radiations to the primary visual cortex. It is most commonly performed by confrontation (Figure 2-2). The patient faces the examiner while covering one eye so that he fixates on the opposite eye of the examiner, directly in front of him.

Testing is performed by covering one of the patient's eyes and having the patient fixate on the examiner's nose. One to three fingers are then shown to the patient in each of the four visual quadrants of each uncovered eye and the patient asked to state the number of fingers seen. Lack of vision in quadrants can then be detected and mapped out to various types of field defect.

If the patient is uncooperative, visual field examination may be grossly tested by asserting a threatening hand to half of a visual field (while cautiously avoiding movement of air that can result in a corneal blink reflex) and observing for a blink to threat.

Monocular visual field deficits are often due to lesions anterior to the optic chiasm, ipsilateral to the field cut as may be seen with lens dislocation, or retinal infarction from occlusion of the ophthalmic artery. Homonymous visual field deficits (toward the same side, e.g., left temporal, right nasal = left homonymous hemianopsia) imply a lesion.
posterior to the optic chiasm (Figure 2-3). The more congruous, (looks the same for each eye), the homonymous field cut; the more posterior the lesion is along the optic radiations. If macular sparing, or sparing of the center of vision, is detected with a homonymous hemianopsia, the lesion is most likely in the occipital lobe, as the macular area of the visual cortex is kept viable after a posterior cerebral artery infarct by terminal branches of the middle cerebral artery.

Figure 2-3: Lesions of the optic nerve, optic chiasm, optic tract, optic radiations and primary visual cortex produce characteristic visual field deficits.

Funduscoppy is performed with an ophthalmoscope. The patient is asked to fixate on an object in the distance while the examiner uses his right eye to examine the patient's right eye and the left eye for examination of the patient's left eye. Once the fundus is visualized, systematic examination of the optic disk, with attention to color and definition of disk margins, arterial supply, venous pulsations, and surrounding retina is conducted.

Swelling of the optic disk may be due to inflammation of the optic nerve, optic neuritis, or papilledema. These conditions may be difficult to differentiate based on fundoscopy alone. Typically, optic neuritis is associated with decreased visual acuity and an enlarged blind spot. Optic pallor implies optic atrophy from retrobulbar neuritis, as seen in multiple sclerosis, or ischemic optic neuropathy from small vessel infarction of the optic nerve secondary to long-standing hypertension. Papilledema implies increased intracranial pressure. Visual acuity is not affected unless there is secondary atrophy of the optic nerve from chronic pressure on the optic nerve. With papilledema, venous pulsations may be lost. Pallor of a segment of the fundus, associated with complaints of a "pie in the sky" loss of monocular vision, suggests branch central retinal artery occlusion.
secondary to embolic or thrombotic occlusion of either the ciliary or ophthalmic arteries, both of which supply the optic nerve.

Cranial Nerves III, IV, and VI–Oculomotor, Trochlear and Abducens Nerves (see Chapter on the Visual System)

The oculomotor (III), trochlear (IV), and abducens (VI), nerves together innervate the extraocular muscles (Figure 2-4). The primary action of the medial rectus is adduction and that of the lateral rectus is abduction. The superior rectus and inferior oblique primarily elevate the eye while the inferior rectus and superior oblique primarily depress the eye.

![Diagram of extraocular muscles](image)

**Figure 2-4:** The action and nerve supply of the extraocular muscles is demonstrated.
The oculomotor nerve (cranial nerve III) also innervates the **levator palpebrae muscle**, which elevates the eyelid, the **pupillo-constrictor muscle**, which constricts the pupil, and the **ciliary muscle**, which controls the thickness of the lens, allowing for accommodation. The nuclear complex of the oculomotor nerve lies medially within the midbrain, ventral to the aqueduct of Sylvius (Figure 2-5). It consists of the oculomotor nucleus, which innervates the skeletal muscles of the eye and the Edinger-Westphal nucleus, which carries parasympathetic innervation to the pupil and ciliary muscle. The superior branch of the oculomotor nerve supplies the superior rectus and levator of the upper lid while the inferior division innervates the medial rectus, inferior rectus, inferior oblique, pupilloconstrictor muscle and ciliary body.
Figure 2-6: A complete left III nerve palsy is illustrated along with clinical presentations of left VI and IV nerve palsies.

A complete oculomotor palsy will manifest as **ptosis, dilated** and **fixed pupil**, and **outward and slightly downward deviation of the eye**. (Figure 2-6). **Pupil-sparing**, isolated oculomotor nerve paresis is often due to ischemia from hypertension, diabetes, tertiary syphilis, or vasculitis, as the pupillomotor fibers travel along the periphery (outside) of the oculomotor nerve, closer to the blood supply of the nerve and are less susceptible to end-arteriole ischemia that tends to affect the center of the nerve. On the other hand, acquired third nerve palsies, which involve the pupil, may be due to compressive lesions such aneurysm of the posterior communicating artery, head trauma,
and tumors of the cerebral hemispheres compressing the oculomotor nerve and the parasympathetic fibers, which run peripherally within it.

The trochlear nerve (cranial nerve IV) nucleus lies in the medial midbrain, and wraps around the midbrain dorsally, alongside the cerebral peduncles, and courses between the posterior cerebral and superior cerebellar arteries (Figure 2-7). As the trochlear nerve has the longest intracranial distance of the cranial nerves, head trauma is the most common cause of nerve injury. A large proportion of fourth nerve palsies, however, are congenital and associated with a superior oblique that is shortened and tethered.

![Figure 2-7: The course of the trochlear nerve in the pons, across the posterior and superior cerebellar arteries, across the petrous ridge of the temporal bone, through the cavernous sinus, and out the superior orbital fissure is illustrated.](image)

The abducens nerve (cranial nerve VI) nucleus lies in the caudal portion of the pons. The axons course ventrally through the pons and then travels in the middle of the cavernous sinus, through the superior orbital fissure and into the lateral rectus muscle, which it innervates. The facial nerve loops around the abducens nerve nucleus within the pons, therefore a pontine lesion in this location will produce ipsilateral paralysis of the lateral rectus and lower motor neuron facial nerve palsy (Figure 2-8).
Figure 2-8: Note how the facial nerve wraps around the nucleus of cranial nerve VI within the pons.

Figure 2-9: The arrows and numbers indicate the sequence of eye movements tested in the six cardinal fields of gaze.
Examination of the extraocular muscles is first conducted by examining the alignment of the patient's eyes in the **primary position** (patient looking straight ahead). Shine a light into the patient's eyes and examine the corneal light reflection. If the light falls off center to a pupil, there is evidence of ocular malalignment, termed **exotropia** if the eye is laterally deviated, **esotropia** if the eye is medially deviated, **hypertropia** if the eye is deviated upwards and **hypotropia** if the eye is deviated downwards. Next, examine ocular motility by asking the patient to follow the examiner's finger as it is moved through the six cardinal fields of gaze (**Figure 2-9**). During conjugate eye movements the yoke muscles are equally stimulated so a lag in eye movement is a subtle sign of extraocular muscle weakness. Complaints of double vision by the patient will not always manifest as visible extraocular muscle weakness. Diplopia is worse in the direction of gaze of the weak muscle.

**Cranial Nerve V–Trigeminal Nerve** [Video]
The trigeminal nerve provides sensation to the face and mucous membranes of the nose, mouth, tongue and sinuses as well as motor innervation to the muscles of mastication.

![Figure 2-10: The subdivisions of cranial nerve V innervation to the face is illustrated.](image)

The cell bodies of most sensory neurons innervating the face lie in the Gasserian ganglion and the rest are in the mesencephalic nucleus. There are three sensory divisions of the
trigeminal nerve, all with their origin in the Gasserian ganglion: the ophthalmic (V1), maxillary (V2) and mandibular branches (V3). The ophthalmic division innervates the conjunctiva, cornea, upper lid, forehead, bridge of the nose and upper scalp to the vertex (Figure 2-10). The maxillary branch carries sensory and motor neurons to the lower jaw, pinna of the ear, anterior portion of the external auditory meatus, ipsilateral tongue, lower teeth, and mucosal surface of the cheeks and floor of the mouth. The motor fibers innervate the temporalis, masseters and medial and lateral pterygoids. The mandibular branch innervates the cheek, lateral surface of the nose, upper teeth, jaw, and mucosal membranes of the nose and upper portion of the oropharynx.

Light touch is assessed by using a cotton wisp and gently touching the areas innervated by the three divisions of the trigeminal nerve while the patient's eyes are closed. The patient is asked to say, "touch" whenever he feels the cotton. To test pain sensation, repeat the above maneuver with the sharp and round end of a safety pin, asking the patient to discriminate between "sharp" and "dull." Temperature sensation can be tested by filling two test tubes individually with cold and warm water, applying the test tubes to the three divisions of the trigeminal nerve and asking the patient to differentiate cold from warm.

The corneal blink reflex tests the integrity of the ophthalmic division of V, which innervates the cornea and constitutes the sensory component of the reflex, and the facial nerve, which constitutes the motor arc of the reflex by innervating the orbicularis oculi and allowing closure of the eyelid. To test the reflex, the end of a cotton Q-tip is twisted into a point. The patient is asked to look laterally and the cotton point applied gently onto the cornea from the direction contralateral to the gaze so as to avoid reflex defensive blinking. In patients who are comatose, the presence of a corneal blink reflex implies that the sensory nucleus of V and the facial nerve nucleus, both in the pons, are intact.

Cranial Nerve VII–Facial Nerve Video

The facial nerve, cranial nerve VII, innervates all the muscles of facial expression, i.e., the muscles around the eyes, mouth, nose, ears and neck. It also innervates the stapedius muscle in the ear, which dampens excessive movement of the ossicles when subject to loud sounds. The facial nerve subserves taste to the anterior two thirds of the tongue and sensation to the outer ear.

The motor nucleus of VII sits in the pons while its axons loop around the nucleus of the abducens nerve and emerges from the pontomedullary junction. The facial nerve then courses through the internal auditory meatus where it is joined by the auditory nerve, and enters the facial canal of the temporal bone. Distal to the geniculate ganglion, the facial nerve gives off the chorda tympani, which supplies taste to the anterior two thirds of the tongue via the lingual nerve. The facial nerve exits the facial canal through the stylomastoid foramen, passing through the parotid gland, before innervating the muscles of the face and the platysma.
Figure 2-11: A right upper motor neuron VII lesion due to a left subcortical stroke is illustrated.
Figure 2-12: A lower motor neuron VII lesion due to a left peripheral facial nerve palsy is illustrated.

To test the facial nerve, first observe the patient's face for symmetry by paying close attention to the nasolabial folds, forehead wrinkles, spontaneous smiling and blinking. Then, ask the patient to show his teeth, raise his eyebrows, squeeze his eyes shut tightly and hold air in his cheeks. Facial weakness may be due to upper motor neuron or lower motor neuron facial palsy. Upper motor neuron palsy implies that there is a lesion contralateral to the side of facial weakness which is disrupting the face motor fibers somewhere in its course from the primary motor cortex to the facial nucleus within the pons (i.e., upper motor neuron to the facial nerve nucleus, Figure 2-11). A typical presentation of an upper motor neuron palsy is a patient with a right subcortical lacunar infarct resulting in flattened left nasolabial fold, decreased upturning of the left corner of the mouth on smiling, and symmetric wrinkling of forehead bilaterally, in addition to a left hemiparesis. Lower motor neuron palsy implies a lesion involving the facial nerve at the nucleus in the pons or along the course of the facial nerve ipsilateral to the side of facial weakness (Figure 2-12). Bell's palsy is a lower motor neuron facial palsy whereby the patient has unilateral flattening of the nasolabial fold with inability to upturn the corner of the mouth upon smiling, inability to wrinkle his forehead, delayed or absent blinking due to weakness of the eyelid, and inability to hold air in the cheeks due to escape of air through the corner of the mouth which is weak. In addition, patients with
Bell's palsy may complain of dry eye from disruption of parasympathetic innervation of the lacrimal gland, hyperacusis or augmented hearing in the ear ipsilateral to the lesion from paralysis of the stapedius muscle and diminished taste from a lesion proximal to the lingual nerve, which inhibits afferent signals concerning taste from reaching the brainstem.

**In summary upper motor neuron facial weakness spares the frontalis (forehead muscle) so the patient can wrinkle his brow. Lower motor neuron facial weakness involves the forehead muscle and the patient can't wrinkle the brow and in addition has unilateral hyperacusis and loss of taste.**

**Facial diplegia**, or bilateral lower motor neuron facial weakness, is seen in such conditions as Guillain-Barré syndrome or sarcoidosis.

**Cranial Nerve VIII—Acoustic Nerve** [Video](#)

The auditory nerve, cranial nerve VIII, is composed of two divisions, the **cochlear** nerve, which subserves hearing, and the **vestibular** nerve, which provides sense of balance. The cochlear nerve sits in the lower pons, near the cerebellopontine angle. Lesions of the cochlear nerve commonly present with ipsilateral decreased hearing and sometimes tinnitus. The vestibular nerve is composed of nerve fibers from the labyrinth of the inner ear, which travel alongside the cochlear nerve to terminate on the vestibular nuclei within the lower pons.

To test the auditory nerve, first check gross hearing in each ear by rubbing your fingers about 30 inches from the patient's ear, with the contralateral ear covered. If hearing in one ear is impaired, perform Rinne and Weber tests. Both tests employ the use of a 256 Hz tuning fork. In the **Rinne** test, the vibrating tuning fork is place over the mastoid process, behind the ear to test bone conduction (BC). Ask the patient to tell you when he no longer hears the vibrating fork, after which the tuning fork is placed in front of the ear and the patient asked if he can hear it (air conduction = AC). Next perform the **Weber** test by placing a vibrating tuning fork over the middle of the forehead and ask the patient if the sound is louder in one ear compared to the other. With conductive hearing loss, from middle ear disease or obstruction of the external auditory meatus with wax, BC will be greater than AC and Weber test will lateralize to the deaf ear. However, with sensorineural hearing loss AC is better than BC and Weber test will lateralize to the good ear.
Figure 2-13: The Hallpike maneuver is illustrated. The patient initially is seated upright and asked to fall backwards, so that his head is below the plane of his trunk. The examiner then turns his head to one side and asks the patient to look in the direction to which his head is turned.

Vestibular nerve function can be tested with postural maneuvers. In patients suspected of benign positional vertigo, presenting with vertigo or dizziness associated with changes in head position, the Hallpike maneuver should be attempted when not contraindicated due to severe cervical spine disease. To perform the Hallpike maneuver, the patient sits up in bed and then quickly lies back on command so that his head hangs over the edge of the bed. The head is tilted backward below the plane of his body and turned to one side by the examiner who holds the patient's head in his examiner who holds the patient's head in his hands. The patient is asked to look in the direction that his head is turned (Figure 2-13). Watch for nystagmus in the direction of gaze and ask the patient if he feels vertigo. If no nystagmus is observed after 15 seconds, have the patient sit up and repeat the maneuver turning the patients head and directing his gaze in the contralateral direction. The absence of nystagmus suggests normal vestibular nerve function. However, with peripheral vestibular nerve dysfunction, such as benign positional vertigo, the patient will complain of vertigo, and rotary nystagmus will appear after a 1 to 5 second latency toward the direction in which the eyes are deviated. With repeated maneuvers, the nystagmus and sensation of vertigo will fatigue and disappear, a sign of peripheral vestibular disease, in contrast to central vestibular disease from stroke or other intrinsic brainstem lesions, which manifests as nonfatigable nystagmus without delay in onset.

Cranial Nerves IX and X–The Glossopharyngeal and Vagus Nerves Video
The glossopharyngeal nerve (cranial nerve IX) contains sensory and motor fibers as well as autonomic innervation to the parotid glands. It mediates taste to the posterior one third of the tongue and sensation to the pharynx.

Like the glossopharyngeal nerve, the vagus nerve (cranial nerve X) contains sensory, motor and autonomic fibers. Motor innervation to the muscles of the soft palate, pharynx and larynx originates in the medulla. Autonomic fibers arise from the dorsal motor
nucleus of vagus and synapse at peripheral ganglia to provide parasympathetic innervation to the trachea, esophagus, heart, stomach, and small intestine.

Figure 2-14: A normal soft palate is illustrated on the left. On the right, a right palatal palsy from a lower motor neuron X nerve lesion has resulted in deviation of the uvula to the left.

To test glossopharyngeal and vagus nerve function, examine the position of the uvula and its movement by asking the patient to say "Ah." the soft palate should elevate symmetrically and the uvula should remain in the midline. The gag reflex can be tested by touching the pharyngeal wall on each side with a cotton tip applicator. This reflex relies on an intact sensory arc, as mediated by sensory fibers of the glossopharyngeal nerve to the soft palate, and an intact motor arc, as mediated by the motor fibers of the vagus nerve to the soft palate and pharynx. Deviation of the uvula to one side implies a lower motor lesion of the vagus nerve contralateral to the side the uvula is deviating to (Figure 2-14). An upper motor neuron vagus nerve lesion will present with the uvula deviating toward the side of the lesion. The presence of a gag reflex does not necessarily imply that the patient can swallow without aspiration after a stroke. Impairment of swallowing is usually due to bilateral vagus nerve lesions. On the other hand, the absence of a gag reflex does not imply inability to swallow. Hoarseness may be seen with tumors encroaching on the recurrent laryngeal nerve, a branch of the vagus nerve. This results in unilateral vocal cord paralysis.

Cranial Nerve XI–The Accessory Nerve Video
The spinal accessory nerve, cranial nerve XI, innervates the sternocleidomastoid and trapezius muscles.

To test the strength of the sternocleidomastoids ask the patient to turn his head against your hand, which is placed over the mandible. Repeat this maneuver with your hand on the contralateral mandible. Observe the sternocleidomastoid, which is contralateral to the
side to which the patient is turning his head. Weakness detected when the patient turns his head to the left implies that the right sternocleidomastoid is weak. To test the trapezius, ask the patient to shrug his shoulders and press down on the shoulders. Trapezius weakness is manifest as difficulty in elevating the shoulders. When the sternocleidomastoid and trapezius are weak on the same side, an ipsilateral peripheral accessory palsy, involving cranial nerves X and XI, is implied as may be seen with a jugular foramen tumor, i.e., glomus tumor or neurofibroma. Because the cerebral hemisphere innervates the contralateral trapezius and ipsilateral sternocleidomastoid, a large right hemisphere stroke will result in weakness of the left trapezius and right sternocleidomastoid. Bilateral wasting of the sternocleidomastoid may be seen with myopathic conditions such as myotonic dystrophy and polymyositis or motor neuron disease, the latter usually associated with fasciculations.

**Cranial Nerve XII—Hypoglossal Nerve** [Video](#)

The hypoglossal nerve, cranial nerve XII, is a pure motor nerve, innervating the muscles of the tongue.

To test the function of the hypoglossal nerve, ask the patient to protrude his tongue and wiggle it from side to side. Look for deviation and atrophy. To check for subtle weakness, ask the patient to push his tongue against the wall of his cheek while you push against it through the outer cheek. Like the forehead, each side of the tongue receives upper motor neuron innervation from bilateral motor cortices. Each half of the tongue pushes the tongue in the contralateral direction, i.e., left half of tongue pushes to the right ([Figure 2-15](#)). Thus, if the tongue deviates to one side, it is pointing to the side that is weak. Tongue deviation, combined with wasting on the side to which it is deviated, implies a unilateral, lower motor neuron, hypoglossal nucleus or nerve lesion as may be seen with syringobulbia (a degenerative cavity within the brainstem), with basilar meningitis, or foramen magnum tumor. If the tongue deviates and is of normal bulk, one should consider an upper motor neuron lesion, such as stroke or tumor in the hemisphere contralateral to the side of deviation, and look for associated hemiparesis on the side of tongue deviation.
Figure 2-15: The opposing action of the two halves of the tongue is illustrated. Note that the tongue, like most muscles in the body derives supranuclear innervation from the contralateral motor cortex.

The Mental Status Examination
As previously noted, the neurologic exam begins with an assessment of the patient's mental status. In most cases, a large part of the mental status exam may be ascertained from observation of the patient as history is provided. A more detailed mental status exam can be divided into the following components:

- Level of consciousness
- Intellectual performance
- Language

Level of Consciousness
Level of consciousness implies awareness of surroundings. If one is examining a patient who is somnolent or comatose, it is important to determine the degree of stimulation that is required to alert the patient, i.e., voice, light touch, sternal rub.
Motor system. In evaluating the motor system, look for lateralizing signs such as asymmetry of movement either spontaneously or to painful stimulation and asymmetric reflexes. Describe any spontaneous posturing. **Decorticate posturing** is characterized by tonic flexion of the arms and extension of the legs and implies a lesion at the level of the midbrain (Figure 2-16). **Decerebrate posturing** is manifest as tonic adduction and extension of the arms and legs and suggests a lesion at the level of the pons. In general, metabolic disturbances do not result in posturing, although anoxia and hypoglycemia can produce posturing. A mass lesion, which previously produced lateralized signs, may result in decorticate or decerebrate posturing when it expands and compresses the brainstem.

Pupils and fundi. Papilledema suggests increased intracranial pressure from a mass lesion or cerebral edema. Check the pupils for size and reactivity to direct light. With metabolic disease the pupils tend to be small and sluggishly reactive. Asymmetry of pupil size and reactivity, particularly the unilateral dilated pupil, suggests mass effect with herniation. **Thalamic** lesions usually produce a 2 mm nonreactive pupils, 4-5 mm fixed pupils suggest a **midbrain lesion** and pinpoint pupils suggest **pontine dysfunction**. Any nonmetabolic sign requires emergent CT scan for evaluation of possible mass lesion.
Ocular movement. Eye movements should be intact with metabolic disease, as noted with spontaneous movement or with Doll's eye maneuver. Doll's eye maneuver should be performed once severe cervical spine disease or fracture has been ruled out (Figure 2-17). The patient's head is moved swiftly from side to side, with the eyes held open. An intact Doll's eye reflex is characterized by the eyes moving conjugately in the direction opposite to which the head is being turned, i.e., head turn to the left should swing both eyes across the midline to the right. This maneuver checks the integrity of the brainstem between the midbrain and pons. If the Doll's eye maneuver does not produce eye movements, cold caloric testing is necessary (Figure 2-18). The head of the bed is raised by 30 degrees. Examination of the tympanic membranes for perforation should be ruled out before cold water is injected into each ear. If the brainstem is intact, injection of cold water into the ear should elicit tonic conjugate deviation of the eyes toward the side of injection. Nystagmus away from the side injected may or may not be present, but is not necessary to assess the integrity of the brainstem. Inability to produce the full range of eye movements with either the Doll's eye maneuver or cold calorics suggests brainstem pathology from pressure on the brainstem (herniation from a subdural hematoma) or from direct brainstem injury (basilar artery stroke). The unilateral third nerve palsy, manifest as a fixed, dilated pupil in an eye that is "down and out" in position, is the classic example of a hemisphere lesion producing brainstem signs of oculomotor and pupillary dysfunction. A mass in one hemisphere causes the uncus of the temporal lobe to herniate over the edge of the tentorium, where it impinges on the third nerve. Compression of the parasympathetic fibers on the outer portion of the nerve results in ipsilateral pupillary dilation and is an early sign of the uncal herniation syndrome.
Respiratory patterns. The respiratory pattern of metabolic disease characteristically produces Cheyne-Stokes respirations however; early mass lesions may also produce Cheyne-Stokes respirations. Central neurogenic hyperventilation, which is manifest as rapid shallow breathing, indicates midbrain dysfunction. Cluster or apneustic breathing suggests pontine injury. Ataxic, shallow breathing is characteristic of agonal respirations from medullary lesion.

In the patient who is somnolent but arousable to stimulation, or confused, the etiology is most likely metabolic or toxic causes unless there are focal neurologic signs to suggest a structural lesion.

Intellectual Performance
Intellectual performance provides the best evidence of organic brain damage and its extent. Diffuse involvement of the brain results in deterioration of general intellectual functions while a structural lesion results in impairment of specific intellectual functions. Difficulties with maintaining attention and perseveration of thought manifest as slowness to shift from one topic to another. These, and poor memory are examples of
specific intellectual deficits which should lead the examiner to more specific testing of memory, calculations, and judgment.

Memory depends on the ability to store and retrieve information both on a short and long-term basis. It is critical for learning. When evaluating memory function, it is important to realize that inattention, decreased motivation, and poor cooperation, all symptoms of depression, can appear to impair memory. However, in depression, memory deficits may be overcome by improving the patient's cooperation and concentration, while organic deficits in memory are not altered with increased effort.

Formation of long-term memory requires both intact sensory store, short-term memory and the consolidation of short-term memory into long-term memory. Most clinical memory deficits involve transfer of information from short term to long-term memory. This deficit is referred to as anterograde amnesia or the inability to form new long-term memory and is classically seen in Korsakoff's psychosis from thiamine deficiency. Once information has been stored in long-term memory it can decay if not rehearsed. Long-term memory is the last memory to be lost in organic disease, with the most remote events, i.e., childhood, retained the longest. This phenomenon is observed in Alzheimer's dementia. The loss of remote memory is referred to as retrograde amnesia and is always accompanied with severe anterograde amnesia. A classic cause of this condition is head trauma with the memory deficit proportional to the severity of the blow.

To test memory, check digit span to make sure attention capacity is intact. The patient is asked to repeat a gradually increasing sequence of numbers, e.g., 2-3-7-4, 5-8-4-6-1, 2-0-5-1-6-9, etc. The normal patient should be able to repeat at least 7 digits. Present the patient with three words (baseball, tree, car) and three complex shapes that are drawn for the patient. Have the patient recall the words and shapes after five minutes. This procedure checks short-term to long-term memory transfer and is an effective screen for anterograde amnesia. Ask the patient about the remote and recent past to check for retrograde amnesia.

References

The Sensory System

Performing this part of the examination may be time consuming because of misunderstanding or lack of patient cooperation. With some experience and practice, useful information can be obtained. If the patient has no sensory symptoms a routine sensory examination is usually performed. If, however, the patient has sensory symptoms, an examination tailored to the symptoms is performed in addition to the usual survey.

We will first go over some basic neuroanatomic pathways so that abnormal findings on the examination can be translated into useful clinical information.

The sensory modalities usually tested are superficial sensation and deep sensation. Superficial sensation encompasses light touch, pain and temperature sensibility. Deep sensation includes joint and vibratory sensibility and pain from deep muscle and ligamentous structures.

Sensory stimuli are picked up at their origin by specialized receptors whose unique firing patterns enable the brain to identify different types of stimuli. The information is relayed upwards to its ultimate destination, the primary sensory cortex of the parietal lobe (post-central gyrus). Here, sensory information is integrated into meaning (e.g., feeling an object and being able to identify it, or experiencing pain and then undergoing suffering and anguish as a result of it). All sensory modality fibers are grouped together in peripheral nerves but once they reach the spinal cord, they split and travel to their ultimate destination over different routes. It is awareness of these pathways and how they are distributed at different levels of the neuraxis that enables the examiner to localize the level of a lesion based on the clinical findings of the sensory examination.
Peripheral nerve lesions can produce sensory deficits, motor deficits, autonomic dysfunction, or all of these. The sensory loss characteristically has sharp borders and if it is a mixed nerve for example, the median nerve, sensory, motor and autonomic fibers are affected. Sensory nerves have no motor fibers and lesions produce sensory loss for all modalities. Partial lesions may produce a disquieting burning or lancinating pain as well. An example of this type of nerve is the lateral femoral cutaneous nerve supplying the skin of the lateral thigh (Figure 2-19). Examples of findings secondary to common peripheral nerve lesions are found at the end of this chapter.

Figure 2-19: Lateral femoral cutaneous nerve sensory loss.
Figure 2-19A: Spinal cord sensory pathways.

The peripheral nerve cell body is located in the dorsal root ganglion near the spinal cord. As the specific central processes of these cells enter the spinal cord (Figure 2-19A) they either synapse and cross in one or two segments to enter the spinothalamic tract (pain and temperature), or remain ipsilateral and travel upwards in the dorsal columns or lateral spino cerebellar tracts (proprioception, joint receptor sensation). The dorsal columns convey information that will ultimately reach consciousness and the spino cerebellar tracts send sensory information to the cerebellum for its use in coordinating motor activity.

If a patient has a lesion involving the nerve root itself there will be sensory and motor loss characterized by the nerve fibers present in the root. Root sensory distribution follows a dermatomal distribution. A dermatome map is shown in Figure 2-20.

Figure 2-20: Dermatome map of spinal sensory nerve roots.

Points to remember about root lesions are the following:

- Most frequent in the cervical and lumbo-sacral regions.
- Associated with pain.
• Commonly caused by intervertebral disc herniations and spondylosis.
• Can also occur secondary to metastatic disease, metabolic or inflammatory/infectious disorders.
• Sensory loss found on exam is not always dramatic because of overlap of sensation with the roots above and below.
• Muscle weakness is characteristic for the root in question.

Once the sensory fibers enter the spinal cord they begin their upward ascent. Pain and temperature fibers travel upwards on the side opposite to their origin in the lateral spinothalamic tract (Figure 2-21). Fibers for facial pain and temperature sensation originate in the Gasserian ganglion and then travel downward in the descending root of V before they cross over to join the contralateral spinothalamic tract. As a result of this unusual arrangement the lateral medulla is characterized by having ipsilateral facial and contralateral body pain and temperature fibers on the same side. For example, a unilateral lesion in the lateral medulla (Wallenberg’s syndrome) demonstrates loss of pain and temperature on the ipsilateral side of the face, and contralateral side of the body.
Proprioceptive fibers and touch fibers travel in the dorsal columns ipsilateral to the side of their origin until they reach the lower medulla; then the fibers cross to the opposite side and travel up to the thalamus where they are joined by facial sensory fibers from the opposite trigeminal sensory nucleus. After synapsing in the thalamus the fibers project to
the primary sensory cortex of the parietal lobe where all sensory modalities are processed and interpreted.

Figure 2-22: Topographic relationship for sensation on the post central gyrus (parietal lobe). Similar topographic representation is present for motor control on the precentral gyrus (frontal lobe).

Some light touch fibers travel in the anterior spinothalamic tract (Figure 2-23) and some vibratory fibers travel in the lateral columns. For this reason there may be sparing of some light touch and vibration sensation with dorsal column lesions.
Figure 2-23: Proprioceptive – light touch sensory pathway.
The Sensory Examination
The patient should be in a comfortable position and undressed except for a gown. Exposure of the feet, abdomen and trunk as well as the perineum is necessary to perform an adequate sensory examination.

Primary Modalities to be Tested

- **Light touch**

  Test item: Cotton wisp. Touch patient lightly with eyes closed and have them say "yes" when touched. Compare sensation on right and left side of body. Ascend from the foot upward and ask the patient to identify the level where touch is first appreciated or becomes more pronounced.

- **Vibration**

  Test item: 256 Hz Tuning fork. Strike the fork and hold it to a bony prominence such as the first toe, ankle malleous, tibial plateau, or ileum. Having to increase the vibration and apply more proximal stimulation implies that the deficit is more pronounced.

- **Pain**

  Test item: Sterile pin. Touch the patient with the sharp or dull end and ask them to identify "sharp or dull" with the eyes closed. One can also ascend from the foot upwards
and ask the patient to identify the level where appreciation of sharpness occurs or where an appreciable increase in sensation occurs.

- **Temperature**

Test item: Cold tuning fork; hot and cold water in a test tube or flask. With eyes closed ask them to identify when touched with hot or cold. Levels and laterality can also be tested as described for pain and light touch.

- **Position sense**

Move patient's finger and, later, toe up or down with the patient's eyes closed, and ask them to identify the direction of the motion. Greater deficits are characterized by having to move a more proximal joint such as ankle, knee or hip for the patient to appreciate the movement.

**Cortical Discrimination Testing (Combined sensation)**

Simple sensations can be appreciated and poorly localized at the thalamic level. It is at the cortical level that sensations are combined and integrated into meaningful and symbolic information. A cortical lesion is usually recognized if there is not a significant absence or loss of primary sensory modalities, and the patient is unable to integrate the appreciated sensations into symbolic information. When sensory recognition functions are impaired a lesion is implied in the contralateral parietal lobe. Basic tests for these modalities are:

**Two point discrimination.** Test item: small calipers. These may be applied to the face, fingertips, palms and tibial regions. The usual sensory thresholds are: face 2-5 mm; finger tips 3-6 mm; palms 10-15 mm; and shins 30-40 mm. Increased distance threshold or loss of this ability implies a contralateral parietal lobe lesion.

**Stereognosis.** This is the ability to identify an object only by feeling it. The patient is asked to close their eyes. A test object is placed in the hand being tested. The patient can manipulate and feel the object with the test hand only and is asked to identify it. Test items can include a key, thimble, coin or bolt. The side suspected to be abnormal is usually tested first.

**Traced figure identification.** Numbers (1-9) are traced on the fingertips or palms of the hands while the patient's eyes are closed. The examiner orients himself so that the numbers are upright to the patient. The patient is asked to identify each number.

**Double simultaneous stimulation.** Homologous parts of the body are touched simultaneously or separately (e.g., right hand, both hands, left hand). The patient is asked to answer right, left or both hands. With a parietal lobe lesion the patient may not identify being touched on the side opposite the lesion when right and left sides are simultaneously stimulated. This phenomenon is termed **sensory extinction.**
It will be through repetition and clinical correlation that one becomes proficient at doing the sensory examination. The more commonly seen sensory loss patterns are listed below.

1. **Isolated nerve lesions (mononeuropathy)**

   - Median nerve (Carpal tunnel syndrome) **Figure 2-25**
   - Ulnar nerve (Elbow entrapment) **Figure 2-26**
   - Lateral femoral cutaneous nerve (meralgia paresthetica) **Figure 2-19**

![Figure 2-25: Sensory distribution of the median nerve – Palm of hand.](image)

![Figure 2-26. Sensory distribution of the ulnar nerve – Palm of hand.](image)

2. **Mononeuritis multiplex**

   Combinations of peripheral nerve lesions occur, usually caused by nerve infarcts secondary to vasculitis or diabetic vasculopathy.
3. Sensory peripheral neuropathy
Disease affecting peripheral nerves may affect the Schwann cell myelin sheath (demyelinating neuropathy) or the nerve axons (axonal neuropathy). These two types are usually clinically indistinguishable in sensory neuropathies. Motor axonal neuropathy is associated with muscle atrophy. Peripheral neuropathy characteristically starts in the feet and is symmetrical. Progression is characterized by rising deficit levels in the legs and eventual involvement of the fingers. In any peripheral nerve or root lesion the sensory or motor arc of the deep tendon reflex can be interrupted leading to diminished or absent deep tendon reflexes. Distal reflexes (ankle) are diminished more than proximal reflexes (biceps).

4. Root lesion
The dermatome maps for the sensory distribution of individual roots are shown in Figure 2-20. Root lesions may manifest a vague sensory alteration or loss following the corresponding dermatome, or no objective sensory loss. Often the patient will have paresthesias in the root distribution. The location of common root paresthesias are C-5, shoulder region; C-6, thumb; C-7, middle finger; C-8, 5th finger; L-3, anterior thigh; L-5, great toe; and S-1, medial sole of the foot. If a patient cannot appreciate the sensation of bladder fullness, passing stools, or sexual sensations, it may imply deficits of the S-3,4,5 sensory roots.

Sensory loss or characteristic paresthesias, when combined with a root pattern of muscle weakness, will confirm the presence of radiculopathy. Root lesions are also, usually characterized by the presence of pain, especially if the root is being compressed.

5. Spinal cord
Lesions of the spinal cord are usually of two different types—external (compressive) lesions and intrinsic lesions.

External compressive lesions affect the spinal cord as a whole, even though one side may be compressed more. As a result all tracts are affected to some degree. Because the corresponding nerve root is also compressed or stretched, pain is a prominent symptom. Ascending and descending pathways are interrupted and sensation is usually diminished distal to the lesion. Localizing signs would be localized root pain, sensory loss below the level of the lesion, an absent root reflex at the level of the lesion, and generally increased reflexes below this level. Compressive lesions can be caused by herniated discs, tumors or abscess, among others.

Because sensory fibers separate into distinct tracts when they enter the spinal cord some are affected by intrinsic spinal cord lesions while others are completely spared. This produces a characteristic finding of intrinsic cord lesions termed sensory dissociation. These lesions may be caused by infarction, tumor or a syrinx. Some common cord syndromes are:

Brown-Séquard syndrome (Figure 2-27)
- Ipsilateral plegia below the lesion.
- Ipsilateral proprioception and light touch loss below the lesion.
- Contralateral pain and temperature loss below the lesion.

![Brown-Séquard Syndrome](image)

**Figure 2-27: Brown-Séquard Syndrome (Unilateral hemi-cord lesion).**

Anterior spinal artery infarction (Figure 2-28)

- Paraplegia below the lesion.
- Pain and temperature loss below the lesion.
- Sparing of dorsal column sensation.
Figure 2-28: Anterior Spinal Artery Infarction.

Central cord syndrome (cervical) (Figure 2-29)

- Shawl distribution pain and temperature loss.
- Sparing of light touch and proprioception.
- Lower motor neuron weakness of the affected cord levels (anterior horn cell involvement).
Figure 2-29: Central cord syndrome.

Complete cord transection. (Figure 2-30)

- loss of all modalities below the level of the lesion

Figure 2-30: Complete spinal cord transection.
6. Brainstem
Brainstem lesions at the level of the medulla have ipsilateral loss of pain and temperature of the face and contralateral loss on the body. Light touch and proprioceptive loss is contralateral. Above this level all sensory modality findings are contralateral to the side of the lesion because all pathways have crossed.

7. Thalamus
Thalamic lesions produce contralateral loss of all sensory modalities in the face, extremities and trunk. In addition, stimulation may be perceived as uncomfortable and painful (dysesthesia).

8. Cortical lesions
Lesions of the cerebral cortex cause diminution of all sensory modalities on the contralateral side of the body. In addition, higher integrative sensory functions are impaired causing defects in stereognosis, two-point discrimination, double simultaneous stimulation and traced figure identification as previously discussed. The extent of the sensory loss parallels the size of the lesion. The pattern of cortical sensory representation in the cerebral cortex is illustrated in Figure 2-22.

The foregoing contains essentials of the sensory examination and should become easier to perform and interpret with continued use. The video on how to perform the neurological examination should be watched as well.

Summary
Characteristics of sensory system lesions:

- **Peripheral nerve**
  - All sensory modalities are affected.
  - The borders are sharply demarcated.
  - There may be hyperesthesia, discomfort and pain.

- **Root**
  - All sensory modalities are affected.
  - Sensory loss is vague but in a dermatomal distribution.
  - Pain is present and may radiate in the dermatome distribution.

- **Spinal cord**
  - There is sensory dissociation.
  - A unilateral lesion produces ipsilateral loss of light touch and proprioception and contralateral loss of pain and temperature.

- **Medulla**
  - There is sensory dissociation.
  - Pain and temperature are lost on the ipsilateral side of the face and contralateral side of the body.
  - Light touch and proprioception are lost on the contralateral side of the body.

- **Upper**
  - There is sensory dissociation.
brainstem  •  All sensory modalities are now crossed and on the same side.
  •  Unilateral lesions cause contralateral loss of sensory modalities.

Thalamus  •  Sensory dissociation is no longer present.
  •  Ipsilateral lesions produce contralateral loss of all modalities.

Cerebral cortex  •  Sensory dissociation is absent.
  •  Ipsilateral lesions produce contralateral loss of all modalities.
  •  Discriminative sensory functions are lost.

The Extrapyramidal System Video
Reflect back to our description of the marionette, lying limp on the floor. (Review Section on System Integration) If the puppeteer wants to simulate normal, life-like action, he first puts tension on the strings that cause the legs, truck and neck to become erect. Similarly, activation of extensor muscle systems finally allows the developing neonate to stand. This function is carried out by an unconscious indirect motor system, called the extrapyramidal system (EPS). It is a primitive system, and is not fully understood.

The EPS basically consists of a group of large subcortical nuclei termed the basal ganglia. They include the caudate nucleus, and putamen (collectively termed the striatum), the globus pallidus, substantia nigra and the subthalamic nucleus. These nuclei receive input from the primary motor cortex (pyramidal system), have multiple reverberating connections among themselves, and send output to the ventral anterior thalamic nucleus, which in turn connects back to the motor cortex. There is also some output to reticulospinal tracts, which travel down the spinal cord and have a modulating effect on anterior horn cells which ultimately initiate movement. By and large, however, the EPS is a reverberating circuit receiving input from the motor cortex, processing it through its nuclei, and then send

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Section Three

The systems, which work on an unconscious level to modulate motor activity, (basal ganglia and cerebellum), do this by inhibiting or damping the effect of other neurons. Loss of their modulating effect will, thus, cause other systems to be overactive. The substantia nigra has a damping effect on the striatum via the neurotransmitter dopamine. Lack of dopamine, such as occurs in Parkinson syndrome, enables the striatum to discharge excessively. This, in turn, produces a slowing and reduction of motor movements termed bradykinesia. There is also an increase in motor tone to passive movements in all directions (rigidity). Abnormal repetitive discharges lead to the third symptom seen in dopamine deficient states, and that is tremor. This is usually seen at rest, and is a regular alternating tremor with a frequency of 3 to 4 per second. If the hands and fingers are involved it produces the classic pill rolling tremor. As mentioned, the tremor is seen at rest, and disappears with initiation of motor activity. It should not be confused with essential familial or senile tremor. These tremors are characterized by being initiated with activity and diminishing at rest. There is no associated bradykinesia or rigidity.

Lack of neuronal activity in the basal ganglia diminishes the damping effect on the cerebral cortex and leads to excessive motor activity. This can be seen with degeneration or loss of some basal ganglia neurons or excessive dopaminergic activity, which damps the caudate nucleus. These states can lead to the production of various movement disorders. The exact mechanism for production of these disorders is not fully understood but some insight into their generation is obtained from knowledge of the specific lesions or biochemical conditions associated with the movement disorder. Some common movement disorders are:

Chorea. This movement consists of brief, random, nonrepetitive movements of fingers, extremities, face and trunk. When present they give the patient the appearance of being fidgety and not being able to sit still. Movements may be exaggerated further by the patients attempt to mask them. (e.g., The patient may attempt to hide an arm elevation movement by following through and scratching his head.) When these actions occur in serial fashion the patient appears to be in constant motion. This may be dismissed by the untrained eye but not the astute observer. If one sees such a patient further evaluation should be performed. The patient should be asked to extend his arms and fingers while extending at the wrist, and at the same time, hold out his tongue. This position enables one to better see the brief choreiform movements, which the patient is unable to prevent. Chorea can be seen with excessive dopamine administration (Sinemet® levodopa/carbidopa), in hereditary diseases (Huntington's Chorea), and in acquired chorea (Sydenham's chorea, during pregnancy (chorea gravidarum) and systemic lupus erythematosus.)

Athetosis. This consists of twisting and writhing movements of the extremities, trunk and sometimes face. It is most commonly seen in cerebral palsy where prenatal or perinatal injury to the motor systems cortex or connections, leaves a fixed motor neurological deficit.
**Dystonia.** This consists of a more sustained abnormal postural movement. It can effect small or larger muscle groups. A common example of dystonia is *torticollis*, whereby the sternocleidomastoid and neck muscles pull the head over to one side.

**Hemiballismus.** This is a dramatic, and fortunately uncommon, movement disorder where an extremity has repetitive flailing movements similar to throwing a ball. These can persist indefinitely and sometimes endanger the person's health via sheer exhaustion. The movement is usually caused by a lesion in the *subthalamic nucleus*, and commonly is caused by a small infarct.

**Speech** is also affected by these disorders and can be characterized as *hypokinetic* (extrapyramidal), or *hyperkinetic*. Hypokinetic speech is low in volume and pitch and may be affected by tremor. The patient sounds like he is mumbling, while whispering. Hyperkinetic speech on the other hand is irregular, explosive and erratic. Patients with cerebellar disorders have some of these characteristics affecting their speech also.

In a simplistic sense one can think of a smoothly functioning EPS as depending on equal interactions and levels of dopamine (DA) and acetylcholine (ACh). When DA is excessive, or ACh depleted, excessive movement or a hyperkinetic state results. The converse (decreased dopamine or increased ACh) leads to bradykinesia, rigidity and sometimes tremor (*Figure 2-32*). These observations form the basis for common pharmacologic treatment of these disorders. Hypokinetic states are treated by supplementing dopamine or adding dopamine agonists. Additionally one can block cholinergic receptors with anticholinergic drugs. Hyperkinetic states are treated by blocking dopamine receptors, i.e., with phenothiazines, risperidone, etc., or by depleting dopamine i.e., with reserpine, etc. Adding ACh has been tried but is not as effective.
Figure 2-32: Biochemical Basis of Extrapyramidal disorders.

The Extrapyramidal System Examination
Each portion of the neurological examination should be initiated by observation of the patient including gait, posture, and activities while sitting during the interview. With abnormalities of the EPS many of the previously described abnormalities will be noted on inspection.

The patient with Parkinson syndrome has a characteristic gait that is produced by his abnormal muscle tone (rigidity) and slowness (bradykinesia). The posture is
characterized by increased flexor tone and he walks stooped forward. This puts the center of gravity in front of the patient. Slowness in initiating gait may cause the trunk to move forward first, and the patient winds up chasing his center of gravity. Rigidity only permits small steps producing a characteristic festinating gait.

At rest, a patient may demonstrate tremor, chorea, or dystonia. The latter two may be seen more readily with the arms outstretched. Dystonia often causes the supinated outstretched arm to pronate.

Rigidity may be appreciated by passive range of motion of the arms or legs of a patient. If the examiner puts his left thumb on the biceps tendon of the patient’s arm and actively flexes and extends that arm at the elbow with his right arm, he will feel increased resistance in both directions with his right arm (rigidity) and a ratcheting sensation with his left thumb (cogwheeling).

It is thus by inspection, palpation and observation that most extrapyramidal abnormalities are detected. There is usually no muscle weakness and no sensory loss. The abnormalities may be symmetric or asymmetric in their distribution. Parkinson's disease or a movement disorder may also begin in a single extremity or part of an extremity, but is usually progressive.

Normal development and functioning of the EPS provides the truncal and extremity support for other activities such as individual extremity movement, walking, or even sitting. Abnormalities of this system disrupt the smooth and accurate functioning of this support matrix and leads to the postural and motion abnormalities described above. The voluntary motor system, which initiates individual volitional motor acts, depends on the support matrix of the EPS to carry out its activities.

Summary

- **Disorders of the EPS** usually present as motor activity which is either hypokinetic or hyperkinetic.
- **Hypokinetic disorders** are characterized by rigidity, bradykinesia and tremor. The most common example is Parkinson's syndrome. There is increased flexor tone, causing a stooped posture with the head, neck, trunk, arms and legs flexed. Tremor and slowness of movement are noted on inspection and cogwheel rigidity may be appreciated by passive range of motion of the extremities. The patient has a festinating gait but no motor weakness is evident.
- **Hyperkinetic disorders** are distinguished by excessive motor activity and may take the form of chorea, athetosis, dystonia or hemiballismus. These abnormalities are due to neurotransmitter derangements, degenerative diseases or structural lesions, and are often defined by the clinical setting in which they occur.

The Pyramidal System [Video]

Our marionette is now standing with his trunk and head erect. In the human infant unconscious (indirect) motor systems are fully activated to maintain this posture and to
provide the framework upon which other motor activity can occur. The **pyramidal system**, consisting of a cortical **premotor, motor** and spinal **motor** area, is what affects **voluntary** motor activity.

The infant looks up and is attracted by the objects on a mobile. He reaches for one and his arm extends forward in a nonsmooth, perhaps erratic fashion, in his attempt to grasp. Such early activity gives some insight into what unmodified pyramidal movements are like. This system initiates voluntary motor activity, but without the modifying effects of a mature EPS and cerebellar system, the activity is crude and poorly coordinated. It is, however, the basic foundation upon which more sophisticated movements are developed.
The motor cortex is located in the precentral gyrus of the posterior frontal lobe (face, hand, arm, trunk) and paracentral lobule (hip, leg, foot). Several layers of pyramidal neurons interconnect and give off long axons that travel through the hemispheric white matter (corona radiata) and converge in topographic fashion in the internal capsule (Figure 2-33). Fibers descend in the brain stem where they keep their topographic representation in the pyramidal tract. The cranial nerve fibers are medial and the leg fibers most lateral. Most of this pathway (80%) crosses to the opposite side in the pyramidal decussation, at the cervico-medullary junction region. Descending fibers now travel in the lateral corticospinal tract. Fibers are given off to anterior horn cells at each level. Fibers from the upper body are arranged more medially since they are given off first.

The pyramidal axons synapse on anterior horn cells, located in the anterior horn of the spinal cord. This is the final common pathway for initiation of voluntary activity. Impulses from pyramidal motor neurons initiate motor activity by stimulating anterior horn cells whose impulses, in turn, cause peripheral skeletal muscle fibers to contract and initiate joint motion.

It is in the premotor area of the cerebral cortex where connections are developed that act as programs for various motor activities. Repetition and practice help these connections develop and serve as templates for certain motor activities. As the infant continues to reach for the mobile he develops more dexterity, through maturation of this and other developing systems.

Similarly, stimulation of the motor cortex with electrical current induces crude uncoordinated movements, much like that of the infant. Previously we discussed how the cerebellum acts to modify motor activity and makes it smooth and coordinated. We will discuss specific functional areas of the cerebellum in the next section.

In experimental situations, production of a pure pyramidal tract lesion leads to flaccidity and hypotonia of affected muscles. In clinical situations most pyramidal lesions are not "pure" and involve premotor and extrapyramidal structures as well. As a result the clinical picture associated with pyramidal system lesions contains the following signs:

**Weakness.** The weakness associated with pyramidal tract lesions has a characteristic distribution.

**Face:** Only the lower facial muscles are affected since the upper facial nucleus receives bilateral cortical innervation.

**Upper extremity:** The extensors are weaker than the flexors. Consequently the arm eventually assumes a flexed position. Therefore the biceps will be stronger than the triceps, the wrist and finger flexors stronger than the extensors. For this reason it is not a
good idea to monitor for stroke progression by testing grip strength. Test finger extensor strength instead.

**Lower extremity:** Here the converse is true. The extensors remain stronger than the flexors. This has the beneficial effect of ultimately permitting standing and possibly walking. On examination the gluteus maximus is stronger than the iliopsoas, the quadriceps stronger than the hamstrings, and the gastrocnemius stronger than the anterior tibial muscle.

The most severely affected muscles are also the ones with the greatest cortical representation. The hand and fingers have a large area of cortical representation since they are capable of complicated and intricate movements. Besides weakness, lesions of these areas also cause clumsiness and loss of the ability to perform intricate movements. This is especially true of lesions in the premotor areas where patterning of movements is coordinated. As a result, even though the finger flexors may have mild weakness, the ability to manipulate small objects in the hand or to button a button may be seriously impaired.

Unlike lower motor neuron lesions, muscle atrophy does not occur with pyramidal tract lesions. The affected muscles may get a little smaller over the years, due to disuse, but true atrophy does not occur.

**Hyperreflexia.** The deep tendon reflexes are increased due to loss of inhibitory motor cortex influences on the anterior horn cell. Sometimes striking or suddenly stretching a muscle tendon will produce repetitive contractions of that muscle. This is called clonus and is a sign of pyramidal tract dysfunction. The abdominal reflexes are lost opposite the affected side. They are normally elicited by gently scratching the abdominal muscles in a supine patient, stroking each quadrant upwards or downwards and inwards towards the umbilicus. A normal response is a contraction of the scratched muscle.

In addition to deep tendon reflexes being increased, certain reflexes that are absent in normal individuals now appear. These are called pathological reflexes. Some pathological reflexes are:

**Babinski's sign:** The examiner scratches the patient's foot starting laterally at the heel, and moving up and crossing medially at the metatarsal head area. If Babinski's sign is present the first toe extends and the others fan outward.

**Grasp reflex:** The patient's palm is rubbed with the examiner's fingers. If the motor system of the contralateral frontal lobe is involved, the patient will involuntarily grasp the examiner's fingers. The examiner's fingers may have to forcefully freed.

**Increased muscle tone:** In the acute phase of a pyramidal tract lesion muscle tone may be diminished and muscles are hypotonic to passive range of motion. Over days to weeks, however, muscle tone increases, albeit in a specific manner. The muscle that are stronger,
as previously described (flexors in the arm and extensors in the leg), also have increased tone. This leads to two observable clinical findings.

**Posture.** The difference in tone causes the patient to keep his upper extremity flexed, and his lower extremity extended. Gait now assumes a characteristic pattern. On the normal side the leg moves smoothly and the arm swings normally as the patient walks. On the affected side the leg has to swing outwards (**circumduction**) to clear the toes because increased extensor tone points the foot down and in. The affected arm stays flexed and does not swing with each step. This is the classic **hemiparetic gait.** As a result patients may fall more frequently due to catching the toes of the affected foot on uneven surfaces such as carpeting.

**Spasticity.** This is the clinical term for the alteration in muscle tone seen with pyramidal tract lesions. When the examiner flexes and extends the patients relaxed arm at a joint he will feel a resistance when he tries to overcome flexion (i.e., when he extends the arm). The resistance is at the beginning of the movement and then it diminishes. The sensation is like that of opening the blade of pocketknife where there is initial resistance to extending the blade. As a result this finding has been termed **clasped-knife spasticity.** It is best appreciated at the elbow and knee joints of affected extremities.

**Summary**

- Pyramidal tract lesions affect the lower face, arm extensors and leg flexors.
- Spasticity causes increased tone in arm flexors and leg extensors, with clasped-knife spasticity noted on passive range of motion.
- The patient walks with the affected arm flexed and leg extended (hemiparetic gait).
- There is hyperreflexia on the affected side.
- Pathological reflexes, such as Babinski's sign and the grasp reflex, may be noted on the affected side.
- Muscle atrophy does not occur in affected muscles.
- There is loss of fine coordinated activity in the affected limb.

This concludes the section on the pyramidal tract or upper motor neuron system. This is intended to be a broad overview and the student should use this as an adjunct along with individual instruction, video materials and clinical experience. These principals will be alluded to again in sections dealing with diseases specifically affecting this system.

**The Cerebellum and Coordination**

At this time our marionette is able to stand erect, and initiate motor activities, albeit crude ones. Our infant is able to stand erect and reach for the mobile also in an uncoordinated fashion. We discussed how the cerebellum, by comparing the intended activity to what is actually being achieved, as communicated by sensory receptors, was able to smooth out motor movements and make them more coordinated. In this fashion, and through learning by multiple repetitions, structural connections are developed between these interactive
systems, which facilitate the performance of often-repeated acts, such as writing or tying shoelaces.

We mentioned that motor incoordination, or ataxia, can be sensory, motor or cerebellar in origin. If motor and sensory functions are intact, then involvement of the cerebellar pathways is suspected. Having determined this our next goal is to localize the lesion to a particular portion of the cerebellum. Cerebellar anatomy is quite complex; but in terms of clinical utilization, the cerebellum can be broken down to a few useful concepts (**Figure 2-34**).

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**Figure 2-34: Cerebellum and Schematic Figure.**
We will divide cerebellar lesions into those that involve the **midline structures**, the **anterior lobe**, and the **lateral hemispheres**.

**Midline Structure Lesions**

A useful way to remember cerebellar functional anatomy is to think in terms of **phylogeny**. The first creatures to require a coordination system basically consisted of a trunk and head (fish and eels). This is, developmentally, the oldest portion of the cerebellum and is termed the *archicerebellum*. The portion of the cerebellum that controls head and trunk movements lies in the midline and consists of the **vermis** and **flocculo-nodular lobe** region. Of interest is that its shape is similar to the elongated trunk and head of the organism (Figure 2-35). Extremities, except for fins, have not evolved yet so the vermis is primarily concerned with truncal coordination. Lesions that affect the vermis produce **truncal ataxia**. An individual who has truncal ataxia is unable to sit up, stand or walk. The reason for this is that the trunk cannot be stabilized to maintain the upright position. Even when the patient is sitting up his trunk will sway and his head may seem to bobble on the shoulders (**titubation**). When lying down, however, the trunk is supported and there is no problem performing coordinated acts with the upper or lower extremities.

![Figure 2-35: Archicerebellum: Truncal control.](image)

Cerebellar midline lesions are usually neoplastic and are most often seen in childhood. An example of such a lesion is the medulloblastoma, a primitive tumor that may develop near the roof of the fourth ventricle. In its early stages it exerts pressure on the flocculus and vermis. The mild degree of truncal ataxia that it induces may cause instability while running, consequently the history of the previously normal child who now has some falls while running. If the neurological exam is normal it is easy to dismiss this complaint or ascribe it to something like a "growth spurt." It is only when the tumor has reached sufficient size to occlude the fourth ventricle or aqueduct of Sylvius, causing acute hydrocephalus, severe headache and projectile vomiting, that the seriousness of the condition is fully appreciated. At this time the child will need an emergency ventriculo-peritoneal shunt and then surgery to remove the tumor.

If one encounters a child with a similar history, early investigation with an MRI scan may demonstrate the lesion. MRI is the test of choice, since CT scans do not demonstrate the posterior fossa as well.
Clinical Testing
If the patient has truncal ataxia he will not be able to sit or stand unsupported. The patient is asked to sit on the edge of a bed or chair with the back unsupported and the arms folded across the chest. If truncal ataxia is present he will tend to fall over in any direction. The head may titubate upon the shoulders. If he is unable to sit without falling over, standing will be impossible as well. Truncal ataxia while standing must meet similar criteria and be unassociated with joint position sense loss, (no difference in ataxia with eyes open or closed), or motor weakness.

Anterior Lobe Lesions
The next major phylogenetic evolutionary step was that certain creatures, which previously only had trunks, became land dwellers. This necessitated the development of extremities (Figure 2-36). The first land dwellers had four extremities and a central nervous system structure (paleocerebellum) that was necessary to coordinate the synergistic movement of these extremities for the action of walking and running. This structure is the **anterior lobe** of the cerebellum and is located superior to the vermis. Lesions or other dysfunctions of the anterior lobe produce **gait ataxia**.

![Figure 2-36: Paleocerebellum: Controls the synergies of walking.](image)

Of all forms of cerebellar ataxia, gait ataxia is the most common. The anterior lobe **Purkinje cells**, or main cerebellar neurons, are very sensitive to certain chemicals especially ethanol. Weekend alcohol consumption increases the incidence of cerebellar gait ataxia and enables police to perform mini-neurological exams on suspected offenders, i.e., by asking the person to walk along a straight line and to tandem walk. Fortunately, this form of ataxia is reversible but may become permanent in chronic alcoholics.

Other toxins that affect the anterior lobe are drugs such as phenytoin, and other anticonvulsants. Toxic levels may induce gait ataxia and nystagmus.

Certain neoplasms may produce cerebellar ataxia in a poorly understood and perhaps autoimmune fashion. Some malignancies known to do this are small cell lung cancer, ovarian cancer and lymphoma. Certain anti-Purkinje cell antibodies can be elevated with this type of remote effect of cancer. Anti-Hu antibodies are seen with small cell lung cancer and anti-Yo antibodies with ovarian cancer. Although rare as causes of cerebellar
ataxia, they should be thought of in any type of acquired cerebellar ataxia where no structural lesion exists, especially if the onset is acute or sub-acute.

**Clinical Testing**
The patient is able to sit or stand unsupported. If he lies on his back he can make normal pedaling motions with his legs and do heel-to-shin testing without any problems. This excludes the presence of truncal and individual extremity ataxia. If he attempts to walk however, he will stagger about and have to hold onto objects to prevent falls.

**Lateral Hemisphere Lesions**
A later stage of evolution sees the development of primates who can ambulate with their lower extremities and have opposable thumbs to grasp and manipulate objects. These intricate and complex movements require large areas of integrating neurons and are seen in the expanded cerebellar hemispheres (*neocerebellum*). These have evolved with topographical representation of the extremities as seen in Figure 2-37. Included also are the related areas for eye movement and speech.

![Figure 2-37: Neocerebellum: Coordination of extremities.](image-url)
Afferent and efferent pathways cross on entering and leaving the cerebellum, therefore representation is ipsilateral. The right upper extremity is controlled by the right upper lobe, the right lower extremity by the right lower lobe, and so forth. Consequently a right upper lobe lesion would produce ataxia of the right upper extremity alone.

Cerebellar lesions produce loss of ability to be the servomechanism that coordinates movement. The abnormal movements thus generated, may be defective in rate, range, direction and force. The loss of coordination leads to a movement abnormality termed dyssynergia. Defects in range are termed dysmetria. The gross movements may have a coarse undulating quality during execution of the movement. This has been called intention tremor. Overall what we see is limb ataxia. The affected extremity usually has decreased muscle tone and diminished ability to correct and change direction rapidly. Thus there is defective performance of rapid alternating movements of the hands, feet and fingers. Finger-to-nose testing will be performed less well with the affected upper extremity.

The lower extremities can be tested individually with rapid alternating movements such as foot tapping or with the heel-to-shin test. This test is performed with the patient supine. On the side being tested, the patient first puts his heel to the ipsilateral knee, and then rapidly slides it up and down the shin. The action should be smooth, and rapid with the heel staying on the shin. If a lower extremity develops ataxia there is some difficulty with ambulation, but is not as severe as gait ataxia secondary to an anterior lobe cerebellar lesion.

Lesions that produce lateral hemisphere dysfunction are usually primary tumors, metastases, infarcts, multiple sclerosis plaques or hemorrhages. Infarcts and hemorrhages are acute in onset and metastases and tumors have a more chronic temporal profile.

Central cerebellar lesions or toxic and degenerative disorders may affect speech and eye movements. Ataxic speech is usually explosive with erratic volume, rate and rhythm.

Cerebellar nystagmus is usually horizontal and most pronounced looking towards the lesion. There may be a null point (no nystagmus) somewhere past the midline in the opposite direction.

Emergency Situation
A patient presents to the emergency department with a history of sudden onset of headache and collapse. On examination he is drowsy but arousable and conversant. He has nausea and vomiting, hypertension and horizontal nystagmus. At this point, determine if the patient can sit or stand unsupported and whether he has any extremity ataxia. If he does, the presumptive diagnosis is cerebellar hemorrhage which may be life threatening. You should proceed to obtain an emergency CT scan and neurology/neurosurgical consultation.

Generalized, slowly developing ataxia may be seen in hereditary spino-cerebellar degenerations or with cumulative lesions such as occur with stroke or multiple sclerosis.
Summary

- Midline cerebellar lesions produce truncal ataxia, and can be seen in children with posterior fossa tumors.
- Anterior lobe cerebellar lesions produce gait ataxia and can be seen with neoplasms, infarcts, toxins, MS (multiple sclerosis) plaques and as a remote effect of cancer.
- Lateral hemisphere lesions produce individual extremity ataxia and are seen with infarcts, neoplasms, hemorrhage, and MS plaques.
- Generalized ataxia is seen with cerebellar degenerative disorders and remote effect of cancer.
- Trauma may produce any combination of the above depending on which portion of the cerebellum is involved.

The Peripheral Nervous System

The peripheral nervous system (PNS) contains the motor, sensory and autonomic nerve fibers that are traveling to, or exiting from, the spinal cord. Many peripheral nerves contain a mixture of the above different nerve types while some branches may be purely motor or sensory in composition.

Peripheral nerve fibers may contain an insulating coating of myelin, which is invested around the nerve cell by Schwann cells (Figure 2-38). This coating aids in axonal metabolism and enables more rapid conduction called saltatory conduction. The depolarization potential travels more rapidly by jumping from node to node. Large rapidly conducting fibers have thick myelin coats. These are the proprioceptive and motor fibers of peripheral nerves. Nerve fibers that subserve pain and temperature sensibility are unmyelinated or poorly myelinated. They conduct impulses more slowly.

![Figure 2-38: Peripheral nerve axon and Schwann cell with myelin sheath.](image)

Myelinated fibers are more prone to pressure injury and may be affected by pressure on bony prominences, e.g., the ulnar nerve at the elbow and the peroneal nerve at the knee.

Clinical symptoms of peripheral nerve disease include:
• Loss of feeling (numbness)
• Abnormal tingling sensations (paresthesias)
• Pain

Clinical signs include:

• Sensory loss
• Weakness
• Muscle atrophy
• Decreased muscle tone
• Diminished or absent deep tendon reflexes
• Distal paresthesias on tapping the lesion site (Tinel's sign)

The characteristics of the above symptoms and signs depend on the extent and pattern of peripheral nerve involvement. Some clinical examples of peripheral nerve involvement include:

• Mononeuropathy: Only one peripheral nerve is affected.
• Mononeuritis multiplex: Multiple peripheral nerves are randomly affected.
• Polyneuropathy or Peripheral neuropathy: Symmetrical, distal greater than proximal, sensory, motor, autonomic, or combined nerve involvement.
• Plexopathy: Involvement of the nerve complexes in the retroperitoneal or brachial regions.
• Radiculopathy: Involvement of the nerve roots prior to exiting or entering the spinal cord. Roots contain all the nerve elements.

Mononeuropathy
Median neuropathy at the wrist (Carpal tunnel syndrome)

• Sensory loss as in Figure2-25.
• Weakness of the abductor and opponens pollicis muscles.
• Thenar atrophy
• Pain in the forearm and arm.
• Tinel's sign at the volar wrist.

Ulnar neuropathy at the elbow (leaning elbow excessively on a hard surface)

• Sensory loss as in Figure2-26.
• Weakness of the interossei, and hypothenar muscles.
• Hypothenar and interosseous atrophy.
• Elbow, forearm and arm pain
• Tinel's sign at the elbow.

Radial neuropathy at the upper arm, i.e., radial groove (usually caused by pressure from leaning or lying on this area for prolonged periods after excessive alcohol or sedative usage)
• Sensory loss on the dorsum of the hand.
• Weakness of wrist and finger extensors. (wrist drop).
• Wasting of dorsal forearm muscles.
• Arm pain and radial groove tenderness.
• Tinel's sign at the radial groove.
• Diminished brachioradialis reflex.

• Sensory loss on the anterior thigh.
• Weakness of the iliopsoas and quadriceps muscle (thigh buckles with weight bearing.
• Quadriceps atrophy
• Thigh pain
• Diminished knee reflex

Sciatic Neuropathy (usually due to pressure or trauma at the sciatic notch)

• Sensory loss below the knee
• Severe distal leg pain
• Weakness of thigh flexors and all muscles below the knee.
• Absent Achilles (ankle) reflex

Peroneal Neuropathy, i.e., deep peroneal nerve, (usually due to pressure from leg crossing or trauma at the fibular head)

• Minimal sensory loss (web space between 1st and 2nd toe).
• Weakness of the anterior tibial, peronei and toe extensor muscles. The posterior tibial muscle (inversion of the foot) is spared.
• Usually not painful.
• Tinel's sign at the fibular head.

Mononeuritis Multiplex
This is due to multiple peripheral nerve lesions. They can occur sequentially and in a random fashion. Any combination of the above nerves or other peripheral nerves can be encountered. The lesions are usually secondary to nerve infarcts due to disease of the vasa vasorum which can be seen in diabetes or vasculitis.

Peripheral Neuropathy
Symmetric, distal greater than proximal, involvement of sensory, motor or autonomic nerves. Numbness or weakness usually starts in the toes and moves proximally, eventually involving the upper extremities. Peripheral neuropathy (PN) is usually due to systemic disease or toxins that affect the Schwann cell or nerve cell body. Metabolic demands on the cell body and axon, or larger number of Schwann cells affected on longer nerves, causes the longest nerves to be more severely affected, thus symptoms begin
distally in the toes. The symptoms and signs of peripheral neuropathy therefore involve: 
**symmetric distal weakness; symmetric distal sensory loss and symmetric diminished deep tendon reflexes.**

**Plexopathy**

**Brachial plexopathy**

**Upper Extremity:** C-5 and C-6.
- Weakness of the deltoid, infraspinatus, biceps and brachioradialis.
- Diminished biceps and brachioradialis reflexes.
- Sensory symptoms or loss in deltid area or thumb.

C-7
- Weakness of the triceps, pronator teres, wrist and finger extensor muscles.
- Diminished triceps reflex.
- Sensory symptoms or loss in the middle finger.

C-8
- Weakness of the wrist flexors and intrinsic hand muscles (median and ulnar).
- Diminished triceps and finger flexor reflex.
- Sensory symptoms or loss in the hand (fifth finger).

**Lower Extremity:** L-3
- Weakness of the iliopsoas, quadriceps and adductor muscles.
- Sensory symptoms or loss on the anterior thigh.
- Diminished or absent knee reflex.

L-5
- Weakness of the anterior tibial, peronei, posterior tibial, and toe extensor muscles.
- Sensory symptoms or loss on the dorsum of the foot and great toe.
- Diminished or absent internal hamstring reflex.
- Pain on straight leg raising.

S-1
- Weakness of the gastrocnemius (can't walk on toes on affected side) and toe flexor muscles.
- Sensory symptoms or loss on sole of foot.
- Diminished or absent Achilles (ankle) reflex.
- Pain on straight leg raising.

**Reflex Testing**
Brisk or diminished deep tendon reflexes often give clues to the presence of disease of the upper or lower motor neuron or sensory portion of the reflex arc. In isolation, however, increased or decreased reflexes may not be pathological. Normal individuals can normally have exaggerated or diminished reflexes. It is the associated clinical findings, which support the presence of a pathological state. Brisk reflexes, associated with spasticity on passive range of motion and upper motor neuron pattern weakness, are abnormal.

Reflexes are tested by stretching the tendon with a brisk tap of a reflex hammer and then observing a contraction of the associated muscle. Technique will be demonstrated on the video portion of the syllabus.

**Deep Tendon Reflexes**

Biceps Tendon: C-5, C-6.

*Figure 2-39*

Triceps Tendon: C-7

*Figure 2-40*
Figure 2-39: Biceps reflex.

Figure 2-40: Triceps reflex.

Brachioradialis Tendon: C-6.

Figure 2-41
Finger Flexor Tendons: C-8, T-1.

Figure 2-42

Figure 2-41: Brachioradialis reflex.
Figure 2-42: Finger Flexor Tendons.

Quadriceps (Knee) Reflex: L-3, L-4.

Figure 2-43

Internal Hamstring Reflex: L-5, S-1.

Figure 2-44

Gastrocnemius (Ankle) Reflex: S-1, S-2.

Figure 2-45
Figure 2-43: Quadriceps (Knee) reflex.

Figure 2-44: Internal Hamstring reflex.
Figure 2-45: Gastrocnemius (Ankle) reflex.

In testing reflexes multiple samples of the reflex should be made to establish its reactivity. Look for asymmetry by testing the reflex on one side and then the same reflex on the other and continue comparing both sides in succession. The patient should be completely relaxed during testing or the results may not be valid.
Section Four

Individual Muscle Testing

A very common complaint encountered in general medical practice is that of weakness. As discussed in the section on the neurological history, this complaint needs further clarification since weakness may be used to denote fatigue, malaise or other non-specific symptoms to certain patients. If the patient does indeed complain of loss of strength in an extremity or elsewhere, then it is the task of the examiner to determine the distribution, degree and type of weakness. The distribution of weakness (e.g., extensors in the arm, flexors in the leg); associated deep tendon reflex (DTR) changes (e.g., increased); presence or absence of atrophy (e.g., absent); and type of motor tone (e.g., spasticity) are the characteristics used to define type of weakness. The previous example defines upper motor neuron weakness. The following is a summary of types of weakness commonly encountered in clinical practice.

Table 1: Patterns of muscle weakness

<table>
<thead>
<tr>
<th></th>
<th>Upper Motor Neuron</th>
<th>Lower Motor Neuron</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distribution</strong></td>
<td>Extensors in arm</td>
<td>Follows root or nerve</td>
<td>Proximal</td>
</tr>
<tr>
<td></td>
<td>Flexors in leg</td>
<td>innervation pattern</td>
<td>Symmetric</td>
</tr>
<tr>
<td><strong>Atrophy</strong></td>
<td>Absent</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td><strong>DTR</strong></td>
<td>Increased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td><strong>Muscle Tone</strong></td>
<td>Increased</td>
<td>Decreased</td>
<td>Not affected</td>
</tr>
</tbody>
</table>

Exceptions to the above may occur in certain specific disease states such as motor neuron disease (amyotrophic lateral sclerosis) where weakness patterns vary, but the above patterns serve in most clinical situations.

How muscle strength is tested is an extremely important and often under emphasized clinical skill. Many extraneous factors may influence the examiner's interpretation as to whether or not the patient has weak muscles. Patients may not exert full effort because of pain, their wish to emphasize their own impairment, or lack of understanding as to what is desired of them during the examination. Individual doctors, as well as patients, vary in their own physical strength. This often leads to inter-examiner variability. The best one can do is to strive for standardization of how he or she performs the test from one patient to the next. By doing this you eventually develop a feel for how strong various types of patients should be when compared to yourself.

A cardinal practice should be that you are the one exerting the force against the muscle being tested. The force you exert becomes the gauge for normality or abnormality. It is also easier to detect break-away or give-away weakness. Here the patient suddenly gives up on the force they exert and the examiner feels a sudden decrease in resistance in the muscle being tested. This is in contradistinction to true weakness where there is a smooth
decrease in resistance as the examiner exerts increasing force. Your ability to recognize this will increase with experience in testing muscle strength. The key to achieving this experience is standardization of your performance of the examination. For each muscle tested, it should be placed in the position of maximal mechanical advantage (vide infra) and then you begin exerting force to try and overcome the muscle. With true weakness there is a smooth movement of the extremity in the direction in which you are exerting force; at the same time you feel a constant steady counter-resistance on the part of the patient.

What follows are descriptions and illustrations of commonly tested muscles as well as their innervations. There will be additional demonstrations of how to test the muscles on the video portion of the module and by your clinical preceptor. Some examiners may vary in just how the test is performed, and you may be exposed to more than one technique. Select the one that works best for you keeping in mind that you are striving for reliability and reproducibility in assessing muscle weakness.

The most common rating system for muscle strength gives a score of 5 for normal, (100%) strength, and 0 for total paralysis. 1, 2, 3, etc. note increasing strength in approximately 20% increments.

Muscles
The underlined root carries the majority of innervation to the listed muscle.

Neck Flexors (C 1-6)
Test: The head is flexed to the chest. The examiner places his hand on the patient's forehead and exerts backward pressure, trying to place the head in the normal upright position. The patient resists. (Figure 2-46)

![Figure 2-46: Neck flexors.](image)
Neck Extensors (C1–T1)
Test: The patient extends the head backward and resists the examiner's attempt to push the head forward (Figure 2-47).

![Neck extensors](image)

Figure 2-47: Neck extensors.

Neck flexors and extensors usually are affected by myopathies, and not by root lesions because of the number of different roots innervating these muscles. Before testing the neck flexors and extensors make sure there is no bony neck injury that might be worsened by these maneuvers. Patients with rheumatoid arthritis may have lax ligaments binding the C1 and C2 vertebrae and the above maneuvers may cause vertebral subluxations.

Upper Extremity

Shoulder Girdle

Infraspinatus (C 5,6: Surascapular nerve)
Action: External rotation at the shoulder.
Test: The patient flexes at the elbow, with his elbows at his side. The examiner exerts force at the dorsal wrist or forearm, trying to push the forearm inwards towards the patient's abdomen (Figure 2-48).

![Infraspinatus muscle](image)

Figure 2-48: Infraspinatus muscle (external rotation at shoulder).

Pectoralis major (C 5–T 1)
Action: Internal rotation at the shoulder.
Test: Same position as above, but the examiner pushes outward against resistance (Figure 2-49).

**Figure 2-49:** Pectoralis major (shoulder adduction).

**Deltoid** (C 5,6: Axillary nerve)
Action: Shoulder abduction.
Test: The patient holds his proximal arm out laterally at 90 degrees of abduction, and the examiner exerts force in a downward direction (Figure 2-50).

**Figure 2-50:** Deltoid muscle (arm abduction and elevation).

**Arm**

**Biceps** (C 5,6: (Musculocutaneous nerve))
Action: Flexion of the forearm at the elbow.
Test: The patient flexes the arm to about 45 degrees, forearm supinated, and the examiner tries to extend it against resistance(Figure 2-51).

![Figure 2-51: Biceps muscle (forearm flexion).](image)

**Triceps** (C6, 7, 8: Radial nerve)
Action: Extension of the forearm at the elbow.
Test: The forearm is flexed to about 70 degrees with the forearm fully supinated. The examiner tries to push it in the direction of flexion against resistance by the patient(Figure 2-52).

![Figure 2-52: Triceps muscle (forearm extension).](image)

**Forearm**

**Brachioradialis** (C 5,6: Radial nerve)
Action: Flexion of the forearm at the elbow.
Test: The forearm is flexed to about 70 degrees with the forearm midway between pronation and supination. The examiner again pulls in the direction of forearm extension, against patient resistance(Figure 2-53).

![Figure 2-53: Triceps muscle (forearm extension).](image)

**Extensor Carpi Radialis Longus and Brevis** (C 6,7: Radial nerve)
Action: Extension of the hand at the wrist.
Test: The patient extends the wrist and holds that position while the examiner pushes downward in the direction of flexion (Figure 2-54).

![Figure 2-54: Extensor Carpi Radialis Longus and Brevis (wrist extension).](image)

**Extensor Digitorum Communis** (C 7,8: Radial nerve)
Action: Extension of the fingers.
Test: The patient keeps the fingers extended. While supporting the wrist with his left
hand the examiner exert downward pressure on the extended fingers, pushing them in the direction of flexion (Figure 2-55).

![Image](image_url)

Figure 2-55: Extensor Digitorum Communis (finger extension).

**Pronator Teres** (C 6,7: Median nerve)
Action: Pronation of the forearm.
Test: The arm is flexed, with elbow at the side of the trunk. The forearm is pronated. The examiner grips the patient's hand and tries to supinate the forearm against resistance (Figure 2-56).

![Image](image_url)

Figure 2-56: Pronator Teres (wrist pronation).

**Flexor Carpi Radialis** (C 6, 7: Median nerve)
Action: Flexion of the wrist at the hand.
Test: The patient flexes the hand at the wrist. The examiner pushes in the direction of extension against resistance by the patient (Figure 2-57).

**Figure 2-57: Flexor carpi radialis (wrist flexion).**

**Flexor Digitorum Sublimis and Profundus** (C 7,8: Median nerve, [ulnar nerve supplies the profundus to the 4th and fifth fingers])
Action: Flexion of the fingers.
Test: Flexion of the fingers, Examiner tries to open them against resistance (Figure 2-58).

**Figure 2-58: Flexor Digitorum Sublimis and Profundus.**

**Hand**

**Abductor pollicis brevis** (C 8, T 1: Median nerve)
Action: Moves the thump perpendicular to the plane of the palm (palmar abduction).
Test: The thumb is placed in palmar abduction and the examiner pushes it towards the dorsum of the hand. (Figure 2-59).

**Figure 2-59: Abductor pollicis brevis (median nerve).**

**Interrosei** (C 8, T 1: Ulnar nerve)
Action: Abduction of the fingers.
Test: It is easiest to test the index finger. The 2-5th fingers are held to support the hand and the index finger is pushed inwards to overcome abduction (Figure 2-60).

![Figure 2-59: Abductor pollicis brevis (median nerve).](image)

**Figure 2-60: Interrosei (1st Dorsal) (finger abduction).**

**Hypothenar** (C 8, T 1: Ulnar nerve)
Test: (ADQ) Push the abducted 5th finger towards adduction. (FDQ) Extend 5th finger, against attempt to keep it flexed (Figure 2-61).

![Figure 2-60: Interrosei (1st Dorsal) (finger abduction).](image)
Figure 2-61: Hypothenar (abductor digiti quinti).

LOWER EXTREMITY

Hip Girdle

Muscles

**Iliopsoas** (L 2,3,4: Femoral nerve)
Action: Flexion of the thigh at the hip.
Test: In the lying or sitting position, the patient flexes the thigh at the hip. The examiner pushes downward at the knee, towards hip extension. *(Figure 2-62).*

![Figure 2-62: Iliopsoas.](image)

**Gluteus Maximus** (L 5, S 1,2: Inferior gluteal nerve)
Action: Extension of the thigh at the hip.
Test: With the patient sitting or standing the patient pushes, (extends), his thigh downward into the chair or bed, against the examiner's attempt to elevate the thigh by lifting upwards under the heel. *(Figure 2-63).*
Figure 2-63: Gluteus Maximus.

Gluteus Medius (L 4, 5, S 1: Superior gluteal nerve)
Action: Abduction of the thigh.
Test: While sitting or lying the patient holds the thigh in the outward abducted position, against the examiner’s attempt to push it inward towards adduction. (Figure 2-64).

Figure 2-64: Gluteus Medius.

Thigh

Quadriceps Femoris (L 2, 3, 4: Femoral nerve)
Action: Extension of the leg at the knee.
Test: The patient extends his leg, at the knee, to about 170 degrees. The examiner tries to flex the leg at the knee while the patient resists. (Figure2-65).
Figure 2-65: Quadriceps Femoris.

Hamstrings

**External** = **Biceps Femoris** (L 5, S 1,2: Sciatic nerve)  
**Internal** = **Semitendinosus; Semimembranosus** (L 4,5, S 1,2: Sciatic nerve)  
Action: Flexion of the leg at the knee.  
Test: The leg is flexed at the knee. The examiner tries to extend the leg against resistance by the patient (**Figure 2-66**).

Figure 2-66: Hamstrings.

**Adductors (Adductor Magnus, Longus, Brevis)** (L 2,3,4: Obturator nerve)  
Action: Adduction of the thigh.  
Test: The patient holds the knees in fairly close proximity. The examiner tries to individually force them apart against resistance by the patient (**Figure 2-67**).
Figure 2-67: Adductors.

**Distal Leg**

**Anterior Tibial** (L 4,5: Deep peroneal nerve)
Action: Dorsiflexion of the foot at the ankle.
Test: The patient dorsiflexes the foot and the examiner pushes downward towards plantar extension. Alternatively, to detect mild weakness, the patient is asked to walk on his heels. With normal strength each foot should stay equally dorsiflexed and the toes not touch the ground while walking. (Figure 2-68).

Figure 2-68: Anterior Tibial.

**Peroneus Longus, Brevis** (L 5, S 1: Superficial peroneal nerve)
Action: Eversion of the foot at the ankle.
Test: The patient holds his foot in the everted position and the examiner pushes inward towards inversion (**Figure 2-69**).

![Figure 2-69: Peroneus Longus.](image)

**Toe Extensors (Extensor Hallucis and Digitorum)** (L 4,5, S 1: Deep peroneal nerve)
Action: Extension of the toes.
Test: The patient extends the toes upward and holds them there against the examiner's attempt to push them downwards towards flexion. (**Figure 2-70**).

![Figure 2-70: Toe Extensors.](image)

**Posterior Tibial** (L 5, S 1: Posterior tibial nerve)
Action: Inversion of the foot at the ankle.
Test: The patient holds his foot in the inverted position while the examiner pushes outward towards eversion. (**Figure 2-71**).
Figure 2-71: Posterior Tibial.

Gastrocnemius (L 5, S 1,2: Tibial nerve)
Action: Plantar flexion of the foot at the ankle.
Test: The patient holds his foot plantar flexed while the examiner tries to dorsiflex it against resistance. Subtle weakness may be detected by having the patient walk on his toes and observing if the heel comes closer to the ground when stepping off the affected side (Figure 2-72).

Figure 2-72: Gastrocnemius.

Toe Flexors (Flexor Hallucis and Digitorum) (L 5, S 1: Posterior tibial nerve)
Action: Flexion of the toes.
Test: The patient flexes his toes and the examiner tries to extend them against resistance by the patient. (Figure 2-73).
**Figure 2-73: Toe Flexors.**

**Abdominal Muscles** (T6–L1)
Action: Flexion of the trunk.
Test: The patient lies supine and flexes his neck. The abdominal muscles are observed to tighten. The mid abdomen (umbilical level) is innervated by T-10, a frequent site of spine metastatic lesions. Spinal lesions at this level often cause weakness below T-10. This can be detected in the abdominal muscles by **Beevor's sign.** The patient lies supine and flexes his neck while the examiner holds a pen over the umbilicus. When the abdominal muscles tense the stronger upper abdominal muscles pull the umbilicus upward which is made easier to observe by holding a pen over the original umbilical location.

**Rectal Sphincter** (S 3,4: Pudendal nerve)
Action: Constriction of the anus.
Test: The examiner performs a rectal examination and notes rectal tone and contractile ability on command. Decreased tone and contractile ability denotes a lower motor neuron lesion. When associated with an atomic bladder (overflow incontinence), it is almost always due to a lesion of the conus medullaris, (distal end of the spinal cord) or the cauda equina (distal lumbar and sacral nerve roots before they exit the spinal canal).

**Summary**

- Weakness is loss of strength in individual muscles or groups of muscles, not fatigue.
- Weakness should be defined in terms of its pattern. *(Table 1)*
- When testing muscle strength the examiner should exert the force and note the degree of resistance of individual muscles to determine degree of weakness.
Evaluation of Speech and Language
Disorders of speech and communication are numerous and some of the neuroanatomical pathways are complex. For purposes of this examination we will be dealing with broad concepts and will limit our discussion to clinically relevant and common disturbances.

**Aphasia (dysphasia).** A disorder of speech where the patient has trouble understanding speech, (in the absence of hearing problems), or in the thought and word finding processes of speech. There is a defect in the comprehension and/or expression of language. Aphasia refers to the absence of speech and dysphasia to a less complete disorder of speech. There are different types of aphasia depending on where the lesion is located (Figure 2-74).

![Figure 2-74: Speech Areas.](image)

**Wernicke's aphasia (sensory aphasia, receptive aphasia, fluent aphasia).** This is caused by lesions of the posterior portion of the superior temporal gyrus (Wernicke's area). The disorder is characterized by copious speech that is not intelligible because of incorrect word and syllable choice. The patient does not understand what he is saying or what is said to him. If a patient is hungry he will speak volumes but not be able to convey the simple message that he wants to eat. If the lesion involves the surrounding cortex there may be contralateral sensory loss or a homonymous visual field defect.

**Broca's aphasia (motor aphasia, expressive aphasia, nonfluent aphasia).** It is caused by lesions of the inferior portion of the left frontal gyrus and its underlying white matter. The patient understands speech but speech production is distorted. There is difficulty with speech fluency and organization and sentences have few words (telegaphic speech). Unlike the patient with a fluent dysphasia, patients can understand what they
themselves and others are saying and can convey ideas. In the example of the starving patient he might communicate his plight by saying "hungry...eat". If the lesion involves the surrounding cortex the patient will also have upper motor neuron right facial and hand weakness.

**Global aphasia.** A large lesion affecting both speech areas and their connections leaves the patient mute and unable to comprehend speech. There is also an associated dense contralateral hemiplegia. This can be seen with acute infarcts in the dominant hemisphere, usually left middle cerebral or carotid artery distribution.

**Dysarthria.** Speech comprehension and expression are intact but an articulation problem exists which affects word pronunciation. There are different types of dysarthria, which reflect the level of the neuraxis affected.

**Dysphonia.** A mechanical or psychological disturbance of voice production. This can be seen in patients with laryngectomies, vocal cord paralysis, or laryngitis. It is recognized by the quality of speech and the diagnosis confirmed by demonstration of the suspected underlying cause.

If you think a patient is confused, test him for aphasia by giving him verbal commands to follow. This will test for Wernicke's aphasia. Be sure not to give the patient visual cues. Families will often insist that an aphasic patient understands them. They demonstrate by asking the patient to wiggle his fingers but at the same time wiggle their fingers in front of him. The patient then responds to the visual cue. If one asks him to wiggle his fingers without simultaneously showing him what is wanted, he will not comply.

References


**Self-Assessment Questions**

Please choose the correct answer for the following.

1. Memory can be impaired with:
   A. decreased motivation
   B. symptoms of depression
   C. inattention
   D. all of the above
2. The anatomy of memory involves all EXCEPT the:
   A. hippocampus
B. subthalamic nucleus  
C. dorsomedial nucleus of the thalamus  
D. fornix  
E. mammillary bodies  

3. Disturbances in calculations are seen in lesions of the:  
A. Non-dominant parietal lobe  
B. thalamus  
C. angular gyrus of the dominant hemisphere  
D. cingulate gyrus  

4. Match pupil size with lesion.  

<table>
<thead>
<tr>
<th>Metabolic disease</th>
<th>A. Pinpoint pupil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midbrain lesion</td>
<td>B. 4-5 mm fixed pupil</td>
</tr>
<tr>
<td>Pontine lesion</td>
<td>C. 2 mm and nonreactive</td>
</tr>
<tr>
<td>Thalamic lesions</td>
<td>D. Sluggishly reactive</td>
</tr>
<tr>
<td>Mass effect with herniation</td>
<td>E. Unilateral dilated pupil</td>
</tr>
</tbody>
</table>

5. The doll's eye maneuver: (Please circle the correct answers for the following)  
A. should only be done after cervical spine disease or fracture is ruled out.  
B. is done with the head of the bed raised 30°.  
C. is positive when the eyes move toward the cold water stimulus on the tympanic membrane  
D. all of the above  

6. Decorticate posturing is:  
A. manifest as tonic adduction and extension of the arms and legs  
B. suggests a lesion at the level of the pons.  
C. manifest as tonic adduction and extension of the lower extremities only  
D. manifest by tonic flexion of the arms and extension of the legs.  

7. The primary sensory cortex is located in the:  
A. frontal lobes  
B. parietal lobes  
C. occipital lobes  
D. precentral gyrus  
E. none of the above  

8. Root lesions are:  
A. associated with pain  
B. most frequent in the thoracic spine  
C. never associated with sensory loss  
D. none of the above  

9. All are true EXCEPT:  
A. proprioceptive fibers and touch fibers travel in the ipsilateral dorsal columns.  
B. pain and temperature fibers travel in the contralateral lateral spinothalamic tract
C. impairment in 2-point discrimination implies a lesion in the thalamus
D. vibration is tested with a 256 Hz tuning fork on a distal bony prominence

10. The extra pyramidal system:
A. receives input from the primary motor cortex
B. consists of subcortical nuclei called the basal ganglia
C. receives input from the motor cortex
D. degeneration can lead to movement disorders
E. all of the above

11. The neurological exam in a patient with Parkinson's disease will show all EXCEPT:
A. tremor
B. rigidity
C. flexed posture
D. hyperkinetic speech
E. Bradykinesia

12. The pyramidal system:
A. effects voluntary movements
B. begins in the cortex, the fibers travels in the internal capsule and travel ipsilateral in the spinal cord fibers
C. descend in the medial corticospinal tract
D. lesions cause loss of legs tendon reflexes

13. The cerebellum helps control motor coordination. Which are true:
A. lesions that affect the vermis produce limb ataxia
B. lesions of the anterior lobe produce gait ataxia
C. lesions of the lateral hemispheres produce truncal ataxia
D. lesions are contralateral to the affected side

14. Peripheral nerve lesions may produce all EXCEPT:
A. muscle atrophy
B. sensory loss
C. weakness
D. increased deep tendon reflexes
E. distal paresthesias on tapping the lesion site

15. MATCHING

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Nerve Roots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadriceps</td>
<td>A. L4-5</td>
</tr>
<tr>
<td>Biceps</td>
<td>B. L2, 3, 4</td>
</tr>
<tr>
<td>Rectal Sphincter</td>
<td>C. L5, S1, S2</td>
</tr>
<tr>
<td>Anterior tibial</td>
<td>D. C5, 6</td>
</tr>
<tr>
<td>Gluteus Maximus</td>
<td>E. S3, 4</td>
</tr>
</tbody>
</table>

16. MATCH TYPE OF APHASIA WITH DEFICIT

Wernicke's A. inability
A 66-year-old retired schoolteacher was referred for headaches. The patient's headaches dated back to age 30, when she developed migraine headaches. They were characterized by right-sided throbbing pain associated with nausea, vomiting, and photophobia. For the most part, her migraines were under good control with propranolol, but occasionally she took sumatriptan subcutaneously for breakthrough headaches. The patient's headaches worsened in the three to four months before consultation. Although they varied in intensity, the overall severity had increased during this period. The headaches occurred daily and were aggravated by activities such as stooping, bending or straining to have a bowel movement. The pain was localized principally at the back of the head now and was dull in character. Within the previous four to six weeks, she avoided gardening because stooping over to pull out weeds exacerbated the severity of the headaches. During the past few weeks, she also experienced intermittent vomiting. The patient ascribed this to "nerves" as she felt increasingly anxious, but could not identify why. On further questioning, the patient admitted that she suffered from a slight limp for several years, which she attributed to an old back injury.

Neurological exam revealed normal tone and moderate impairment of strength in the left leg. Pin prick, vibration and proprioception were intact. Deep tendon reflexes were equal in the arms, but increased in the left leg, compared to the right. Left Babinski was present while the right Babinski was equivocal. On ambulation, circumduction of the left leg was apparent.

17. What features of the patient's exam suggest an upper motor neuron lesion?
A. weakness  
B. hyperreflexia  
C. Babinski  
D. circumduction  
E. all of the above  
F. all but D

18. The most likely cause of the patient's leg weakness is:
A. poorly controlled complicated migraines  
B. lumbar cord compression from an old vertebral fracture  
C. meningioma of the falx  
D. ependymoma of the upper cervical cord  
E. pontine glioma

Discussion: Meningiomas are benign, slow growing neoplasms and the brain accommodates to slow growth. Consequently clinical signs may not develop until the tumor reaches significant size. The leg is primarily affected since this tumor overlies the parasagittal primary motor cortex representing the lower extremity. (See Figure 2-22 [make this a link]). Parasagittal meningiomas may also produce focal motor seizures (starting in the leg), which may then secondarily generalize.

A 52-year-old housewife presented with generalized weakness. Her illness commenced about ten days ago when she suffered from nausea, vomiting and diarrhea. About four to five days later, she experienced tingling in both hands so that she was unable to hold a cup or use a knife and fork effectively. During the next few days, the weakness extended into her legs. At this stage, she was referred for consultation. Her past medical history was remarkable for a gastric ulcer, which was successfully treated medically. She has had no further symptoms of ulcer and her weight has slightly increased in the past year.

The patient was afebrile and blood pressure was 180/90 mm Hg. Physical examination was remarkable for palpable lymph nodes on both sides of the neck which were discrete, mobile and non-tender, the largest being about 2 cm in diameter. On neurologic examination, facial expression was immobile. She had difficulty holding air in both of her cheeks or pursing her lips. Blinking was diminished. The patient could not close her eyes completely on request and when she attempted to do so, it could be seen that the eyeballs turned upwards. There was hypnotic and weakness of all limbs to the point that the patient had great difficulty lifting her limbs off the bed. Sensory exam revealed loss of pinprick, vibration and proprioception in the hands and feet. Deep tendon reflexes were absent in the arms and legs. Babinski could not be elicited bilaterally. Chest X-ray was normal. CBC demonstrated normal WBC and hemoglobin. Chem 7 revealed mild hyponatremia of 128. Lumbar puncture yielded clear CSF with an opening pressure of 170 mm of water. CSF protein was 220, glucose 60, WBC 0 and RBC 10.

19. The patient's inability to close her eyes completely is due to:
A. bilateral upper motor neuron weakness of the facial nerve
B. bilateral lower motor neuron weakness of the facial nerve
C. bilateral frontalis muscle weakness
D. bilateral oculomotor nerve palsies
E. an abnormality of neuromuscular transmission

20. Weakness of the limbs is due to:
   A. acute inflammatory demyelinating polyneuropathy (Guillian-Barre syndrome)
   B. subacute combined degeneration of the spinal cord from B12 deficiency
   C. cytomegalovirus polyradiculopathy
   D. myasthenia gravis
   E. lead neuropathy

21. Loss of pin prick, vibration, and proprioception may be due to:
   A. cytomegalovirus polyradiculopathy
   B. infectious myelopathy
   C. dorsal column dysfunction and sensory neuropathy from B12 malabsorption
   D. the effect of botulinum toxin at the neuromuscular junction
   E. none of the above

22. Loss of deep tendon reflexes may due to:
   A. acute inflammatory demyelinating polyneuropathy
   B. sensory neuropathy from B12 deficiency
   C. subacute combined degeneration of the spinal cord from B12 deficiency
   D. A or B
   E. B or C

The patient is a 58-year-old lawyer who was referred with the complaint of weakness. Apart from an illness affecting her legs at age of 9 years, which had been diagnosed as poliomyelitis, she was in good health until 2.5 years prior to presentation. She first noticed that her left foot and leg became "tired and tended to drag" when she walked for several minutes. After a few weeks she noted a definite weakness in the left leg even at rest. This weakness progressed to involve the right leg and foot similarly within two or three months. Her hands later became weak so that she experienced difficulty writing or unscrewing bottle tops, and frequently dropped objects such as cups and utensils. During the last six months her speech became less distinct and solid foods often stuck in her throat upon swallowing. There was no nasal regurgitation of liquids, but at night, in bed, she frequently had difficulty clearing mucus from the back of her throat. In the past month, she required assistance with ambulation, complaining of easy fatigue. Her fingers felt clumsy and weak such that dressing became laborious, particularly when buttoning was required. During this period of illness, the patient's weight dropped from 136 lbs. to 100 lbs.

Neurologic examination was remarkable for normal cognitive function. There was nasal intonation of voice and mild slurring of speech. The tongue was wrinkled. Fasciculations appeared to be present when the tongue as at rest in the floor of the
mouth. Upon gross observation of the body, generalized loss of muscle bulk was evident. In general, the legs were more wasted than the arms. The intrinsic hand muscles were atrophic. Fasciculations were conspicuous in the shoulder girdle, biceps, triceps, quadriceps and calf muscles. Tone was diminished throughout, particularly in the arms. Strength was diminished throughout, with the greatest weakness noted where muscle atrophy was present. Sensory exam was normal. No difficulty with finger-nose-finger and heel-to-shin tests. Deep tendon reflexes were exaggerated and Babinski was elicited bilaterally. Jaw jerk was brisk. Gait was slow with short shuffling steps and evinced a poverty of knee flexion.

23. The most likely cause of generalized weakness is:
   A. cervical cord compression from a herniated disc
   B. Chronic inflammatory demyelinating polyneuropathy
   C. brainstem glioma
   D. none of the above

24. What feature of the patient's exam suggests lower motor neuron disease?
   A. wrinkled tongue with fasciculations
   B. diffuse hyperreflexia
   C. slurred speech
   D. slow, shuffling gait
   E. none of the above

25. Which of the following suggests upper motor neuron disease?
   A. brisk jaw jerk
   B. fasciculations
   C. atrophy of intrinsic hand muscles
   D. A and B
   E. A and C

26. What feature(s) of the patient's exam is compatible with myopathy?
   A. weakness
   B. wrinkled tongue
   C. fasciculations
   D. B and C
   E. none of the above

27. Brisk deep tendon reflexes in the limbs and bilateral Babinski may be due to:
   A. poliomyelitis
   B. C2-3 herniated disc with cord compression
   C. pontine glioma
   D. A or B
   E. B or C
   F. A or C

28. Nasal intonation of speech, slurred speech and difficulty swallowing in this patient is due to pathology involving the
   A. motor cortex
   B. Broca's area
   C. white matter of the brain
   D. brainstem
E. none of the above

**Answers**

1. D  
2. B  
3. C  
4. Metabolic disease D  
   Midbrain lesion B  
   Pontine lesion A  
   Thalamic lesions C  
   Mass effect with herniation E  
5. A  
6. D  
7. B  
8. A  
9. C  
10. E  
11. D  
12. A  
13. B  
14. D  
15. Quadriceps B  
   Biceps D  
   Rectal sphincter E  
   Anterior tibial A  
   Gluteus maximus C  
16. Wernicke's E  
   Broca's C  
   Conduction A  
   Global B  
   Transcortical D  
17. E  
18. C  
19. B  
20. A  
21. C  
22. D  
23. E  
24. A  
25. A  
26. A  
27. E  
28. D
Chapter 2 – Visual Problems

VISUAL PROBLEMS

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VISUAL LOSS
Perhaps the most challenging and frequent neuro-ophthalmological problem that one encounters is unexplained visual loss. In assessing vision, one needs to evaluate:
Visual acuity
Afferent pupillary defect
Visual fields
Fundus

Visual Acuity
In testing visual acuity one is actually assessing central or macular vision. This portion of the retina, which consists entirely of cones, is responsible for color perception and the sharpness and clarity of the images that we see. In testing visual acuity the patient can be examined at a distance of twenty feet with the use of a Snellen chart. Each eye is tested individually. Alternatively, a hand held near card may be used at a distance of fourteen inches. When using the near card, always allow the patient to use their reading glasses. The need for reading glasses, termed presbyopia, usually develops in everyone after the age of 40 years. It is due to weakness of the ciliary muscle, which in turn controls the thickness of the lens. If vision is still defective with use of reading glasses, check vision on the Snellen chart as well.

If you have a patient with unexplained visual loss, potential problems include:

- Optical disturbances
- Refractive error
- Disturbances of ocular media (tear film, cornea, lens, vitreous)
- Disturbance of the retina or central neurologic pathways (neuroretinal disturbance)

Tests for Optical Disturbances
Refractive errors of vision are those that can be corrected with proper lenses (glasses). Disturbances of the ocular media can be of several types:

- The tear film can be reduced in conditions causing "dry eyes" such as Sjogren's syndrome, or other collagen vascular diseases.
- Corneal infections (keratitis), and corneal edema are sometimes associated with acute closed angle glaucoma.
- Lens disorder (cataracts).
• Vitreous disorder (hemorrhage, detachment, etc.).

The pinhole test is an effective technique to improve subnormal acuity that is caused by an optical disturbance. One can construct a simple pinhole occluder for office use by taking a piece of cardboard as shown in Figure 1, and punching a central ~2.5 mm hole, with surrounding holes as shown. If the visual acuity is better with the pinhole than without, then it is much more likely that we are dealing with an optical disturbance. If the acuity is not improved with the pinhole, the examiner should now investigate for a neuroretinal disturbance by searching for a relative afferent pupillary disturbance (RAPD). This abnormality is most commonly seen with disorders of the optic nerve.

To understand the concept of the RAPD, we must briefly review the anatomy of the light reflex pathway (see Figure 2). The pupillary light reflex begins in the retina. Light stimulates photoreceptor cells, which eventually synapse with the ganglion cells. The axons of the ganglion cells that subserve the light reflex undergo hemidecussation in the chiasm (note, in Figure 2, that only the nasal fibers decussate in the chiasm to the opposite optic tract). Ipsilateral temporal and contralateral nasal fibers continue through the optic tract and then synapse in the pretectal nucleus of the midbrain. Each pretectal nucleus receives light input from the opposite homonymous visual field. Recall that a homonymous visual field consists of the temporal field in one eye and the nasal field in the opposite eye. Each pretectal nucleus then innervates both Edinger-Westphal nuclei. The result of this arrangement is that unequal light input arising from lesions of the optic nerve or tract does not result in anisocoria (unequal pupils). For example, if one optic nerve is severed both pupils will be of equal size.

To demonstrate the RAPD we perform the swinging-flashlight test (Figure 3). The patient is seated in a room with very little background illumination. Have the patient fixate on a distant object so as not to invoke a near response (miosis, convergence, and accommodation). Shine a bright light into one eye and observe the direct response (the response to light directly focused on the pupil). Remember, the consensual response (the response of the opposite eye) will be the same as the direct response because of the light reflex pathway. Then quickly shift the light from the first eye to the second one. Under normal circumstances, there should be no change in the pupillary size. Figure 3 is an example of findings of the swinging flashlight test in a patient with a defective left optic nerve. Note in panel 2 that both pupils constrict equally. When the flashlight is quickly moved to the defective left eye both pupils dilate equally. And if we were to move the flashlight rapidly to the normal right eye, both pupils would again constrict. Because we are only viewing one pupil at a time, when we move the flashlight to the defective pupil we observe an apparent paradoxical dilatation to light. Actually, of course, both pupils are dilating because of the defective afferent input due to the defective left optic nerve.

In the evaluation of the patient with unexplained monocular visual acuity loss, a RAPD is strongly correlated with ipsilateral optic nerve pathology. Although less likely it may be observed in retinal nerve fiber layer pathology macular disease, amblyopia, and optic tract pathology. If RAPD is present, visual fields should be evaluated. If there is no
RAPD, and the pinhole test is negative, one needs to consider amblyopia (congenital blindness due to cortical suppression of vision).

**Visual Field Testing**
Visual field testing is performed in order to anatomically localize the neuroretinal lesion. In the office setting, confrontational fields are performed. Each eye should be tested individually. The examiner should face the patient and align himself so that he can evaluate the patient's field by comparing it to his own. The patient should fixate on the examiner's eye opposite to his. The index fingers of both hands can be used to check all four quadrants (see Figure 4). It is imperative to observe whether the field defect respects the vertical meridian (vision is lost or returns when the test object cross the midline of the patients face. See Figure 2.3; Chapter 1). If it does, the lesion is located at the level of the chiasm or posterior to it. The central field also needs to be examined. This area is especially important in assessing prechiasmatic pathology such as optic nerve or macular dysfunction. These areas are especially sensitive to color desaturation. A red match tip or red bottle cap can be utilized. The patient with optic nerve disease will frequently have a central scotoma. When the small red object is placed in their central field the color may desaturate and look gray or yellow.

**Unexplained Visual Loss**
Unexplained loss of visual field with normal visual acuity is usually due to retinal receptor dystrophies and peripheral retinal diseases. Optic neuropathies that spare the papillomacular bundle (fibers from the macula to the optic disc that subserve color and central vision) can result in normal acuity. This would include glaucoma, ischemic optic neuropathy, pseudotumor cerebri and rarely, optic neuritis.

Two important facts to note:
Many cases of chiasmatic lesions, and all retrochiasmatic lesions will spare visual acuity. All retrochiasmatic lesions are homonymous hemianopsias (Figure 2.3, Chapter 1). If one looks at the lesion G in Figure 2.3, you will note the heminanopsia has macular or central sparing. This is only seen with occipital lobe lesions because of the large macular representation in the occipital lobe. When observed, this finding is almost always caused by a vascular insult in the occipital cortex.

**Funduscopic Examination**
A thorough examination of the fundus is vital in the evaluation of unexplained visual loss. This is especially true of monocular loss. The disk, macula, retinal vessels, and retina need to be carefully examined. One especially interesting presentation is that of the patient who presents with unexplained visual loss, a RAPD, and a swollen or elevated optic disk. Some of the common etiologies would include optic nerve drusen (congenital hyaline bodies within the optic nerve, sometimes familial in origin), papillitis (inflammation of the optic nerve), ischemic optic neuropathy (arteritic or nonarteritic), and metastatic tumors. Arteritic ischemic optic neuropathy must be diagnosed quickly and accurately. If not treated immediately and aggressively the patient may go blind in a matter of days. This disease is almost exclusively seen in the elderly. There are generally systemic symptoms of myalgia, malaise, anorexia, and headache. Frequently the
Westergren sedimentation rate is elevated. In suspicious cases a temporal artery biopsy is indicated; the treatment is high dose steroids.

**PUPIL ABNORMALITIES**
The two most common pupillary problems encountered by the clinician are anisocoria (unequal pupils) and decreased pupillo-constriction to light. The parasympathetic system controls pupillo-constriction. (See Figure 2, the light reflex pathway). Pupillo-dilatation is controlled by the sympathetic system. The size and shape of the pupil is determined by balance between these two opposing branches of the autonomic nervous system.

However, the parasympathetic system is dominant because the iris sphincter is a stronger muscle than the iris dilator.

In evaluating the patient who presents with anisocoria, the clinician should first determine whether the anisocoria is physiological or pathological. Perhaps 20% of the adult population will have an inequality of 0.3 to 0.4 millimeters; only 2% will have an inequality of 1 mm or more. If the amount of anisocoria does not change, despite different amounts of background room light and the pupillary reactions to light are equal, physiological anisocoria, is the probable diagnosis.

The first step in the assessment of pathological anisocoria is to determine whether the inequality is greatest in dim light or in bright light.

If the anisocoria is increased in a darkened room, one may conclude that the dilator muscle is deficient. The most common etiology would be a Horner's pupil, due to a sympathetic system deficiency. First, inspect carefully for ptosis. A newly acquired Horner's syndrome in an adult must be thoroughly investigated inasmuch as there is a significant possibility that there is an underlying malignancy. The clinician must assess the structures along the sympathetic pathway including the carotid artery, the apex of the lung, and the base of the brain.

If the anisocoria is greatest in bright light one could conclude that there is dysfunction of the iris sphincter. The differential diagnosis includes disturbances of the parasympathetic system such as Adie's tonic pupil, third nerve palsy, and mydriasis due to pharmacological instillation of drugs that pharmacologically dilate the pupil, such as atropine. Other possibilities include iris damage and acute angle glaucoma causing iris ischemia and subsequent iris sphincter paresis.

**Case 1**
A 25-year-old female presents with mild headache, and a newly noted large left pupil. Examination demonstrates the inequality of the pupils is increased in bright light, suggesting deficient iris constriction of the left eye. Adie's pupil, a defect in the ciliary ganglion, is a definite possibility. This entity includes:

- relative mydriasis in bright illumination, poor to absent light reaction.
- a slow contraction to prolonged near effort.
- a slow re-dilatation after completion of the near effort (the near stimulus is removed).
This condition demonstrates light-near dissociation, in which the pupil constricts better to near stimulus, than to light stimulus. It is most frequently seen in women, and when associated with hypo- or areflexia is termed the Holmes-Adie syndrome. Adie's syndrome is generally benign. Further examination fails to demonstrate light-near dissociation. The above patient is now examined for third nerve palsy.

**Third Nerve Palsy**

One needs to examine ocular motility as well as ptosis. In the absence of those findings, it would be extremely rare for an ambulatory patient to present with a third nerve palsy manifested solely as an isolated dilated pupil. If there is a suspicion that the patient has instilled an atropine-like substance into the eye one can confirm this by instilling 1% pilocarpine solution into the dilated eye. If there is no constriction than one may assume that a mydriatic has previously been in contact with that eye. In a third nerve palsy, the pupil will constrict to the pilocarpine. If the above techniques fail to provide the diagnosis, the patient should be referred to an ophthalmologist in order to inspect the iris with a slit lamp and measure the intraocular pressure. Glaucoma, 2° to acute angle block, is a medical emergency that may present with headache and a fixed pupil.

**OCULAR MOTILITY**

The final portion of this discussion will be devoted to the evaluation of the patient with ocular motility problems, complaining of diplopia.

First, determine whether the diplopia is monocular or binocular. If the diplopia is still present with one eye covered, it is monocular. The common causes of monocular diplopia include cataract, refractive error, corneal abnormalities, retinal surface abnormalities, and psychogenic. If one pinholes the patient and the diplopia clears, one can assume that the etiology was optical.

Binocular diplopia is most common; the ocular misalignment is such that if the patient closes either eye the diplopia will resolve. The clinician can get some clues as to the misalignment by asking a few pertinent questions. Are the images separated horizontally, vertically, or obliquely? In what direction of gaze is the separation maximal?

Let's begin our evaluation with a patient that presents with horizontal diplopia. Upon further questioning we learn that the diplopia is worse in gaze to the right. This suggests that there is a defective right lateral rectus muscle or a defective left medial rectus muscle. These two muscles are responsible for horizontal ocular movement to the right. To determine which muscle is responsible, the examiner should check ocular excursions. If, for example, the right lateral rectus fails to fully abduct on gaze right, than the right lateral rectus is deficient. More commonly however, the ocular misalignment is more subtle, and other examination techniques are necessary.

One such technique is the alternating cover-uncover test (Figure 5). The cover-uncover test is based on evoking a fixational eye movement. Remember, if there is ocular misalignment, only one of the eyes fixates on the object of regard while the other eye deviates. Therefore, if the fixating eye is covered, the deviating eye must re-fixate in order to be aligned with the object of regard. In the cover-uncover test, have the patient fixate
on a distant object, then cover one eye. Observe whether the uncovered eye makes a fixational movement, and if so what is the direction of the movement? If no movement is seen, remove the occluder, and place it front of the other eye. Again observe for any fixational movements of the uncovered eye.

Some common causes of an abduction deficit include:

- Sixth nerve palsy
- Myasthenia gravis
- Extraocular myopathy
- Duane's syndrome
- Spasm of the near reflex

The most common extraocular myopathy is Graves' disease. Duane's syndrome is a congenital condition, felt to be a miswiring of the brainstem. On adduction of the involved eye, the palpebral fissure narrows secondary to retraction of the globe. Interestingly, these patients generally do not complain of diplopia. Spasm of the near reflex is usually secondary to psychological circumstances, and invokes the near triad of convergence, miosis, and accommodation. Convergence mimics the abduction deficit, i.e., the patient converges as you ask them to look left to right, giving the impression that they cannot abduct.

Testing for the specific muscle imbalance in vertical diplopia is much more complex than horizontal diplopia. There are a total of eight muscles, the recti and the obliques, any of which can be responsible for vertical diplopia. In addition, one can have vertical diplopia secondary to skew deviation, a central nervous system abnormality. For those interested in the evaluation of vertical diplopia, please consult the many standard ophthalmological and neuro-ophthalmological texts.

This brief chapter provides the examiner with a basic approach to the evaluation of patients presenting with visual, pupillary, or ocular motility symptoms, as well as some of the more common etiologies. It is imperative that the clinician familiarizes himself with the basic neuroanatomy of these systems.

REFERENCES


MULTIPLE CHOICE QUESTIONS
1. The pinhole test may improve subnormal acuity caused by:

A. Cataract.
B. Retinal detachment.
C. Optic neuritis.
D. Occipital lobe lesions.
E. None of the above

2. A relative afferent pupillary defect is seen most commonly with:

A. Macular degeneration.
B. Vitreous hemorrhage.
C. Amblyopia.
D. Optic neuropathy.
E. None of the above.

3. Physiological anisocoria may be seen in what percent of the adult population?

A. 10%
B. 20%
C. 30%
D. 40%
E. None of the above

4. An Adie's tonic pupil is sometimes associated with:

A. Horner syndrome
B. Optic neuropathy
C. Color vision abnormalities
D. Areflexia  
E. None of the above

5. Common causes of monocular diplopia include:

A. Cataract

B. Refractive error

C. Corneal abnormalities

D. Retinal surface abnormalities

E. All of the above

6. Which of the following will not cause an abduction deficit?

A. Sixth nerve palsy
B. Spasm of the near reflex
C. Duane's syndrome
D. Ischemic optic neuropathy
E. All of the above

7. When testing visual fields by direct confrontation, it is critical to note whether the field defect respects the:

A. Horizontal meridian

B. Vertical meridian

C. Neither
8. When testing for a Horner pupil, there is a greater discrepancy in the anisocoria in:

A. A darkened room

B. A well-lit room

C. The ambient lighting makes no difference whatsoever

9. (True or False) In a patient with optic nerve disease, the swinging flashlight test will demonstrate a subtle anisocoria.

10. (True or False) When using the swinging flashlight test to demonstrate the relative afferent pupillary deficit, the direct response is usually stronger than the consensual response.

ANSWERS:

1. A
2. D
3. B
4. D
5. E
6. D
7. B
8. A
9. False
10. False
Chapter 3 – Numbness: A Practical Guide Form Family Physicians

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Localizing The Problem By History And Examination

Numbness can result from either a disease process located in the central nervous system (brain or spinal cord) or the peripheral nervous system (nerve root, dorsal root ganglion, or nerve). Often, localization of the problem can be identified by the patient's history alone. Recognition of both the timing and onset of the patient's symptoms and the distribution of the patient's signs and symptoms are essential.

Localizing a patient's deficits to a specific area of the nervous system can frequently be accomplished by attention to:

- **Distribution of symptoms**
  - Right vs. left
  - Presence of facial involvement
  - Arm vs. leg
  - Proximal vs. distal
  - Symmetric vs. asymmetric

- **Characteristics of symptoms**
  - Sensory and motor
  - Painless or Painful
  - Sensory only
  - Autonomic involvement

- **Temporal Features**
  - Acute or Chronic
  - Static or Progressive

History: The Chief Complaint
Patient complaints of "numbness" can include a range of true sensory disturbances. "Tingling," "burning," or true loss of sensation can each be described simply as "numbness." Specific questioning, therefore, can help in identifying the etiology of the disease process, and simultaneous evaluation of the distribution of these complaints can significantly limit the differential diagnosis. Prompt recognition of these common symptoms has a major impact on appropriate treatment and ultimately can minimize long-term residual deficits for the patient.

Table 1.

<table>
<thead>
<tr>
<th>Patient's Description of Sensory Loss</th>
<th>Likelihood of the localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Tingling&quot;</td>
<td>Peripheral NS &gt; Central NS</td>
</tr>
<tr>
<td>&quot;Burning&quot;</td>
<td>Peripheral NS &gt; Central NS</td>
</tr>
<tr>
<td>&quot;Total loss of feeling&quot;</td>
<td>Central NS1 &gt; Peripheral NS²</td>
</tr>
<tr>
<td>&quot;Poor coordination&quot;²</td>
<td>Central NS = Peripheral NS</td>
</tr>
</tbody>
</table>

¹Localization to the central nervous system would most commonly involve unilateral signs and symptoms except with spinal cord lesions where symptoms are usually bilateral. ²Peripheral nervous system lesions can be either multifocal or, commonly, bilateral and symmetric. Early signs in a neuropathy may involve only one extremity (usually the feet) but peripheral involvement would be much less likely with all unilateral complaints. ³Poor coordination can result from either central (cerebellar, brainstem) or peripheral (impaired proprioception, nerve, dorsal root ganglion) pathology.

The neuronal projections determine the extent and characteristics of the patient's symptoms. Individual populations of neurons are vulnerable in specific disease states. This vulnerability may arise from the effect of a disease on a specific vascular territory (i.e., stroke, vasculitis, aneurysm), a space occupying lesion (tumor, herniated disk) or an autoimmune, inflammatory attack on the nervous system. By history alone one can frequently appreciate the basics of localization (Table 1, 2).

Table 2: Distribution and selected characteristics of localizing patient complaints along the neuraxis

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Facial Involvement</th>
<th>Characteristic</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Unilateral</td>
<td>often</td>
<td>sensory + motor</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Bilateral</td>
<td>no</td>
<td>sensory + motor</td>
</tr>
<tr>
<td>Nerve Root</td>
<td>Unilateral</td>
<td>no</td>
<td>sensory + motor</td>
</tr>
<tr>
<td>Nerve</td>
<td>Unilateral or bilateral</td>
<td>possible</td>
<td>sensory, motor, autonomic or combinations</td>
</tr>
<tr>
<td>Neuromuscular junction</td>
<td>often bilateral</td>
<td>yes, but not always</td>
<td>motor</td>
</tr>
</tbody>
</table>
The distribution of lesions affecting the brain or spinal cord (central nervous system) are usually distinct from those affecting nerve root, nerve, neuromuscular junction or muscle (peripheral nervous system).

Table 2: Classification of etiologies affecting the central vs. peripheral nervous system. These conditions can result in common patient complaints of "numbness, tingling, pain or weakness"

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Central Nervous System</th>
<th>Peripheral Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>stroke, arterial-venous malformation, claudication</td>
<td>peripheral vascular disease</td>
</tr>
<tr>
<td>Structural</td>
<td>tumor, disk</td>
<td>tumor, disk</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>infection, vasculitis</td>
<td>neuropathy, vasculitis, infection, myositis</td>
</tr>
<tr>
<td>Genetic</td>
<td>myopathy, motor neuron disease</td>
<td>neuropathy</td>
</tr>
<tr>
<td>Immune mediated</td>
<td>Multiple sclerosis, myelopathy</td>
<td>neuropathy, neuromuscular junction disease</td>
</tr>
</tbody>
</table>

Brain

A presenting symptom of numbness may be secondary to lesions of the parietal lobe or thalamus (ventral postomedial nucleus, VPM). As described in Chapter 1, thalamic lesions produce contralateral sensory loss and numbness, which may be painful. Abrupt onset suggests stroke and often is seen with lacunar infarcts secondary to hypertension. The patient typically has sudden onset of contralateral sensory loss without other symptoms (such as weakness). The MRI examination may confirm the presence of a lacunar infarct, in the VPM thalamus or more significantly a hemorrhagic infarction usually accompanied with significant hypertension. The thalamus is more vulnerable to hemorrhage resulting from hypertension in the brain, relative to other brain regions. Control of the patient's precipitating hypertension may constitute the major treatment modality along with addressing other stroke risk factors.

Parietal lobe lesions are characterized by sensations of contralateral numbness but on examination we find loss of discriminatory sensation, possibly accompanied by neglect of that extremity. The patient may feel touch but may not localize it well and may also demonstrate extinction (see Chapter 1). Patients may feel you touch their fingertips but may not be able to identify a number that you trace on the fingertip (impaired graphesthesia). Depending upon localization within the parietal lobe or involvement of the underlying white matter, patients may also experience weakness as well as numbness. Sensory complaints should be more prominent than motor symptoms, however, both sensory and motor signs may occur in many affected regions of the brain due to interruption of fibers affecting both functions.
Spinal Cord
Lesions in the spinal cord resulting only in numbness are less common than complaints of both numbness and weakness due to the close proximity of motor and sensory neurons and their pathways in the spinal cord. This is especially true of structural (herniated disk, trauma, tumor) and ischemic lesions.

Inflammatory lesions, however, can selectively affect sensory pathways and result in profound, usually bilateral, sensory disturbance. Inflammatory disorders such as acute myelitis and multiple sclerosis can present as only sensory disturbances. The dorsal columns (fasciculus gracilis and cuneatus) as well as the spinal thalamic tract carry distinct sensory modalities through the spinal cord. Sensory disturbance characterized by selective abnormality of position sensation (proprioception) suggests a selective involvement of the large myelinated fibers found in the dorsal columns and disorders such as multiple sclerosis, vitamin deficiencies/toxicity, and tertiary syphilis should be explored further. Temperature, light touch and pain are mediated by the smaller fibers of the spinal thalamic pathway. These fibers are not usually selected affected in the spinal cord.

Nerve Root/Dorsal Root Ganglion
Dorsal (sensory) and ventral (motor) nerve roots are separate as they exit the spinal cord until their fibers combine at the level of the dorsal root ganglion. The most common nerve root pathology results from a herniated vertebral disk causing compression on the nerve roots. This usually results in pain with radiation into the affected dermatome. Due to the proximity of dorsal and ventral roots, motor involvement is also commonly detected. The hallmark of selective nerve root involvement is a pattern of unilateral symptoms limited to the distribution of that nerve root.

The involvement of multiple nerve roots suggests a process other than a structural lesion. Inflammatory (Guillian Barré, CIDP, amyloidosis, vasculitis), neoplastic (carcinomatous meningitis) or infectious (syphilis, Lyme) processes need to be considered. Often appropriate serology and a lumbar puncture is required to further resolve this differential diagnosis.

Selective involvement of the dorsal root ganglion cells causes a profound sensory disturbance. Fortunately, the differential diagnosis of a dorsal root ganglionopathy is limited and careful attention to the physical examination can identify the proper etiology.

Cis-platinum toxicity following chemotherapy can result in a significant disability due to large fiber (position sense) sensory loss. The onset can be delayed by several months and some resolution may be expected when the dose is reduced or stopped. Paraneoplastic (anti-Hu) syndrome can result in painful, asymmetric sensory loss to all modalities with normal motor function. This pathology predominantly affects women and is commonly associated with concurrent small cell carcinoma.

Nerve
Sensory disturbances caused by neuropathy are common. More commonly, however,
neuropathy presents with both motor and sensory symptoms reflecting the involvement of both fiber types in the nerve. An etiology for a predominantly sensory neuropathy can be focused by recognition of some discriminating features of the patient's sensory complaints at presentation. Small fiber sensation includes light touch, pain and temperature while large fiber sensation includes position sensation (proprioception) and partial vibratory sensation. Pain and/or autonomic complaints can also limit the evaluation of possible etiologies and work-up. The list of possible etiologies resulting in sensory neuropathy is long and it is not necessary to evaluate every patient for all possible causes. Table 4 lists both common and uncommon causes of sensory predominant neuropathy.

Along with the recognition of distinguishing features of the patient's sensory disturbance, identification of significant features of the past history and family history is essential. Diabetes, alcohol abuse, chronic use of medication or vitamins, and history of similar sensory problems in the family are significant clues to identifying a proper etiology. In this country, and in many European countries, diabetes is the most common cause of neuropathy while leprosy remains the most common etiology worldwide.

**Table 4**

<table>
<thead>
<tr>
<th>Primary Characteristic</th>
<th>Toxic</th>
<th>Immune</th>
<th>Metabolic</th>
<th>Inherited</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Alcohol Metals: thallium, arsenic, Meds: cis-platinum, disulfiram, nitrofurantoin, taxol</td>
<td>Guillain Barré syndrome, HIV, Sjogren's, Vasculitis, Cryoglobulinemia</td>
<td>Diabetes, Vitamin related</td>
<td>Fabry's disease (a-galactosidase), Hereditary Sensory Neuropathy, Amyloidosis, Porphyria</td>
<td></td>
</tr>
<tr>
<td>Large &amp; Small Fiber</td>
<td>Metals: thallium, mercury, Drugs: thalidomide, taxol, metronidazole, phenytoin</td>
<td>Paraneoplastic (anti-Hu), Anti-MAG, anti-sulfatide, Sjogren's, Cryoglobulinemia</td>
<td>Diabetes</td>
<td>Hereditary Sensory Neuropathy (AR)</td>
<td></td>
</tr>
<tr>
<td>Large Fiber</td>
<td>Vitamin</td>
<td>Miller Fischer</td>
<td>Friedreichs</td>
<td>Syphilis-tabes</td>
<td></td>
</tr>
<tr>
<td>&amp; Ataxia related, Cisplatinum, Taxol</td>
<td>variant of Gillian Barre syndrome, CIDP1, Anti-MAG syndrome2, GALOP syndrome3</td>
<td>ataxia, Sensory ataxic neuropathy, Ataxia telangectasia</td>
<td>dorsalis</td>
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</tr>
<tr>
<td>Small Fibers Mostly</td>
<td>Chronic Metronidazole, or misonidazole</td>
<td>HIV-Associated</td>
<td>Amyloidosis Hereditary Sensory Neuropathy, Tangier's Disease, Fabry's disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Leprosy, 1° biliary, cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autonomic Symptoms</td>
<td>Guillain Barré, Paraneoplastic (anti-Hu)</td>
<td>Diabetes</td>
<td>Amyloidosis, Porphyria, Lepra</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>MNGIE4,#Chronic intestinal, Encephalopathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Chronic Inflammatory Demyelinating Polyneuropathy; 2 Syndrome of Gait disorder, Autoantibody, Late age, Organomegaly, Polyneuropathy; 3 Syndrome of detectable antibodies directed against Myelin Associated Glycoproteins; 4 A mitochondrial etiology: Myopathy and external ophthalmoplegia, Neuropathy, Gastro-Intestinal, Encephalopathy

**History of the Present Illness**

**Onset**

**Slow progressive course.** Slow progressive numbness or sensory disturbance is most commonly described as distal numbness or tingling in the toes. This usually progresses proximally into the feet and then up the legs [distal to proximal progression or "dying back" pattern]. The most distal segments of the nerve are most dependent upon axonal transport for delivery of vital proteins and neurotransmitters. Interruption of axonal transport, or any lesion affecting the function and viability of the nerve along its course will be recognized by the patient as symptoms occurring referred in the most distal aspects of the affected nerve. Recognizing a dying back process, i.e., a slow progressive distal to proximal progression (usually symmetric) would strongly implicate neuropathy in the differential diagnosis. Sensory complaints due to radiculopathy can also evolve slowly, however they are frequently characterized by pain in the affected root distribution, which is exacerbated by activity. Sensory complaints from a radiculopathy or neuropathy can be episodic, especially earlier in their course.
Sensory disturbances from pathology in the brain or spinal cord usually evolve more acutely. Ischemia or inflammatory disease in the central nervous system also evolves rapidly over several days. Numbness or paresthesias due to multiple sclerosis are examples of such a process.

**Acute or subacute onset with rapid progression (Table 5).** Rapidly progressive sensory complaints, usually accompanied by weakness are compatible with localization to either the **brain spinal cord, nerve root or nerve**. In general, ischemic injury is most commonly implicated in sudden onset of sensory symptoms. As mentioned above, inflammatory disorders can evolve rapidly over several days and also can affect any area of the neuraxis.

In the brain, acute onset of significant sensory symptoms is usually accompanied by either weakness and/or encephalopathy. Common etiologies include: stroke, multiple sclerosis, cancer (lymphoma, metastasis), and infection. In the nerve root, acute sensory symptoms are most commonly due to compression from a disk or trauma as discussed above. In the nerve, the differential diagnosis of potential etiologies is longer but equally critical. Acute inflammatory demyelinating neuropathy (Guillain-Barré syndrome) often requires prompt attention to maintain life support and initiate treatment. Arsenic, thallium, tick paralysis and porphyria may also result in rapidly progressive disability for the patient warranting emergent treatment.

**Table 5: Considerations of differential diagnosis for neuropathy in patients with sensory complaints using the onset and progression as criteria.**

<table>
<thead>
<tr>
<th></th>
<th><strong>ACUTE (Days)</strong></th>
<th><strong>CHRONIC (Weeks - Months)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Immune</strong></td>
<td>Guillain-Barré &amp; variants, Vasculitis</td>
<td>Chronic demyelinating neuropathy</td>
</tr>
<tr>
<td><strong>Toxins</strong></td>
<td>Botulism, Buckthorn, Diphtheria; Tick; Arsenic; Organophosphates; Thallium; Vacor</td>
<td>Heavy Metals, Environmental Chemicals</td>
</tr>
<tr>
<td><strong>Drugs (see Table 6)</strong></td>
<td>Captopril (few case reports); Gangliosides; Gold; Nitrofurantoin; Suramin; Zimeldine</td>
<td>Chemotherapeutic Agents</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td>Porphyria</td>
<td>Porphyria, Diabetes</td>
</tr>
<tr>
<td><strong>Nutritional</strong></td>
<td></td>
<td>Vitamin toxicity or deficiency</td>
</tr>
<tr>
<td><strong>Hereditary</strong></td>
<td>Hereditary motor and sensory neuropathy (HMSN), hereditary sensory neuropathy (HSN)</td>
<td></td>
</tr>
</tbody>
</table>
the brain or spinal cord can be aided by identification of similar disease in the family, however, the symptoms are usually not limited to sensory complaints or numbness.

Identification of genetic lesions resulting in inherited neuropathy has significantly increased our understanding of normal biology of nerve, myelin and their interaction. The hereditary motor and sensory neuropathies (HMSN, Charcot-Marie-Tooth neuropathies) comprise a group of disorders with overlapping clinical characteristics but distinct pathology. Some of these disorders can be identified by currently available commercial laboratory tests (see below). Inherited disorders affecting only sensation (hereditary sensory neuropathy, HSN) are more rare and may involve either small fiber sensory loss (pain and temperature) or loss of larger sensory fibers (proprioception, vibration). Distinguishing the type of sensory loss on examination, therefore, can limit the differential diagnosis and an accurate family history can lend further support for a diagnosis even prior to definitive genetic testing when available. Genetic markers screening for these disorders have not been established for general clinical use at this time and the diagnosis is made based on the clinical observations and family history.

**Occupational Exposure**

Incidental exposure to agents, which are toxic to nerve, may be easily missed on a routine history and review of systems. Contact with solvents, glues, fertilizer, oils and lubricants can result in a neuropathy indistinguishable from other causes of idiopathic or hereditary etiology. **Table 6** includes a summary of several categories of neurotoxic exposure leading to neuropathy.

**Table 6: Selected agents found in various industrial applications associated with neuropathy affecting sensation.**

<table>
<thead>
<tr>
<th>Solvents, Glues &amp; Lacquers</th>
<th>n-hexane</th>
<th>Hexacarbons</th>
<th>Trichloroethylene(TCE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides</td>
<td>methylbromide</td>
<td>Organophosphates</td>
<td>Thallium</td>
</tr>
<tr>
<td>Oils/Lubricants</td>
<td>Spanish &quot;toxic&quot; oil</td>
<td>Triorthocresylphosphate (TOCP)</td>
<td></td>
</tr>
<tr>
<td>Disinfectants</td>
<td>ethyleneoxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>carbon disulfide, acrylamide</td>
<td>DMAPN</td>
<td>Polychlorinatedbiphenyls (PCBs)</td>
</tr>
</tbody>
</table>

**Medications**

Inadvertent or iatrogenic injury to nerve caused by medications or vitamins is likely not fully recognized in a routine history and physical evaluation. Over-the-counter oral preparations can result in a profound sensory predominant neuropathy even when taken at therapeutic doses. Patients who have neuropathy not associated with or caused by a medication may still be vulnerable to exacerbation of their symptoms by taking these neuropathic agents and should be advised to avoid these preparations (**Table 7**).
Table 7: Selected medications, which are associated with a sensory or a sensory predominant neuropathy. These medications should also be avoided in patients with other etiologies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Sensory Predominant Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloramphenicol</td>
<td>metronidazole</td>
</tr>
<tr>
<td>cis-platinum</td>
<td>nitrous oxide</td>
</tr>
<tr>
<td>ethambutol</td>
<td>nucleosides</td>
</tr>
<tr>
<td>glutethemide</td>
<td>[didanoside (ddI)]</td>
</tr>
<tr>
<td>hydralazine</td>
<td>dideoxycytosine (ddC)</td>
</tr>
<tr>
<td>isoniazid</td>
<td>stavudine (d4T)</td>
</tr>
<tr>
<td>phenytoin</td>
<td>Nitrofurantoin</td>
</tr>
<tr>
<td>pyridoxine</td>
<td>taxol</td>
</tr>
<tr>
<td>thalidomide</td>
<td></td>
</tr>
</tbody>
</table>

**Evaluating Changes In Sensation**

**Examination**

**The clinical signs.** Few signs in the neurological examination are as localizing and sensitive as the deep tendon reflexes (DTRs). Intact DTRs require both an afferent (sensory) component to carry input from the muscle tendon to the spinal cord and an efferent (motor) component to produce a muscle twitch during a reflex. Furthermore, the motor neurons are affected by descending cortical-spinal inputs that effect the reflex arc. Nerve impulse conduction throughout this entire afferent/efferent loop is, therefore, vulnerable to injury, which could exaggerate, diminish or obliterate the corresponding reflex.

**Pathology in the central nervous system** is characterized by pathologically brisk reflexes and extensor plantar reflexes (abnormal Babinski sign). In addition, increased tone and spasticity are consistent features. By contrast, with pathology in the peripheral nervous system diminished or absent reflexes are seen along with atrophy and reduced muscle tone. Asymmetric or absent reflexes should generate clinical suspicion for a neuropathy or radiculopathy.

In a sensory (or sensory predominant) neuropathy the type of sensory loss can localize the process to small, large or both small and large, axons as discussed above. The primary modalities of sensory loss which should be evaluated include those listed below.

Table 8: Sensory modalities which should be included on a through examination and their anatomic correlates.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Fiber type (Periphery)</th>
<th>Tract (Central)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light touch</td>
<td>small fiber</td>
<td>Spinothalamic</td>
</tr>
<tr>
<td>Temperature</td>
<td>small fiber</td>
<td>Spinothalamic</td>
</tr>
<tr>
<td>Pinprick</td>
<td>small fiber</td>
<td>Spinothalamic</td>
</tr>
</tbody>
</table>
The nature of the sensory examination relies on a patient's subjective report and is therefore prone to additional variability. Differences between patient perceptions and their ability to relate subtle differences in pinprick or temperature can make this the most challenging part of the physical examination. In general, absolute differences in sensation are not as important for localization or diagnosis as are the relative differences in perceived sensation. The most useful information from the sensory examination results, therefore, from the distribution of the deficit (symmetric vs. asymmetric) and the quality of the sensory loss.

Sensory loss and neuropathy associated with systemic disease. Clinical signs on the general examination can be essential clues to the etiology of sensory loss (Table 9). Systemic diseases commonly involve multiple organ systems. The nervous system is frequently implicated due to its widespread distribution, long projections and unique metabolic demands. Autoimmune, inflammatory, metabolic, and neoplastic disease are among the categories of systemic illness, which can involve the peripheral nerve resulting in numbness, paresthesia, and/or weakness. Careful attention to key clinical signs on general examination can result in the underlying disease as well as the etiology for the neuropathy.

Table 9.

<table>
<thead>
<tr>
<th>Clinical Sign</th>
<th>May suggest:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>Lupus</td>
</tr>
<tr>
<td>Funduscopic examination</td>
<td>Diabetes, Vasculitis</td>
</tr>
<tr>
<td>Adenopathy</td>
<td>Infection, Cancer</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Diabetes, Cancer, Endocrinopathy</td>
</tr>
<tr>
<td>Bony or Cutaneous abnormalities</td>
<td>Inherited neuropathy, Endocrinopathy</td>
</tr>
<tr>
<td>Organomegaly</td>
<td>&quot;POEMS&quot; syndrome1</td>
</tr>
</tbody>
</table>

1 Syndrome of: Polyneuropathy: sensory & motor Organomegaly: liver; spleen; lymph nodes Endocrinopathy or Edema: diabetes; hypothyroid; gynecomastia M-protein: Usually IgG or IgA Skin changes: hypertrichosis; hyperpigmentation; clubbed fingers; white nails

Evaluation: Work-Up
The primary goal in identifying a proper localization is to identify treatable etiologies of the underlying process. Each localization along the neuraxis mentioned above (brain–spinal cord–nerve root–nerve) has treatable conditions associated with it. Evaluation should include serologic and radiographic evaluation where appropriate to identify overt contributing conditions and proper referral to a neurologist for assistance in further resolution of the differential diagnosis and treatment plan.
Central Nervous System
As discussed above, sensory loss or numbness localized to the central nervous system most commonly is associated with stroke or inflammatory disease.

Proper evaluation of a patient with a suspected stroke, primarily involving sensation, should include screening for the commonly accepted risk factors (HTN, diabetes, cholesterol, tobacco use, arrhythmia). In addition, an MRI scan of the brain with gadolinium contrast is usually indicated as this can illustrate the extent of the current lesion and reflect prior, perhaps subclinical, lesions.

Ischemic or inflammatory disease localized to the spinal cord by both a gadolinium enhanced MRI scan and a lumbar puncture. The presence of elevated protein and an increased number of white blood cells in the cerebrospinal fluid is consistent with inflammation (myelitis). A specific etiology for an inflammatory lesion in the spinal cord is often more elusive. Specific viral pathogens such as varicella, HTLV-1, and HIV have been identified. Multiple sclerosis is a clinical diagnosis requiring multiple signs and symptoms at more than one point in time.

Table 10. Initial screening evaluation for suspected localization of sensory loss.

<table>
<thead>
<tr>
<th>Localization</th>
<th>Lab tests</th>
<th>Radiology</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Hb-A1c, lipid profile, ESR, ANA, CBC, electrolytes, RPR</td>
<td>MRI with contrast Transcranial doppler, Carotid doppler</td>
<td>EKG, ECHO, possible Holter</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>Routine lab screen evaluating underlying illness, B12</td>
<td>MRI with contrast</td>
<td>LP with opening pressure, protein, chemistry and cytology</td>
</tr>
<tr>
<td>Nerve Root</td>
<td>Not usually indicated</td>
<td>CT or MRI of the suspected area. Myelogram may be indicated</td>
<td>Nerve conduction and electromyography including F and H wave evaluation</td>
</tr>
<tr>
<td>Nerve</td>
<td>Hb-A1c, ESR, ANA, CBC, electrolytes, RPR, SPEP, immunofixation, B12 As indicated: ANCA, cryoglobulins</td>
<td>Not usually indicated</td>
<td>Nerve conduction and electromyography Possible nerve &amp; muscle biopsy as indicated</td>
</tr>
</tbody>
</table>

Electrodiagnosis (Table 11)
The evaluation of electrical impulses along affected nerves (nerve conduction studies) and within affected muscles (electromyography) often provides an essential aspect to the work-up, localizing nerve/muscle pathology and etiology. These tests are highly dependent upon multiple variables impacting the technical quality of the study. Consequently it is important to have confidence in the referral as interpretation of the data can be markedly affected by these technical issues.

Nerve conduction studies are especially helpful in identifying treatable causes of neuropathy by revealing evidence of demyelination. Impaired speed of conduction or a complete block of conduction over a defined segment are compatible with demyelinating neuropathy. Conversely, a reduced amplitude of the conducted response is characteristic of an axonal neuropathy. It is important to note that axonal loss can either result from a primary pathologic process or secondary to demyelination. Ultimately, the goal of the nerve conduction study is to determine whether a treatable process is present. This goal is usually realized by noting pathology that is selective or focal (i.e., nerve compression, radiculopathy) or compatible with demyelination.

Table 11: Summary of common patterns found on nerve conduction studies in various areas of neuromuscular pathology

<table>
<thead>
<tr>
<th>Result</th>
<th>Axonal neuropathy</th>
<th>Demyelinating neuropathy</th>
<th>Radiculopathy</th>
<th>Myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced amplitude</td>
<td>Common</td>
<td>Possible secondary change</td>
<td>Not common and only in motor nerves affected by the root</td>
<td>Possibly due to reduced impulse in the disease muscle, not disease in the nerve</td>
</tr>
<tr>
<td>Slow conduction velocity</td>
<td>Not common</td>
<td>Common. Also look for focal conduction block</td>
<td>Not commonly found</td>
<td>Not found</td>
</tr>
<tr>
<td>Prolonged distal latency</td>
<td>Possible</td>
<td>More common</td>
<td>Not expected</td>
<td>Not usually found</td>
</tr>
<tr>
<td>Sensory nerves</td>
<td>Can be affected</td>
<td>Can be affected</td>
<td>Not found</td>
<td>Not Found</td>
</tr>
</tbody>
</table>

Psychological Considerations
A number of the conditions described above may be associated with psychological and behavioral complications. In some cases the condition itself produces psychological changes (e.g., stroke). In other cases the effects of the condition may precipitate those changes (e.g., depression over loss of independence). Studies have found an incidence of depression after stroke as high as 60%, and the risk of suicide is increased for patients with conditions such as stroke or multiple sclerosis. Occasionally our treatment interventions may be associated with adverse psychological effects.

Depression may decrease a patient's ability and willingness to take part in needed therapy, thus resulting in prolonged or increased disability. Caregivers of patients with
some of the chronic conditions described in this chapter are also often affected. Many of these patients require intense and ongoing efforts by family members, which can lead to depression and anxiety among these caregivers. Physicians must be attentive and proactive in searching for this co-morbidity, both in the patient and in the family members.

**Community Resources**

As noted in the section on weakness, ongoing needs will vary tremendously from patient to patient. The effects of neuropathy, stroke or multiple sclerosis will span the range from incapacitation to minimal impact. Physical therapy, occupational therapy, and speech therapy can be provided in various settings, including the acute care hospital, extended care facilities, and the home. In the case of stroke, education can play a valuable role in reducing the likelihood of reoccurrence through lifestyle changes (e.g., lowering of cholesterol, management of blood pressure, smoking cessation). Education may also be valuable to the multiple sclerosis patient in terms of management of symptoms and avoidance of exacerbation triggers (e.g., avoidance of overheating). Often, patient education regarding the site and nature of pathology can be a powerful tool to helping a patient cope with progressive disability. This may be especially true in distinguishing demyelinating, axonal and inherited neuropathy.

National organizations for specific conditions offer a number of services, including literature directed to the lay audience, lists of local support groups, and treatment advances. Some of those for the conditions discussed in this chapter include:

**The Neuropathy Association**
60 East 42nd Street
New York, NY 10165
(800) 247-6968, 212-692-0662
info@neuropathy.org
Regularly published informative newsletter is also available.

**Charcot Marie-Tooth Association**
800-606-CMTA

**Sjogren's Syndrome Foundation**
516-933-6365
Patient Support Group

**Guillain-Barré Syndrome Foundation International**
P.O. Box 262
Wynnewood, PA 19096
(610) 667-0131
Website
gbint@ix.netcom.com
Questions

1. All of the following statements are true except:
   A. brain lesions usually cause unilateral numbness without associated pain
   B. spinal cord lesions usually cause bilateral sensory loss
   C. nerve root lesions usually are associated with sensory loss or symptoms and pain.
   D. myopathies are commonly associated with severe pain

2. A brain lesion that may be associated with painful sensory loss is located in the:
   A. thalamus
   B. frontal lobe
   C. motor cortex
   D. parietal lobe

3. Motor and sensory symptoms in a multiple nerve root distribution can be seen:
   A. carcinomatous meningitis
   B. Guillain-Barré syndrome
   C. Lyme disease
   D. diabetes mellitus
   E. all of the above

4. The most common pathology to affect a single nerve root is:
   A. diabetic radiculopathy
   B. Guillain-Barré Syndrome
   C. herniated intervertebral disc
   D. disc space infection

5. Neuropathy in Charcot-Marie-Tooth disease is:
A. due to nutritional deficiency
B. secondary to benzene exposure
C. a genetically determined degenerative disorder.
D. reversible in most cases

6. Chronic nitrofurantoin use can cause peripheral neuropathy. True or False?
7. Slowly progressive numbness, beginning slowly in the feet and moving proximally may be secondary to the "dying-back" phenomenon characteristic of multiple sclerosis. True or False?
8. Absent reflexes may be seen with:
   1. neuropathy
   2. radiculopathy
   3. myelopathy
   4. A and B
   5. none of the above

9. (True or False) Nerve conduction studies are sensitive in detecting areas of demyelination on peripheral nerves that result in slowing of nerve conduction velocities. True or False?
10. Electromyography is useful in distinguishing a neuropathic process from a myopathic process. True or False?

Answers

1. D
2. A
3. E
4. C
5. C
6. True
7. False
8. D
9. True
10. True

Navigation

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Chapter 4 – Weakness: Practical Guide For Family Physicians

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A common complaint of many patients in a primary care setting is "Doctor, I am weak." One could accept this outright as a manifestation of loss of strength in some muscle groups but a wiser approach is to ask the patient to specifically define what he or she means by weakness. The answer is often surprising and may encompass complaints as varied as fatigability, apathy, loss of sensation, imbalance or excessive drowsiness. If, indeed, the complaint is actual loss of strength in muscle groups, then an accurate history directed to causes of weakness must be obtained.

Information important for the evaluation of weakness includes:

- The temporal profile of weakness onset
  - Acute
  - Subacute
  - Chronic
- The distribution of the weakness:
  - Proximal
  - Distal
  - Symmetric
  - Asymmetric
    - Hemiparesis (one half of the body)
    - Paraparesis (lower extremities)
    - Monoparesis (one extremity)
    - Focal weakness (portion of an extremity or the face)

Once the history is obtained the neurological examination should confirm the presence of any weakness as well as its distribution. Important associated findings are muscle atrophy, pain and tenderness, swelling, fasciculations (a visible twitch under the skin caused by the spontaneous firing of a motor unit [one anterior horn cell and all the muscle fibers it innervates]), deep tendon reflex changes and sensory loss.
The following cases will illustrate different types of weakness, with their associated histories and physical findings.

Case 1
A 71-year-old male is eating breakfast and has abrupt onset of visual loss in the left eye and weakness in the right arm and leg. There is some tingling of the right hand and right corner of his mouth. He has difficulty standing and is taken to the emergency room where you are called to see him. On exam his vision has recovered but he has weakness of the right arm involving the triceps, wrist and finger extensors and the right leg involving the hamstrings (lower leg flexors) and anterior tibial (foot dorsiflexors). The deep tendon reflexes are more brisk on the right, and he has a right Babinski sign. Sensory exam reveals decreased sensation in the right hand and arm, and less on the right the face and leg. He has difficulty identifying objects placed in his hand by sensation alone. The patient has no difficulty understanding speech, but speaks infrequently and with a paucity of otherwise meaningful words.

General physical examination reveals a left carotid bruit and a normal sinus rhythm.

**Analysis.** The patient is elderly and had abrupt onset of weakness (acute), with a distribution best classified as a hemiparesis. Associated symptoms are ipsilateral sensory loss and contralateral monocular blindness. The acute onset suggests a vascular etiology and the clinical findings best fit the brain location supplied by the left internal carotid artery.

The first branch of the left internal carotid artery is the ophthalmic artery (OA). Decreased blood flow in this artery would produce transient monocular visual loss, known as amaurosis fugax (fleeting blindness). The patient usually experiences this as a curtain being pulled down over the eye, lasting several minutes, then clearing. The retina often recovers due to collateral circulation from the external carotid artery (ECA), and vision returns.

The carotid artery then divides into the middle and anterior cerebral artery. The middle cerebral artery (MCA) supplies the lateral hemisphere (see homunculus, Chapter 1, **Figure 2.22**). The prefrontal motor area supplied by the MCA encompasses the face, hand, upper extremity and trunk. The motor cortex supplied by the anterior cerebral artery (ACA), encompasses the leg. The MCA and ACA supply analogous sensory areas (parietal).

The best diagnosis is stroke in the distribution of the left internal carotid artery (ICA), due to involvement of the ophthalmic, middle and anterior cerebral arteries. Another clue on examination is the left carotid bruit. Bruits are due to turbulent blood flow, which can in turn be caused by vessel stenosis. When a vessel completely occludes, the bruit disappears.
Summary. Abrupt onset (vascular) of left visual loss (left OA) and right hemiparesis (MCA and ACA = ICA ) is suggestive of a stroke in the left internal carotid artery distribution. This could be embolic or thrombotic in etiology.

If the patient presents to an Emergency Department or is a hospital in-patient and is seen within three hours of symptom onset, he/she should be evaluated for possible treatment with tissue plasminogen activator.

Table 1: Characteristics of upper motor neuron weakness

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Lower face, Extensor muscles in the arm Flexor muscles in the leg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Tone&lt;</td>
<td>Spasticity, Increased resistance overcoming flexion in the arm and overcoming extension in the leg (Like opening a clasped knife)</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Deep tendon reflexes are increased and clonus may be elicited</td>
</tr>
<tr>
<td>Pathological Reflexes</td>
<td>Clonus at the patella or ankle Babinski sign in the lower extremity</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Does not occur with UMN weakness Mild disuse atrophy may be seen</td>
</tr>
<tr>
<td>Coordination</td>
<td>There is slowness or incoordination of fine motor movements, e.g.,tapping fingers or wiggling toes</td>
</tr>
</tbody>
</table>

Case 2
A 33-year-old male construction worker has been in good health except for a recent bout of gastroenteritis. Initially he noted some paresthesias in his feet and less so in his fingers. The following day he noted difficulty climbing a ladder. He presented to the Emergency Department and was noted to have hypoactive deep tendon reflexes, no sensory loss and was able to walk unassisted. A diagnosis of "flu" was given and he was given symptomatic treatment. He spent the remainder of the day resting in bed. The following morning he fell while attempting to walk to his bathroom and at that time, was unable to stand without support. Re-evaluation, at the Emergency Department, revealed distal leg weakness and absent deep tendon reflexes. There was no objective sensory deficit.

Other studies included normal EKG, CPK and troponin and normal chest x-ray. Neurology consultation was obtained. Nerve conduction/EMG studies revealed prolonged distal motor latencies and slowed nerve conduction velocities. CSF was obtained and showed a protein level of 80 mg/dl with no cells and normal glucose. Treatment was started.

The following day the patient noted difficulty grasping and elevating his arms but then stabilized. After one week of treatment strength started to return in the upper, then lower extremities.
Discussion. This individual had a subacute process causing progressive weakness that started distally and progressed proximally over days, ultimately affecting the patient's ability to walk. Over time, the deep tendon reflexes disappeared, suggesting a lower motor neuron or peripheral nerve lesion. Associated findings are elevated CSF protein with a normal cell count (albumino-cytologic dissociation) and slowed motor nerve conduction velocities (demyelination). The disorder that is most likely to produce this profile is acute inflammatory demyelinating polyradiculoneuropathy (AIDP) also known as Guillain-Barré syndrome.

Current treatment involves alternate day plasmapheresis or daily administration of intravenous immune globulin (IVIG). These treatments have significantly improved the outcome of patients with this immune mediated disorder.

Failure to provide timely treatment could lead to progressive weakness, and respiratory failure, with need for assisted ventilation. Prolonged disease duration could also produce axonal nerve damage with subsequent prolonged recovery times, muscle atrophy, contractures and motor disability. With severe untreated disease autonomic involvement could lead to hypo- or hypertension and life threatening cardiac arrhythmias.

Table 2: Characteristics of lower motor neuron weakness

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Peripheral neuropathy, distal and symmetrical; or, follows the distribution of root, plexus or peripheral nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Tone</td>
<td>Decreased in the affected muscles</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Present in the affected muscles</td>
</tr>
<tr>
<td></td>
<td>Fasciculations may be noted</td>
</tr>
<tr>
<td>Coordination</td>
<td>There is motor ataxia proportional to the degree of weakness</td>
</tr>
</tbody>
</table>

There is current evidence that peripheral neuropathies whether generalized or focal may have an immune basis if no other etiology is found. If certain criteria are met these neuropathies may be classified as a form of chronic inflammatory demyelinating polyradiculonueopathy and respond to treatment with IVIG or plasmapheresis. Chronic progressive or recurrent neuropathies without an apparent etiology should be referred for detailed neurological investigation.

Case 3
A 68-year-old male was diagnosed with prostate cancer two years earlier. His biopsy showed an undifferentiated carcinoma and he was treated with surgical excision and local radiation therapy. Several months later chemotherapy was started because of rising prostatic alkaline phosphatase and prostate specific antigen (PSA) levels. Three months later he noted increasing leg fatigue when he went for his daily walk. Two weeks later he fell while walking his dog but sustained no injuries. There were several subsequent falls followed by increasing complaints of low thoracic mid back pain. Finally one fall caused
a right proximal humerus fracture and he was admitted to the hospital. Initial evaluation revealed mild to moderate proximal bilateral leg weakness and he was kept on bed rest. Spine x-rays revealed anterior compression fractures at several levels in the upper lumbar, lower and mid thoracic spine. A technetium bone scan showed uptake in the spine corresponding to the fracture sites and other areas.

Difficulty initiating urination and occasional small volume incontinence prompted insertion of an indwelling Foley catheter. On insertion the initial volume drained was 800 cc.

Physical therapy was ordered but discontinued on day 2 because of lack of cooperation. Oncology consultation was requested.

On day 4 after admission, nursing service informed the admitting physician that the patient could no longer move his legs to cooperate with bathing. Repeat examination disclosed that the patient had flaccid paraplegia of both lower extremities. Neurological consultation confirmed flaccid lower extremity paraplegia, a sensory level at T-10 and diminished rectal sphincter tone. **Beevor's sign**, was present (upward motion of the umbilicus with neck flexion while lying supine, caused by weakness of abdominal muscles below T-10).

An emergency MRI scan showed some lysis of the T-10 vertebral body with a posterior tumor mass compressing the conus medullaris and distal spinal cord. Emergency radiation therapy to the area was started. Six months later the patient had some return of antigravity leg movement, but was unable to ambulate independently.

**Discussion.** The above case illustrates how spinal cord lesions can progress, subacutely, to full paraplegia even when the patient is in a setting where he/she is observed. Once the patient is on bed rest, progressive leg weakness is harder to detect, by medical staff or the patient.

Numerous early warning signs could have alerted the physician to the presence of an early myelopathy in this patient:

- Multiple spine compression fractures; and an abnormal bone scan with a known malignancy (prostate carcinoma), that is known for bone metastasis.
- Increased frequency of falls most likely due to progressive leg weakness.
- Development of spine pain as part of the current symptomatology, secondary to metastases and compression fractures.
- Overflow urinary incontinence, with a large residual volume on catheterization, due to evolving weakness of the bladder detrusor muscles secondary to sacral outflow interruption.
- Daily neurological examination would have led to earlier detection of evolving leg weakness, a rising sensory level, and the development of lower abdominal wall weakness (Beevor's sign). The weakness would have had the characteristic upper motor neuron distribution with extensor muscle groups being stronger than
the corresponding flexors. *(Gluteus maximus stronger than iliopsoas, quadriceps stronger than hamstrings and gastrocnemius stronger than anterior tibial, posterior tibial stronger than peronei. It is this distribution of weakness that produces the classic leg posture in upper motor neuron weakness; leg extended at the hip and knee with the foot pointed down and inverted).*

The importance of this case lies in the fact that, once paraplegia develops, and lasts for up to 24 hours, surgical or radiation intervention may not be as beneficial in terms of restoration of normal neurological function. Any spinal cord lesion, once suspected should be monitored closely for progression, while the work-up proceeds to determine the cause, and thus the treatment of the pathological process.

This particular patient had spinal metastases that produced spinal cord compression with clinical signs that evolved in a subacute fashion. Spinal cord metastases frequently involve the T-10 region because a main arterial feeder; the artery of Adamkewicz, arises around the L1 level and supplies the distal spinal cord. The practitioner must beware of ordering just a "lumbar" MRI scan or "lumbar" myelogram on a patient with evolving leg weakness. This study, as ordered, will visualize the spine up to T12-L1 and potentially miss lower thoracic spine lesions.

**A key clinical pearl is always to suspect an evolving spinal cord lesion in a patient with spine pain, progressive leg weakness, and urinary incontinence or retention.**

The presence of the above clinical findings in a known cancer patient should be particularly alarming, especially primary cancer of the prostate, breast, colon, and kidney. Another malignancy that commonly causes spine involvement is multiple myeloma.

Early recognition can lead to prompt treatment, which will prolong survival and hopefully preserve the ability to walk and maintain bladder control.

**Table 3. Characteristics of spinal cord lesions**

<table>
<thead>
<tr>
<th></th>
<th><strong>Intrinsic</strong></th>
<th><strong>Extrinsic</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness</td>
<td>Upper motor neuron; below level of cord involvement</td>
<td>Upper motor neuron; below level of cord involvement.</td>
</tr>
<tr>
<td>Sensory</td>
<td>Sensory dissociation (Some pathways severely affected, others are normal)</td>
<td>All modalities affected, fairly equally. May have Brown-Séquard distribution (Chapter 1)</td>
</tr>
<tr>
<td>Pain</td>
<td>Usually none</td>
<td>Root pain at the level of compression</td>
</tr>
<tr>
<td>Root lesion</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Brisk below level of lesion</td>
<td>Decreased at level of lesion (root) and increased below</td>
</tr>
<tr>
<td>Example</td>
<td>Multiple Sclerosis</td>
<td>Tumor, Disc</td>
</tr>
</tbody>
</table>
Case 4

A 23-year-old female, first noted difficulty exercising on the stair-climber at her local health spa. She had been in top physical condition, engaging in daily aerobic workouts for the past 18 months. Her first symptoms were a feeling of heaviness in her legs after stair climbing for about 15 minutes. As she continued, the weakness would worsen. She sought the advice of her personal trainer who thought she should vary her routine and exercise her upper body more. She changed her routine so that once she tired on the stair climber she would switch to the rowing machine. This seemed to solve the problem for the next several weeks.

Over the ensuing weeks she noted increasing fatigue and actual weakness as she continued her workouts. Variation in her program and new routines seemed to give very transient relief. She stopped her exercise program on the advice of a friend and noted that she symptomatically improved. Things went along well for another few weeks as she substituted reading for exercise in her leisure hours. A visit to her physician was finally prompted by some new episodes consisting of diplopia and ptosis after about an hour of reading. She noted improvement when she rested, only to have the diplopia recur when she began reading again.

Examination by her primary care physician noted her to be in good health otherwise. Her peripheral strength appeared normal. Her reflexes were on the brisk side but normal and there were no sensory deficits. Coordination and cranial nerve examination was normal.

Laboratory studies revealed normal CBC, chemistry profile, sedimentation rate, ANA, thyroid function studies, CPK, urinalysis and RPR. Chest X-ray, and EKG. Pulmonary function studies were also normal.

She was referred for neurological consultation. Physical findings confirmed that the patient demonstrated weakness with sustained muscle activity. If she held her gaze upward, after two minutes some ptosis was noted in the right and then left eye. With sustained upward gaze she reported vertical diplopia. In a similar fashion she had difficulty doing deep knee bends after 8 repetitions and then could not stand upright without assistance. After a brief period of rest the weakness resolved, only to recur with repeated exercise.

Exercise was then repeated to demonstrate observable ptosis, dysconjugate gaze and inability to stand up from a squatting position. At this point the patient was given 5 mg of edrophonium chloride (Tensilon®) intravenously, after a 1 mg test dose. This led to immediate resolution of weakness for several minutes.

A repetitive nerve stimulation test demonstrated a neuromuscular transmission defect and a blood test revealed a high titer of antibodies directed against acetylcholine receptor antigen. (ACh receptor Ag).

By now you have surmised that the patient has myasthenia gravis (MG), an autoimmune disease. The hallmark of this disease process is the development of muscle weakness with
exercise. Patients are usually stronger in the mornings and after rest, and weaker after exercise and later in the day. The distribution of weakness can be ocular (ptosis and diplopia), bulbar (dysarthria, dysphagia), or generalized, (extremity weakness and difficulty breathing).

The diagnosis depends on demonstrating a defect in neuromuscular transmission by:

- Specialized nerve conduction studies such as repetitive stimulation and single fiber EMG.
- Transiently overcoming the neuromuscular blockage using edrophonium chloride, which is an acetylcholinesterase inhibitor.
- Demonstrating antibody directed against the ACh receptor antigen.

Treatment of MG consists of two major components:

- Symptomatic: Varying doses of pyridostigmine (Mestinon®), at 4-6 hour intervals provide improvement in muscle fatigability. This drug is a long acting acetylcholinesterase inhibitor.
- Immunosuppression:
  - Prednisone initiated in small alternate day doses (12.5 mg) and slowly increased by 12.5 mg every other dose. Full benefit is usually obtained at doses of 60 to 100 mg every other day. Once improvement is achieved the dosage can be gradually reduced to the smallest one that maintains benefit.
  - Azathioprine may be a better agent if long-term use is contemplated due to fewer overall side effects than steroids. However, the potential toxic effect on bone marrow and liver function must be carefully monitored. Long-term use on a young patient may increase the risk of oncogenesis.
  - Plasmapheresis will provide short-term improvement in function by lowering antibody titer. It is a useful modality to prepare myasthenic patients for surgery (thymectomy) or as an adjunctive treatment in myasthenic crisis (situations of disease worsening when patients may be unable to swallow or breathe adequately without assistance).
  - IVIg is a newer form of therapy that may have fewer risks than plasmapheresis, e.g., central venous catheter infection or thrombosis, but is expensive. IVIg is currently achieving wider use in treating patients with MG that is more difficult to control with conventional therapy. IVIg has a duration of action that may last several weeks and sometimes several months in patients being treated with other immunosuppressive drugs. It is easier to administer than plasmapheresis especially in patients with poor venous access. Potential risks in adults with other health problems are congestive heart failure, acute renal failure and deep vein thrombosis.
  - Thymectomy may be a curative procedure or result in clinical improvement with reduction of medication requirements. The thymus gland appears to have a major role in promulgating this disease process and removal may lead to disease remission in a significant number of patients. The patient should be at maximal functional capacity prior to surgery. This may require pretreatment with steroids and plasmapheresis. The thymus should be removed with a sternal splitting procedure and not
through mediastinoscopy. Any remaining thymus tissue may interfere with attainment of remission and mediastinoscope procedures may miss rests of thymic tissues located deep in the mediastinal gutters.

Finally, the thymus gland should be evaluated in all patients diagnosed with myasthenia gravis. Typically, it is hypertrophied. However, about 15 percent of myasthenic patients have a malignant thymoma, which can be locally invasive and requires surgical as well as radiation therapy. MG in this setting is more difficult to treat and these myasthenics appear to be more resistant to conventional therapy.

**Table 4. Characteristics of weakness in myasthenia gravis**

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Cranial nerves: diplopia, dysphagia, dysarthria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Proximal or distal, usually symmetric</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal or increased</td>
</tr>
<tr>
<td>Muscle tone</td>
<td>Normal</td>
</tr>
<tr>
<td>Coordination</td>
<td>Affected in proportion to degree and distribution of weakness</td>
</tr>
<tr>
<td>Unique features</td>
<td>Weakness increases with exercise and improves with rest</td>
</tr>
</tbody>
</table>

**Case 5**

A 28-year-old construction worker was injured on the job, twisting his back to the right. He initially complained of soreness but was able to continue working the remainder of the day if he avoided lifting. The following morning he noted increased low back pain, which radiated down the posterior aspect of his left leg. There was also paresthesia in the left first toe.

He reported the injury and was sent to the company physician who ordered plain LS spine X-rays. These showed some loss of the L4-5 disc height but were otherwise normal. Light duty, NSAIDs and muscle relaxants were prescribed, but to no avail. His symptoms were particularly bad at night, although sleeping in a reclining chair with his knees and back flexed helped.

He remained off work and attended physical therapy daily for the next three weeks. He noted no further improvement and towards the end of the three-week period noted he had to purposefully lift his left leg higher to prevent the toes from scraping the ground when he walked.

Neurologic examination at this time, revealed pain with straight leg raising at 50 degrees on the left and 80 degrees on the right. He was unable to heel walk on the left and there was specific weakness of the left anterior tibial, posterior tibial, peronei and toe extensor muscles. The left internal hamstring reflex was reduced and there was vague subjective sensory loss over the dorsum of the left foot.

This history and associated clinical findings strongly suggest the subacute development of a left L-5 radiculopathy. In this setting the most likely diagnosis is a herniated
intervertebral disc, which could be demonstrated on MRI. Had the onset been acute, in a known diabetic with a negative MRI scan, consideration to nerve root infarction should be given. Chronic onset of similar symptoms in a patient with multiple myeloma or prostate cancer should make one investigate metastatic disease as a likely possibility.

He reported back pain radiating down the posterior leg, now with paresthesias on the sole of the foot, weakness with toe walking, and a diminished Achilles tendon reflex, makes S1 radiculopathy the underlying cause. Pain in the neck, which radiates to an upper extremity, is often due to cervical radiculopathy. The most common roots affected are C7 and C6. C7 root lesions are associated with pain, paresthesias in the middle fingers, usually weakness of the triceps, pronator teres and finger extensors. There is usually a diminished triceps reflex. C6 weakness involves the biceps, deltoid, brachioradialis and pronator teres, with associated paresthesias in the index finger and a diminished biceps and brachioradialis reflex.

If weakness is present with any radiculopathy, an imaging study should be done to identify the underlying cause. With cervical spondylosis or herniated disc, immobilization with a soft cervical collar for one to two weeks may be curative.

With lumbar radiculopathy, associated with weakness, conservative measures may be less successful and surgery may be indicated. Needless to say, if he patient has weakness, he should be monitored closely for progression while undergoing conservative management. If weakness is progressive during therapy, and a surgical lesion is responsible, neurosurgical consultation should be obtained.

**Table 5. Characteristics of nerve root weakness**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Pain in a radicular distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Paresthesias in the sensory distribution on the affected nerve root</td>
</tr>
<tr>
<td></td>
<td>Aggravated by activities that lengthen the involved nerve root, e.g., straight leg raising</td>
</tr>
<tr>
<td></td>
<td>Weakness in the distribution of the involved nerve root</td>
</tr>
<tr>
<td>Distribution</td>
<td>Cervical: upper extremity Thoracic: chest or abdominal wall</td>
</tr>
<tr>
<td></td>
<td>Lumbar: lower extremity</td>
</tr>
<tr>
<td>Muscle Tone</td>
<td>Decreased in the affected muscles</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Decreased or absent in the affected dermatome or myotome</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Present in the affected muscles</td>
</tr>
<tr>
<td></td>
<td>Fasciculations may be noted</td>
</tr>
<tr>
<td>Coordination</td>
<td>Usually unaffected</td>
</tr>
</tbody>
</table>
Case 6
A 45-year-old male had been working late at home doing accounting deskwork. He had been to a social affair earlier and had consumed some alcohol. To unwind he had another drink while working. He next recalls awakening in a leaned back position in his rigid-back wooden chair. He noted an aching pain in his right triceps area. He cleared his head and then attempted pick up his pen. He noted he could not open his right hand or elevate his wrist and the dorsal surface of the hand was tingling. He assumed he was having a stroke and had his wife take him to the nearest Emergency Room. Examination there revealed right fingers and wrist extensor weakness and a diminished right brachioradialis reflex. There was vague subjective sensory loss on the dorsal hand, but no other findings. A CT scan of the head was obtained which was normal. Routine laboratory studies were normal and the patient was normotensive. There were no other stroke risk factors, and a chest x-ray and EKG were normal. The local neurologist was consulted to determine if the patient was a candidate for treatment with tissue plasminogen activator (tPA).

The neurologist evaluated the patient and decided the weakness was fairly acute in onset and had occurred during sleep. The weakness, as previously described, involved wrist and finger extensors, with dorsal hand sensory loss and a diminished brachioradialis reflex. He concluded that the problem was an acute radial neuropathy, caused by prolonged pressure of the nerve at a vulnerable point (the radial groove of the humerus), while the patient slept. He told the patient to wear a neutral wrist splint to prevent a flexion contracture and to follow up in the ambulatory clinic. If the weakness persisted beyond three weeks, nerve conduction and EMG studies were planned.

This case illustrates that some cases of acute onset weakness can have etiologies other than stroke. The history and examination help establish the correct diagnosis. Inappropriate administration of tPA, in the above case, may have led to unnecessary complications. Fortunately, the patient would have been excluded from tPA treatment since the exact time of onset of weakness was not known.

Other peripheral nerve syndromes that may have acute or subacute onset include:

- Peroneal neuropathy or "crossed leg palsy": In this condition there is inability to dorsiflex the foot and the person lifts the involved leg higher to enable the foot to clear the ground. Weakness is noted in the anterior tibial, peronei and toe extensor muscles. The posterior tibial muscle is spared and the deep tendon reflexes are normal. Usually the superficial peroneal nerve is spared and only mild sensory loss is noted in the webspace between the first and second toe. The condition is usually caused by pressure on the peroneal nerve as it goes across the fibular head. This is most frequently caused by crossing of the legs while sitting and is also called "crossed leg palsy." Treatment is discontinuation of leg crossing or other activity that puts pressure on the peroneal nerve. Recovery develops over a few weeks if the lesion is only demyelinating.

- Ulnar neuropathy: This is one of the most common compression neuropathies. Normally the ulnar nerve is protected at the elbow because it lies in the ulnar groove. The olecranon usually rests on a hard surface when the elbow is leaned
on, thereby protecting the ulnar nerve. As one ages the ulnar groove may become shallower, which exposes the ulnar nerve. Common activities involving leaning on the elbows, may now compress the ulnar nerve leading to the following symptoms:

- Numbness and sensory loss involving the fifth and lateral half of the fourth finger and medial portion of the palm on the affected hand.
- Weakness of the interossei and fourth and fifth lumbrical muscles (claw hand deformity).
- Atrophy of the involved muscles.
- Tinel's sign may be present at the ulnar groove.

See Table 2 for characteristics of lower motor neuron weakness.

Case 7

A 46-year-old female stock clerk noted increasing pain in her shoulders and thighs at the end of the workday. She was somewhat better in the mornings but worsened at work. Her workload had not changed and she had no work related injuries. She also noted difficulty elevating stock boxes to shelves above shoulder level and some difficulty stepping up onto high platforms. The pain and weakness slowly worsened and within six months she had difficulty keeping her arms up when setting her hair, climbing stairs at home, and getting out of the bathtub.

She sought medical attention and was initially diagnosed as having myalgia and musculoskeletal pain related to her job. She was treated with muscle relaxants and NSAIDs with only minimal relief of symptoms.

A second visit to her physician revealed some difficulty getting out of a chair. Laboratory values showed mildly elevated transaminases and a CPK of 12,000 U/L, which fractionated to predominantly MM bands. Neurological consultation was requested.

On neurologic examination she was found to have symmetric weakness of the neck flexors, shoulder and hip girdle muscles. She had difficulty getting out of a low chair and in attempting to get up from a prone position, she had to extend her trunk by pushing upward with her hands on her thighs or using furniture to pull her trunk erect with her arms (Gower's Sign).

This type of weakness is illustrative of myopathy, which may have many causes. A common acquired form is polymyositis, an autoimmune inflammatory disorder. Metabolic myopathies can be due to hypothyroidism or Cushing's disease among others. Congenital dystrophies can also present with proximal muscle weakness.

Once suspected, diagnosis is confirmed with NC/EMG studies and muscle biopsy. A muscle biopsy should only be performed and interpreted by someone with sufficient training and experience. A routine muscle biopsy, i.e., a sample of any muscle is placed in formalin and then sent to the pathology laboratory, is not sufficient. Formalin actually
distorts muscle architecture, so the specimen must be frozen in liquid nitrogen before being processed. Normal values have been ascertained for only a few muscles such as the biceps and quadriceps femoris. This information should be obtained from the myologist before a muscle is selected for biopsy. Special staining and architecture measurement techniques performed by the myologist give useful information about the etiology of the myopathy.

Accurate diagnosis depends on family history, laboratory evaluation, muscle biopsy and sometimes, genetic studies. Consultation with a specialist familiar with these disorders is frequently required. Treatment is directed to the underlying etiology.

**Table 6. Characteristics of myopathic weakness**

<table>
<thead>
<tr>
<th>Distribution</th>
<th>Proximal: involves neck flexors, shoulder and hip girdle muscles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Problems climbing stairs, stepping up onto high steps, getting out of low places such as deep chairs, and holding arms over head for prolonged periods Pain, tenderness, and sometimes swelling of involved muscles</td>
</tr>
<tr>
<td>Muscle Tone</td>
<td>Normal or diminished Severe weakness and contractures may develop</td>
</tr>
<tr>
<td>Reflexes</td>
<td>Normal or diminished in proportion to weakness</td>
</tr>
<tr>
<td>Atrophy</td>
<td>Present with moderate to severe involvement</td>
</tr>
</tbody>
</table>

**Summary.** The preceding cases represent some of the more common presentations of weakness including some that require urgent treatment intervention. When evaluating weakness, important considerations are the temporal profile, distribution of weakness, historical progression of the weakness, and associated symptoms such as pain and sensory changes. A thorough clinical examination to determine whether the weakness involves the upper or lower motor neuron, the neuromuscular junction or muscle itself, is mandatory. Once the above features are categorized, one can then establish a differential diagnosis and proceed with a proper workup designed to establish the correct clinical diagnosis. The appropriate treatment can then be chosen.

**Psychological Impact**

Although weakness may be a sign of a serious neurological condition, many patients with no neurological disorder present with a complaint of weakness. As noted in the introduction to this chapter, "weakness" doesn't always mean a true loss of motor function. Patients who are depressed often complain of weakness. Hypothyroidism may present this way, as can patients with anemia, coronary artery disease, and numerous other non-neurological conditions. Thus, it is critical that the physician considers not only the patient's description of the problem and the physical examination, but also the context in which the patient presents.
Patients have a great fear of loss of neurological function. The resulting loss of control, independence, and dignity is often more frightening to patients than cancer or myocardial infarction. It is critical that the physician be willing and able to address these fears. Many of the conditions discussed in the chapter will lead to permanent and even progressive disability. The physician must strike a balance between truthfully sharing information and taking away all hope. In most cases, some positive information can be provided. For example, it may be comforting for a stroke patient to know that many similar patients do recover some or all of their function over time. Remember, also, that the shock of a new diagnosis may make it difficult for the patient and family to fully absorb your information. Be prepared to repeat and elaborate it over time.

Community Resources

Ongoing needs will vary tremendously from patient to patient. For example, the patient with a large CVA may require skilled care in an extended care facility, while patients with small strokes may recover complete function. Most patients, though, benefit from various community resources. Home health services are a wonderful way to allow patients to remain in their home, at the same time receiving needed therapy. Physical therapy, speech therapy, and occupational therapy can all be given in the home, as well as in acute and extended care facilities. Family members can often be taught to provide these services. A growing array of supportive devices exists for helping patients compensate for their disabilities. Some "low tech" examples include eating utensils that can be strapped to the hand, splints, bathroom rails and elevated toilet seats. Sophisticated technology also comes into play, including motorized wheelchairs and scooters, seat lifters, symbol keyboards, text-to-speech systems, and speech recognition devices.

National organizations for specific conditions offer a number of services, including literature directed to the lay audience, lists of local support groups, and treatment advances.

**National Stroke Association**
96 Inverness Drive East, Suite I
Englewood, Colorado  80112-5112
800-787-6537
Website:

Review article "Evaluation of the patient with muscle weakness" in *American Family Physician*

**Myasthenia Gravis**

**Patient Support Group**

**Guillain-Barré Syndrome**

**Patient Support Group**
Peripheral Neuropathy

Spondylotic myelopathy

Myopathy and Neuromuscular junction disorders

Peripheral nerve injuries

Cervical radiculopathy

Lumbar radiculopathy

American Heart Association
National Center
7272 Greenville Avenue
Dallas, Texas 75231
800-242-8721

The ALS Association National Office
27001 Agoura Road, Suite 150
Calabasas Hills, California 91301-5104
800-782-4747
Email: alsinfo@alsa-national.org

Myasthenia Gravis Foundation of America
123 W. Madison Street, Suite 800
Chicago, IL 60602
800-541-5454
E-Mail: myasthenia@myasthenia.org

The Neuropathy Association

PO Box 2055
Lenox Hill Station
New York, NY 10021
800-247-6968
Email: info@neuropathy.org

Self-Assessment Questions

1. All of the following clinical findings are important to determine the etiology of muscle weakness EXCEPT:
   A. distribution of weakness
   B. presence of atrophy
   C. muscle tone
   D. deep tendon reflexes
2. A feature of upper motor neuron weakness is:
   A. muscle atrophy
   B. fasciculations
   C. fibrillations
   D. diminished muscle tone
   E. increased deep tendon reflexes

3. In weakness due to motor peripheral neuropathy, all of the following are true EXCEPT:
   A. the weakness is symmetric
   B. the weakness is distal.
   C. the weakness is proximal
   D. the weakness is usually greater in the lower extremities
   E. there may be associated muscle atrophy

4. Upper motor neuron weakness from a cortical lesion has the following distribution:
   A. upper, flexors; lower, flexors
   B. upper, extensors; lower, flexors
   C. upper, flexors; lower, extensors
   D. upper, extensors; lower, extensors

5. Progressive weakness in the lower extremities associated with back pain and urinary retention can be seen with:
   A. myelopathy secondary to a herniated thoracic disc.
   B. myasthenia gravis
   C. acute stroke
   D. inflammatory myopathy.
   E. all of the above

6. Acute or subacute onset of cervical pain with radiation to an upper extremity may be caused by:
   A. herniated cervical disc
   B. spondylosis of the cervical spine
   C. Herpes zoster
   D. nerve root infarction secondary to diabetes
   E. all of the above

7. Clinical findings associated with inflammatory myopathy include all EXCEPT:
   A. muscle pain
   B. elevated CPK level
   C. proximal symmetric muscle weakness
   D. Babinski's sign
   E. dysphagia

8. Abnormal laboratory findings in myasthenia gravis include:
   1. elevated CPK level
   2. elevated transaminase levels.
   3. reduced acetylcholine antibody titer
   4. elevated smooth muscle antibody titer.
   5. none of the above
9. Characteristics of radiculopathy include:
   A. numbness, pain and increased muscle tone
   B. weakness, atrophy and increased deep tendon reflex
   C. spasticity, atrophy and diminished deep tendon reflex
   D. none of the above

10. Progressive bilateral, distal muscle weakness, distal paresthesias, and loss of deep tendon reflexes over one to two weeks is suggestive of:
   A. myasthenia gravis
   B. polymyositis
   C. Guillain-Barré syndrome
   D. diabetic peripheral neuropathy

11. Proximal and bulbar muscle weakness that worsens with exercise and improves with rest may be associated with:
   A. lung cancer
   B. AIDS
   C. thymoma
   D. sepsis

12. All of the following may be seen with ulnar neuropathy EXCEPT:
   A. numbness of the fourth and fifth fingers
   B. hypothenar atrophy
   C. interosseous atrophy
   D. Tinel's sign at the ulnar groove (elbow).

13. CPK elevations are most commonly associated with:
   A. stroke
   B. myelopathy
   C. inflammatory myopathy
   D. Guillain-Barré syndrome

14. Amaurosis fugax may be a premonitory symptom of:
   A. respiratory arrest
   B. facial weakness
   C. stroke
   D. none of the above

Answers:

1. E
2. E
3. C
4. B
5. A
6. E
7. D
8. E
9. A
10. D
11. C
12. D
13. C
14. D

Navigation

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Chapter 5 – The Dizzy Patient: A Clear-Headed Approach


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Boston, MA

INTRODUCTION
The problem of dizziness is one of the most exasperating in the practice of medicine. Physicians all know that sinking feeling elicited by the patient who sits down and, when you ask, "What can I do for you?" says, "I'm dizzy." The goal of this discussion is to offer practitioners a reasoned approach to dizziness that will lead expeditiously to diagnosis and effective therapy.

Before getting down to cases, a caveat: "Dizziness" may or may not mean vertigo. More often than not, if a patient proclaims that the problem is vertigo, it's because he or she has heard the term and thinks it sounds medical. It's really dizziness that brought this patient to you.

Case 1
A 61-year-old woman comes to the office complaining of dizziness. When asked to describe the sensation, she says that it is a feeling of violent motion, a sensation of being pulled to the right. It occurs in waves a moment after she lies down on her right side in bed. If she remains motionless, the sensation will pass in about 30 seconds. However, if she then sits up, the phenomenon recurs, although less severely, this time with the environment moving from left to right and a sensation of falling to the left. There is no history of hearing loss or tinnitus, nor is there an associated diplopia, dysarthria, or weakness. Many years before, she was thrown from a horse and struck her head, with resultant severe vertigo, which cleared gradually over a six-week period.

On examination, vital signs including orthostatic blood pressure and pulse determinations are normal. General examination and routine neurologic examination are normal. The findings on examination of cranial nerve VIII include mildly abnormal hearing in the right ear, equal air and bone conduction, and intact speech discrimination. There is no spontaneous nystagmus. However, with Bárány position testing (see Figure 2), rotatory nystagmus develops five seconds after the patient attains the right-ear-down position, with fast phase in the counter-clockwise direction and slow phase in the clockwise direction. The patient reports vertigo, with the environment spinning right to left, which she says is the same as her symptomatology at home. The nystagmus and vertigo stop after 30 seconds, but when she sits up, there are a few beats of nystagmus in the opposite direction with recurrence of vertigo but in the reverse direction. Head-hanging and left-ear-down positions fail to elicit vertigo or nystagmus. The tympanic membranes are
intact, but when air is insufflated via the otoscope into the right external auditory meatus, the patient complains of vertigo, and a few beats of nystagmus develop.

**DIFFERENTIAL DIAGNOSIS**
The first principle to observe in evaluating a dizzy patient is not to put any words in the patient's mouth. This is, of course, a good rule in taking any medical history, but it is particularly applicable in this instance. When the patient says to you, "I am dizzy," sit back in your chair, slowly spin around, perhaps stare aimlessly out the window, and reply, "What do you mean, dizzy?" Then wait for the response. This may take what seems to be a long time; nonetheless, don't ask, "Does the room spin?" "Do your legs get weak?" "Do you feel as if you might stagger?" "Are you lightheaded?" because the answer to all these questions will nearly always be yes. If you're lucky enough to be the first physician to examine a patient complaining of dizziness, always take the undirected approach. Merely say to the patient, "What do you mean, dizzy?" and wait for the response. There are several responses that the patient may give (see Figure 1).

**SYNCOPE OR NEAR-SYNCOPE**
"I feel as if I might faint," or "I feel giddy or light-headed." Some patients do faint or report that they have done so; others have never actually fainted (near-syncope). Pathophysiologically, both syndromes suggest several cardiovascular disorders that produce a generalized decrease in cerebral blood flow; there is no qualitative difference between syncope and near-syncope with respect to the differential diagnosis.

*Circulatory syndromes* that should be considered in the differential include orthostatic hypotension, which may have a number of causes, most of them iatrogenic (e.g., antihypertensive agents and/or vasodilators). Cardiac arrhythmias are a very frequent cause of syncope and near-syncope. If the history suggests arrhythmic episodes, Holter monitoring may be required. Hypersensitive carotid sinus is relatively uncommon. Vasovagal attacks are otherwise known as the simple faint or the simple swoon. Neurocardiogenic syncope is probably due to over activity of the baroreceptor reflex such that brief periods of hypertension result in disproportionate bradycardia and hypotension resulting in decreased cerebral blood flow and consequent loss of consciousness. Any faintness that occurs during or immediately after exercise suggests a possible serious cardiac disorder, such as aortic stenosis, anginal equivalents, or asymmetric septal hypertrophy.

**DISEQUILIBRIUM**
"I feel as if I might fall." This version of dizziness generally reflects one of two major categories of neurologic disease, apart from disorders of the vestibular system.

*Cerebellar ataxia* is due either to a primary disease of the cerebellum, e.g., cerebellum degeneration, or to a tumor in or near the cerebellum, e.g., in the cerebellopontine angle. Neurologic examination will ordinarily reveal such pathology.

The **multiple sensory deficits syndrome**, reflects multiple abnormalities in the various sensory proprioceptive systems. When several of these systems fail in a given individual,
the central nervous system receives conflicting proprioceptive input, with consequent dizziness. The typical patient is rather elderly, perhaps with some visual disorder due to cataracts, some auditory disorder due to presbyacusis, and peripheral neuropathy due to diabetes and/or chronic use of alcohol. Such a patient typically complains of dizziness at night, for instance, when the lights are out or dim and he or she has to go to the bathroom. On occasion, the patient may fall.

The treatment of this extremely common syndrome is common sense: As many of the sensory abnormalities as can be corrected, should be. Cataracts and hearing disorders can be treated, and the progression of peripheral neuropathy can be prevented by abstinence from alcohol. You might also advise your patient to keep the lights on at night, which would help the visual system compensate for other sensory abnormalities. Such patients should not be treated with drugs that might sedate them, as antivertigo medications would do. Mistaking this syndrome for vertigo would, in fact, make matters worse.

ANXIETY AND/OR DEPRESSION

There are patients who when asked, "What do you mean, dizzy?" respond, usually after a pause, "Dizzy." If the physician persists with "Do you mean you might faint?" or "Do you mean that you might fall?" or "Do you mean that the room spins?" the patient repeats, "No, I mean I'm dizzy." This disorder can only be called true dizziness, and it generally arises from various psychological disorders, most commonly anxiety (with or without hyperventilation) and/or depression.

Affective disorders can often be recognized because of the effect that the patient has on the examiner. If you feel depressed or anxious yourself after spending time with a patient, it may well be because the patient is depressed or anxious. It is extremely important to recognize instances when dizziness represents a metaphor for depression, because treatment for vertigo is likely to exacerbate depression, whereas treatment for depression might dramatically relieve the dizziness.

VERTIGO

The fourth and last category of disorder found in patients who complain of dizziness is true vertigo, or illusion of motion. Some patients insist that they themselves are moving, others-such as the one presented at the beginning of this chapter-that the environment is moving. In either case the patient says, "I feel as if I am tilting, rocking, or moving in some other way," or "I feel as if the room is spinning."

Vertigo indicates a disturbance in the vestibular system, which is responsible for keeping the central nervous system informed of the head's position in space, its relation to the pull of gravity, and its acceleration in various planes. The question is whether the vertigo is due to a disorder in the peripheral nervous system (the end organ or the peripheral nerve) or in the central nervous system (the brainstem or its projections to parts of the cerebral cortex, particularly the temporal lobe). Each lesion has its own differential diagnosis and treatment.
Evaluation of Vertigo
The first step is to do a complete history and physical examination and a general neurologic examination with particular attention to the VIII cranial nerve. The VIII cranial nerve is in fact two separate cranial nerves, the vestibular and cochlear. (Unfortunately, it received only one number, and generations of medical students have been confused ever since.) These two nerves have closely juxtaposed end organs, run close to each other in the internal auditory meatus, and have two completely different pathways in the central nervous system. Because of the close proximity of these two nerves and their end organs, it is common for disease of one to affect the other. The physician should therefore examine both aspects of the VIII cranial nerve whenever there is a complaint of vertigo.

COCHLEAR VIII NERVE FUNCTION
Pure Tone Hearing Loss
Auditory testing.
Examination of the cochlear system involves three steps whether or not the patient complains of hearing loss. The first is to test for pure tone hearing loss. This can be done quite reliably in the office by comparing the sensitivity of the patient's ears or comparing the patient's ears with your own, using a ticking watch or the sound of your fingers rubbing together.

Sensory Neural vs. Conductive Hearing Loss
If there is a pure tone hearing loss, the next step is to determine whether it is a sensory neural hearing loss, i.e., a neurologic problem, or a conductive hearing loss, i.e., a disorder in the middle ear interfering with the functions of the ossicles. These determinations are made by using two tests, the Weber and Rinne.

1. The Weber test is performed by placing a vibrating tuning fork at the midline of the skull and asking the patient on which side the sound can be heard. If there is a definite lateralization to one side, you can determine whether there is sensory neural or conductive hearing loss. For example, if the Weber lateralizes to the left, this may be interpreted as either a left-sided conductive hearing loss or right-sided sensory neural hearing loss. Combining this information with the knowledge of which ear has the hearing loss, you can determine whether that loss is sensory neural on the right or conductive on the left.

   However, as the reader probably knows, the Weber test is often difficult to use. Effectively in actual office circumstances. Frequently, when asked where the sound is heard, the patient points directly at the tuning fork and cannot appreciate a definite lateralization.

2. The Rinne test is of greater use in an office setting. Bone and air conduction are compared by placing the tuning fork first over the mastoid bone and then in front of the ear. Under normal circumstances, air conduction is better, because the ossicles in the middle ear amplify and intensify the sound as it passes through the
middle ear to the inner ear. If the ossicles are not functioning because of otosclerosis, cholesteatoma, or perhaps fluid in the middle ear, air conduction may suffer, which leads to a situation in which air and bone conduction are equal or bone conduction is the better of the two. If, however, there is sensory neural hearing loss, air conduction remains better than bone conduction.

Unfortunately, generations of physicians have been taught to do the Rinne test by placing the vibrating tuning fork on the mastoid process and saying to the patient, "Tell me when that stops." Time passes, and passes, other patients line up in the waiting room, and this patient is still just sitting there quietly. Finally the physician asks, "Has it stopped yet?" and the patient replies, "Oh, yes, it stopped a long time ago." The frustrated physician repeats the test, this time interrupting every second or two to ask whether the patient still hears the sound. The talking-physician approach does tend to interfere with a hearing test—by drowning it out. It is easier simply to put the vibrating tuning fork over the mastoid process (number 1) and then in front of the ear (number 2) and ask the patient which is louder. If the patient says number 2, you know that air is better than bone conduction. End of test. This finding, along with hearing loss, tells you unequivocally that there is a sensory neural problem.

Cochlear vs. Retrocochlear Hearing Loss
The third step in the hearing examination, needed only if there is a sensory neural loss, is perhaps the most important of the differential procedures but paradoxically the one least well known to many physicians. The question being asked is whether the sensory neural deficit is due to end organ disease (cochlear) or to peripheral or central neural disease (retrocochlear).

Speech discrimination testing can be done in your office to differentiate a cochlear from retrocochlear sensory neural hearing loss. (There are a number of ways to make this distinction, but many require the services of an audiologist.) The physician whispers words in the affected ear (e.g., hot dog, ice cream) loud enough for the patient to hear. At the same time, you make a sound in the other ear so that the patient cannot hear your words through that ear. Putting a finger in the patient's other ear and moving it around will serve the purpose. Do this on both sides five or 10 times, have the patient repeat your words each time, and compare the two ears.

In people with cochlear-type sensory neural hearing loss, such as occurs in Ménière's disease, speech discrimination is not perfect, but it is relatively preserved. On the other hand, in patients with retrocochlear hearing loss, such as accompanies a vestibular schwannoma, there is a disproportionate loss of speech discrimination. Thus a patient with a cochlear hearing loss should be able to understand 70% or more of the words heard, whereas a patient with a retrocochlear hearing loss might understand only two out of 10 words. If there is any question of a retrocochlear hearing loss, one should order an audiogram.
VESTIBULAR VIII NERVE-FUNCTION
Testing for nystagmus.
The vestibular aspect of the VIII cranial nerve may be examined by testing for nystagmus. First, ask the patient to sit on the end of the examining table and to look about 45° to the right and to the left. (Asking the patient to look beyond 45° is not useful, since when asked to look too far in either direction, about 10 percent of the normal population show some degree of gaze-evoked end-point nystagmus.) If nystagmus develops when the gaze is directed to 45°, note the direction of the fast phase, the direction of the slow phase, and in what position of the eyes they occur.

Next the patient should be put through a series of positions called the Dix-Hallpike maneuver (see Figure 2). All vertigo is positional to some extent, but if vertigo is positional only, there are specific pathogenetic and prognostic implications. Once position testing has been done, the physician knows in which direction the world seems to be spinning and in which direction the patient seems to be falling when the vertigo develops. The directions of the fast and slow phases of the nystagmus have been recorded. The question now is how to interpret these data.

PERIPHERAL OR CENTRAL NERVOUS SYSTEM?
A brief review of the neuroanatomy and neurophysiology of the vestibular system may be helpful at this point. The text that follows should be considered as a unit with the illustrations above, which depict the normal structural components (Figures 3A and 3B) and neurologic events pertinent to vertigo and nystagmus.

Vestibulo-Ocular Reflex
The end organ of the vestibular nerve is located in the semicircular ducts, utricle, and saccule. The lateral, or horizontal, semicircular duct is oriented in the inner ear so that it tilts at about 30° above the horizontal plane (see Figure 3A). When the head is held in the usual carrying position, this duct is approximately parallel to the ground. Thus turning the head right and left would be expressed almost entirely in a vector within the plane of the lateral semicircular duct.

The series of events that make up the active phase of the vestibulo-ocular reflex is schematized in Figure 3D. When the head turns to the left, a series of impulses is initiated (beginning with stimulation of the hair cells in the left lateral semicircular duct) that leads to contraction of the right lateral rectus muscle (right eye abductor). This sequence, taken no further, would of course lead to a situation in which the eyes are pointed in two different directions, which produces diplopia, an unacceptable situation for the nervous system. Therefore, a corresponding series of impulses must also reach the left medial rectus muscle in order for the left eye adductor to contract as well.

In a comatose patient with an intact brainstem but with cortical signals in abeyance, the vestibulo-ocular reflex can be elicited by turning the patient's head, which produces the oculocephalic reflex, or the so-called doll's eyes. In an awake patient the reflex may be demonstrated by having the patient fix his or her gaze on a distant object or by infusing the ears with warm or cold water (the caloric reflex). Although the caloric reflex should
be a routine part of the evaluation of a comatose patient, in an awake patient it is a procedure perhaps best left to the otologist or neurologist.

**Cerebral Cortex**
In the hypothetical situation illustrated in Figure 3D, the eyes have deviated to the right. This information is transmitted to the cerebral cortex by more than one mechanism. The movement of images on the retina sends information to the occipital cortex through the usual visual pathways. However, it is presumed that information regarding the movement of the eyes may reach the cerebral cortex even in the absence of visual stimuli, since proprioceptive organs in the orbit probably convey information to the parietal cortex.

The cerebral cortex, however, finds itself in a dilemma. It asks itself, "Have I, in fact, turned the eyes to the right?" The left frontal eye fields could, of course, turn the eyes under normal circumstances to produce a voluntary saccade (rapid conjugate eye movement) to the right. However, in this instance the left frontal eye fields have not fired. It is possible that the right parietal-occipital region could have turned the eyes to the right by producing a conjugate pursuit or tracking eye movement. But in this case, these areas have not fired either. Thus the cerebral cortex has received conflicting information.

On the one hand, it seems that the eyes have turned to the right. On the other hand, it seems as if the eyes have not been moved to the right. What conclusion can the cerebral cortex draw? It concludes not that the eyes have moved to the right but that the world has moved to the left! This arrogant conclusion is based on the cerebral cortex's assumption that it alone is capable of moving the eyes, although of course the brainstem can also move them.

**Frontal Lobe**
Parts of the cerebral cortex, however, are not so egocentric. The frontal lobe, for example, knowing that the eyes have turned to the right, decides to make a correction. The corrective phase of the vestibulo-ocular reflex arises from the frontal eye fields and results in rapid turning of the eyes back to the left.

In the circumstance postulated, the stimulus has arisen from the left vestibular system and caused a slow conjugate eye movement to the right followed by intermittent rapid conjugate correction back to the left. It is associated with a vertigo in which the patient has a feeling that the world is spinning to the left while he or she is being pulled to the right.

The patient's feeling of being pulled may become worse when the eyes are closed, because closing the eyes removes another proprioceptive system that would help to compensate. Romberg's sign, i.e., when a person's balance becomes worse with the eyes closed, can be seen in any abnormality producing a proprioceptive disorder, including peripheral neuropathy and disease of the spinal cord as well as disease of the vestibular system.
The Two Phases of Nystagmus
Thus vestibular imbalance nystagmus consists of two components. The first (active) phase originates in the brainstem or vestibular system, is caused by different vestibular input from the ears, and is associated with slow eye movement. The second (corrective) phase is initiated by the cerebral cortex via the frontal eye field and is associated with fast eye movement. Both phases act through the final common pathway of the ocular motor system of the brainstem.

Under normal circumstances (see Figure 3B), the entire vestibular system functions bilaterally with all of its central connections. There is no vertigo or nystagmus with ordinary accelerations of the head. In fact, the situation depicted in Figure 3D, although useful as a model for understanding the mechanics of vertigo and nystagmus, hardly ever happens in real life. It is relatively rare for the pathology to produce an excess of stimuli from the affected side.

More likely is the pathologic situation illustrated in Figure 3C, which depicts a "lesion" in the right ear, perhaps functional, perhaps anatomic. In this situation, an imbalance develops between the two sets of vestibular apparatus in the ears. With disruption of the vestibular impulses from the right ear, it is as if the left side has been stimulated or the head has been turned with acceleration to the left. What symptomatology does such a lesion produce? The eyes are driven conjugately toward the side of the lesion. This movement is interrupted by intermittent rapid corrective movement away from the side of the lesion. The patient has a sensation of vertigo, with the world spinning away from the lesion (or toward the fast phase) and a feeling of falling toward the side of the lesion (or toward the slow phase).

Criteria For Locating The Lesion
There are four criteria for a peripheral type of vertigo and nystagmus (see Table 1). If there are 1) fast-phase nystagmus away from the lesion, 2) slow-phase nystagmus toward the lesion, 3) environment spinning away from the lesion, and 4) Romberg's sign toward the lesion, one can say with confidence that there is a lesion of the peripheral nervous system, probably in either the end organ or the peripheral nerve.

Table 1: Criteria for peripheral lesion of vestibular system

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<tbody>
<tr>
<td>Rapid-phase nystagmus</td>
<td>away from lesion</td>
</tr>
<tr>
<td>Slow-phase nystagmus</td>
<td>toward lesion</td>
</tr>
<tr>
<td>Environment</td>
<td>spinning away from lesion</td>
</tr>
<tr>
<td>Romberg's sign</td>
<td>toward lesion</td>
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</table>

If any of these four rules fails to hold, one can assume by exclusion that the lesion is in the central nervous system. Central nervous system lesions can cause bilateral nystagmus in the same position of the head, vertical nystagmus of any kind, and any conditions in which the directions of the fast and slow phases, the Romberg's sign, and the spinning of the environment do not strictly fit the four criteria specified. Those criteria specify only...
the anatomic localization without implying anything about the severity or seriousness of the underlying disease. Peripheral diseases can be trivial (e.g., vestibular neuronitis) or very serious (e.g., acoustic schwannoma). Central diseases can range from the trivial complications of many drugs to vertebrobasilar insufficiency.

**Synthesizing the Data**

Thus by testing the auditory system and the vestibular system, one can divide all cases of vertigo into three categories:

1. Peripheral (by vestibular criteria) cochlear disease (by auditory criteria and signs)
2. Peripheral (by vestibular criteria) retrocochlear disease (by auditory criteria), and
3. Central disease

With this in mind, we can now consider the major diseases in each category.

**Peripheral Cochlear Lesions**

*Labyrinthitis* is thought to be a result of viral infection of the endolymph and perilymph affecting both the vestibular and cochlear components of the system. The usual history is viral illness followed by acute onset of severe spinning vertigo and sensory neural deafness with tinnitus. Examination shows a classic peripheral picture by vestibular criteria and a classic cochlear picture by auditory criteria. Paracentesis of the perilymph may show growth of common ubiquitous viruses, such as coxsackievirus or echovirus. Despite its severe onset, labyrinthitis is a benign illness, which resolves completely in three to six weeks. Patients regain normal hearing and vestibular function.

*Vestibular neuritis*, or acute vestibulopathy, is thought to be pathogenetically identical to labyrinthitis but without any hearing symptomatology. If the patient has vertigo unaccompanied by a hearing abnormality, it is strictly speaking impossible to be sure whether the disease is cochlear or retrocochlear. However, its natural history is also benign, and it clears up completely in three to six weeks, which makes a retrocochlear illness very unlikely.

*Ménière disease* is caused by a cryptogenic hydrops of the endolymph such that there is intermittent swelling of the semicircular ducts, with damage to the hair cells. An attack of Ménier's syndrome is classically characterized by a dull ache in the region of the mastoid process or around the ear associated with severe tinnitus, a cochlear kind of sensory neural hearing loss, and a classic peripheral type of vestibular syndrome with severe spinning vertigo. It is identical in almost every respect with an acute attack of labyrinthitis. However, it does not clear up completely in three to six weeks, and patients are left with residual hearing loss. Several months or years later a similar attack may occur, leaving the patient with even more severe hearing loss. Tinnitus, a nonspecific sign of auditory system disorder, is a major problem for these patients, who can be terribly disabled for weeks at a time by the vertigo that accompanies acute attacks.
Many therapies have been tried, including shunting of the perilymphatic system and diuretics, but none has proved effective. About 15% of these patients will have bilateral disease in subsequent years. Management of such cases is complex and often best entrusted to an otolaryngologist or otoneurologist.

Benign positional vertigo, or Bárány's vertigo, usually occurs in older patients and is characterized by the sudden onset of a peripheral vestibular syndrome with no auditory aspect. It is present only in certain positions, which are specific to the individual.

Typically, the patient reports that a few moments after attaining a certain position, perhaps in bed at night, a severe vertigo occurs in which the world spins in one direction while the patient has a sensation of falling in the other direction. If he or she does not move, the vertigo stops, which implies that it is transient in type. If the patient sits up, the vertigo recurs, but this time in reverse. If the patient repeats the posture several times, the tendency toward vertigo and nystagmus will fade. All the symptoms can be reproduced using the Dix-Hallpike maneuver. Benign positional vertigo has a natural course, which improves gradually over a six-month period and ends with complete recovery.

ETIOLOGY OF BENIGN VERTIGO

Cupulolithiasis

Two major theories have been proposed to explain benign vertigo. The theory of canalolithiasis maintains that bits of calcium break off from the otolithic apparatus in the ear, perhaps as a consequence of aging or minor head trauma. If these bits of calcium are floating in the endolymph, they can, in certain positions, put pressure on the end organ, which initiates an impulse arising from that ear. Since the calcium tends to fall into the most dependent of the three semicircular ducts, the canalolithiasis tends to affect the posterior vertical semicircular duct resulting in rotatory nystagmus in the dependent ear and vertical nystagmus in the other ear maximum when the affected ear is down.

Perilymphatic fistula.

The second theory for benign positional vertigo is the development of a perilymphatic fistula. Normally the middle ear and inner ear are separated by the oval and round windows, which are completely sealed. If for some reason (e.g., head trauma) a crack develops in the oval or round window, some of the perilymph may leak from the inner ear into the middle ear. Such patients may have intermittent episodes of conductive hearing loss superimposed on a sensory neural hearing loss. This pathology is established by an audiogram.

The presence of the fistula can be detected by placing the otoscope in the ear and closing the glass window, which produces an air-tight space. Air is then pumped into the external ear using the ordinary balloon attachment to the otoscope. This air distorts the tympanic
membrane, which briefly increases the pressure in the middle ear. Under normal circumstances, a mild sensation in the ear is produced but no vertigo. If, however, there is a pathologic connection between the middle ear and the inner ear, increased pressure in the middle ear will be transmitted to the perilymphatic space in the inner ear, which produces an abnormal stimulus and causes vertigo and nystagmus.

**Case Diagnosis and Treatment**

The 61-year-old woman described at the beginning of this discussion was found to have perilymphatic fistula. This diagnosis—established by the findings of benign positional vertigo, a syndrome of conductive and sensory neural hearing loss, and a positive fistula test—may be less rare than was once thought. It is important to recognize it, because it is completely treatable surgically. Microsurgery, performed in this patient, repaired the defect in the oval window by filling it with fat from the earlobe, with complete relief of her vertigo.

**PERIPHERAL RETROCOCHLEAR SYNDROMES**

**Vestibular Schwannoma**

A second category of disease is a peripheral type of vertigo but with retrocochlear hearing loss, i.e., patients are found to have poor speech discrimination. Such patients should always have an audiogram; if the audiogram confirms retrocochlear hearing loss, a CT scan with special views of the internal auditory meatus is indicated. If a CT scanner is not available, conventional tomography of the internal auditory meatus should be done.

It is important to recognize the presence of a tumor while it is still contained within the internal auditory meatus and thus surgically resectable. Vestibular schwannomas (often incorrectly called acoustic neuromas) are histologically benign tumors, but they can become quite dangerous. If a vestibular schwannoma is allowed to grow into the brainstem, treatment requires a posterior fossa craniotomy, with significant morbidity and even some mortality. *Any patient with a history of progressive hearing loss should at some time during the evaluation have a careful audiogram, and if any retrocochlear characteristics are found, a CT scan with careful views of the internal auditory meatus should be ordered.*

**Central Lesions**

The last category of vertigo is central disease, i.e., patients with vestibular symptomatology that does not meet the criteria for peripheral disease. This group includes patients with vertical nystagmus or bilateral nystagmus in the same position of the head.

**Drugs**
All drugs that act by intoxicating the reticular activating system in the core of the brainstem—including all anticonvulsants, all sedatives, and some sleeping pills—will by their nature produce nystagmus in two different directions in the same position of the head. When the patient looks to the right, the nystagmus beats to the right; when the patient looks to the left, it beats to the left. Overdosage can produce vertigo.

The fact that the lesion is central does not necessarily mean that it is serious. In fact, the appearance of this form of nystagmus may prove that a given drug is in the therapeutic range. Such patients should be asked specifically about their use of drugs, including alcohol; before any invasive studies are performed, it is useful to order blood and urine toxic screening.

Demyelinating Illness

Demyelinating illnesses, such as multiple sclerosis, can and often do produce vertigo, presumably because there are lesions somewhere in the vestibular system in the brainstem. Although such vertigo usually has characteristics that indicate a central lesion, occasionally it can resemble peripheral vertigo and be misdiagnosed as vestibular neuronitis. If the same patient returns a year later with optic neuritis, it would be clear in retrospect that the first disorder was due to multiple sclerosis. However, nothing has been lost in the interim, because multiple sclerosis of this mild degree would not be treated.

Vascular Disease Affecting the Brainstem

In approaching vascular disease affecting the brainstem, it should be remembered that the most common manifestation of vertebrobasilar insufficiency is vertigo, but vertigo is almost never the only manifestation. Such patients can also be expected to complain of double vision, weakness of the limbs, sensory loss, dysarthria, and dysphagia. It might be possible for disease of the small branch of the vertebral artery to produce vertigo as its only symptom, but in such instances there is no specific therapy anyway.

Disorders Of The Temporal Lobe

Temporal lobe seizures arising from trauma, tumors, or prior strokes can, as one of their manifestations, produce vertigo.

TREATMENT OF VERTIGO

Anticholinergic- and Antihistamine-Type

There are three categories of drugs for treating true vertigo. Anticholinergic- and antihistamine-type drugs include dimenhydrinate, diphenhydramine, meclizine, and cyclizine. All of these drugs are effective if the dosage is adequate—about 50 mg every six hours (see Table 2). They produce major sedation as their side effect, but this is
usually of no concern: Patients who have been dizzy and vomiting for hours tend to be more than happy to go to sleep.

Table 2. Drugs useful in symptomatic treatment of vertigo

<table>
<thead>
<tr>
<th>Duration of Activity</th>
<th>Useful Adult Oral Dosage</th>
<th>Sedative Effects</th>
<th>Other Modes of Administration</th>
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<tbody>
<tr>
<td><strong>Ethanolamines</strong></td>
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<tr>
<td>Dimenhydrinate</td>
<td>4-6 hr</td>
<td>50 mg ev. 6 hr</td>
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<tr>
<td>Diphynhydromine</td>
<td>4-6 hr</td>
<td>50 mg ev. 6 hr</td>
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<td><strong>Piperazines</strong></td>
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<tr>
<td>Meclizine</td>
<td>12-24 hr</td>
<td>25-50 mg ev. 6 hr</td>
<td>+</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>4-6 hr</td>
<td>50 mg ev. 6 hr</td>
<td>+</td>
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<td><strong>Phenothiazine</strong></td>
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<tr>
<td>Promethazine</td>
<td>4-6 hr</td>
<td>25 mg ev. 6 hr</td>
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<td><strong>Belladonna alkaloid</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Scopolamine</td>
<td>4 hr</td>
<td>0-6 mg ev. 6 hr</td>
<td>+</td>
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+ Mild ++ Moderate

The Phenothiazines: Promethazine

Promethazine is the only phenothiazine that works against the nausea associated with vestibular imbalance and vertigo. Other phenothiazines, useful for chemical nausea, are of no help whatsoever in this setting. Promethazine may be effective primarily because it is an anticholinergic, not because it is a phenothiazine; it is useful also because it can be given together with the antihistamines or the antiserotonin drugs. A combination of promethazine and antihistamine is particularly effective for acute vertigo.

Beladonna Alkaloids

A belladonna alkaloid, usually scopolamine, is used only for severe recurrent vertigo (e.g., in difficult cases of Ménière’s disease) because it is a dangerous drug with many cardiovascular and psychiatric side effects. Transdermally absorbed scopolamine,
although helpful for motion sickness, is of inadequate dosage for use in treating an acute vestibular syndrome. Benzodiazepines are often useful in treating the anxiety components of dizziness, but are not particularly useful for true vertigo.

**SUMMARY**

To evaluate dizziness, you must first decide whether it can be categorized as near-syncope, disequilibrium, ill-defined light-headedness, or vertigo. If it is vertigo, vestibular and auditory testing will allow you to place the patient in one of three categories: peripheral cochlear disease, peripheral retrocochlear disease, or central disease. When this distinction is made, you can create a reasonable differential diagnosis and arrive at the likely diagnosis. Some of these disorders (e.g., vestibular schwannoma) require specific evaluation and treatment, whereas others have a benign natural history and require only symptomatic relief for the duration. Symptomatic therapy is straightforward and makes use of the three categories of drugs discussed.

This approach should allow you to diagnose and treat your dizzy patients quickly and effectively.

**SELECTED READING**


Fife TD. Bedside cure for benign positional vertigo. BNI Quarterly 1994;10(3).


**SELF-ASSESSMENT QUESTIONS**

1. Endolymph
   A. is the intracellular fluid
2. The following are all true statements about the vestibular system EXCEPT:

A. the semicircular ducts sense angular acceleration
B. the cells of origin of the vestibular hair cells are bipolar neurons in Scarpa's ganglion
C. the utricle and saccule sense linear acceleration
D. the vestibular nerve travels in the internal auditory meatus
E. impulses conveying vestibular sensation travel in the vestibular portion of the cranial nerve VIII

3. The vestibular nuclei connect the ocular-motor system via the:

A. posterior columns
B. Clark's column
C. the medial lemniscus
D. the medial longitudinal fasciculus
E. the lateral lemniscus

4. The vestibulo-ocular reflexes

A. utilize the frontal eye fields as a command center
B. bypass the pontine paramedial reticular formation
C. utilize the lateral lemniscus to transmit impulses to the oculomotor nuclei
D. may be utilized to distinguish a nuclear from an infranuclear gaze palsy
E. may be utilized to distinguish a supranuclear from a nuclear or infranuclear gaze palsy

ANSWERS:

1. A
2. B
3. D
4. E

Navigation

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INTRODUCTION

Headache is a nearly universal symptom. Migraine and other headaches can be highly disabling, and impose a significant burden, both in economic terms and in personal suffering. For migraine alone, missed workdays and disability at work have been estimated to cost American employers approximately $13 billion per year (Hu et al). Head pain is a common complaint by patients presenting to physicians' offices and emergency departments (Barton). The characteristics and treatment of the primary headaches disorders including migraine, tension-type, and cluster will be discussed, as well as secondary headache disorders (including benign-appearing recurrent headache due to underlying disease). The recognition and treatment of chronic daily headache and its relationship to medication overuse will also be addressed.

CLINICAL SYMPTOMS AND SIGNS: APPROACH TO THE PATIENT

To properly diagnose a patient presenting with headache it is necessary to take a careful history and examine the patient. The history should include the date of onset, duration and timing of the headache attacks, as well as the frequency, severity, duration of pain episodes, triggers, quality of the pain, factors increasing and decreasing the pain, previous and current medications (including over-the-counter remedies), social history and family history. History of trauma, other medical conditions, and a psychiatric history should be obtained. A careful and complete history is important in earning the patient's confidence and in establishing the correct diagnosis. A complete medical and neurologic examination, based on clues from the history or other physical findings, should be performed on every patient complaining of headache. Head and neck examination is
particularly important. The results of this evaluation will dictate the physician's choice of additional investigations.

Neuroimaging (CT scanning or MRI), blood work, lumbar puncture, angiography, etc., are necessary when a secondary cause of headache is suspected. Testing is generally not indicated when history and examination are strongly consistent with a primary (benign) headache disorder. When neuroimaging is suggested by history or examination (see Table 1—"Red Flags" in Headache), MRI is usually superior to CT, although CT scanning is best when acute intracerebral or subarachnoid hemorrhage is suspected. Lumbar puncture is appropriate in three settings: 1) suspicion of meningitis or encephalitis, 2) suspicion of subarachnoid hemorrhage or 3) suspicion of high or low intracranial pressure. Prior to LP, neuroimaging to rule out intracranial mass is usually necessary.

Table 6-1—"Red Flags"—Clues to diagnosing secondary causes of headache

- Sudden onset
- Progressive worsening
- Constant pain
- Change in pattern
- Effort-induced pain
- Positional pain
- Onset in middle age or later
- Recent head trauma
- Setting of chronic illness (e.g., cancer, AIDS)
- Fever, abnormal vital signs
- Any neck stiffness
- Change in personality or behavior
- Neurologic findings on examination

SECONDARY HEADACHES

Secondary headaches include those headaches resulting from known structural or pathologic causes. Some can be exceedingly difficult to sort out from primary causes such as migraine and tension-type headache. The following case report is presented to stimulate thinking about secondary headaches that may mimic primary headache disorders.

Case Report (Part 1)

Case 6-1. A 20-year-old man came to the office complaining of pain over his forehead and into the left orbit. He rated the severity of his pain as a 10/10. He was previously seen in another office where he was diagnosed with tension-type headache and given acetaminophen/caffeine/butalbital (Fioricet®), resulting in mild relief. He had continued pain. He had been given 28 Fioricet® of which only 7 remained after 20 hours. He complained of nausea and had vomited once at home. He denied photophobia, fever, ear or abdominal pain.
He has a history of asthma and had had an upper respiratory tract infection about two weeks prior to his presentation with stuffy nose, cough and tearing eyes. He had been coughing green-brownish material for the three days. Medications included albuterol (Proventil®) and acetaminophen (Tylenol®). On examination he had equal pupils that were round and reactive to light without tearing, injection or nystagmus. He was able to read and count fingers in both visual fields. His fundi showed what was thought to be early papilledema. He had marked tenderness on palpation of his left frontal sinus and was non-tender to palpation over the other sinuses. He had a non-focal neurological examination. His initial temperature was 100.4 orally and vital signs were stable. A stat head CT scan without contrast was arranged and read as normal.

The course and workup of this patient will be discussed later. This case illustrates the potential hazard of diagnosing a primary headache disorder too soon as will be seen later.

Because of a number of shared clinical features among the many causes of headaches, diagnostic problems may occur. These problems may be grouped into four categories and are reviewed below (Mathew, 1994).

1. **Organic conditions presenting with acute headache that may cause difficulty in diagnosis.**

   Clues to diagnosing secondary (threatening) headaches include: new, worsening, or constant headaches, sudden onset of headache, a deficit on neurological examination (including abnormal mental status), abnormal vital signs, a history of trauma, older age, or a history of drug abuse or systemic illness.

   - Intracranial aneurysms
   - Unruptured - "sentinel headache," "thunderclap headache"
   - Ruptured
     - Cerebral venous thrombosis
     - Encephalitis (e.g. herpes simplex encephalitis)
     - Carotid artery dissection, vertebral artery dissection
     - Cerebral venous thrombosis

   Subarachnoid hemorrhage (SAH) from ruptured intracranial aneurysm is usually a dramatic clinical presentation. Some individuals collapse and expire immediately. Survivors generally have an explosive, severe headache with nausea and/or vomiting. Seizures may occur, as can stupor or coma. On examination, stiff neck (Brudzinski and Kernig signs), hypertension, and subhyaloid ( preretinal) hemorrhages may be found, as well as focal neurologic deficits. Work-up proceeds promptly to a CT scan, which if negative (CT misses 10–15 percent SAH) is followed by a lumbar puncture. If SAH is confirmed, a 4-vessel cerebral angiogram is performed (up to 20 percent of aneurysms are multiple). CT angiography in some centers is nearly as sensitive. Neurosurgical consultation is required.
Up to 5 percent of the general population harbors asymptomatic intracranial aneurysms. Unruptured intracranial aneurysms may cause headache due to sudden expansion or thrombosis within the aneurysm. If sufficient clinical suspicion is present, magnetic resonance angiography (MRA) or CT angiography may be performed, or even conventional angiography.

Patients with encephalitis or meningitis usually have fever (unless on antipyretics or steroids), and stiff neck. (However, with patients in a deep coma, stiff neck may not be present). Headache is common, and focal neurologic deficits may develop. Seizures may occur, possibly followed by stupor and coma. CT scan or MRI is usually performed to rule out an abscess or other mass lesion, followed by a lumbar puncture.

Herpes simplex encephalitis, a progressive necrotizing encephalitis with a predilection for the temporal and frontal lobes, presents with fever and cognitive changes. Headache is common. MRI is positive early in some cases; polymerase chain reaction on CSF may be diagnostic. Treatment with acyclovir is initiated as soon as the diagnosis is suspected to try to limit the degree of brain damage. Neurologic and infectious disease consultation is appropriate.

Dissection of the carotid or vertebral arteries may occur spontaneously, or in the setting of trauma or underlying vascular disease. Symptoms include neck pain, headache, and neurologic deficits in the distribution of the involved blood vessel. The dissection may be revealed by ultrasound, MR angiography, CT angiography, or conventional angiography.

Cerebral venous thrombosis (CVT) may be present with headaches, seizures, paraparesis (cortical parasagittal leg area), or other focal neurologic deficits. Predisposing conditions include pregnancy (or the immediate post-partum period), dehydration, cancer, coagulation disorders, or trauma. CVT is often missed with conventional neuroimaging. MR angiography is generally very sensitive.

2. **Organic conditions associated with recurrent headaches mimicking primary headache disorders**
   - Symptomatic cluster headaches
   - Posterior fossa brain tumor
   - Arteriovenous malformation
   - Cough and exertional headache due to intracranial lesion (generally posterior fossa)
   - Antiphospholipid antibody syndrome
   - Isolated CNS vasculitis
   - Pheochromocytoma

The pain of cluster headache is so severe that many patients feel certain there must be an underlying mass lesion. Imaging is generally normal. However,
symptomatic cluster headache may be due to a lesion in or near the cavernous sinus. The duration of the pain attacks may become progressively shorter, and a fixed neurologic deficit may appear.

Cough headache is usually a sudden head pain triggered by coughing or other Valsalva maneuvers. The headache is sudden in onset and severe, but brief (seconds or minutes). It may be followed by a longer duration posterior or holocranial dull ache. Perhaps 10–20 percent are due to a posterior fossa lesion such as a Chiari malformation. MRI is indicated as part of the evaluation. (CT is a poor choice as it is less sensitive for lesions in the posterior fossa due to bony artifact). If imaging is negative, treatment with indomethacin is usually dramatically effective. Lumbar puncture may also be therapeutic (Raskin, 1995).

Sex may trigger headaches in several ways. First and most disturbing is the sudden onset "explosive" or "orgasmic" headache which mimics and must be differentiated from SAH. CT, LP, even angiography, may be required. Secondly, the "pre-orgasmic" muscle contraction type headache may be precipitated (gradual onset, without nausea or vomiting). Both of these are considered primary headaches as causes have not been identified. Lastly, a postural headache may follow intercourse, presumably due to a nerve root sleeve or other dural tear with CSF leakage. The headache is relieved by recumbency and aggravated by standing, as is typical for "low-pressure" headaches such as the post-LP headache.

Antiphospholipid antibodies (the lupus anticoagulant, anticardiolipin antibodies, antiphosphatidylserine antibody) may occasionally be associated with migraine with prolonged (1 hour) aura or migrainous infarction. A previous history of recurrent miscarriages or venous thrombosis should arouse suspicion. An elevated partial thromboplastin time (PTT) on routine coagulation testing and a false positive VDRL may provide a clue to their presence.

CNS vasculitis may be present with headaches, seizures, and focal neurologic deficits. Laboratory parameters consistent with collagen vascular diseases may be present, but may be absent if disease is confined to the CNS (a privileged area). Imaging may reveal strokes, CSF may contain red and white cells, and rising protein. Angiography may demonstrate beading of blood vessels, segmental narrowing or occlusions. Occasionally meningeal biopsy is performed. Rheumatologic, neurologic, and neurosurgical consultation may be necessary.

Mild essential hypertension is typically not associated with headache. Severe paroxysmal elevations of blood pressure, as occurs with pheochromocytoma or the tyramine reaction in patients on MAO inhibitors, is associated with headache. The headache of pheochromocytoma is generally paroxysmal—sudden, but brief (less than one-hour duration). Dramatic elevations of blood pressure, with tremor and diaphoresis occur. The headache is often holocranial, pounding, and
nausea/vomiting may be present. A 24-hour urine evaluation for products of the tumor (VMA, metanephrines) is diagnostic.

3. **Organic conditions associated with chronic persistent headache or facial pain, often without abnormal physical findings**
   - Arnold-Chiari Malformation-Type 1
   - Idiopathic intracranial hypertension (pseudotumor cerebri) without papilledema
   - Temporomandibular joint (TMJ) dysfunction
   - Giant Cell Arteritis (temporal arteritis)

Arnold-Chiari Malformation-Type 1 (without other malformations) can produce a secondary cough headache or more non-descript aching head pain. Patients may eventually develop diplopia, vertigo, ataxia from brainstem compression, but this is unusual.

Idiopathic intracranial hypertension (IIH, "pseudotumor cerebri") typically presents with headache and signs of increased intracranial pressure such as papilledema. However, some patients do not exhibit papilledema, and diagnosis hinges then on finding increased opening pressure on lumbar puncture.

Temporomandibular joint dysfunction (TMD) may produce headache, but jaw pain radiating to the ear is generally noted. Clues include "popping" and clicking at the joint, increased pain on use (chewing, talking, laughing), and limitation of jaw opening (less than 30 mm). TMD usually responds to physical measures such as physical therapy, heat, and massage. Non-steroidal anti-inflammatory medications are of use as well. Surgery is usually best avoided.

Giant cell arteritis ("temporal arteritis") is usually manifested as temporal pain, often constant, sometimes with jaw claudication (increased pain with jaw use). The scalp and superficial temporal arteries may be tender. Most patients are over 50 years old and have an ESR over 50 mm/hr. Untreated, this disease carries a significant risk of blindness and stroke. If the diagnosis is suspected, prednisone is started immediately (60–80 mg per day initially), the patient is then sent for temporal artery biopsy (due to patchy involvement, a substantial length of vessel needs to be obtained. If one side is negative, the opposite side should be considered for biopsy).

4. **Intracranial pathology occurring in a patient with established primary headache**
   - Brain tumor
   - Brain Abscess
   - Subdural hematoma

Carrying the diagnosis of a primary headache type, such as migraine, in no way prevents a patient from developing a second type of headache. Brain tumors
certainly can occur in patients who also have primary headache disorders. Therefore, if a patient with an established headache disorder develops new or progressive signs or symptoms, or becomes refractory to previously effective therapy, the possibility of the presence of a secondary headache should be considered.

**Case Report (Part 2)**

Case 6.1 (continued). Examination of the patient's CSF showed 3 mononuclear cells with protein 22, glucose 77, and later, negative cultures. His blood WBC was 15,000. Later in the evening, after the results of the brain CT became available, he was diagnosed as having migraine or cluster headache. The next morning his temperature reached 102.5 (rectal) and he complained of chills. Subsequently his temperature rose to 104.1 (oral) with normal vital signs. His left eyelid and conjunctiva became swollen, with tenderness to percussion over the left frontal sinus.

He was admitted and treated with nafcillin 2 grams and cefuroxime 1.5 grams, intravenously. Acetaminophen and ibuprofen were prescribed for his pain. Repeat CT scan of the brain this time with additional views of the paranasal sinuses showed fluid collections in both maxillary and ethmoid sinuses, as well as the left frontal and sphenoid sinuses. He underwent bilateral intranasal antrostomies, a left intranasal ethmoidectomy and a left sphenoidotomy. Subsequently his WBC normalized and he did well, with complete resolution of headache.

This case illustrates the potential hazard of diagnosing primary headache disorder too soon. Over 100 secondary causes of headache are possible, many of which may mimic primary headache (Levin 2002). Table 2 lists the most commonly encountered causes.

**Table 6-2—Differential diagnosis of secondary causes of headache**

- **Vascular**
  - Subarachnoid hemorrhage
  - Arteriovenous malformation
  - Cerebral venous thrombosis
- **Infectious**
  - Meningitis—bacterial, viral, fungal, protozoal, Lyme disease syphilis
  - Encephalitis
  - HIV infection
  - Subdural empyema
  - Brain abscess
  - Sinusitis
  - Dental abscess
- **Trauma**
  - Subdural hematoma
  - Intracerebral hematoma
  - Carotid or vertebral dissection
• Post-concussive syndrome
• Occipital or supraorbital neuralgia
• Dural leak—low pressure syndrome

• Autoimmune
  • Vasculitis affecting CNS
  • Giant cell arteritis
  • SLE

• Metabolic/Toxic
  • Thyroid disease
  • Pheochromocytoma
  • Drug intoxication or adverse effect
  • Hyperparathyroidism
  • Oxygen abnormalities—COPD, sleep apnea, altitude sickness
  • Carbon monoxide toxicity
  • Anemia

• Idiopathic
  • Trigeminal neuralgia
  • Benign intracranial hypertension (pseudotumor cerebri)

• Neoplastic
  • Glioma
  • Meningioma
  • Pituitary region mass
  • Cerebellopontine angle tumor (e.g. acoustic neuroma)
  • Lymphoma
  • Metastatic tumor of brain, skull, meninges

• Structural, Psychiatric
  • Depression, Anxiety
  • Hydrocephalus
  • Chiari malformation
  • Upper cervical spine disease
  • Epilepsy

**DIAGNOSIS AND MANAGEMENT OF PRIMARY HEADACHES**

International Headache Society diagnostic criteria are now used to classify and diagnose headache (IHS Headache Classification Committee). We will discuss the major primary headache disorders (migraine and tension-type) and their management. Patients often complain about headaches when they interfere with their routine- our goal is to keep this interference to a minimum.

**Migraine**

Migraine is a common problem, affecting approximately 6 percent of children, 6 percent of men, and 18 percent of women (Stewart). It is an episodic headache that is often a unilateral throbbing pain associated with photophobia, phonophobia, nausea and vomiting. It is made worse by exertion. If there are neurological symptoms associated
with the headache it is called "migraine with aura" (IHS1.2; old term—"classic migraine"), without these symptoms it is known as "migraine without aura" (IHS 1.1; old term—"common migraine").

The object of therapy is to ameliorate or terminate patients' migraine attacks, and when necessary, to reduce the frequency and severity of attacks via behavioral treatment, lifestyle changes, and preventative pharmacotherapy. Migraine is often precipitated by various triggers (i.e., foods, menses, sun glare, missing a meal, stress, sleep deprivation, etc.). Therapy begins with identification and modification or avoidance of these triggers when possible.

It is also important to be sure other medications are not contributing to headache causation. A number of medications and substances have the potential to directly cause headaches in some patients (see Table 3). Additionally, the overuse of symptomatic medication such as analgesics can transform migraine into a chronic daily headache. This is termed analgesic rebound or medication overuse headache (MOH) and is a significant problem in headache management. The mechanism of MOH is not well understood, but most, if not all, medications used for acute relief of migraine can lead to increased frequency of headaches in susceptible individuals. The frequency of analgesic use necessary to cause MOH seems to vary with respect to medication type and individuals, but restricting acute treatment to twice weekly is generally sufficient to prevent this phenomenon.

When MOH does occur, prophylactic medication is ineffective and the offending medications must be stopped. Preventive pharmacotherapy is thus usually appropriate when patients need to use acute headache medications more than 2 days per week, if the headaches do not respond to abortive medications, (perhaps resulting in visits to the emergency room), or if the patient has had complicated migraine (a prolonged neurologic deficit, or migrainous infarction).

Table 6-3—Medications and drugs which may cause headache

- Hydralazine
- Isosorbide
- Nitroglycerin
- Nifedipine
- Enalopril (Vasotec)
- Ranitidine, famotidine, cimetidine
- Sidenafil (Viagra)
- Trimethoprim-Sulfa, Tetracyclines
- Estrogen, Progesterone, Tamoxifen
- Theophylline
- Pseudoephedrine
- Amphetamines
- Cocaine
**Prophylactic Treatment**

Prophylactic therapy is initiated to reduce the frequency, duration, and severity of migraine attacks. Fortunately, a number of good choices exist. Patients in the childbearing years requiring preventative treatment generally should be using an effective form of contraception. However, oral contraceptives may not be appropriate for some migraine patients.

It generally takes two to three months to ascertain a medication's preventative effect. Ideally, therapy starts with the lowest dose which is increased slowly until headache control is achieved or unacceptable side effects are encountered. ("start low, go slow"). After the headaches are controlled for six months or more the medication may be gradually decreased and stopped, as tolerated. Preventative migraine therapy choice should be guided by co-morbid/co-existent conditions such as mitral valve prolapse, Raynaud's phenomenon, epilepsy or, depression, since one can often choose a drug that might help both headache as well as a coexistent condition. In addition, it is essential to avoid medications which might exacerbate a coexisting illness.

The major classes of prophylactic drugs include beta-blockers, anticonvulsants, calcium channel drugs, and heterocyclic antidepressants. There are also several miscellaneous drugs, which are sometimes useful (Ward, 2000).

**Antidepressant**

*Amtriptyline, Nortriptyline, Doxepin*

Many patients with migraine have co-morbid depression. If sleep disturbance is prominent, consider using a heterocyclic antidepressant. Amtriptyline (Elavil®, others) has the most support in the literature. Its effect on migraine is separate from its effect on depression. Its mechanism of action may be through modulation of serotonergic and noradrenergic pathways. Start patients on a 10mg or 25mg bedtime dose and increase the dose slowly to achieve headache control. Doses of 150mg or less are generally employed. Side effects include weight gain, dry mouth, cardiac arrhythmias, urinary retention, blurred vision, and constipation. The medication should be avoided in patients with untreated glaucoma and prostatic hypertrophy. The dry mouth side effect can be managed by using hard sugarless candies or with pilocarpine (Salagen®) 5–10mg tid.

Nortriptyline (Pamelor®, others) may be tried if the side effects of amitriptyline are unacceptable. It causes less drowsiness. Again, the initial dose is generally 10–25 mg hs, but as it is also available in a liquid formulation, even lower doses can be employed if necessary. Doxepin (Sinequan®) is another potential option, and is also available in a liquid form. Heterocyclic antidepressants are contraindicated in patients with cardiac arrhythmia, narrow angle glaucoma, prostatism, and uncontrolled seizures (Saper).

Antidepressants exemplify the fact that medications within the same pharmacologic group produce various side effects that are more, or less, acceptable to each individual
patient. If one agent is poorly tolerated, consider either a lower dose or a trial of another agent in the same family.

**Beta-Adrenergic Antagonist Drugs**

*Propranolol, Timolol, Metoprolol, Nadolol, Atenolol*

The beta-blockers are widely used for the prevention of migraine. They were discovered to have an effect serendipitously, and are postulated to work via an effect on 5-HT2 receptors, preventing the generation of nitric oxide. Propranolol (Inderal®) and timolol (Blocadren®) have FDA indications for migraine prevention. Propranolol is often the first choice and is used in doses ranging from 40–320mg daily, in divided doses. It is also available in several extended-release forms that can be given once or twice daily. Nadolol (Corgard®) can be given once daily, as can atenolol (Tenormin®). Side effects are common and include hypotension, bradycardia, fatigue, weight loss, and bronchospasm (Welch). This class of medications is contraindicated in patients with asthma, diabetes, Raynaud's phenomenon, depression, and sometimes heart failure. Some authorities avoid beta-blockers in migraine with aura.

**Calcium-Channel Blocking Drugs**

*Verapamil, Diltiazem, Amlodipine*

This class of drugs is especially useful in those migraineurs suffering from Raynaud's. Verapamil (Calan®, Isoptin®, others) is the best studied. Like other preventative agents, benefit may not become apparent for weeks to months (Welch). Verapamil is usually started at doses of 80mg twice or three times a day. It may be increased to 480mg per day as tolerated. There are sustained-release formulations (Calan SR®, others) that may be used once or twice daily, to enhance compliance. Common side effects include constipation, hypotension, and pedal edema. The vasodilation associated with some drugs in this category (particularly nifedipine [Procardia®]) occasionally causes a migraine-like headache.

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

*Naproxen, Naproxen Sodium*

These drugs have a role in both acute and preventative migraine therapy (see below). Naproxen (Naprosyn®) has been demonstrated to be an effective prophylactic in clinical trials. It decreases the intensity and duration of headache, nausea, vomiting, and other analgesic use. It may be particularly useful for predictable menstrually-associated migraine attacks. The initial dose is 550mg naproxen sodium (Anaprox DS®) BID beginning two days prior to the expected onset of headache and continued through the usual time of headache susceptibility (Raskin, 1988). Patients may be switched to another NSAID to find the most effective and tolerable relief.
Aspirin

Aspirin is useful in migraine prophylaxis (Welch). A single 325mg dose daily may reduce the frequency of migraine attacks. Side effects of aspirin and other NSAIDs are well known and include dyspepsia, gastritis, and GI hemorrhage. These side effects can be ameliorated with concurrent treatment with misoprostol (Cytotec®). It is given as 200 mcg tablets 4 times a day, with meals. The dose may be reduced if necessary to 100mcg 4 times a day.

Anticonvulsants

Valproic Acid, Gabapentin, Topiramate.

Migraine is known to be co-morbid with epilepsy. Valproic acid (Depakote®, others) has an FDA indication for migraine prevention. It is usually administered as the enteric-coated formulation, Depakote® with superior GI tolerability. The initial dosage is usually 250 mg BID. After 6-8 weeks, the dose may be increased to 500 mg BID, and eventually to 750 mg BID. A once-a-day formulation is available. The most important parameter to monitor is headache control. Blood levels do not correlate with clinical effect. Side effects include GI irritation, tremor, hair loss, weight gain, and hepatic dysfunction. Pancreatitis occurs rarely. Spina bifida may occur during pregnancies in fetuses exposed to valproic acid.

Gabapentin (Neurontin®) has been reported to have efficacy in selected migraine patients (Ward, 2000). It is not hepatically-metabolized and has little potential for drug interaction. Adverse effects do include cognitive impairment in some patients. Dosing typically begins at 300 mg tid, and may be slowly raised as high as 1200 mg tid.

Topiramate (Topamax®) has been shown in randomized controlled trials to be effective in preventing migraine (Brandes, Silberstein). Adverse effects include metabolic acidosis and paresthesias as well as occasional sedation and cognitive dysfunction. This drug is a weak carbonic anhydrase inhibitor, and therefore should not be given to patients with a history of renal stones. Higher doses are often associated with significant sedation. It is actually associated with weight loss, which may be of benefit to some migraineurs. For migraine prevention, dosing is begun at 15–25 mg at hs, and slowly raised to as high as 100 mg BID.

Lamotrigine (Lamictal®) seems promising as migraine prophylaxis. But adverse effects include severe skin rash.

Miscellaneous Headache Preventive Agents

Methysergide, Cyproheptadine

Numerous other drugs have been used as for migraine prophylaxis, with variable success, and often limited support in the literature. Methysergide (Sansert®) has an FDA
indication for migraine prevention. It is highly and rapidly effective, but its use is limited by rare but serious side effects including retroperitoneal, cardiac valvular, and pulmonary fibrosis. Therefore it cannot be given for longer than 6 months without a "drug holiday" of at least one month. Other side effects are related to vasoconstriction and include: chest pain, abdominal pain, cold numb painful extremities with or without paresthesiae, and diminished or absent pulses. These effects usually regress when the medication is stopped. Nausea and vomiting may also occur. The medication may make patients feel strange (chemically similar to LSD), especially at the initiation of therapy. The 2 mg tablet is started once daily for 3–4 days, then increased slowly to tid or qid. Methysergide is often useful for intractable episodic cluster headache. It is no longer available in the US but is available in Canada.

Cyproheptadine (Periactin®) is an agent with anti-serotonergic, antihistamine, and calcium channel blocking properties. It has been advocated particularly as a preventative agent for children with migraine. The usual starting dose is 2mg (1/2 a 4mg tablet) twice or thrice daily. The dose may be increased slowly, usually to 4 mg twice or three times daily. It is available as syrup as well, enabling lower dosage titration. Side effects include sedation and weight gain.

Symptomatic Migraine Treatment

Simple Analgesics

Aspirin, Acetaminophen, Combinations

Both aspirin and acetaminophen are superior to placebo in decreasing migraine pain (Welch). Aspirin is the most commonly used non-prescription analgesic selected by patients for the management of headache pain. An initial dose of 975–1000 mg is recommended at the onset of the attack. Subsequent doses of 650 - 1000 mg every 4 hours may be given as needed (maximum 4–6 grams in a 24-hour period). Buffered and effervescent forms of aspirin may reduce gastric irritation. Delayed absorption with enteric-coated aspirin precludes the use of this product in acute pain management. Aspirin is also available for rectal administration. It has been used intravenously with good results (Welch) but is only available outside of the U.S.A.

Acetaminophen is a non-prescription alternative in patients who cannot tolerate aspirin. Several pain models demonstrate the equivalent analgesic efficacy of aspirin and acetaminophen on a milligram to milligram basis. A study in patients with tension and tension-vascular headaches observed no difference between 1000 mg acetaminophen and 650 mg aspirin in relieving headache pain.

Gastric stasis may occur during a migraine attack and impedes the absorption of medications, such as aspirin and acetaminophen. Concomitant administration of metoclopramide (Reglan®) significantly increases serum concentrations of both these agents, by increasing gastrointestinal motility. (Volans). Oral medications may be limited in their utility by their incomplete absorption and the frequent vomiting accompanying
migraine. The use of the rectal route of administration is available for aspirin and acetaminophen. Codeine and other drugs may also be prepared in this fashion by pharmacists (Ward). Dependence can occur in patients who use these products uninterrupted for 48 hours or more.

Aspirin and acetaminophen are commonly combined with caffeine and/or butalbital to enhance analgesic activity and are sold as Fiorinal®, Esgic® and Fioricet® (with acetaminophen). This combination works for many patients with headache, but is very prone to cause medication overuse headache. When this occurs, it is important to detoxify these patients from all rebound-producing medications, including simple analgesics, when using excessive quantities (e.g., more than 2 days a week).

**Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

*Naproxen Sodium, Ketorolac*

Nonsteroidal anti-inflammatory drugs (NSAID) may be considered good choices in first line abortive therapy of migraines, due to their effectiveness and lack of a dependency cycle. Naproxen (Naprosyn®) is the most frequently studied NSAID for the treatment of migraine. Naproxen and naproxen sodium (Anaprox/Anaprox DS®) achieve peak plasma concentrations after 2 and 1 hour, respectively. Naproxen sodium is preferred for abortive therapy because onset of analgesic activity corresponds with its earlier peak plasma concentration.

Ketorolac (Toradol®), the first parenteral NSAID available in the United States, is effective in the treatment of migraine. However, relief from pain and disability with I.M. ketorolac are significantly less than the combination of IV DHE 45® and metoclopramide. Ketorolac may also be administered intravenously.

Other NSAIDs found to be effective in the treatment of migraine include diclofenac sodium, flufenamic acid, flurbiprofen, ibuprofen and mefenamic acid (See Table 4). The most common adverse effect with all NSAIDs is dyspepsia.

**Table 6-4—Dosing Guidelines For NSAIDs For Treating Migraine**

- Naproxen sodium (Anaprox®) 550 mg–850 mg BID
- Diclofenac sodium (Voltaren®) 50-100 mg in 2 divided doses
- Flufenamic acid Not available in the United States
- Flurbiprofen (Ansaid®) 300 mg in 2–4 divided doses
- Ibuprofen (Motrin®, Advil®) 600-800 mg TID
- Indomethacin (Indocin®)
  25–50 mg TID
- Mefenamic acid (Ponstel®)
  500 mg, then 250 mg every 6 hours
- Tolfenamic Acid
  Not available in the United States

**Antiemetics**

*Metoclopramide, Chlorpromazine, Prochlorperazine, Promethazine*

Antiemetics are useful in the management of disabling nausea and vomiting frequently associated with migraine headaches. In addition to antiemetics properties, metoclopramide (Reglan®) can also reverse the gastric stasis accompanying migraine attacks. Metoclopramide enhances the effectiveness of analgesics such as aspirin, acetaminophen, naproxen as well as ergotamine in migraine by improving absorption (Raskin, 1988). It should be used sparingly as it may cause dystonia and akathisia, especially in adolescents (Welch). Keeping the dose below 30 mg per day decreases the chance such a reaction will occur. Patients should be warned of the potential dystonic reaction and have 25 mg of diphenhydramine (Benadryl®) available. Administration of a narcotic analgesic (e.g., meperidine-Demerol®) or anticholinergic agents may antagonize increased gastrointestinal motility produced by metoclopramide.

Recent studies suggest that some antiemetics may be useful as single agents in the treatment of migraine attacks. Controlled studies have shown intravenous chlorpromazine (Thorazine®) 0.1 mg/kg and prochlorperazine (Compazine®) 10 mg effectively terminate migraine attacks (Lane/Jones cited in Raskin 1988) Chlorpromazine may be useful when treating migraine with intravenous dihydroergotamine (DHE-45®) (Welch). Chlorpromazine and prochlorperazine may cause tardive dyskinesia that occasionally is irreversible. Promethazine (Phenergan®) suppositories (12.5mg–25 mg-50mg) are effective in treating nausea and vomiting, with little likelihood of dystonia.

**Isometheptene**

Isometheptene (Midrin®) is suitable for patients to try for mild to moderate migraine attacks. Midrin® contains isometheptene in combination with dichloralphenazone (a sedative) and 325 mg of acetaminophen. It is generally well-tolerated. Adverse reactions are unusual. Isometheptene is a vasoconstrictor possessing antispasmodic activity. It was more effective in treating mild to moderately severe migraine in a placebo-controlled trial (Raskin 1988). In a comparative trial, no difference in headache duration was observed between Midrin® and ergotamine/caffeine (Cafergot®). However, the incidence of nausea and vomiting was significantly lower with Midrin® (6.5 percent versus 24.6 percent). The recommended dose for Midrin® is 2 capsules at the onset of the attack, followed by 1 capsule every hour as needed, up to a maximum of 5 capsules per 12 hours.
Ergot Preparations

Ergotamine Tartrate, Dihydroergotamine

Ergotamine tartrate was a very important medication for symptomatic treatment of migraine. It is available in oral, rectal, and sometimes sublingual forms. Availability of some of these formulations has been intermittent. Dihydroergotamine (DHE-45®) is the only parenteral ergot available. The absorption rates of ergotamine are variable, depending on the route of administration. Caffeine enhances ergotamine's absorption. Metoclopramide is likely to improve absorption of oral ergotamine (Welch). Parenteral treatment is most effective; rectal ergotamine achieves higher serum levels than the oral route. Therapeutic responses will, of course, vary among different patients and route and dose of medication.

Oral ergotamine (Cafergot®, Wigraine®, and others) is given initially as two 1 mg tablets followed by 1 tablet every 30 minutes until relief occurs. The dose is limited to 6 tablets daily and 10 tablets weekly. Nausea and vomiting are common side effects of the medication. Metoclopramide can be used to help control the nausea and vomiting associated with ergotamine.

Rectal ergotamine (Cafergot® or Wigraine®) is available in 2 mg suppositories. It is useful to take one-quarter to one-half of a suppository initially, followed by one-quarter every 30 minutes as needed to a maximum daily dose of two suppositories or 4 mg.

Gradual overuse of oral or rectal ergotamine may lead to dependency and the development of ergotamine headache. The patient develops a rebound or withdrawal ergotamine headache that is successfully treated with another dose of the drug. The total daily dose may slowly increase over years transforming a migraine headache into a chronic daily headache (Mathew, 1993). Other side effects include nausea, vomiting, abdominal pain, diarrhea, muscle cramps, paresthesias of the extremities, vasoconstriction and loss of pulses, and angina.

Dihydroergotamine (DHE-45®) is effective in aborting migraine, and is more effective than meperidine plus hydroxyzine and butorphanol (Raskin, 1986) (Silberstein, 1990) (Welch). Up to 90 percent of migraines treated with intravenous DHE 45® abated - it is also useful in treating drug-induced headache (Silberstein 1990). Patients can be taught to give themselves subcutaneous or intramuscular injections. DHE-45® comes in ampules (1 mg in 1 ml) - the dose may be titrated between 0.5-1.0 mg twice daily, as needed. The goal is to use the smallest effective dose.

Initially metoclopramide or another antiemetic should be taken prior to DHE-45® to help control drug-induced nausea and vomiting. Many patients later find the metoclopramide is no longer necessary. The side effects of DHE-45® are similar to those of ergotamine but less severe. An intranasal formulation, Migranal®, is also available.
The ergots and their derivatives are contraindicated in patients with severe hypertension, peripheral vascular disease, ischemic heart disease and thrombophlebitis. They should be used cautiously in patients with peptic ulcer disease, bradycardia, renal and hepatic abnormalities. The ergots can not be used with "triptan" drugs (see below) within 24 hours.

**Triptan medications**

Sumatriptan (Imitrex®) is the first medication engineered to work at the 5-HT receptor to treat migraine. It is an effective treatment and has been used extensively since it became available in the United States in 1993. Sumatriptan is currently available for patients orally, intranasally, and with an autoinjector for subcutaneous injection. Sumatriptan suppositories are available in some countries outside the USA.

Physicians may administer the drug without the use of an autoinjector. Subcutaneous sumatriptan reaches peak plasma level within 15 minutes. Extensive clinical trials have shown marked relief of head pain, nausea, vomiting, phonophobia, and photophobia within 1–2 hours after treatment with 6 mg in approximately 80 percent of patients. This formulation is most effective for headache occurring early in the morning (upon awakening), those which escalate to maximum severity rapidly, and those attacks with vomiting.

Oral sumatriptan (25, 50, and 100 mg) produces relief less rapidly, within 2 to 4 hours. Sumatriptan produced better relief from nausea and vomiting than ergotamine and had a similar effect to aspirin with metoclopramide. Intranasal sumatriptan is available in 5mg and 20mg single use devices (20mg BID prn is the usual adult dose). It is another option for use during attacks with vomiting.

The side effects of subcutaneous, nasal, and oral sumatriptan are similar. Most common is an injection site reaction after subcutaneous administration. Also, flushing, heat sensation, chest pressure, heaviness, tingling and jaw or neck pain may occur. Occasional patients report chest pressure with pain going into the left arm suggestive of myocardial ischemia. After 3 million documented headache attacks treated with sumatriptan, 4 patients had documented myocardial ischemia (Welch). More extensive data suggests the occurrence of serious cardiac events is rare.

Usually side effects are mild to moderate in severity, short-lived, and resolve on their own. Some authorities advocate giving the initial dose of "triptans" under medical supervision. It is contraindicated to use "triptans" in patients with previous myocardial infarction, ischemic heart disease, Prinzmetal's angina, or uncontrolled hypertension. They should only be used 24 hours before or after an ergot preparation is ingested. They should be avoided when patients are taking methysergide because of the vasoconstrictor properties of both medications.

Other "triptan" drugs available include zolmitriptan (Zomig®), naratriptan (Amerge®), rizatriptan (Maxalt®), eletriptan (Relpax®), almotriptan (Axert®), and frovatriptan.
(Frova®). In the USA, these agents are all presently available oral treatments, and zolmitriptan is available in nasal spray form. Zolmitriptan and rizatriptan are also available in rapidly dissolving tablets which are preferred by some patients although they have not been shown to be more rapid or effective in clinical trials. Failure to respond to one triptan does not preclude a successful response to another (Ward 2000). These agents give superior results if used as early in the migraine attack as possible.

**Narcotics**

*Butorphanol, Codeine, Oxycodone, Hydrocodone, Meperidine*

Codeine has been shown to be superior to placebo in aborting a migraine attack (Raskin 1988). Butalbital, aspirin or acetaminophen, and caffeine combinations (see above) may become more effective in selected patients when codeine is added (Kunkel). These agents are potentially addictive: the addition of codeine increases the risk and severely limits its utility. Oxycodone (Percodan®) and hydrocodone (Vicodin®) have similar effects and concerns. Parenteral meperidine (Demerol®) is often used for the emergent treatment of migraine. It should be limited to those patients with infrequent attacks that cannot be treated effectively with another agent. This includes patients with peripheral vascular or coronary artery disease (Welch).

It is important to note that the efficacy of oral meperidine is approximately 25 percent of the IM preparation. Oral meperidine should be used in a very limited way for selected patients with severe migraine and as a rescue medication when other measures fail. Medication use should be closely monitored.

Transnasal butorphanol (Stadol NS®) has been used in the treatment of migraine. While US regulatory agencies formerly did not view it as a narcotic, it does contain the morphine molecule, and its major side effect is sedation. As a mixed agonist-antagonist, it may have less addiction potential, although this is controversial. Overuse may occur, and it seems capable of causing rebound. The initial dose of 1 mg (1 puff) in one nostril is approximately equipotent to 5 mg of morphine. Onset of action is rapid (minutes).

In pregnancy, there are very few medications that can be safely used. Acetaminophen, metoclopramide and meperidine can be used judiciously, as they are in FDA category B (Codeine is category C). Combination analgesics are to be avoided. Fortunately many migraineurs experience fewer headaches during pregnancy.

**TENSION-TYPE HEADACHE**

Previously known as muscle contraction headache and tension headache, the IHS classified it as tension-type headache: episodic. The episodic type is the headache that almost everyone experiences and usually responds to simple analgesics. The chronic type (more than 15 days per month) may be difficult to treat.
Patients with tension-type headache often complain of a dull ache across their forehead or in the back of their neck or both. It may feel as if a tight band is compressing the head. The pain location may vary and may even be unilateral at times. The neck muscles are usually tight. Patients do not often complain of photophobia, nausea or vomiting. Routine activity is generally not impaired, and there is less disability associated with headache episodes than there is with migraine. In primary tension-type headache the neurologic examination is normal, except for possible tightness/spasm in pericranial and cervical muscles. When the headache is chronic, depression and anxiety may be present.

Tension-type headache and episodic migrane headache may coexist. In addition episodic tension-type headache may be exacerbated or transformed to chronic tension-type headache by drug-induced or rebound headache caused by increasing symptomatic medication use over time. It is important to find out exactly how much medication the patient uses, including over-the-counter, and herbal, remedies, as well as prescription medications.

**Treatment of Tension-Type Headache**

Episodic tension-type headache may respond to the medications discussed for the symptomatic relief of migraine. Acetaminophen, aspirin, NSAIDs, and the isometheptene combination are the mainstays of episodic treatment. Chronic tension-type headache is difficult to treat. It is important that symptomatic medications are not overused leading to rebound headache. If so, the patient must be withdrawn from the offending medications. This often causes the patient to have a brief exacerbation of headache ("withdrawal headache"). DHE-45 may be used to treat this withdrawal headache (Raskin, 1986) (Silberstein). It takes approximately 8 to 12 weeks for the abused analgesics to "wash out" of the patient (Rapoport); only then may prophylactic medication, if necessary, become fully effective.

Incidentally, caffeine, present in medications, beverages and foods, often causes rebound headache. If the patient is taking over 500 mg daily, it is useful to slowly taper the caffeine ingestion. When the patient reports that caffeine ingestion provides headache relief within 1 hour, it virtually confirms the diagnosis of caffeine withdrawal headache.

Amitriptyline, nortriptyline or doxepin can be used for prophylactic therapy (see above). Elderly patients often cannot tolerate the smallest dose tablets or capsules because of their increased sensitivity to medication. Doxepin (Sinequan®) comes in a concentrate that may be added to juice or other drink. This gives precise control over the dose and permits these patients to be successfully treated. Nortriptyline is also available in liquid form.

Non-pharmacological treatments may also be useful. Biofeedback seems helpful, especially in combination with relaxation training and psychotherapy (Kunkel). Physical therapy and, if appropriate, an exercise program may be useful.

**CLUSTER HEADACHE**
Cluster headache occurs predominantly in men and occurs daily in approximately 50 percent of patients, twice a day in 33 percent, and more often in the remainder. Attacks range in frequency from 8 (or more) a day to one every other day. The attack may last from 15 minutes to 3 hours, although the mean duration is 45 minutes. The attack often awakens the patient from sleep, occurring with the first stage of REM sleep (Kudrow). It is described as an extremely severe, boring pain that begins in or above one eye radiating to the frontal or temporal regions. The pain may also radiate into the teeth or the neck. It is associated with autonomic phenomena including ipsilateral rhinorrhea and lacrimation, nasal stuffiness, and conjunctival injection. A partial Horner's syndrome may occur with the attack (miosis and ptosis). Most cluster headache patients feel the urge to pace about and find that they are unable to lie still during an attack (Kudrow).

The headaches of cluster patients usually occur in episodes or bouts lasting 2 to 4 months. During this time the attacks occur spontaneously or may be provoked by alcohol, histamine, or nitroglycerin). The time between bouts is a "remission" that may last from 1 month to 20 years, in episodic cluster headache. Occasionally, remissions are permanent. Some patients have chronic cluster headache, without remission.

There are some entities which may be misdiagnosed as cluster headache including:

- Migraine
- Trigeminal neuralgia
- Temporal arteritis
- Pheochromocytoma
- Cervical carotid artery dissection
- Chronic and episodic paroxysmal hemicrania

**Treatment of Cluster Headache**

*Symptomatic Treatment of Cluster Headache*

As in migraine, symptomatic treatment is the second line of defense against attacks, if prophylactic therapy fails (Ward 1997, 1998). Oxygen inhalation is effective and safe. The patient should be given 100 percent oxygen at 7 or more liters/minute via a facemask (non-rebreather). It has been effective in 90 percent of patients within 15 minutes (Kudrow). DHE-45® (1 mg) may be given IV to provide relief (preceded by an antiemetic such as metoclopramide 10 mg). Sumatriptan (Imitrex®) subcutaneously is highly effective in treating cluster attacks. Caution is advised, as many cluster patients are middle-aged males with multiple risk factors for coronary artery disease, a contraindication to the use of sumatriptan. Transnasal butorphanol (Stadol NS®) is another option.

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• **Prophylactic Treatment**

Prophylactic therapy is initiated to reduce the frequency, duration, and severity of migraine attacks. Fortunately, a number of good choices exist. Patients in the childbearing years requiring preventative treatment generally should be using an effective form of contraception. However, oral contraceptives may not be appropriate for some migraine patients.

It generally takes two to three months to ascertain a medication's preventative effect. Ideally, therapy starts with the lowest dose which is increased slowly until headache control is achieved or unacceptable side effects are encountered. ("start low, go slow"). After the headaches are controlled for six months or more the medication may be gradually decreased and stopped, as tolerated. Preventative migraine therapy choice should be guided by co-morbid/co-existent conditions such as mitral valve prolapse, Raynaud's phenomenon, epilepsy or, depression, since one can often choose a drug that might help both headache as well as a coexistent condition. In addition, it is essential to avoid medications which might exacerbate a coexisting illness.

The major classes of prophylactic drugs include beta-blockers, anticonvulsants, calcium channel drugs, and heterocyclic antidepressants. There are also several miscellaneous drugs, which are sometimes useful (Ward, 2000).

**Antidepressant**

*Amitriptyline, Nortriptyline, Doxepin*

Many patients with migraine have co-morbid depression. If sleep disturbance is prominent, consider using a heterocyclic antidepressant. Amitriptyline (Elavil®, others) has the most support in the literature. Its effect on migraine is separate from its effect on depression. Its mechanism of action may be through modulation of serotonergic and noradrenergic pathways. Start patients on a 10mg or 25mg bedtime dose and increase the dose slowly to achieve headache control. Doses of 150mg or less are generally employed. Side effects include weight gain, dry mouth, cardiac arrhythmias, urinary retention, blurred vision, and constipation. The medication should be avoided in patients with untreated glaucoma and prostatic hypertrophy. The dry mouth side effect can be managed by using hard sugarless candies or with pilocarpine (Salagen®) 5–10mg tid.

Nortriptyline (Pamelor®, others) may be tried if the side effects of amitriptyline are unacceptable. It causes less drowsiness. Again, the initial dose is generally 10–25 mg hs, but as it is also available in a liquid formulation, even lower doses can be employed if
necessary. Doxepin (Sinequan®) is another potential option, and is also available in a liquid form. Heterocyclic antidepressants are contraindicated in patients with cardiac arrhythmia, narrow angle glaucoma, prostatism, and uncontrolled seizures (Saper).

Antidepressants exemplify the fact that medications within the same pharmacologic group produce various side effects that are more, or less, acceptable to each individual patient. If one agent is poorly tolerated, consider either a lower dose or a trial of another agent in the same family.

**Beta-Adrenergic Antagonist Drugs**

*Propranolol, Timolol, Metoprolol, Nadolol, Atenolol*

The beta-blockers are widely used for the prevention of migraine. They were discovered to have an effect serendipitously, and are postulated to work via an effect on 5-HT2 receptors, preventing the generation of nitric oxide. Propranolol (Inderal®) and timolol (Blocadren®) have FDA indications for migraine prevention. Propranolol is often the first choice and is used in doses ranging from 40–320mg daily, in divided doses. It is also available in several extended-release forms that can be given once or twice daily. Nadolol (Corgard®) can be given once daily, as can atenolol (Tenormin®). Side effects are common and include hypotension, bradycardia, fatigue, weight loss, and bronchospasm (Welch). This class of medications is contraindicated in patients with asthma, diabetes, Raynaud's phenomenon, depression, and sometimes heart failure. Some authorities avoid beta-blockers in migraine with aura.

**Calcium-Channel Blocking Drugs**

*Verapamil, Diltiazem, Amlodipine*

This class of drugs is especially useful in those migraineurs suffering from Raynaud's. Verapamil (Calan®, Isoptin®, others) is the best studied. Like other preventative agents, benefit may not become apparent for weeks to months (Welch). Verapamil is usually started at doses of 80mg twice or three times a day. It may be increased to 480mg per day as tolerated. There are sustained-release formulations (Calan SR®, others) that may be used once or twice daily, to enhance compliance. Common side effects include constipation, hypotension, and pedal edema. The vasodilation associated with some drugs in this category (particularly nifedipine [Procardia®]) occasionally causes a migraine-like headache.

**Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)**

*Naproxen, Naproxen Sodium*

These drugs have a role in both acute and preventative migraine therapy (see below). Naproxen (Naprosyn®) has been demonstrated to be an effective prophylactic in clinical trials. It decreases the intensity and duration of headache, nausea, vomiting, and other
analgesic use. It may be particularly useful for predictable menstrually-associated migraine attacks. The initial dose is 550mg naproxen sodium (Anaprox DS®) BID beginning two days prior to the expected onset of headache and continued through the usual time of headache susceptibility (Raskin, 1988). Patients may be switched to another NSAID to find the most effective and tolerable relief.

**Aspirin**

Aspirin is useful in migraine prophylaxis (Welch). A single 325mg dose daily may reduce the frequency of migraine attacks. Side effects of aspirin and other NSAIDs are well known and include dyspepsia, gastritis, and GI hemorrhage. These side effects can be ameliorated with concurrent treatment with misoprostol (Cytotec®). It is given as 200 mcg tablets 4 times a day, with meals. The dose may be reduced if necessary to 100mcg 4 times a day.

**Anticonvulsants**

*Valproic Acid, Gabapentin, Topiramate.*

Migraine is known to be co-morbid with epilepsy. Valproic acid (Depakote®, others) has an FDA indication for migraine prevention. It is usually administered as the enteric-coated formulation, Depakote® with superior GI tolerability. The initial dosage is usually 250 mg BID. After 6-8 weeks, the dose may be increased to 500 mg BID, and eventually to 750 mg BID. A once-a-day formulation is available. The most important parameter to monitor is headache control. Blood levels do not correlate with clinical effect. Side effects include GI irritation, tremor, hair loss, weight gain, and hepatic dysfunction. Pancreatitis occurs rarely. Spina bifida may occur during pregnancies in fetuses exposed to valproic acid.

Gabapentin (Neurontin®) has been reported to have efficacy in selected migraine patients (Ward, 2000). It is not hepatically-metabolized and has little potential for drug interaction. Adverse effects do include cognitive impairment in some patients. Dosing typically begins at 300 mg tid, and may be slowly raised as high as 1200 mg tid.

Topiramate (Topamax®) has been shown in randomized controlled trials to be effective in preventing migraine (Brandes, Silberstein). Adverse effects include metabolic acidosis and paresthesias as well as occasional sedation and cognitive dysfunction. This drug is a weak carbonic anhydrase inhibitor, and therefore should not be given to patients with a history of renal stones. Higher doses are often associated with significant sedation. It is actually associated with weight loss, which may be of benefit to some migraineurs. For migraine prevention, dosing is begun at 15–25 mg at hs, and slowly raised to as high as 100 mg BID.

Lamotrigine (Lamictal®) seems promising as migraine prophylaxis. But adverse effects include severe skin rash.
Miscellaneous Headache Preventive Agents

*Methysergide, Cyproheptadine*

Numerous other drugs have been used as for migraine prophylaxis, with variable success, and often limited support in the literature. Methysergide (Sansert®) has an FDA indication for migraine prevention. It is highly and rapidly effective, but its use is limited by rare but serious side effects including retroperitoneal, cardiac valvular, and pulmonary fibrosis. Therefore it cannot be given for longer than 6 months without a "drug holiday" of at least one month. Other side effects are related to vasoconstriction and include: chest pain, abdominal pain, cold numb painful extremities with or without paresthesiae, and diminished or absent pulses. These effects usually regress when the medication is stopped. Nausea and vomiting may also occur. The medication may make patients feel strange (chemically similar to LSD), especially at the initiation of therapy. The 2 mg tablet is started once daily for 3–4 days, then increased slowly to tid or qid. Methysergide is often useful for intractable episodic cluster headache. It is no longer available in the US but is available in Canada.

Cyproheptadine (Periactin®) is an agent with anti-serotonergic, antihistamine, and calcium channel blocking properties. It has been advocated particularly as a preventative agent for children with migraine. The usual starting dose is 2mg (1/2 a 4mg tablet) twice or thrice daily. The dose may be increased slowly, usually to 4 mg twice or three times daily. It is available as syrup as well, enabling lower dosage titration. Side effects include sedation and weight gain.

Symptomatic Migraine Treatment

Simple Analgesics

*Aspirin, Acetaminophen, Combinations*

Both aspirin and acetaminophen are superior to placebo in decreasing migraine pain (Welch). Aspirin is the most commonly used non-prescription analgesic selected by patients for the management of headache pain. An initial dose of 975–1000 mg is recommended at the onset of the attack. Subsequent doses of 650 - 1000 mg every 4 hours may be given as needed (maximum 4–6 grams in a 24-hour period). Buffered and effervescent forms of aspirin may reduce gastric irritation. Delayed absorption with enteric-coated aspirin precludes the use of this product in acute pain management. Aspirin is also available for rectal administration. It has been used intravenously with good results (Welch) but is only available outside of the U.S.A.

Acetaminophen is a non-prescription alternative in patients who cannot tolerate aspirin. Several pain models demonstrate the equivalent analgesic efficacy of aspirin and acetaminophen on a milligram to milligram basis. A study in patients with tension and tension-vascular headaches observed no difference between 1000 mg acetaminophen and 650 mg aspirin in relieving headache pain.
Gastric stasis may occur during a migraine attack and impedes the absorption of medications, such as aspirin and acetaminophen. Concomitant administration of metoclopramide (Reglan®) significantly increases serum concentrations of both these agents, by increasing gastrointestinal motility. Oral medications may be limited in their utility by their incomplete absorption and the frequent vomiting accompanying migraine. The use of the rectal route of administration is available for aspirin and acetaminophen. Codeine and other drugs may also be prepared in this fashion by pharmacists (Ward). Dependence can occur in patients who use these products uninterrupted for 48 hours or more.

Aspirin and acetaminophen are commonly combined with caffeine and/or butalbital to enhance analgesic activity and are sold as Fiorinal®, Esgic® and Fioricet® (with acetaminophen). This combination works for many patients with headache, but is very prone to cause medication overuse headache. When this occurs, it is important to detoxify these patients from all rebound-producing medications, including simple analgesics, when using excessive quantities (e.g., more than 2 days a week).

**Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**

*Naproxen Sodium, Ketorolac*

Nonsteroidal anti-inflammatory drugs (NSAID) may be considered good choices in first line abortive therapy of migraines, due to their effectiveness and lack of a dependency cycle. Naproxen (Naprosyn®) is the most frequently studied NSAID for the treatment of migraine. Naproxen and naproxen sodium (Anaprox/Anaprox DS®) achieve peak plasma concentrations after 2 and 1 hour, respectively. Naproxen sodium is preferred for abortive therapy because onset of analgesic activity corresponds with its earlier peak plasma concentration.

Ketorolac (Toradol®), the first parenteral NSAID available in the United States, is effective in the treatment of migraine. However, relief from pain and disability with I.M. ketorolac are significantly less than the combination of IV DHE 45® and metoclopramide. Keterolac may also be administered intravenously.

Other NSAIDs found to be effective in the treatment of migraine include diclofenac sodium, flufenamic acid, flurbiprofen, ibuprofen and mefenamic acid (See Table 4). The most common adverse effect with all NSAIDs is dyspepsia.

**Table 6-4—Dosing Guidelines For NSAIDs For Treating Migraine**

- Naproxen sodium (Anaprox®)
  550 mg–850 mg BID
- Diclofenac sodium (Voltaren®)
  50-100 mg in 2 divided doses
- Flufenamic acid
  Not available in the United States
• Flurbiprofen (Ansaid®)
  300 mg in 2–4 divided doses
• Ibuprofen (Motrin®, Advil®)
  600-800 mg TID
• Indomethacin (Indocin®)
  25–50 mg TID
• Mefenamic acid (Ponstel®)
  500 mg, then 250 mg every 6 hours
• Tolfenamic Acid
  Not available in the United States

Antiemetics

*Metoclopramide, Chlorpromazine, Prochlorperazine, Promethazine*

Antiemetics are useful in the management of disabling nausea and vomiting frequently associated with migraine headaches. In addition to antiemetics properties, metoclopramide (Reglan®) can also reverse the gastric stasis accompanying migraine attacks. Metoclopramide enhances the effectiveness of analgesics such as aspirin, acetaminophen, naproxen as well as ergotamine in migraine by improving absorption (Raskin, 1988). It should be used sparingly as it may cause dystonia and akathisia, especially in adolescents (Welch). Keeping the dose below 30 mg per day decreases the chance such a reaction will occur. Patients should be warned of the potential dystonic reaction and have 25 mg of diphenhydramine (Benadryl®) available. Administration of a narcotic analgesic (e.g., meperidine-Demerol®) or anticholinergic agents may antagonize increased gastrointestinal motility produced by metoclopramide.

Recent studies suggest that some antiemetics may be useful as single agents in the treatment of migraine attacks. Controlled studies have shown intravenous chlorpromazine (Thorazine®) 0.1 mg/kg and prochlorperazine (Compazine®) 10 mg effectively terminate migraine attacks (Lane/Jones cited in Raskin 1988). Chlorpromazine may be useful when treating migraine with intravenous dihydroergotamine (DHE-45®) (Welch). Chlorpromazine and prochlorperazine may cause tardive dyskinesia that occasionally is irreversible. Promethazine (Phenergan®) suppositories (12.5 mg–25 mg-50 mg) are effective in treating nausea and vomiting, with little likelihood of dystonia.

Isometheptene

Isometheptene (Midrin®) is suitable for patients to try for mild to moderate migraine attacks. Midrin® contains isometheptene in combination with dichloralphenazone (a sedative) and 325 mg of acetaminophen. It is generally well-tolerated. Adverse reactions are unusual. Isometheptene is a vasoconstrictor possessing antispasmodic activity. It was more effective in treating mild to moderately severe migraine in a placebo-controlled trial (Raskin 1988). In a comparative trial, no difference in headache duration was observed between Midrin® and ergotamine/caffeine (Cafergot®). However, the incidence of nausea and vomiting was significantly lower with Midrin® (6.5 percent versus 24.6...
percent). The recommended dose for Midrin® is 2 capsules at the onset of the attack, followed by 1 capsule every hour as needed, up to a maximum of 5 capsules per 12 hours.

**Ergot Preparations**

*Ergotamine Tartrate, Dihydroergotamine*

Ergotamine tartrate was a very important medication for symptomatic treatment of migraine. It is available in oral, rectal, and sometimes sublingual forms. Availability of some of these formulations has been intermittent. Dihydroergotamine (DHE-45®) is the only parenteral ergot available. The absorption rates of ergotamine are variable, depending on the route of administration. Caffeine enhances ergotamine's absorption. Metoclopramide is likely to improve absorption of oral ergotamine (Welch). Parenteral treatment is most effective; rectal ergotamine achieves higher serum levels than the oral route. Therapeutic responses will, of course, vary among different patients and route and dose of medication.

Oral ergotamine (Cafergot®, Wigraine®, and others) is given initially as two 1 mg tablets followed by 1 tablet every 30 minutes until relief occurs. The dose is limited to 6 tablets daily and 10 tablets weekly. Nausea and vomiting are common side effects of the medication. Metoclopramide can be used to help control the nausea and vomiting associated with ergotamine.

Rectal ergotamine (Cafergot® or Wigraine®) is available in 2 mg suppositories. It is useful to take one-quarter to one-half of a suppository initially, followed by one-quarter every 30 minutes as needed to a maximum daily dose of two suppositories or 4 mg.

Gradual overuse of oral or rectal ergotamine may lead to dependency and the development of ergotamine headache. The patient develops a rebound or withdrawal ergotamine headache that is successfully treated with another dose of the drug. The total daily dose may slowly increase over years transforming a migraine headache into a chronic daily headache (Mathew, 1993). Other side effects include nausea, vomiting, abdominal pain, diarrhea, muscle cramps, paresthesias of the extremities, vasoconstriction and loss of pulses, and angina.

Dihydroergotamine (DHE-45®) is effective in aborting migraine, and is more effective than meperidine plus hydroxyzine and butorphanol (Raskin, 1986) (Silberstein, 1990) (Welch). Up to 90 percent of migraines treated with intravenous DHE 45® abated - it is also useful in treating drug-induced headache (Silberstein 1990). Patients can be taught to give themselves subcutaneous or intramuscular injections. DHE-45® comes in ampules (1 mg in 1 ml) - the dose may be titrated between 0.5-1.0 mg twice daily, as needed. The goal is to use the smallest effective dose.

Initially metoclopramide or another antiemetic should be taken prior to DHE-45® to help control drug-induced nausea and vomiting. Many patients later find the metoclopramide
is no longer necessary. The side effects of DHE-45® are similar to those of ergotamine but less severe. An intranasal formulation, Migranal®, is also available.

The ergots and their derivatives are contraindicated in patients with severe hypertension, peripheral vascular disease, ischemic heart disease and thrombophlebitis. They should be used cautiously in patients with peptic ulcer disease, bradycardia, renal and hepatic abnormalities. The ergots can not be used with "triptan" drugs (see below) within 24 hours.

**Triptan medications**

Sumatriptan (Imitrex®) is the first medication engineered to work at the 5-HT receptor to treat migraine. It is an effective treatment and has been used extensively since it became available in the United States in 1993. Sumatriptan is currently available for patients orally, intranasally, and with an autoinjector for subcutaneous injection. Sumatriptan suppositories are available in some countries outside the USA.

Physicians may administer the drug without the use of an autoinjector. Subcutaneous sumatriptan reaches peak plasma level within 15 minutes. Extensive clinical trials have shown marked relief of head pain, nausea, vomiting, phonophobia, and photophobia within 1–2 hours after treatment with 6 mg in approximately 80 percent of patients. This formulation is most effective for headache occurring early in the morning (upon awakening), those which escalate to maximum severity rapidly, and those attacks with vomiting.

Oral sumatriptan (25, 50, and 100 mg) produces relief less rapidly, within 2 to 4 hours. Sumatriptan produced better relief from nausea and vomiting than ergotamine and had a similar effect to aspirin with metoclopramide. Intranasal sumatriptan is available in 5mg and 20mg single use devices (20mg BID prn is the usual adult dose). It is another option for use during attacks with vomiting.

The side effects of subcutaneous, nasal, and oral sumatriptan are similar. Most common is an injection site reaction after subcutaneous administration. Also, flushing, heat sensation, chest pressure, heaviness, tingling and jaw or neck pain may occur. Occasional patients report chest pressure with pain going into the left arm suggestive of myocardial ischemia. After 3 million documented headache attacks treated with sumatriptan, 4 patients had documented myocardial ischemia (Welch). More extensive data suggests the occurrence of serious cardiac events is rare.

Usually side effects are mild to moderate in severity, short-lived, and resolve on their own. Some authorities advocate giving the initial dose of "triptans" under medical supervision. It is contraindicated to use "triptans" in patients with previous myocardial infarction, ischemic heart disease, Prinzmetal's angina, or uncontrolled hypertension. They should only be used 24 hours before or after an ergot preparation is ingested. They should be avoided when patients are taking methysergide because of the vasoconstrictor properties of both medications.
Other "triptan" drugs available include zolmitriptan (Zomig®), naratriptan (Amerge®), rizatriptan (Maxalt®), eletriptan (Relpax®), almotriptan (Axert®), and frovatriptan (Frova®). In the USA, these agents are all presently available oral treatments, and zolmitriptan is available in nasal spray form. Zolmitriptan and rizatriptan are also available in rapidly dissolving tablets which are preferred by some patients although they have not been shown to be more rapid or effective in clinical trials. Failure to respond to one triptan does not preclude a successful response to another (Ward 2000). These agents give superior results if used as early in the migraine attack as possible.

**Narcotics**

*Butorphanol, Codeine, Oxycodone, Hydrocodone, Meperidine*

Codeine has been shown to be superior to placebo in aborting a migraine attack (Raskin 1988). Butalbital, aspirin or acetaminophen, and caffeine combinations (see above) may become more effective in selected patients when codeine is added (Kunkel). These agents are potentially addictive: the addition of codeine increases the risk and severely limits its utility. Oxycodone (Percodan®) and hydrocodone (Vicodin®) have similar effects and concerns. Parenteral meperidine (Demerol®) is often used for the emergent treatment of migraine. It should be limited to those patients with infrequent attacks that cannot be treated effectively with another agent. This includes patients with peripheral vascular or coronary artery disease (Welch).

It is important to note that the efficacy of oral meperidine is approximately 25 percent of the IM preparation. Oral meperidine should be used in a very limited way for selected patients with severe migraine and as a rescue medication when other measures fail. Medication use should be closely monitored.

Transnasal butorphanol (Stadol NS®) has been used in the treatment of migraine. While US regulatory agencies formerly did not view it as a narcotic, it does contain the morphine molecule, and its major side effect is sedation. As a mixed agonist-antagonist, it may have less addiction potential, although this is controversial. Overuse may occur, and it seems capable of causing rebound. The initial dose of 1 mg (1 puff) in one nostril is approximately equipotent to 5 mg of morphine. Onset of action is rapid (minutes).

In pregnancy, there are very few medications that can be safely used. Acetaminophen, metoclopramide and meperidine can be used judiciously, as they are in FDA category B (Codeine is category C). Combination analgesics are to be avoided. Fortunately many migraineurs experience fewer headaches during pregnancy.

**TENSION-TYPE HEADACHE**

Previously known as muscle contraction headache and tension headache, the IHS classified it as tension-type headache: episodic. The episodic type is the headache that almost everyone experiences and usually responds to simple analgesics. The chronic type (more than 15 days per month) may be difficult to treat.
Patients with tension-type headache often complain of a dull ache across their forehead or in the back of their neck or both. It may feel as if a tight band is compressing the head. The pain location may vary and may even be unilateral at times. The neck muscles are usually tight. Patients do not often complain of photophobia, nausea or vomiting. Routine activity is generally not impaired, and there is less disability associated with headache episodes than there is with migraine. In primary tension-type headache the neurologic examination is normal, except for possible tightness/spasm in pericranial and cervical muscles. When the headache is chronic, depression and anxiety may be present.

Tension-type headache and episodic migraine headache may coexist. In addition episodic tension-type headache may be exacerbated or transformed to chronic tension-type headache by drug-induced or rebound headache caused by increasing symptomatic medication use over time. It is important to find out exactly how much medication the patient uses, including over-the-counter, and herbal, remedies, as well as prescription medications.

**Treatment of Tension-Type Headache**

Episodic tension-type headache may respond to the medications discussed for the symptomatic relief of migraine. Acetaminophen, aspirin, NSAIDs, and the isometheptene combination are the mainstays of episodic treatment. Chronic tension-type headache is difficult to treat. It is important that symptomatic medications are not overused leading to rebound headache. If so, the patient must be withdrawn from the offending medications. This often causes the patient to have a brief exacerbation of headache ("withdrawal headache"). DHE-45 may be used to treat this withdrawal headache (Raskin, 1986) (Silberstein). It takes approximately 8 to 12 weeks for the abused analgesics to "wash out" of the patient (Rapoport); only then may prophylactic medication, if necessary, become fully effective.

Incidentally, caffeine, present in medications, beverages and foods, often causes rebound headache. If the patient is taking over 500 mg daily, it is useful to slowly taper the caffeine ingestion. When the patient reports that caffeine ingestion provides headache relief within 1 hour, it virtually confirms the diagnosis of caffeine withdrawal headache.

Amitriptyline, nortriptyline or doxepin can be used for prophylactic therapy (see above). Elderly patients often cannot tolerate the smallest dose tablets or capsules because of their increased sensitivity to medication. Doxepin (Sinequan®) comes in a concentrate that may be added to juice or other drink. This gives precise control over the dose and permits these patients to be successfully treated. Nortriptyline is also available in liquid form.

Non-pharmacological treatments may also be useful. Biofeedback seems helpful, especially in combination with relaxation training and psychotherapy (Kunkel). Physical therapy and, if appropriate, an exercise program may be useful.

**CLUSTER HEADACHE**
Cluster headache occurs predominantly in men and occurs daily in approximately 50 percent of patients, twice a day in 33 percent, and more often in the remainder. Attacks range in frequency from 8 (or more) a day to one every other day. The attack may last from 15 minutes to 3 hours, although the mean duration is 45 minutes. The attack often awakens the patient from sleep, occurring with the first stage of REM sleep (Kudrow). It is described as an extremely severe, boring pain that begins in or above one eye radiating to the frontal or temporal regions. The pain may also radiate into the teeth or the neck. It is associated with autonomic phenomena including ipsilateral rhinorrhea and lacrimation, nasal stuffiness, and conjunctival injection. A partial Horner's syndrome may occur with the attack (miosis and ptosis). Most cluster headache patients feel the urge to pace about and find that they are unable to lie still during an attack (Kudrow).

The headaches of cluster patients usually occur in episodes or bouts lasting 2 to 4 months. During this time the attacks occur spontaneously or may be provoked by alcohol, histamine, or nitroglycerin. The time between bouts is a "remission" that may last from 1 month to 20 years, in episodic cluster headache. Occasionally, remissions are permanent. Some patients have chronic cluster headache, without remission.

There are some entities which may be misdiagnosed as cluster headache including:

- Migraine
- Trigeminal neuralgia
- Temporal arteritis
- Pheochromocytoma
- Cervical carotid artery dissection
- Chronic and episodic paroxysmal hemicrania

Treatment of Cluster Headache

Symptomatic Treatment of Cluster Headache

As in migraine, symptomatic treatment is the second line of defense against attacks, if prophylactic therapy fails (Ward 1997, 1998). Oxygen inhalation is effective and safe. The patient should be given 100 percent oxygen at 7 or more liters/minute via a facemask (non-rebreather). It has been effective in 90 percent of patients within 15 minutes (Kudrow). DHE-45® (1 mg) may be given IV to provide relief (preceded by an antiemetic such as metoclopramide 10 mg). Sumatriptan (Imitrex®) subcutaneously is highly effective in treating cluster attacks. Caution is advised, as many cluster patients are middle-aged males with multiple risk factors for coronary artery disease, a contraindication to the use of sumatriptan. Transnasal butorphanol (Stadol NS®) is another option.

Prophylactic Treatment of Cluster Headache

Many of the prophylactic treatments for cluster are similar to those for migraine. Patients with episodic cluster experience tremendous pain. Vigorous attempts to prevent the
attacks are warranted. Treatment in the early phases of a cluster headache cycle with prednisone will usually stop the bout or decrease its severity within 24 hours. The initial dose is 60-80 mg daily instituted immediately. Then after 2 to 3 days at this level the dose is slowly tapered over 10-14 days. This immediate control permits the initiation of another medication that will be safer over the long-term than prednisone.

Prednisone can cause immediate bone loss, even when given for a short time. Bone loss may be prevented by taking Vitamin D 50,000 units weekly and calcium, one gram per day. Measures to protect the stomach (such as H2 blockers, antacids, or proton pump inhibitors) may be advisable.

Methysergide (Sansert®) is used as described under the treatment of migraine (see above). It tends to be most effective early in the course of the cluster cycle. It has been reported to have an efficacy of 65 percent (Kudrow).

Verapamil (Calan®, others) has been effective in several studies. Patients may require up to 480 mg per day (e.g., as Calan SR 240 BID) or, cautiously, even higher doses. Adding oral ergotamine 2 mg 1 hour prior to bedtime increases the effect of the verapamil (Kudrow). Lithium is effective in episodic cluster and chronic cluster. The dose has to be gradually built up to avoid untoward reactions. This dose escalation takes place while controlling the cluster with the prednisone treatment. Lithium can be prescribed at 300 mg daily for 3 days then increased every 3 days until it is taken three times daily. It is necessary to follow the lithium serum level to monitor for toxicity. The concomitant use of diuretics, NSAIDS, and severe sodium-restricted diets are contraindicated, since this may cause toxicity. Thyroid function should be assessed in patients taking lithium as it can interfere with thyroid function. The symptoms of lithium toxicity include tremor, polyuria and mild nausea initially. Diarrhea, vomiting, drowsiness, muscular weakness, and incoordination occur with greater lithium intoxication. Stopping the lithium and monitoring the patient is necessary in this situation.

Valproic acid (Depakote®) appears to be another useful treatment for cluster headache. Recent studies suggest that for refractory cases, gabapentin (Neurontin®), and topiramate (Topamax®) might be useful. Combinations of verapamil and lithium, or verapamil and valproic acid, for example, may be effective when monotherapy fails.

When all medical treatment fails surgical treatment may be appropriate. Current surgical options include percutaneous radiofrequency lesions directed against the trigeminal ganglion, and deep brain stimulation of the hypothalamus. Both have risks for potential complications.

LESS COMMON PRIMARY HEADACHES

- Chronic Paroxysmal Hemicrania (CPH)
- Short-lasting unilateral neuralgiform headaches with conjunctival injection and tearing (SUNCT)
- Hemicrania continua (HC)
Chronic paroxysmal hemicrania (CPH) is in many ways similar to cluster headache—periorbital location, severe pain intensity, usually accompanied by tearing and other autonomic facial symptoms—but duration of headaches is very brief, usually around 5 minutes, and headaches can occur many times per day. CPH affects young women predominantly, and is particularly responsive to indomethacin (25–50 mg tid).

SUNCT is characterized by even briefer paroxysms of pain (seconds), also in the periorbital region. Up to 200 attacks may occur per day. It too is usually accompanied by tearing and other autonomic facial symptoms, but it does not respond to indomethacin.

Hemicrania continua (HC) consists of constant unilateral head pain, also often accompanied by tearing, nasal congestion and other autonomic facial symptoms. Like CPH, HC is highly responsive to indomethacin.

CONCLUSION

Many different causes of headaches confront medical practitioners. A first step in the approach to the patient with headache is to rule out secondary causes, keeping common "red flags" in mind. Fortunately, the vast majority of patients with headache will be found to have a primary cause, such as migraine or tension-type headache. Many effective treatments are available for these conditions, but with primary headaches too, diagnosis is essential to ensure proper treatment.

SELF-ASSESSMENT QUESTIONS

1. A 35-year-old woman, with a past history of occasional migraine, has sudden onset of severe generalized headache and nausea, causing her to stop her activities and lie down. The headache persists and her family takes her to the emergency room. The primary diagnostic consideration for the examining physician is:
   A. migraine headache
   B. subarachnoid hemorrhage
   C. posttraumatic headache
   D. cluster headache
   E. none of the above

2. The above individual undergoes a noncontrast CT scan of the head which is read by the radiologist as negative. The next step for the examining physician is:
   A. administer an analgesic and observe for headache resolution.
   B. lumbar puncture.
   C. refer to a neurologist for his next available appointment.
   D. schedule for an outpatient MRI and MRA of the brain.
   E. administer 6 mg of sumatriptan subcutaneously.

3. The following organic conditions can mimic recurrent primary headache disorders:
   A. pituitary adenoma
   B. cerebral arteriovenous malformation
   C. isolated CNS vasculitis.
D. pheochromocytoma
E. all of the above

4. A 68-year-old female presents with a three week history of severe unilateral headache and scalp tenderness. She has had one episode, the day prior, of transient ipsilateral monocular visual loss, which has completely resolved. An erythrocyte sedimentation rate is 65 mm/hr. The following steps should be instituted:
   A. schedule cerebral angiography.
   B. start prednisone, 60 -80 mg/daily immediately
   C. obtain a stat CT scan of the brain.
   D. schedule for a temporal artery biopsy
   E. a,b,c.
   F. b,c,d

5. Pick the one true statement among the following:
   A. oral or rectally administered ergotamines rarely lead to dependency, despite frequent use.
   B. ergotamines and sumatriptan cannot be used concomitantly within 24 hours of each other.
   C. ergotamine or sumatriptan can be used safely during pregnancy.
   D. sumatriptan can be used safely six months after myocardial infarction.
   E. dihydroergotamine has only marginal benefit in the treatment of migraine headache.

6. The mainstay drug(s) for treatment for episodic tension-type headache are:
   A. ergotamines, sumatriptan
   B. beta-adrenergic antagonist drugs
   C. calcium channel blockers
   D. steroids
   E. aspirin, acetaminophen, non-steroidal anti-inflammatory drugs

7. Overuse of medications which symptomatically treat tension-type headache may lead to:
   A. transformed migraine.
   B. cluster headache
   C. chronic daily headache.
   D. hemicrania continua
   E. classic migraine

8. The following medication should not be used for migraine prophylaxis:
   A. valproic acid (Depakote®)
   B. verapamil
   C. nadolol
   D. nortriptyline
   E. butorphanol

9. New-onset headache, followed shortly by confusion and/or seizures, may be secondary to:
   A. encephalitis
   B. brain abscess
   C. subdural empyema
D. aseptic meningitis
E. a,b,c

Label the following statements True (T) or False (F):

A. valproate serum levels correlate with clinical effectiveness in migraine prophylaxis.
B. metoclopramide (Reglan®) may enhance analgesic absorption during a migraine attack.
C. oxygen inhalation is a safe and effective treatment for cluster headache attacks.
D. nonsteroidal anti-inflammatory drugs are an effective first line abortive therapy for mild to moderate migraine headaches.
E. fronto-maxillary headache with associated local tenderness is almost always due to a benign headache disorder.

Answers

1. B
2. B
3. E
4. F
5. B
6. E
7. C
8. E
9. E

True or False:

A. False
B. True
C. True
D. True
E. False

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Chapter 7 – Episodic Disorders

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Case 1

A 13-year-old boy is attending his grade school commencement, which is being held outdoors on a hot day. Near the end of the ceremony he feels nauseated, his vision fades, and he falls limply to the ground unconscious. His friends try to sit him up and his body shakes for several seconds. He awakens quickly and is seen to be pale and sweaty.

Case 2

A 25-year-old law student is studying in the library. Suddenly her left hand begins to twitch. This is followed several seconds later by twitching of the left side of her face. She loses consciousness and falls stiffly to the floor, where her body and limbs shake rhythmically for one minute. She is incontinent, and confused for 15 minutes after she awakens.

Case 3

A 65-year-old diabetic, hypertensive man is working in his garden when he experiences the sudden onset of weakness of the right arm and leg. He slumps to the ground. When his wife runs over to him he appears to be awake, but does not speak. The symptoms clear completely over the next 30 minutes.

The above are simple paradigms of episodic neurological disorders: **vasovagal syncope, seizure, and transient ischemic attack (TIA).**

In these illustrative cases, the combination of age, risk factors, circumstance, and attack characteristics leaves little room for doubt. A careful, detailed history of the episode is the most crucial aspect of accurate diagnosis.

What are the features of the cases above which make the diagnosis obvious; and what are the common variants of these disorders, which may make their diagnosis more difficult, albeit ultimately achievable?
Let us start with the principle that the sudden onset of neurological symptoms (regional loss of function, focal symptoms, loss of consciousness) is generally due to an electrical (seizure) or vascular (TIA, stroke, syncope) event. Such symptoms may also be due to psychogenic causes, i.e., conversion disorder, but this relatively infrequent cause will not be discussed here.

Syncope or loss of consciousness is the direct result of a transiently inadequate supply of blood to the brain. Such reduction of cerebral perfusion may occur because of lowered cardiac output due to arrhythmias, and in such cases may be referred to as a Stokes-Adams attack. By far the most common form of syncope, however, is that associated with abnormal autonomic regulation of blood pressure and/or heart rate, and it is then called vasovagal syncope.

**Vasovagal and Cardiac Synopies**

**Epidemiology.** Vasovagal syncope, the most common type of faint encountered in office practice, occurs most commonly in children, adolescents, and young adults. [We will avoid its more recent designation, 'neurocardiogenic syncope,' a term which misleadingly implies that cardiac disease may be involved.]

True cardiac syncope, formerly known as Stokes-Adams attack, consists of transient loss of consciousness due to reduction of cerebral blood flow directly due to abrupt, reduced cardiac output secondary to arrhythmia. Cardiac syncope usually occurs in older patients with a history of other forms of heart disease such as coronary artery disease or angina. Cardiac syncope is typically recurrent, and is potentially lethal when due to cardiac arrhythmia such as ventricular tachycardia. Accurate diagnosis is vital.

Orthostatic syncope is most commonly seen in the context of antihypertensive drug treatment, or in association with autonomic neuropathies, for example, in patients with diabetes or uremia.

Clinical symptoms and signs. Vasovagal syncope usually occurs in certain provocative circumstances which trigger an overactive autonomic reflex, which acutely reduces cardiac output and lowers blood pressure.

Syncope may be triggered by a Valsalva maneuver such as that occurring with **micturition.** The young man with micturition syncope may be dehydrated after an evening of drinking alcohol; he gets up in the night to urinate, stands at the toilet, and performs a Valsalva maneuver as he initiates urination. The older person with chronic obstructive pulmonary disease is at risk for **cough syncope** during long bouts of severe coughing.

Long periods of **standing** upright, particularly when combined with **cutaneous vasodilation,** can trigger syncope, e.g., when standing on a hot parade ground or emerging from a prolonged, hot shower.
Sudden rushes of sympathetic nerve activity such as those associated with a frightening experience (eg, pain or the sight of blood) may trigger a vagal reflex with bradycardia and/or lowered blood pressure. The doctor or dentist's office is a favorite site for such syncopes, and occurrence there should always raise the possibility of that diagnosis.

Fainting which occurs shortly after arising from a sitting or lying position, especially in patients taking antihypertensive drugs, should always suggest orthostatic hypotension. Orthostatic faints are particularly common upon arising first thing in the morning or during nocturnal trips to the bathroom, when blood pressure reflexes may be relatively inefficient. There may be a brief prodrome of faintness or dizziness, or loss of consciousness may be abrupt.

Dehydration, such as that following heavy alcohol use, may be a contributing factor, lowering the "safety factor" for adequate cerebral perfusion. Postprandial diversion of blood flow to the splanchnic blood vessels, which do not contribute significantly to sustaining systemic blood pressure, increases vulnerability to orthostatic hypotension.

Cardiac syncope, in contrast, may occur in any situation, is unrelated to postural change or circumstance. It is related directly to abrupt insufficiency of cerebral blood flow due to reduce cardiac output, as from severe bradycardia, heart block, or a systole.

Premonitory Symptoms. Vasovagal syncope rarely happens without characteristic premonitory symptoms: fading of vision, nausea, sweating, weakness, tinnitus, or a feeling of an impending faint are the most common. Such symptoms may last several seconds to a half-minute or so before consciousness is lost.

The person with syncope usually slumps limply to the ground and does not fall stiffly or assume a rigid position. Twitching or myoclonic movements of the limbs may occur briefly, and may suggest to on-lookers that a seizure is occurring. Unlike the clonic movements of a seizure, however, which lasts 30–60 seconds, in so-called "convulsive" syncope the jerks last only a few seconds. Urinary incontinence may occur, and should not automatically suggest a diagnosis of seizure.

Patients awaken quickly, usually within 15–30 seconds, and are immediately oriented. Vomiting may occur on awakening, and pallor or sweating persisting for some minutes may be noted by witnesses.

Cardiac syncope, on the other hand, characteristically occurs without warning; the patient loses consciousness abruptly. Occasionally brief palpitations preceding the attack or at other times may be reported, but this is by no means invariable.

MARGIN NOTES:

1. Epileptic seizures occur in any circumstances, while syncope is usually due to common physical, emotional, or situational triggers.
2. The convulsive movements of epilepsy last longer and are more violent than the twitches often seen in syncope.
3. The prodromal symptoms of vasovagal syncope (nausea, faintness, weakness, diaphoresis, fading of vision) are diagnostic, and usually well recalled by the patient.
4. An observer of an attack of loss of consciousness often provides crucial diagnostic information.

The physical examination. The physical examination in vasovagal syncope, including routine blood pressure measurements, is typically normal.

If orthostatic syncope is suspected, the blood pressure should be measured after keeping the patient supine for 10 minutes. The pressure is retaken immediately after having the patient stand up, and again three minutes after standing upright. A systolic drop of 15 mm, or a diastolic drop of more than 10 mm is abnormal; a smaller change may be significant if it reproduces the patient's prodromal symptoms.

On the other hand the patient with cardiogenic syncope may have physical signs of heart disease such as cardiomegaly, irregular heart rate, or murmur. Massaging the carotid sinus, the physiologic blood pressure detector in the neck, to look for the unusual condition of carotid sinus hypersensitivity has been blamed for strokes and life-threatening changes in blood pressure or heart rhythm, and is best avoided without ECG monitoring and emergency resuscitation teams nearby. It should not be an office procedure.

Diagnostic tests. No diagnostic tests are necessary when a diagnosis of vasovagal syncope is made because of a typical history and circumstances. If cardiac syncope is suspected, a 12-lead EKG followed by a 24-hour Holter monitor is indicated. An (M-mode 2D) echocardiogram ($600) will look for valvular disease such as aortic stenosis. If all of these tests are normal, it is unlikely that further tests will be required because the diagnosis of cardiogenic syncope is unlikely. Recurrent episodes in the face of normal initial cardiac evaluation warrant referral to a cardiologist.

Tilt-table testing does not usually contribute to the diagnosis of vasovagal syncope, and is indicated only in cases when diseases of the autonomic nervous system causing orthostatic hypotension are suspected. Such conditions may be accompanied by other autonomic symptoms or signs, and if they are suspected a neurological consultation would be more cost-effective and appropriate. In the face of a typical history of vasovagal syncope, even one associated with a few myoclonic jerks, an EEG is unnecessary and may even be counter-productive, since the number of falsely positive "epileptic" EEG abnormalities emerging from some laboratories is distressingly high. This leads to mistaken labeling of the patient.

Treatment of syncope depends upon the cause. Vasovagal syncope usually requires no treatment other than a reassuring explanation to the patient. Understanding the benign nature of the attacks, being aware of the kind of circumstances which put him or her at
risk and being prepared to lie down or put the head down at the first sign of a syncopal prodrome is generally enough.

Cardiac disorders are treated in the usual fashion. Adjustment of dosage or changes in antihypertensive drugs may be necessary.

Treatment of orthostatic hypotension due to autonomic neuropathies centers around measures designed to increase water retention. Nocturnal elevation of the head of the bed is the simplest initial step. If this fails, fludrocortisone may be tried.

**Referral.** Because of the life-threatening nature of an episode, when a diagnosis of cardiac syncope is suspected a cardiologist should be consulted. If cardiac syncope is strongly suspected clinically but unproven, the cardiologist may recommend specialized tests of cardiac conduction or prolonged event monitoring, in which cutaneous or subcutaneously implanted EGK electrodes enable continuous cardiac monitoring over weeks or months.

When the clinical history is ambiguous, or when an imprudently ordered EEG shows unexpected "epilepsy" in the patient with classical symptoms of vasovagal syncope, a neurologist may help reinforce the correct diagnosis and avoid years of inappropriate antiepileptic treatment. Most neurologists will also provide a treatment plan for severe orthostatic hypotensive syncope due to neuropathies.

Referral to a cardiology or neurologic specialist is usually less expensive and provides more useful information than an inappropriately ordered brain image or electroencephalogram.

**Psychosocial impact.**

Syncopal injuries are rare, and disability negligible, but the events are often frightening to the patient and onlookers, and may contribute to unnecessary investigations (brain imaging, EEGs) or even treatment (beta blockers, fludrocortisone). Patients who have fainted once are at risk for recurrences, but attacks usually disappear with age.

Orthostatic syncope may cause injury in the elderly on antihypertensive drugs, emphasizing the need for careful dosing in this age group.

Cardiac syncope often heralds the presence of life-threatening cardiac arrhythmias, so that a typical history in an at-risk individual should always prompt immediate action.

**Seizures**

Seizures occurring in the context of an acute illness such as meningitis, eclampsia, alcohol withdrawal, or high fever (in infants) do not constitute epilepsy, and generally are not an indication for chronic treatment.
In contrast, epilepsy consists of spontaneous, recurrent seizures appearing at unpredictable intervals. It is most logically regarded as a symptom rather than as a disease per se. Just as the acute seizure raises the immediate question, "What is the cause?" similarly chronic epilepsy should prompt the question, "What is causing it?"

**Epidemiology**

**Age and Incidence.**

Acute symptomatic seizures are very common, with a lifetime incidence of about 10 percent. Chronic epilepsy has a prevalence of about 0.5 percent across all age groups. The incidence of epilepsy is highest in the first year of life, falls slowly until a plateau is reached at about 10 years of age, and rises steeply again in the elderly.

Risk factors include intracranial lesions (tumor, hemorrhage), a family history of epilepsy, a history of acute symptomatic seizures, or a history of meningitis or encephalitis. Minor head trauma does not increase the risk of epilepsy, but a history of loss of consciousness for more than 30 minutes, focal neurological signs, skull fracture, or seizures at the time of the trauma do so. Abuse of cocaine, amphetamine, or PCP, and therapeutic doses of some antidepressants, particularly newer serotonin-sparing drugs, can provoke seizures. "Birth injury" is probably over-rated as a cause of epilepsy. In at least half the patients with adult-onset epilepsy, no cause can be found.

The most common seizure syndrome is the febrile seizure of childhood, affecting up to 5 percent of children, with a family history as a major risk factor.

**Clinical symptoms and signs.**

The most common seizures are **focal** or **partial**, that is, they begin (as in Case 2) in a localized cortical area. The clinical manifestation of the seizure depends upon the function of the cortical area involved, e.g., seizures beginning in the motor cortex cause contralateral twitching, in the visual cortex flashing lights, in the limbic cortex the experience of nausea, fear, or memories. The subjective "warning" of a seizure or aura reported by some patients actually represents the start of the attack, often identifies the cortical site of seizure onset, and is a reliable indication of the focal nature of the seizure.

Seizures which stop after such experiences are called simple partial seizures, while attacks which start with or proceed to altered consciousness or start with it are called **complex partial** seizures. Complex partial seizures are the most common type of focal seizure. Patients usually remain seated or standing, stare or look around, and often smack their lips, fiddle with their clothing, or rub their bodies. These movements are called **automatisms** and are the same in each seizure, in each patient. Focal seizures last only a minute or two, and are stereotypical for each patient.

If the focal seizure activity spreads throughout the brain, the result is a **tonic-clonic seizure**, also known as a **grand mal** or **generalized** seizure. The tonic-clonic seizure
starts with stiffening of the body and limbs ("tonic"), followed within half a minute by bilaterally synchronous jerking ("clonic") of the limbs and face. Respirations are halted or ineffective, and cyanosis is common. The clonus usually slows, then stops abruptly. The entire seizure usually lasts less than two minutes, although shocked observers may often offer an exaggerated "five minutes" estimate of its length. Reactive hyperventilation, excessive salivation, and confusion or drowsiness are often seen postictally, resolving over 10–30 minutes.

Consciousness is invariably lost during a tonic-clonic seizure, with amnesia for the tonic-clonic movements, and disorientation and sleepiness during recovery.

The most common non-focal seizures are an absence or petit mal seizures, which consist of abrupt immobility and loss of awareness (in effect, loss of continuity of consciousness), usually lasting no more than 15 seconds, with immediate recovery of mental functions after the attack. Patients themselves may be unaware of these brief seizures. Absence attacks occur mainly in children.

Another common nonfocal seizure type is the myoclonic seizure, which consists of sudden, bilateral jerks of the arms. Like absences, they last only a few seconds, and have no warning. Both absence and myoclonic seizures may be repetitive, culminating in a tonic-clonic seizure.

**Common epilepsy syndromes**

**Febrile seizures** are common, age-specific, symptomatic seizures with a high recurrence rate in the individual and the family. Seen mainly between 18 months and 2 years, they are usually brief, tonic-clonic seizures triggered by rapid rise of temperature, as may occur in roseola infantum. Chronic antiepileptic drugs are not indicated. Parents should be instructed to use cool baths and acetaminophen at the first sign of fever.

Simple febrile seizures do not occur after the age of 5 years.

**Infantile spasms** or "salaam" attacks are brief motor seizures consisting of sudden flexion or extension of the neck, trunk, or limbs. This is an age-related seizure type, usually limited to the ages of 6 months to 2 years. Infantile spasms usually occur many times daily. Although they may occur in healthy infants, many children with infantile spasms have pre-existing cerebral damage, and most of them show developmental delay with or without chronic epilepsy as they mature. Neurological consultation is generally indicated, both for treatment and for elucidation of the cause of the syndrome, e.g., tuberous sclerosis.

**Childhood absence epilepsy** is a benign genetic disorder, which usually begins between 5 and 10 years of age with typical petit mal seizures. Tonic-clonic seizures may occur several years later. The great majority of cases go into permanent remission by young adulthood, when medication may be stopped.
Benign Rolandic epilepsy is a common epileptic syndrome of childhood beginning between 5 and 10 years of age. Typically a healthy child has infrequent nocturnal tonic-clonic seizures, or seizures beginning with facial twitching. A family history of similar attacks or of febrile seizures is common. A correct diagnosis is important, both for appropriate treatment (see below) and because the prognosis of complete remission by the end of puberty may be given to the parents with confidence.

Juvenile myoclonic epilepsy is another common epilepsy syndrome. Onset is usually between 10 and 20 years with bilateral myoclonic jerks of the arms, but the condition usually comes to the attention of the physician only after the first tonic-clonic seizure occurs, usually in the early to late teens. Most attacks happen shortly after arising in the morning, and may be provoked by lack of sleep or alcohol ingestion. Although usually easily controlled by treatment (see below), juvenile myoclonic epilepsy is thought to be a lifelong condition.

Even when presenting as tonic-clonic seizures without warning or apparent focal onset, virtually all adult-onset epilepsies are characterized by seizures beginning focally. Many are symptomatic of significant focal cerebral pathology. Unprovoked seizures in an adult are therefore an indication for MR scanning of the brain.

In all cases, taking a careful history of the attack from the patient and whenever possible from a witness is the key to an accurate diagnosis of seizures. Important seizure characteristics are:

1. Time course: 1-2 minutes for focal and tonic-clonic seizures, 5–15 seconds for absence, myoclonic, and atonic seizures;
2. Stereotypy: although seizures and their auras may take many forms, in the single patient seizures do not vary from one to another;
3. Testimony of a witness, as with syncope, may be vital, e.g., the patient may be unaware of loss of responsiveness or automatisms during a complex partial seizure.

Diagnostic Pitfalls

Episodes of loss of consciousness without loss of postural tone are almost always complex partial seizures in adults, but are commonly absences in children. Misdiagnoses are common, but a careful history is almost always diagnostic. The distinction is important, as treatments of these seizure types may differ.

Table 1. Differential features of complex partial and absence seizures

<table>
<thead>
<tr>
<th>Complex Partial</th>
<th>Absence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aura</td>
<td>Sometimes</td>
</tr>
<tr>
<td>Duration</td>
<td>0.5 - 2 minutes</td>
</tr>
<tr>
<td>Behavior</td>
<td>Motionless or Automatisms</td>
</tr>
</tbody>
</table>
Syncope with accompanying twitching of the limbs is often misdiagnosed as epilepsy. Children and adolescents are at highest risk, and attacks are situational. A careful history of the usual presyncopal symptoms usually makes the diagnosis clear.

Breath-holding attacks in children are easily diagnosed with a good history. They usually occur around 2 to 3 years of age, and usually follow angry crying. The child suddenly stops, becomes cyanotic and apneic, and then slumps unconscious. There is also a pallid form, often triggered by minor head trauma. The child turns pale and becomes briefly unconscious and apneic. Recovery from both forms is rapid.

Panic attacks are usually accompanied by typical emotional and autonomic symptoms: some combination of fear, a feeling of impending death, chest pain, palpitations, shortness of breath, tingling in the hands or lips, weakness, tachycardia or sweating. Attacks usually last a few minutes but may recur continuously or repetitively for hours.

Pseudoseizures are non-epileptic episodes which behaviorally mimic various types of seizures. They are not true seizures, however, and are most commonly symptoms of a conversion disorder. The diagnosis should be considered in patients who fail antiepileptic therapy; referral to a neurologist is indicated.

The physical examination in the patient with epilepsy is often normal. The neurological examination and developmental profile in most of the common genetic epilepsies, for example, are typically normal.

Adults with new onset seizures should be carefully examined for signs of focal cerebral dysfunction. Children should be scrutinized for skin changes typical of neurocutaneous syndromes such as Sturge-Weber disease or tuberous sclerosis.

Diagnostic Tests

The electroencephalogram (EEG) records electrical potentials generated by neurons in the cerebral cortex, and in patients with epilepsy often showing interictal cerebral activity called spikes or epileptiform discharges.

The EEG is best used to:

1. Confirm a diagnosis of the type of seizure disorder. When positive, for example, it clearly distinguishes between absence and complex partial seizures. Myoclonic epilepsy and benign Rolandic epilepsy also produce characteristic EEG patterns.
2. Assess the efficacy of antiepileptic drug (AED) therapy in patients with absence seizures; discharges generally stop or are greatly attenuated by successful treatment. Other types of seizure disorders may continue to show spikes, despite clinically adequate treatment.
3. Assess the prognosis for withdrawal of antiepileptic drugs. (See below.)
Although traditionally used in diagnosis, the EEG does not meet modern criteria for an accurate diagnostic test for epilepsy. It is diagnostically insensitive in many types of epilepsy, a single EEG giving false negative results in 30 percent to 40 percent of cases of focal seizure disorders. Diagnostic sensitivity for absence and myoclonic epilepsies is better, reaching 80 percent to 90 percent.

The diagnostic specificity of EEG abnormalities is also unsatisfactory: inaccurate, "over-read" EEG readings are distressingly common, especially in children. In addition, some children or adolescents who have never had a seizure but who have a positive family history of epilepsy have true epileptiform discharges on their EEGs. One to three percent of adults without epilepsy may also have EEG spikes. Because an incorrect diagnosis of epilepsy may have profound effects on self-esteem, employment, medical insurance availability, driving, and long-term use of pharmaceuticals, such false positive rates make the EEG inappropriate as the sole or major basis for a diagnosis.

The 24-hour ambulatory EEG is not indicated in most epilepsies. The test is most appropriately used in the diagnosis of frequent (every day or two), episodic, possibly ictal symptoms which need to be "caught" on the EEG for diagnosis.

MR brain imaging with and without contrast ($1000-$2000) is indicated for every newly diagnosed seizure disorder, with the exception of those known to be genetic and unassociated with detectable cerebral pathology, eg, benign Rolandic epilepsy, childhood absence epilepsy, or juvenile myoclonic epilepsy. MR scanning is more sensitive than CT for certain neoplasms, tuberous sclerosis, small vascular malformations, and cortical migrational anomalies.

Treatment

Many seizure disorders can be successfully treated by primary care doctors. In most cases this includes initiation of treatment.

An accurate diagnosis of the type of seizure is essential, since it dictates the appropriate choice of antiepileptic drug (AED).

For first-line therapy, not necessarily in order of choice, see Table 2.

Table 2. Treatments according to seizure type

**Simple partial, complex partial, tonic-clonic seizures**
- carbamazepine (Tegretol XR®, Carbatrol®)* **
- gabapentin (Neurontin ®)
- lamotrigine (Lamictal®)
- levetiracetam (Keppra®)
- oxcarbazepine (Trileptal®)**
- phenytoin (Dilantin®)* **
- pregabalin (Lyrica®)
primidone (Mysoline®)* **
tiagabine (Gabitril®)
topiramate (Topamax®)
valproate (Depakote®)*
zonisamide (Zonegran®)**

Absence, myoclonic, atonic seizures
valproate *
ethosuximide (Zarontin®)*
lamotrigine
zonisamide

*older, less costly drugs

**available as generic preparation

Other Principles of choice

- Phenobarbital may be appropriate in the neonatal period, but is best avoided for chronic use due to side effects such as sedation, cognitive dysfunction, and, in children, behavior abnormalities.
- Valproate, especially in combination with other AEDs, is generally not used in infants under 2 years of age because of potential hepatic toxicity.
- Valproate is absolutely contraindicated in pregnancy due to at least a 5 percent association with neural tube defects, and is best avoided in young women.
- Ethosuximide is effective for absence seizures only.
- Phenytoin is better used in adults than children, in whom it more commonly has significant unwanted effects such as acne, gum hypertrophy, hirsutism, and possibly coarsening of facial features.

Using AEDs

1. In general it is good to aim for the lower therapeutic level of the AED that you choose.
2. If seizures recur, slowly increase the dose until seizures are controlled or the patient reports dose-related side effects (Table 4).
3. If the first AED fails, cautiously add a second and follow the same dosing strategy.
4. Monotherapy is preferred to polytherapy; if the second drug is effective, taper the ineffective one.
5. Use "therapeutic blood levels" only as guides; some patients are well controlled at lower levels, others are comfortable at higher levels, and need the higher dosage for seizure control.
6. Prices of AEDs vary widely, from about $30 per month for phenytoin; $100 for carbamazepine; $130 for valproate; to several hundred dollars per month for most of the other drugs.
Because their therapeutic doses are very close to their toxic doses, and because patient compliance is vital to successful therapy, management of AEDs often requires careful attention to drug kinetics and interactions. Dosing frequency, for example, should be based on the drug's half-life (Table 3), avoiding more than three times per day dosing.

Table 3: Average half-lives of common AEDs (hours)

<table>
<thead>
<tr>
<th>AED</th>
<th>Half-life (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine</td>
<td>8</td>
</tr>
<tr>
<td>ethosuximide</td>
<td>12</td>
</tr>
<tr>
<td>gabapentin</td>
<td>6</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>12 used with inducers</td>
</tr>
<tr>
<td></td>
<td>20 used with inducer + valproate</td>
</tr>
<tr>
<td></td>
<td>70 used with valproate</td>
</tr>
<tr>
<td>levetiracetam</td>
<td>16</td>
</tr>
<tr>
<td>oxcarbazpine</td>
<td>12</td>
</tr>
<tr>
<td>phenytoin</td>
<td>24</td>
</tr>
<tr>
<td>pregabalin</td>
<td>8</td>
</tr>
<tr>
<td>primidone</td>
<td>6</td>
</tr>
<tr>
<td>tiagabine</td>
<td>6</td>
</tr>
<tr>
<td>topiramate</td>
<td>10</td>
</tr>
<tr>
<td>valproate</td>
<td>8</td>
</tr>
<tr>
<td>zonisamide</td>
<td>12</td>
</tr>
</tbody>
</table>

Some AEDs have clinical effects on the hepatic P450 enzyme system, which metabolizes AEDs and other drugs, so interactions are often significant. Those which induce greater enzyme activity may reduce the serum levels of other drugs, and those which inhibit them may raise levels. Enzyme-inducing AEDs, for example, may impair the effectiveness of oral contraceptives or alter the effect of anticoagulants.

Inducers:
- carbamazepine
- phenytoin
- primidone
- topiramate

Inhibitor:
- valproate

Dose related side effects of the AEDs are predictable, occur in nearly everyone who takes a high enough dose, and are reversible by lowering the dose. Idiosyncratic side effects are
uncommon to rare, unpredictable, unrelated to dose, and sometimes serious. Most AEDs can cause a hypersensitivity syndrome with rash. Other characteristic side effects are listed in Table 5.

**Table 5.**

<table>
<thead>
<tr>
<th>AED</th>
<th>Dose Related</th>
<th>Idiosyncratic or chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>carbamazepine</td>
<td>diplopia, nausea</td>
<td>neutropenia, hyponatemia</td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td>blurred vision</td>
<td></td>
</tr>
<tr>
<td>phenytoin</td>
<td>ataxia, dizziness,</td>
<td>gingival hyperplasia, acne, hirsutism</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>blurred vision, insomnia</td>
<td>severe skin rash</td>
</tr>
<tr>
<td>levetiracetam</td>
<td>cognitive changes</td>
<td>weight gain</td>
</tr>
<tr>
<td>primidone</td>
<td>drowsiness, ? libido</td>
<td></td>
</tr>
<tr>
<td>valproic acid</td>
<td>fine tremor</td>
<td>weight gain, alopecia, hepatitis*</td>
</tr>
<tr>
<td>gabapentin</td>
<td>drowsiness</td>
<td>weight gain</td>
</tr>
<tr>
<td>topiramate</td>
<td>cognitive changes</td>
<td>numb face, hands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>weight loss, nephrolithiasis</td>
</tr>
<tr>
<td>zonisamide</td>
<td>cognitive changes</td>
<td>weight loss, nephrolithiasis</td>
</tr>
</tbody>
</table>

*rare, mainly seen in children under 2 years of age on polytherapy

Many epilepsies remit in time. The rate varies between 80 percent–90 percent (for childhood absence) and as low as 0 percent (for juvenile myoclonic epilepsy), with most focal epilepsies somewhere in between. Except in juvenile myoclonic epilepsy, after 2 years of successful therapy discontinuation of AEDs should be considered. Recurrence rates average about 30 percent.

**Referral to a neurologist**

If there is any doubt about the *initial diagnosis*, or about the specific type of epilepsy, a diagnostic consultation may be appropriate, and inappropriate tests avoided. Most patients or parents facing a new diagnosis of seizure disorder have questions about the implications of the condition, treatment, genetics, driving, and prognosis, which may often best be addressed by the neurologist.

If two AEDs *fail to control* the seizures, consultation by a neurologist is indicated to review and confirm the diagnosis and to offer an alternative treatment plan. Surgical treatment is thought to be appropriate after the failure of three or four AEDs, and can prevent irreparable educational, vocational, and psychosocial damage. Such medically intractable seizures are estimated to occur in 10 percent of people with epilepsy.
All of the AEDs are thought to increase the risk of fetal malformations or developmental delay if used during pregnancy. How or whether to take AEDs during pregnancy should be discussed with every woman or girl of childbearing potential prior to pregnancy. The neurologist can usually provide the most recent relevant facts, advise the least risky AED therapy, and provide reassurance that will enable the patient to make informed choices.

*Tapering AEDs* after a two-year remission of most epilepsies should be considered, but may be fearsome for the patient and the physician. Since an unsuccessful taper can have negative implications for the patient's job, driving, and safety, a thorough discussion with a neurologist of the relative risks and benefits of stopping AEDs can be provided in a single visit.

**Psychosocial impact**

A diagnosis of epilepsy may have significant effects on self-esteem, employment, and mood. Depression has been reported in up to 30 percent of patients, and is under diagnosed. Cognitive abnormalities in children are common, and many adults complain of memory deficits. The inability to drive can be socially and economically crippling. The mortality rate in uncontrolled epilepsy is at least double that expected in peers, and occurs most commonly from sudden death in a seizure, or drowning.

**Utilization of resources**

The *Epilepsy Foundation of America* [www.efa.org or 800-332-1000] has regional offices in most areas of the US, where group and individual counseling, help with insurance and employment problems, information about epilepsy, and other supports are free. These offices also will provide the names of local neurologists or centers with particular expertise in epilepsy.

The Epilepsy Pregnancy Registry at Harvard is an on-going study of the effect of AEDs on the exposed fetus, gathering vital data on the comparative effects of these drugs hitherto unavailable. All women beginning pregnancy while taking an AED should be informed of the voluntary registry and provided with its phone number, 1-888-233-2334.

**Strokes and Transient Ischemic Attacks**

**Epidemiology**

*Cerebrovascular accident* (CVA) is the *third most common cause of death* in the United States and causes more physical and mental disability than any other neurological disorder. Although the most obvious risk factor for stroke is advancing age, strokes can occur in young adults or even in children. In the young, additional risk factors include migraines, intravenous drug use or the use of cocaine or amphetamines by any route, AIDS, and pregnancy.
Hypertension is the most important modifiable risk factor for stroke. Even small reductions in blood pressure produce detectable reductions in stroke incidence. This also includes lowering of systolic hypertension (>140) in the elderly. Careful, skillful management of hypertension is the single most important contribution to stroke prevention that the primary care physician can make. Hypertension is also an important risk factor for multi-infarct dementia, which, once established, is untreatable.

Atrial fibrillation, whether or not it is due to rheumatic heart disease, is an independent risk factor for embolic stroke. If the heart rhythm cannot be normalized, anticoagulation can lower the incidence of stroke (see below).

Cigarette smoking roughly doubles a person's risk of stroke, an increase that is reversible within five years of smoking cessation. The combination of hypertension and cigarette smoking is associated with a stroke risk that is greater than the sum of the individual risks.

Other risk factors include diabetes, a family history of stroke, occurrence of a previous stroke, high cholesterol level, heavy alcohol use (particularly for intracerebral hemorrhage), sedentary lifestyle, hypercoagulable states, and anticardiolipin antibodies. Some of these conditions are also modifiable through counselling and other interventions.

Transient ischemic attacks (TIAs) are a "risk factor" for impending stroke. For this reason, urgent diagnosis and proper preventive treatment are important.

Clinical symptoms and signs

Essential features of a cerebrovascular event are:

1. abrupt onset, within seconds to minutes;
2. a focal neurological deficit such as hemiparesis or aphasia;
3. a clinical pattern conforming to a vascular territory.

Most strokes are ischemic, that is, they are due either to blockage of a cerebral artery from a thrombus, which develops at a site of atherosclerotic narrowing or from a fatty deposit (plaque), or to platelet emboli from such a site. Emboli originating in the heart are usually thrombotic in nature. Such ischemic strokes can involve the territory of a major artery such as the middle cerebral (the most common such site), or may be small, deeply located, and even asymptomatic. Even tiny strokes can cause significant clinical symptoms, eg, hemiplegia, if they involve a vital area such as the internal capsule. Multiple small strokes are one of the major causes of chronic, progressive dementia, accounting for 30 percent in some studies.

The symptoms of a transient ischemic attack (TIA) usually resolve within five to 30 minutes. TIAs are thought to be caused by platelet emboli arising at an arterial plaque or in the heart. Prompt diagnosis of a TIA and its cause are urgent, because of the high early
stroke risk, up to 10 percent within the first 90 days with most of the risk within the first week.

Hemorrhagic stroke may appear clinically identical to an ischemic stroke. Large intrahemispheric hemorrhages, however, more commonly produce initial loss of consciousness which is usually associated with a flaccid hemiplegia, often with tonic eye deviation.

Common neurological features of cerebrovascular events involving the anterior (carotid) or posterior (vertebro-basilar) circulation are found in Table 6. When all of the patient's abnormal neurological findings "fit" onto one side of the cerebrum (eg, right-sided hemiparesis, right-facial paresis, aphasia), the CVA involves the anterior circulation. When the findings are "crossed," that is, they involve both sides of the body, the brainstem is usually the site of the event and the posterior circulation is involved (eg, numbness of the right side of the face and the left side of the body).

Table 6: A guide to localization

Carotid circulation

- monocular visual loss ("amaurosis fugax")
- hemiparesis
- hemi-sensory loss or numbness
- homonymous hemianopsia
- aphasia
- apraxia
- conjugate eye deviation

Vertebral-basilar circulation

- diplopia
- vertigo
- ataxia
- limb tremor/incoordination
- dysarthria
- "crossed" sensori-motor loss*
- homonymous hemianopsia
- nausea

Loss or depression of consciousness can occur in the context of severe stroke involving the brainstem or most of the left hemisphere, but as an isolated sign or as a transient phenomenon it is generally not suggestive of a vascular event.

The physical examination of the patient with suspected TIA or stroke should include a careful cardiovascular exam (murmurs, arrhythmias, signs of peripheral vascular disease),
and neurological exam (limb weakness, facial asymmetry, sensory deficit, monocular or homonymous visual loss, carotid bruits).

A CBC, metabolic panel, prothrombin and thromboplastin times, fasting lipid profile, and EKG should be done (20 percent of strokes are associated with acute myocardial infarction). A brain CT will rule out or detect intracranial hemorrhages. Urgent MR with diffuse weighted imaging is increasingly available, and can identify ischemic strokes at a very early stage, even before detection by CT or standard MR. Neck pain and/or a history of localized trauma, especially in the young, may raise the question of carotid dissection; CT angiography or MRA (magnetic resonance angiography) are appropriate investigations.

If cardiac embolism is suspected on the grounds of previous myocardial infarct or valvular disease, a cardiac echo exam is indicated. When large vessel disease is suspected, a carotid Doppler ultrasound examination should also be done, along with a transcranial Doppler. The latter are noninvasive tests which measure the presence and speed of bloodflow in the carotid, vertebral, and large intracranial arteries. Magnetic resonance angiography (MRA) is noninvasive, and gives somewhat more detailed information about these and some of the smaller arteries. It can be done at the time of a routine MR scan, the most sensitive imaging test for stroke. MR scans often reveal asymptomatic cerebral infarctions in patients with TIAs.

**Evaluation and treatment of TIAs.**

Patients recounting a history compatible with transient ischemia should be treated urgently. Those with symptoms in the anterior circulation have a risk of completed stroke risk of up to 20 percent within the first month, with the highest risk within the first 72 hours.

Many TIAs and ischemic strokes are thought to be caused by clumps of platelets which embolize from areas of stenosis in the carotid artery. Carotid stenting or endarterectomy has been shown to be more effective than medical therapy when tight carotid stenosis is present. For TIAs in the vertebrobasilar circulation, or when surgically treatable carotid stenosis is not found in patients with anterior circulation TIAs, medical therapy is indicated.

Aspirin can reduce the risk of stroke in patients with TIAs, and is also recommended for acute ischemic stroke. The usual dose is 50 to 325 mg per day. For TIAs some stroke experts recommend clopidogrel (Plavix®) or a combination of long-acting dipyridamole and aspirin (Aggrenox®). The treating physician should be familiar with the side effects of the drugs.

When a cardiac source of thrombotic embolization is found, anticoagulation is indicated. Coumadin producing an INR of 2 to 3 has been found to reduce the incidence of stroke in patients with atrial fibrillation, even when TIAs have not occurred.
For the long term, modification of risk factors should be stressed, i.e., control of hypertension, statins for hypercholesterolemia, weight management, control of serum glucose, regular exercise.

This is an area which is evolving quickly. If available, consultation with a neurologist or stroke specialist may help the patient receive the most effective treatment for his or her specific type of vascular disease.

**Evaluation for Hyperacute Stroke Treatment**

Tissue plasminogen activator or tPA has been approved for the treatment of acute stroke within the first three hours of onset, and if and only if certain other clinical indicators are present. The risk of hemorrhage, including cerebral hemorrhage, is significant, and tPA is best used in consultation with a neurologist or trained stroke or emergency physician. The drug improves the chance of a good outcome only in patients treated within three hours of a stroke, so that its use generally depends upon the efforts of a well-organised, dedicated emergency team.

Required tests include CBC, metabolic panel, EKG, and brain CT. Charting the neurological examination according to the NIH Stroke Scale ensures that the patient's deficit is neither too mile nor too severe to qualify for tPA.

A plain computed tomograph (CT) of the head should be done immediately, to look for hemorrhage or neoplasm. An acute ischemic stroke may not be seen well, or at all, on an early CT scan.

**Initial management.** At this point nearly all patients with an apparent CVA will be admitted to a hospital. The presence or absence of acute bleeding on CT will determine whether initial intervention can be done, often suggests the cause of the stroke, and in some cases forecasts the prognosis. For example, small, basal ganglia hemorrhage is often associated with chronic hypertension, can cause acute hemiplegia, but may have a relatively good outcome. A large hemispherical ischemic infarct which is seen on an initial CT scan may be followed within 48 hours by cerebral edema causing worsening focal signs, coma, and death. A large hemispherical or cerebellar hemorrhage may cause death immediately or within hours from intracranial hypertension or pressure on the brainstem. Neurosurgical intervention for such hemorrhages to relieve intracranial pressure, although infrequently done, can be life saving and should be considered by consulting a neurosurgeon.

Reduction of malignant hypertension (>220/120) is vital, because it can cause focal neurological symptoms and signs, which usually resolve when blood pressure is reduced. But overly aggressive lowering of blood pressure can reduce cerebral perfusion and cause worsening of the neurological symptoms, particularly in the context of significant cerebral atherosclerosis and the abnormal autoregulation of cerebral blood flow caused by a stroke. If the patient is known to be hypertensive, and malignant hypertension is not present, urgent lowering of blood pressure is not necessary.
Steroids as a treatment of ischemic stroke have not been found to be helpful in reversing the symptoms and signs of stroke.

If intracranial hemorrhage seems unlikely or has been ruled out by CT, 300 mg aspirin should be given. Anticoagulation in the face of an acute stroke may be indicated, depending upon the cause and the risk of subsequent stroke, and is best considered with the aid of a neurologist.

Hyperglycemia has been associated with worse stroke outcomes, and should be corrected. For the same reason fever should be lowered. Proper hydration should be managed carefully.

Consultation with a stroke service has been found to be associated with better outcome, and can be cost-effective. In addition, consultation with physical therapy, occupational therapy, and speech therapy are often useful.

Subsequent Diagnostic tests. Unless another cause of the stroke is found, a carotid ultrasound examination or magnetic resonance angiogram should be done to look for evidence of carotid artery occlusion, stenosis, or dissection. This is not merely to seek or confirm the cause of the current stroke, but to look for a preventable cause of the next one. Cerebral angiography is not indicated unless the carotid ultrasound is suggestive of significant carotid stenosis. A normal carotid Doppler examination makes surgically treatable carotid stenosis unlikely. If a cardiac embolic source is suspected and echocardiography is unrevealing, the addition of transesophageal leads is often helpful.

MR scanning with contrast is sensitive for ischemic stroke, particularly for lacunar infarcts, and is indicated if the acute CT scan is uninformative.

Referral.
Prompt initiation of physical and/or speech therapy is important for stroke outcome. Patients with significant residual disability should be referred to Physical Medicine, and evaluated for inpatient or outpatient rehabilitative therapy. Many patients with stroke have dysphagia which may not be obvious, so a swallowing evaluation is generally indicated. A home evaluation by an occupational therapist is valuable for patients with incomplete recovery, to adapt the home environment to the patient's disability.

The occurrence of a stroke is a risk factor for subsequent stroke. Referral to a neurologist or stroke specialist is appropriate both for management of acute severe stroke, and for accurate diagnosis of the cause of the stroke and preventive management.

Margin Teaching Points

1. An acute stroke is a neurological emergency. Immediate evaluation of the patient and formulation of a working diagnosis and treatment plan are essential.
2. CT scans can usually be done on a STAT basis and can rule out or display acute cerebral hemorrhage.
3. Malignant hypertension should be treated as an emergency. Less dramatic increases in blood pressure should not be treated.

**Psychosocial impact.** Both the patient and the family need information about what has happened, and continuing reports about the patient's progress or lack of it. Usually no clear prognosis can be provided during the first 24 hours, unless massive cerebral hemorrhage has occurred.

In the case of a completed stroke, the pace of recovery slows quickly over the subsequent days and weeks, and in most cases only very gradual, mild functional improvement occurs after the first three months. Post-stroke depression is very common, especially after left-sided hemispheral stroke, and is under-diagnosed.

**Utilization of community resources.** The American Stroke Association (ASA) [www.strokeassociation.org] is a good source of information about prevention of stroke, and coping with its aftermath. Raising public awareness of the signs and symptoms of ischemic "brain attacks" is a goal of the ASA and the American Academy of Neurology, so that patients may be evaluated quickly enough for the use of tPA if appropriate.

**Some Special Cases**

Strokes can occur in young adults and even in children. Risk factors include migraines, pregnancy, renal failure, lupus, AIDS, intravenous drug use or the use of amphetamines and cocaine by any route. The diagnostic workup of the patient under 50 should include serum for HIV, antiphospholipid antibodies, proteins S and C, antithrombin III, hemoglobin electrophoresis, and an autoimmune profile. Localized neck pain or recent trauma should raise the possibility of carotid or vertebral artery dissection, generally detectable by CT angiography or MRA. A four-vessel angiogram should be considered for the young person who has an intracerebral hemorrhage, to look for arteriovenous malformation or aneurysm.

**Questions**

1. The most important diagnostic aid in the diagnosis of epilepsy is the:
   A. electroencephalogram
   B. history of the attacks
   C. MRI head scan
   D. family history
   E. B and C

2. Shaking or twitching in an attack of loss of consciousness:
   A. may occur during vasovagal syncope
   B. is diagnostic for epilepsy
   C. occurs in all seizure types
   D. rules out a diagnosis of syncope
   E. A and C
3. Syncope caused by cardiac arrhythmias is characterized by:
   A. vertigo at the start of an attack
   B. sweating and nausea at the start of an attack
   C. loss of consciousness lasting 1 to 2 hours
   D. sudden loss of consciousness
   E. may be associated with all of the above

4. Complex partial seizures:
   A. are the most common focal seizure type
   B. may included stereotyped movements of the lips or body
   C. usually last 30 seconds to 2 minutes
   D. may be caused by tumors or other focal brain lesions
   E. all of the above

5. Early morning jerks of the limbs, tonic-clonic seizures, and good therapeutic response to valproate are characteristic of:
   A. juvenile myoclonic epilepsy
   B. salaam attacks
   C. atonic seizures
   D. many focal epilepsies
   E. any of the above

6. In suspected epilepsy, the electroencephalogram:
   A. may help confirm the type of seizure disorder
   B. is rarely useful
   C. should be repeated every two years
   D. should be run for at least 24 hours
   E. A and D

7. A newly diagnosed focal epilepsy:
   A. means a lifetime of medication
   B. should be followed by an MRI scan of the head
   C. may be treated by ethosuximide
   D. requires a search for other cases in the family
   E. none of the above

8. Effective drug treatment for tonic-clonic seizures may include:
   A. carbamazepine
   B. lamotrigine
   C. clonazepam
   D. valproate
   E. all but one of the above

9. Symptoms occurring at the start of a syncopal episode include:
   A. nausea
   B. sweating
   C. fading of vision
   D. none of the above
   E. all of the above

10. Risk factors for stroke include:
    A. older age, hypertension, and HIV
    B. older age, seizures, and atrial fibrillation
C. hypertension, use of phenytoin, and migraine
D. all of the above
E. none of the above

11. Common symptoms of an anterior circulation (carotid artery territory) stroke include:
   A. hemiparesis
   B. aphasia
   C. loss of sensation on one side of the body
   D. two of the above
   E. all of the above

12. The diagnosis of syncope, seizure, or transient ischemic attack is best made by:
   A. a 24 hour electroencephalogram
   B. an MRI of the brain
   C. a careful neurological examination
   D. a detailed history
   E. none of the above

13. The risk of stroke in patients with atrial fibrillation can be best reduced by:
   A. aspirin
   B. Coumadin
   C. either
   D. neither

14. An EKG in the patient with an acute stroke:
   A. is not cost-effective
   B. often reveals a myocardial infarction
   C. is indicated only if the pulse is irregular
   D. is irrelevant
   E. should not be done until the second day

15. An immediate CT scan of the head in the patient with a new stroke can identify:
   A. carotid stenosis
   B. intracerebral hemorrhage
   C. an acute lacunar infarction
   D. none of the above
   E. all of the above

Answers

1. B
2. A
3. D
4. E
5. A
6. A
7. B
8. E
9. E
10. A
11. E
12. D
13. B
14. B
15. B

Navigation

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Chapter 8 – Gait and Movement Disorders

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DEFINITION
The term "movement disorder" refers to the group of central nervous system diseases in which the control of movement is altered with relative preservation of strength, muscle bulk, and mechanical range of motion. Instead, there are changes in the patient's muscle tone, rapidity and smoothness of voluntary movements, or movements may occur involuntarily. Movement disorders are grossly segregated into hyperkinetic movements (tremor, dystonia, chorea etc.) and hypokinetic movements (Parkinsonian conditions).

EPIDEMOLOGY AND SCOPE OF THE PROBLEM AS A HEALTH CARE ISSUE
Movement disorders probably affect about 20 percent of the population. Restless legs syndrome accounts for half of this. Essential tremor is estimated to affect up to 5–10 percent of the population. Parkinson's disease in persons over the age of fifty is approximately 1 percent. However, some studies indicate that up to 10 percent of the population over age 60 have early symptoms not yet diagnosed as Parkinson's disease. Although early studies suggested that Parkinson's disease was more common in Caucasians, some prevalence studies comparing other racial groups and Caucasians in the same geographic areas have demonstrated approximately equal numbers. Other movement disorders may also be more common than previously thought. The various dystonias, especially spasmodic torticollis, may affect up to 0.4 percent population.

Although most movement disorders are not life threatening, they are certainly a threat to the patient's quality of life. The impact can be enormous, with loss of employment, inability to drive an automobile, and impairment in activities of daily living including personal hygiene. Most do not spontaneously remit so they become lifelong issues. In addition, physicians and patients often face a challenge in obtaining insurance coverage for treatment of these conditions, since many treatment modalities, both pharmacologic and surgical, are relatively new.

CLINICAL SYMPTOMS AND SIGNS
The motor control system is the part of the nervous system that integrates sensory input and organizes and directs motor output. The structures involved include proprioceptive sensory receptors in the muscles, the spinal cord, brainstem, cerebellum, thalamus, basal ganglia, and cerebral cortex (Figure 1).
The approach to the patient with a movement disorder is to first determine which aspects of motor control are clinically affected, and then to combine the cluster of symptoms and signs found into a specific diagnosis and etiology whenever such can be identified. Treatment is directed toward the individual symptoms as well as the underlying etiology.

Most movement disorders begin insidiously. A co-worker, spouse, or even child of the patient may notice the problem before the patient does. Patients may complain of "weakness" or "stiffness" in their muscles, or they may have noticed involuntary movements, such as tremors, twitches, or gross movements of their head or extremities. Symptoms may be noticed as they try to perform their routine activities, or may be present only at certain times, such as when walking, turning the head, or handwriting. Thus, in addition to testing strength, examination of the motor system should include testing of tone, kinesis, posture, observation for any spontaneous involuntary movements, and evaluation of coordination and gait with various provocative maneuvers. If the patient tells you that the abnormal movement occurs only with a certain activity or position, such as when writing, always try to reproduce it in your office (Table 1).

Table 1: Clinical signs of abnormal motor control

<table>
<thead>
<tr>
<th>Movement</th>
<th>Speed/Phenotype</th>
<th>Location</th>
<th>Hallmark Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest Tremor</td>
<td>4-6 Hz</td>
<td>Arms&gt;legs</td>
<td>Parkinson's disease</td>
</tr>
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</tr>
<tr>
<td><strong>Postural Tremor</strong></td>
<td>6-12 Hz</td>
<td>Hands</td>
<td>Essential Tremor</td>
</tr>
<tr>
<td><strong>Intention Tremor</strong></td>
<td>2-5 Hz</td>
<td>Arms/legs</td>
<td>Cerebellar lesions</td>
</tr>
<tr>
<td><strong>Dystonia</strong></td>
<td>Tonic Patterned</td>
<td>Any part</td>
<td>Torticollis</td>
</tr>
<tr>
<td><strong>Stereotype</strong></td>
<td>Slow, semi- rhythmic</td>
<td>Any part</td>
<td>Tardive dyskinesia Restless legs syndrome</td>
</tr>
<tr>
<td><strong>Athetosis</strong></td>
<td>Slow, irregular &quot;writhing&quot;</td>
<td>Proximal limbs</td>
<td>Brain lesion</td>
</tr>
<tr>
<td><strong>Chorea</strong></td>
<td>Fast, irregular</td>
<td>Any part</td>
<td>Huntington's disease</td>
</tr>
<tr>
<td><strong>Myoclonus</strong></td>
<td>Fast, Simple</td>
<td>Any part</td>
<td>Juvenile myoclonic epilepsy Cerebral hypoxia</td>
</tr>
<tr>
<td><strong>Tics</strong></td>
<td>Fast, Patterned</td>
<td>Face&gt;neck, shoulders</td>
<td>Tourette's syndrome</td>
</tr>
</tbody>
</table>

**Muscle tone** refers to the resting activity of agonist and antagonist muscles. Normally, no resistance should be felt when passively flexing and extending the patient's arm. When the legs are tested by lifting and letting go (in the supine position), the foot should drag on the bed and the whole leg should drop when released. Rigidity and spasticity are two types of increased tone indicating deficits in the basal ganglia or corticospinal tracts, respectively. Cogwheel rigidity refers to increased tone with a ratchety feel when passively moving a limb, as seen in Parkinson's disease. Tone can vary with certain extrinsic factors. Pain, for example will temporarily increase tone and even deep tendon reflexes, but this is usually to an equal degree in all four limbs. The inability to relax may artificially increase apparent tone. Muscle relaxants and antispasmodics, such as diazepam, carisoprodol, baclofen, and related agents will decrease tone symmetrically.

**Dystonia**, by definition, means a sustained abnormality ("dys-") in muscle tone ("-tonia"). Dystonia can be thought of as a sustained contraction of a group of muscles that produces altered posture of the head, neck, trunk, or limbs. There should be a consistent pattern. Usually this is because of an imbalance of resting tone between agonist and antagonist muscle groups in the same limb, or in the neck. Patients may notice pain before the dystonia becomes visibly apparent. Involuntary movements, especially tremors, are sometimes associated with dystonias. Usually volitional movement initiates or augments the dystonia, although fixed dystonias at rest also occur, usually associated with brain injury. As the dystonia worsens and begins to interfere with daily activities, patients may develop certain compensatory maneuvers. For example, a patient may change the way they hold a pen to overcome hand dystonia known as writer's cramp.

**Tremor** is the most common presenting symptom in patients with movement disorders. It is a rhythmic oscillation around one or more focal points, usually a joint. Tremor may be seen in the head, face, especially the chin, one or both arms or legs. Tremor occurs when...
agonist and antagonist muscles supplying the same limb contract involuntarily. They may alternate or actually be synchronous. Tremors vary in frequency, anatomy, quality, and precipitating actions. With loss of neuronal function in the basal ganglia, cerebellum, or certain other structures involved in motor control, this balance is lost, and tremor occurs (Figure 2).

Figure 2: Finger-to-nose test. A. Normal: Smooth trajectory throughout movement. B. Cerebellar hemisphere dysfunction: Tremor increases in amplitude as finger approaches target. C. Parkinsonian: Tremor may be present at initiation of movement, but smoothes out as finger approaches target. D. Essential tremor: Low-amplitude fast tremor throughout trajectory, may worsen as finger approaches target.

Tremor should be observed at rest (muscle not in use), with the arms held forward, and with directional movements, such as the finger-to-nose task. The three main types of tremor and their treatment will be discussed later in this chapter.

There are various types of tremor, which point the neurologist to particular anatomical structures within the central nervous system. Because of the complex neurochemical pathways subserving the basal ganglia, localization is important in determining appropriate treatment (Table 3).
Table 3: Classification and differential diagnosis of tremor

**Rest Tremors**

- Parkinson's disease
- Other Parkinsonian syndromes
- Midbrain (rubral) tremor: rest<postural/action
- Wilson Disease
- Essential Tremor-only if severe: rest<postural/action

**Action Tremors**

Postural

- Essential tremor (familial or sporadic)
- Task specific tremors (i.e. isolated writing tremor)
- Orthostatic tremor
- Physiological tremors
  - Endocrine: Hypoglycemia, thyrotoxicosis, pheochromocytoma, adrenocorticosteroids stress, fatigue, anxiety
  - Drugs: beta, agonists, dopamine agonists, amphetamines, lithium, SSRI neuroleptics, theophylline, caffeine, valproic acid
  - Toxins: alcohol withdrawal, mercury ("hatters shakes"), lead, arsenic, others

Intention (action) tremors:

- Cerebellar tremor (postural<action)
  - Focal cerebellar or brainstem lesions due to multiple sclerosis, trauma, tumor
    - Drugs and Toxins: Chronic Dilantin®, mercury, others

Miscellaneous rhythmic movement disorders (not technically tremor)

- Asterixis, myoclonus, epilepsy partialis continua, myorrhythmia, others

**Myoclonus** is a rapid, very brief (<.25 seconds), simple contraction. It may affect any body part, may be rhythmic or non-rhythmic. Although myoclonus can be seen with several epilepsy syndromes, metabolic derangements (hepatic or renal) and brain ischemia are the most common etiologies.

**Asterixis, also called negative myoclonus**, refers to sudden loss of tone while attempting to maintain a limb in a certain position. Typically, it appears as a "flapping" of the hands when the patient holds the arms out with palms extended as if halting traffic. Asterixis is a classic sign of hepatic encephalopathy, hence the term "liver flap."
**Kinesis** simple means movement. Bradykinesia means slowed ("brady-") movement and hypokinesia means small movements. These are characteristic of Parkinson's disease. Observe the patient performing various tasks, such as opening and closing the fist or finger-tapping rapidly. PD patients have slowness, and more specifically smallness to these. Often, the amplitude will start normally then decrement. Tapping may stop altogether, then restart at a larger amplitude only to decrement again. This is much more specific for PD compared to general slowness, which could be seen in many disorders. Other PD symptoms and signs such as the "masked facies" (hypomimia), micrographia are consequences of hypokinesia. Retropulsion on pull testing (backward movements caused by the inability to move the feet fast or big enough) is also a sign of hypokinesia.

**Dyskinesia** technically means any disorder of kinesis. The term is used to describe multiple phenotypes, usually hyperkinetic. It is most commonly used in association with tardive syndromes (below), and levodopa (Sinemet®) when used for PD.

**Chorea** refers to involuntary movements, which are rapid and unpredictable. Each movement involves one part of the body at a time, but "skips" from one part to another in seemingly random fashion.

**Athetosis** is a pattern of dyskinesia in which the random involuntary movements occur slowly, seeming to "flow" rather than "skip" to different parts of the body. Athetosis and chorea may actually represent different severities of the same pathophysiology, but have traditionally been individually defined.

**Tics** are another type of involuntary movements which differ from chorea in that they involve smaller groups of muscles, are more "jerky" in quality, and tend to be stereotyped, recurring with the same or a very similar pattern in the same muscles. Tics are often partially suppressible, and may involve an urge to tic, which grows if the tics are suppressed. They are also suggestible and increase when they are discussed. Tics are most commonly seen in the face but can occur anywhere.

**Ataxia** means any breakdown of smooth, coordinated movement. It is often segregated into limb ataxia and gait ataxia. When examining the limbs look for "past pointing" on finger to nose testing (the subject misses your finger), breakdown of rapid alternating movements (alternately tapping the plantar and dorsal surface of the hand against the leg is arrhythmic. The inability to quickly stop movements "overshoot" is also characteristic of limb ataxia. When examining for gait ataxia, observe the patient's posture, the speed of the swing phase, the stride length (normal is 24–26" for women, 30" for men). Also note the looseness and symmetry of the arm swing and watch for the foot pivoting when the patient makes turns. A true cerebellar ataxic gait is wide-based and the patient has difficulty walking in tandem ("tightrope walk"). The arms are often abducted to improve balance. The hallmark of sensory ataxia (a pseudo-ataxia caused by impaired sensory input, usually from a neuropathy) is a positive Romberg; gait improves if the patient looks at his feet. Gait impairment due to basal ganglia dysfunction is manifested by slowing, shuffling and poor postural reflexes, most easily observed when the patient makes turns.
DIAGNOSTIC EVALUATION

The focus of the diagnostic work-up will be guided by the information acquired from the history and physical examination (Table 2A and 2B). All differential diagnosis are mostly based on the neurologic examination.

The Neurologic Examination

Table 2A. Additional clues from the history

- Was the onset acute, subacute, or chronic?
- Was the onset related to another illness (cardiac arrest, an auto accident or fall)?
- Are there other "unrelated" symptoms or illnesses (e.g., liver disease, headaches, dysphagia, visual, speech, or memory disturbance)?
- If there is syncope or other alteration of consciousness, or if the movement disorder is episodic, the patient should be evaluated for a seizure disorder.
- Was the onset associated with ingestion of a drug (accidentally or prescribed)?
- Has the patient identified aggravating or relieving factors, such as caffeine to worsen or a sip of alcohol to relieve tremor?
- Is motor function better or worse with the time of day?
- Does it disappear or worsen during sleep (ask the spouse)?
- How does the movement problem interfere with daily life (walking, driving, eating, talking, sports, and public appearances)?

Table 2B. Additional clues from the examination

- Seborrhea and abnormalities in sweating are associated with Parkinson's disease and other conditions of the basal ganglia.
- Orthostatic hypotension and other cardiovascular symptoms may point to a problem with autonomic nervous system regulation, which also lies in the domain of the basal ganglia.
- Psychiatric disease may be a clue to drugs as the etiology, even prescribed drugs, such as the neuroleptics or antiemetics.
- Dementia is part of some movement disorders, such as the late stages of Parkinson's disease.
- Hepatic insufficiency may be a clue to certain entities, some common (alcoholism) others less so (Wilson disease).

Serological and other laboratory examinations depend entirely on the phenotype. Recommended serologies range from none (classic PD phenotype) to many (ataxia and chorea have large differentials). A large number of metabolic abnormalities may result in movement disorders. Screening for hepatic failure, uremia, electrolyte abnormalities, including calcium and parathyroid, thyroid testing, inflammatory/rheumatological screening, and metals (serum and urine copper, heavy metals, may be considered.
Neurology consultation should be sought when no etiology is found to explain the patient's symptoms after routine office and laboratory evaluations have been performed. Imaging studies such as CT and MRI may reveal structural lesions such as strokes, tumors, or severe atrophy, but since the basis of most movement disorders is biochemical rather than structural, these are helpful only in a minority of cases. For example, brainstem and cerebellar atrophy is seen in olivopontocerebellar atrophy.

Neurophysiologic studies should be performed whenever there is pain, numbness, weakness, or paresthesias. Electromyography (EMG) is valuable in identifying patterns of muscle hyper- and hypo-activity in various types of movement disorders, especially the dystonias, however this would have to be specifically ordered as standard EMG usually concentrates on neuropathy and myopathy. Nerve conduction studies (NCV) are indicated in the evaluation of movement disorders associated with sensory disturbances.

Electroencephalography (EEG) should be performed if the abnormal movements are paroxysmal (sudden onset with brief duration of seconds to minutes) or if there is associated alteration of consciousness or behavior. As mentioned above, myoclonus is often part of an epileptic syndrome that may include absence and generalized tonic-clonic seizures in later life. Myoclonus is also associated with metabolic, toxic, and hypoxic encephalopathies. Therefore it is imperative to perform electroencephalography in any patient with myoclonus.

**DISEASE OVERVIEWS**

**Essential tremor** is one of the most common movement disorders. Prevalence studies indicate that it is about 5–20 times more common than Parkinson's disease. Onset is usually in early adulthood, although it can occur at any time. Progression is variable but as a rule, the amplitude increases and the frequency decreases over years. High amplitude correlates with disability so patients often have tremor for many years before presenting to a physician. A positive family history can frequently be elicited. Amelioration by alcoholic beverages is another common feature. The hands are almost always involved but any part may tremor.

The most commonly used medications for ET include propranolol and primidone. Propranolol and nadolol are probably the most effective beta blockers for ET, and can be used on a "as needed" basis. Their effect is dose dependent and they help most cases to some extent. Primidone is less dose dependent, can not be used as needed, and usually either helps significantly or does not help at all. The usual dose should begin at 25 mg to minimize side effects. Many other medications may help ET: topiramate, pregabalin, gabapentin, zonisamide, benzodiazepines. Botulinum toxin and brain surgeries can also be used. (see below)

**Orthostatic tremor** is a very interesting tremor disorder that does not present with tremor. Rather, patients complain of balance difficulties specifically while standing. The subjective balance immediately improves with walking. Although patients report a dramatic feeling of decreased balance and exhibit distress while standing, they do not
actually fall. Upon close examination while standing, a very fine, rapid (14 Hz) tremor can be palpated, and sometimes seen, in the calves. This stops when walking. Numerous medications may improve orthostatic tremor (clonazepam, gabapentin, topiramate, phenobarbital, and dopaminergics) but the efficacy often lessens over time.

**Physiologic tremor** is the term used to describe a tremor that is enhanced by certain physiologic states, such as hyperthyroidism. All people have some tremor, the amplitude of which can be enhanced in a variety of situations. Physiologic tremor is usually low amplitude and high frequency and seen with posture or during activity of the upper limbs, rather than at rest. Treatment should be aimed first at the underlying etiology (*Table 4*) although propanolol is very effective.

**Table 4. Drugs or toxins that may potentiate physiologic tremor**

<table>
<thead>
<tr>
<th>Beta-adrenergic agonists</th>
<th>Psychiatric drugs</th>
<th>Methylxanthines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terbutaline</td>
<td>Lithium</td>
<td>Caffeine</td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>Neuroleptics</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Isoetharine</td>
<td>SSRI</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Stimulants</strong></td>
<td><strong>Heavy metals</strong></td>
<td></td>
</tr>
<tr>
<td>Amphetamine</td>
<td>Mercury</td>
<td></td>
</tr>
<tr>
<td>methylphenidate</td>
<td>Lead</td>
<td></td>
</tr>
<tr>
<td>midodrine</td>
<td>Arsenic</td>
<td></td>
</tr>
<tr>
<td>cocaine</td>
<td>Bismuth</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methyl bromide</td>
<td></td>
</tr>
<tr>
<td><strong>Anticonvulsants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproate sodium</td>
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</tr>
</tbody>
</table>

**Cerebellar outflow tremor**, aka **intention tremor**, is a tremor that worsens with directed movement. Closed head trauma and alcoholic cerebellar degeneration are common causes in adults. Numerous hereditary ataxias, multiple sclerosis, Wilson disease, and posterior fossa tumors may also present this way. Certain drugs and toxins affecting these pathways, such as phenytoin and carbamazepine, may cause intention tremor.

**Idiopathic Parkinson's disease**

Idiopathic Parkinson's disease (PD) is the most common degenerative movement disorder. Men are affected somewhat more commonly than women, and rural areas have a somewhat high prevalence of disease. PD is manifested, and clinically diagnosed, by rigidity, bradykinesia, postural instability, and tremor. Motor symptom onset is usually unilateral, and that side will always be worse. The most common symptom that leads the patient to seek medical attention is tremor. However, tremor is not necessarily the first symptom to appear, nor is it the most disabling symptom. Patients may not suspect that bradykinesia and rigidity are early symptoms. In fact non-motor symptoms such as REM
behavioral disorder (acting out dreams), impaired olfaction, and constipation may precede the motor symptoms of PD by more than a decade. This suggests that the neurodegeneration occurs for many years prior to the motor symptom onset. Multiple genetic causes of PD have been identified, although most subjects do not have any family history. PD is in fact multiple different diseases that present with similar symptoms caused by dopaminergic cell loss.

**Treatment**

The treatment of PD is complex. Many non-motor aspects (depression, psychosis, urinary urgency, constipation, sleep disorders, dementia) often need to be addressed pharmacologically. Non-pharmacologic treatments, especially specific physical therapies (visual cuing, rhythmic training etc.) also aid the movement problems. The following summary included only pharmacological treatments for the cardinal motor symptoms.

1. **Levodopa** (combined with carbidopa as Sinemet®) is the most potent treatment for Parkinson's disease. (Figure 3) Unfortunately, the short dose response of the drug requires frequent dosing as the disease progresses, at intervals as short as every 1–1/2 to 2 hours. Sustained-release Sinemet CR® can reduce this inconvenience, but absorption is reduced, requiring higher total daily doses. Side effects include orthostatic hypotension, dyskinesias, hallucinations, and nausea. Dyskinesia (involuntary excessive chorea type movements) develop over time and are the greatest limitation with levodopa, and greatest argument for alternative dopaminergic therapies.

2. **Dopamine agonists**, such as bromocriptine (Parlodel®) and pergolide (Permax®), pramipexole (Mirapex), ropinirole (Requip), rotigotine (Newpro), and apomorphine (Apokyn) were initially introduced to help control fluctuations in movement control that patients with Parkinson's disease often develop on levodopa. It is often recommended that therapy begin with these drugs as they do clearly delay the onset of dyskinesia. They are somewhat less potent than levodopa and tend to have more hallucinations, peripheral edema, and sedation, and impulsivity (increased spending, gambling, sex drive) than levodopa. They also require more titration.

   Monoamine oxidase (MAO) is one of the enzymes that breaks down dopamine. MAO inhibitors (selegiline, rasagiline) increases brain concentrations of dopamine and should lead to improvement of Parkinson's disease symptoms. In practice, however, the efficacy is modest, although side effects are also mild.

3. **Anticholinergics** (Artane®, Cogentin®) may be prescribed as adjunctive therapy to levodopa-carbidopa, and may be helpful early in the course of Parkinson's disease if tremor is significant. Unfortunately, elderly patients are less tolerant to these agents because of side effects, such as cognitive impairment, dry mouth, and urinary retention. In recent years, the use of anticholinergic medications in the treatment of Parkinson's disease has waned, but these drugs are very addictive and difficult to wean off.
Although the availability of a growing armamentarium of pharmacologic agents for Parkinson's disease has changed the outlook for many patients, the degree of functional impairment may still be prohibitive. Initially, early onset Parkinson's disease patients, who often became disabled by the disease in their prime employable years, were the prime candidates for surgery, but advances in techniques have occurred so rapidly that surgery is considered an option for all ages as long as the patient meets the medical screening criteria.

4. Before L-dopa became available, **thalamotomy** was one of the few treatment options available for persons with Parkinson's disease and certain tremors (Markham et al, 1966). Unfortunately, cumulative experience with thalamotomy showed that this procedure is beneficial only for a few months after it is performed. Moreover, thalamotomy appears to effectively decrease contralateral tremor, but bradykinesia usually remains, and rigidity improves variably.

Collaboration among neurologists, neurosurgeons, neurophysiologists and neuroradiologists led to the development of a thalamic stimulation technique that could reproduce the benefits seen early in response to thalamotomy. The ventral intermediate (VIM) nucleus of the thalamus was found to be the locus of neurons that appear to be responsible for tremor; thus, it was predicted that the VIM would be a useful lesioning target for the reduction of tremor. High-frequency stimulation at rates over 100 Hz reproduces the same physiologic effect as lesioning. Known as "DBS" (for Deep Brain Stimulation), the procedure involves the insertion of an electrode wire that is inserted into the VIM under electrophysiologic guidance. The other end of the wire is connected to a pulse generator, which resembles a cardiac pacemaker in size and shape. This pulse generator unit is implanted subcutaneously at the pectoral area. The patient activates this unit by passing a small (about 2 inches) hand-held magnet over the chest. Within 30 seconds to 5 minutes, the tremor resolves on the contralateral side, and the patient can go about his usual activities until he chooses to pass the magnet over the unit again to turn off the stimulation. Although bradykinesia and rigidity usually remain, for patients whose tremor is the primary disabling feature the results are dramatic.

5. **Pallidotomy**, a procedure in which the medial portion of the globus pallidus is lesioned permanently, gained popularity among the general public after several anecdotal reports of success appeared in the news media and the Internet in the mid-1990s. There is greater morbidity with bilateral procedures, with complication rates greater than 15 percent. If the procedure is performed under careful electrophysiologic monitoring and restricted to one side, preferably the nondominant, results are more favorable, with reduction in dyskinesia, but lesser effect on rigidity, bradykinesia and tremor. Pallidotomy is rarely performed now that the technique of Deep Brain Stimulation has been standardized and more widely accepted.

6. More recently, the **subthalamic nucleus** has emerged as the DBS surgical treatment of choice for Parkinson's disease. This DBS approach was first reported
Subthalamic DBS ameliorates Parkinsonian features other than tremor, including bradykinesia, rigidity and even dyskinesias and motor fluctuations (Limousin et al, 1995; Obeso, 6/2000). It reduces dyskinesia and allows reduced medication doses. The ideal candidate for a STN DBS is relatively young, cognitively intact, and has a dramatic change with levodopa. In fact most surgical centers will not implant a STN DBS unless the patient has marked dyskinesia. Symptoms that do not respond to levodopa i.e. voice, balance, psychiatric, autonomic, do not respond to STN DBS.

**Multiple Systems Atrophy** is pathologically related to PD and may present with similar symptoms. Later, however patients may develop marked autonomic abnormalities (orthostatic hypotension, incontinence, inspiratory strider, etc.) and/or true ataxic features. The prognosis is much worse as patients do not respond as well to medications.

**Progressive Supranuclear Palsy** (PSP) and **Cortical Basal Degeneration** (CBD) are pathologically related conditions that present with parkinsonism. PSP is manifest by loss of upgaze, marked balance problems, and early bulbar symptoms. CBD presents very unilaterally (often isolated for three years prior to involvement of the other side). Patients present with apraxia (an inability to use their hand or leg, despite normal strength. They may also have PSP symptoms. The prognosis for both is poor and the medications do not respond to treatment.

**Dystonias**
The dystonias are usually classified by anatomical involvement: "generalized," "hemi-," segmental," or "focal." Most generalized dystonias are genetically inherited, or at least idiopathic, and present in childhood. Hemidystonia usually results from a brain lesion (stroke etc. Adults usually have focal dystonias of the face, neck, and limbs. When multiple contiguous areas are involved, the term segmental is applied.

**Idiopathic Torsion Dystonia,** formerly termed, "Dystonia Musculorum Deformans," is a generalized dystonia that usually begins in childhood with twisting of one foot while walking. Dystonic posturing may be precipitated by ant specific action, which the patient can often reproduce on request. Other actions that use the same muscles, such as walking backward, often do not exhibit dystonia. The hereditary forms may show an autosomal dominant, recessive, or X-linked pattern. Only one (DYT-1) is commercially available for testing.

**Blepharospasm** is involuntary bilateral contraction of the peri-ocular muscles, sometimes with sustained bilateral eye closure. The eyes are not actually involved. This may be so severe as to impede the patient's functioning and pose great risk, particularly when driving. It may spread to other parts of the face and be called "cranial dystonia." Interestingly blepharospasm improves while patients are talking. It often worsens with lights, especially headlights, or other objects coming at the patient i.e. walking in a crowd. There is usually a gritty sensory component, and many patients are mis-diagnosed with "dry eyes." It is usually idiopathic but may be seen with Parkinsonian disorders.
**Spasmodic torticollis** (cervical dystonia) is a common focal dystonia of the neck muscles that results in abnormal neck and head posturing. The could result is rotation (torticollis), tilt (laterocollis), flexion or extension (antero- or retrocollis). As with all dystonias, the pattern, although not necessarily intensity, should be stable. A head tremor very much resembling an essential tremor is often seen in patients with cervical dystonia.

**Writer's cramp and other task specific dystonias** occur in the setting of repetitive motor tasks. Writing is the most common task specific dystonia. It may begin with an involuntary movement (flexion more often than extension) of the hand precipitated by a single letter. Eventually it will occur with any word writing and later with any movement involving a writing instrument (drawing a straight line). Patients may notice the actual movement or just report "tightness" or "muscle fatigue." Writing is the classic precipitant of this form of dystonia, but many other activities may produce it as well. Musicians commonly develop task specific dystonias, often ending their careers. Typing and sports i.e., "golf yipps" are other examples.

**Dystonia treatment** depends on the severity and anatomy of the muscle involvement. Botulinum toxin injections are widely considered to be the most effective treatment for all focal dystonias. These compounds (BOTOX, Dysport, Myobloc) eloquently inhibit the release of acetylcholine from the nerve into the neuromuscular junction. Without this trigger, the muscle will not contract, and begins to atrophy. The toxin is extremely potent and must be injected into the muscle that is targeted. Therefore a good knowledge of muscle activity and function is essential for proper injection technique. There are many debated technical issues to identify the appropriate muscles and optimize placement of the toxin into those muscles. In general activity lessens for 3–5 months, then gradually returns. Repeat injections are then required. The greatest problem with botulinum toxins are the high cost, especially when large muscles require injections. Numerous muscle relaxant medications can be used for dystonia but their effect is very inconsistent and they have numerous side effects, especially sedation. In general muscle relaxants have relatively greater utility in generalized or hemi-dystonia, when botulinum toxin becomes impractical. Finally baclofen pumps and seep brain stimulation of the globus pallidus internus are also commonly used for generalized and segmental dystonias.

**Restless legs syndrome** (RLS) is a very common condition affecting women more than men. It manifests as an urge to move the legs, which improves with movement, worsens with inactivity, and worsens at night. Subjects with RLS usually have **periodic leg movements of sleep** (PLMS) seen on sleep studies, but this is not part of the diagnosis, which is made exclusively on history. RLS pathology shows reduced iron in the brain, even is body stores of iron, and iron testing, are normal. Several medical conditions including systemic iron deficiency, uremia, pregnancy, and possibly neuropathy are associated with RLS. Most other patients have a family history, and multiple genetic loci have been found.

RLS usually responds dramatically to low doses of dopamine agonists. The dose should be administered 1–2 hours before the onset of symptoms. Other treatments include levodopa, gabapentin, and opioids.
Hemifacial spasm (HFS) refers to rapid synchronous, involuntary unilateral contractions of the facial muscles, which may range in severity from simple twitching of the corner of one eyelid, to sustained and even painful contraction of one entire side of the face. All involved muscles are innervated by the facial nerve (CN VII). HFS is usually caused by a compression of the facial nerve near its exit from the brainstem, usually a blood vessel. This causes a "short circuit" in the nerve and spontaneous firing. Hemifacial spasm may occur months or years following Bell's palsy in association with synkinesis due to aberrant reinnervation.

HFS responds dramatically to low doses of botulinum toxin. Seizure medications are sometimes moderately effective. A surgical procedure where the offending blood vessel is stented away from the nerve is also usually effective.

Drug induced movement disorders
There are five main drug induced movements disorders. All are associated with the use of medicines that block dopamine receptors. These include neuroleptics, nausea and GI drugs. Although data is lacking metoclopramide may be the most common offender.

- **Tardive dyskinesia** may occur while on an offending medication or only after stopping it. The phenotype is variable but most commonly involved repetitive, loose perioral and lingual muscles. The movements appear with the patient at rest and can be volitionally suppressed for a few seconds at a time. They also tend to decrease with voluntary activity requiring use of the involved muscle groups. Risk factors include a longer duration of use, older age, and female sex.

- **Acute dystonic reactions** occur within days of starting a dopamine blocker. Children are most commonly effected by this dramatic dystonic extension posturing. Although it looks serious, it almost always resolves with a single dose of anti-histamine and will not usually recur. Therefore, it does not preclude the continued use of the drug.

- **Akathisia** is an intense urge to move the body. Patients will stand up, pace, and rock back and forth. In most cases it resolves upon discontinuation of the offending agent.

- **Neuroleptic malignant syndrome** is a severe life threatening condition manifest by acute rigidity, fever, and altered mental status. Muscle breakdown may result in renal failure. Treatment is supportive along with dopamine agonists, and possibly other muscle relaxants. Recovery can take months.

- **Drug induced parkinsonism** can not be consistently differentiated from idiopathic PD on clinical grounds. It may be more symmetric and have a higher frequency tremor. Removing the offending agent results in improvement but this may take months. Up to 40 percent of patients with drug induced parkinsonism may actually have latent PD that was unmasked by the drug.

Wilson disease is a systemic illness caused by accumulation of copper primarily in the liver and brain. The characteristic flapping tremor of the arms is seen proximally, and best brought out with the patient's arms in "chicken wing" position. The phenotype is actually quite broad. The well-known finding of Kayser-Fleischer rings at the
circumference of the irises might not be detected without a slit-lamp examination. Lever functions may be abnormal but are not needed to suspect the diagnosis. A low serum ceruloplasmin and "reversed" serum/urine copper ratio confirm the diagnosis.

If found early, therapies that chelate copper can completely ameliorate the disease, and result in a normal life. Without treatment the disease is usually fatal.

**Choreas**

**Huntington's disease** is an autosomal dominant hereditary form of chorea that is relentlessly progressive. It can be associated with other central nervous system manifestations, especially dementia, personality changes, gait disorders, and bulbar symptoms. Interesting the same disease in childhood has nearly opposite symptoms including parkinsonism and tremor. Genetic and neuroimaging studies of large families have led to the discovery of the autosomal dominant Huntington's disease gene on chromosome 4. The question of whether to conduct testing presents an ethical dilemma. While there is no "right" decision, a team counseling approach involving the patient's family physician, neurologist, and significant relatives, can result in peace of mind.

The chorea can be treated with amantadine, dopamine antagonists, or tetrabenazine. Anti-depressants appear to help but there is not effective treatment for the entire disease.

**Sydenham's chorea**, now rare, tends to occur in children and teenagers after streptococcal infection. The exact relationship to the Strep infection is unknown, some have negative ASO titers. Although steroids have been used with some success in shortening the duration of the initial attack, the condition usually remits spontaneously over 3–5 months and may nevertheless relapse years later.

Numerous other rare conditions can cause chorea. Chorea is associated with pregnancy, lupus and other autoimmune disorders, several other genetic conditions, and brain ischemia.

**Tourette's syndrome** is defined by having multiple motor tics and at least one sound tic. It is not thought to be intrinsically different from other arbitrarily defined tic disorders (multifocal motor tic disorder etc.). Often patients also have features of obsessive-compulsive disorder. The mean age of onset is seven but peak intensity is the early teens. Boys are affected more than girls. There is a strong familial tendency for both the tic and behavioral components of this condition that appears to be transmitted in autosomal dominant fashion. Although the motor and vocal tics can be willfully suppressed by the patient, this requires significant effort and produces great anxiety. The anxiety that builds up is released upon allowing the movements or vocalizations to occur.

**Psychogenic movement disorders** are relatively common and can present diagnostic difficulties. The most common is probably tremor, followed by dystonia. In general these have an acute onset, which is fairly uncommon in organic movement disorders. Psychogenic tremor tends to have variable frequencies, is distractible, and will entrain (take the same frequency when the subject is asked to volitionally mimic tremor in the
other limb). Psychogenic dystonia tends to be fixed (most commonly foot plantar flexion that can not be pushed back). The psychopathology ranges from a true conversion disorder to frank malingering. This diagnosis should be made by someone with expertise in movement disorders.

COMMUNITY RESOURCES
Because the psychosocial impact of movement disorders is so great, a number of organizations have been created to provide support and medical information in lay terms, largely through the efforts of patients and families. On-line question-and-answer "newsgroups" have also proliferated through the Internet in recent years. These sources can answer questions about legal issues, such as driving, and can offer help to the caregivers.

PATIENT SUPPORT GROUPS AND FOUNDATIONS
The following is a list of active movement disorder foundations and support groups in the United States. A comprehensive "Resource Handbook for Movement Disorders" and a directory of international organizations can be obtained from:

WE MOVE (Worldwide Education and Awareness for Movement Disorders)
204 W. 84th Street
New York, NY 10024
www.wemove.org/

Benign Essential Blepharospasm Research Foundation, Inc.
2929 Calder Avenue, Suite 304
Beaumont, TX 77702
(409) 832-0788
www.blepharospasm.org/

Dystonia Medical Research Foundation
8383 Wilshire Blvd.
Beverly Hills, CA 90211
(310) 852-1630
www.dystonia-foundation.org/

Huntington's Disease Society of America
140 West 22nd Street
New York, NY 10011-2420
(800) 345-HDSA
www.hdsa.org

National Parkinson Foundation, Inc.
1501 Ninth Avenue NW
Miami, FL 33136
(800) 327-4545
www.parkinson.org
The Parkinson's disease Foundation
640 West 168th Street New York, NY 10032
(212) 305-3480 or (800) 457-6676
www.pdf.org/

Society for Progressive Supranuclear Palsy
2904-B Marnat Road
Baltimore, MD 21209
www.psp.org

Shy-Drager Syndrome Support Group
Dorothy Trainor-Kingsbury
1607 SE Silver Avenue
Albuquerque, NM 87106
(505) 243-5118
www.shy-drager.org/

National Spasmodic Dysphonia Association
PO Box 266
Birmingham, MI 48012
www.dysphonia.org

National Spasmodic Torticollis Association, Inc.
PO Box 873
Royal Oak, MI 48068-0873
Fax: (313) 362-4552
www.torticollis.org/

International Essential Tremor Foundation
P.O. Box 14005
Lenexa, Kansas 66285-4005
913-341-3880
FAX: 913-341-1296
Toll-free: 888-387-3667
www.essentialtremor.org/

Wilson Disease Association
PO Box 75324
Washington, DC 20013
(202) 208-0934
www.wilsonsdisease.org/

Restless Legs Syndrome Foundation
819 Second Street SW
Rochester, MN 55902-2985
Phone: 507-287-6465
REFERENCES


**SELF-ASSESSMENT QUESTIONS ON GAIT AND MOVEMENT DISORDERS**

Please select one BEST answer to each of the questions below.

1. Spasmodic torticollis is an example of:
   A. a variant of Parkinson's disease
   B. a movement disorder caused by botulinus toxin
   C. a genetic disorder caused by triplicate nucleotide repeat sequences
   D. a form of dystonia affecting the neck
   E. a form of epilepsy affecting the neck

2. Among the following, the most prevalent movement disorder is:
   A. Parkinson's disease
   B. essential tremor
   C. Huntington's disease
   D. Amyotrophic Lateral Sclerosis
   E. idiopathic torsion dystonia

3. Dystonic reactions may be associated with any of the following except:
   A. Compazine
   B. benadryl
   C. haloperidol
   D. metoclopramide
   E. Navane

4. Ataxia is the term used to describe:
   A. a jerking or "flapping" of the hands seen in hepatic disease
B. repetitive jerking movements of the body seen in certain drug withdrawal states
C. the shuffled gait seen in Parkinson's disease
D. the wide-based gait seen in cerebellar disease
E. a tremor exhibiting irregular frequency

5. A patient complains of neck pain and on examination you find that his head posture is asymmetric, with enhanced drifting to the right when the patient closes his eyes. The remainder of the physical examination is normal, without sensory or motor deficit of the upper or lower limbs and symmetric reflexes. The next step in the management of this patient should be:
   A. brain MRI
   B. cervical spine MRI
   C. cervical spine CT scan
   D. treat with clonazepam
   E. refer for consideration of botulinus toxin injections

6. An 11-year-old child is described as having facial twitching during sleep. Birth and development history are normal. The next step in the management of this patient should be:
   A. electroencephalography (EEG)
   B. brain MRI
   C. botulinus toxin injections for hemifacial spasm
   D. prednisone for idiopathic Bell's palsy
   E. serum and urine copper and serum ceruloplasmin levels

7. On a routine follow-up examination of a 61-year-old man with a ten-year history of Parkinson's disease you find new weakness and hyperactive reflexes on the right arm and leg. The significance of these changes is:
   A. motor fluctuations commonly seen in advanced Parkinson's disease
   B. the dose of Levodopa is too low
   C. a brain MRI scan should be obtained
   D. the patient is exhibiting dominant-side dystonia
   E. these changes may be a side effect of bromocriptine

8. A 56-year-old woman comes to see you because of a tremor she has developed in her arms. She is also reports recent symptoms of anxiety and excessive sweating. Your next step in the management of this patient is:
   A. prescribe carbidopa-levodopa for probable Parkinson's disease
   B. prescribe primidone for her tremor
   C. order thyroid function studies
   D. order MRI scan of the neck
   E. all of the above

9. Blepharospasm is:
   A. seen in association with cranial dystonia
   B. a type of partial epilepsy
   C. seen in association with idiopathic Parkinson's disease
   D. a movement disorder manifested by twitching of one side of the face and eyelid
   E. A and C
10. A 26-year-old schoolteacher comes to your office because of painful cramping of the hand brought on by writing. You are able to reproduce the symptom in your office by having her write a few words down on paper, and, in addition, you note that her wrist assumes a hyperflexed posture with the digits hyperextended, so that she is unable to continue writing. Your next step in the management of this patient is to:
   A. administer calcium IV STAT, for hypocalcemic tetany
   B. prescribe trihexiphenidyl (Artane®) for writer's cramp
   C. refer the patient to an orthopedist for carpal tunnel release surgery
   D. administer Benadryl iv STAT for acute dystonic reaction
   E. refer the patient to a neurologist

11. A 45-year-old man with a long history of schizophrenia returns to see you after being lost to follow up for about one year. On examination, you note that his posture is stooped, his gait and overall mobility are slow, and his right hand exhibits a tremor when resting on his lap. You decide to:
   A. start carbidopa-levodopa (Sinemet®)
   B. refer the patient back to the psychiatrist for evaluation of impending catatonia
   C. order MRI of the brain
   D. review his list of medications to look for iatrogenic causes
   E. administer a test dose of Benadryl®

12. A sixty-year-old woman with recently diagnosed Parkinson's disease complains of nausea. You believe this may be related to the Sinemet® prescribed last week by the neurologist. Your next step in management should be to:
   A. discontinue the Sinemet®
   B. add bromocriptine to the patient's regimen
   C. treat the nausea with prn metoclopramide (Reglan®)
   D. tell the patient to take Sinemet® on an empty stomach
   E. contact the neurologist

13. A 70-year-old man with Parkinson's disease complains of visual hallucinations. He is currently treated with Sinemet CR®® and bromocriptine (Parlodel®). The best approach to manage the hallucinations is to:
   A. discontinue Mirapex® and begin Requip®
   B. decrease the dose of Mirapex® and increase the dose of Sinemet CR®
   C. decrease the dose of Sinemet CR® and add regular Sinemet® to the regimen
   D. begin clozapine 25mg po bid
   E. begin Haldol® 0.5 to 1.0 mg po tid and increase the dose gradually as needed

14. A 45-year-old bank executive whose essential tremor had initially responded to propranolol (Inderal®) complains of problems with concentration and memory. He is certain that the drug is responsible because he discontinued it and his performance at work improved, according to his colleagues. You decide to:
   A. discontinue Inderal® and begin Artane® for treatment of the tremor
   B. refer the patient to a psychiatrist for possible dementia
   C. add donezepil (Aricept®) to his treatment regimen
D. refer the patient to a neurologist for medication change
E. order MRI of the brain

15. A patient reports problematic unpleasant sensations in the legs at night with an urge to move. She often gets up and walks around to temporarily improve the symptoms. They also occur some evenings when she is forced to sit still. It would be most reasonable to:
   A. obtain a sleep study
   B. treat with a dopamine agonist
   C. obtain serologies including thyroid tests, B12, and folate
   D. treat with a sleeping pill
   E. treat with low dose haloperidol

16. Resources that are available to patients with movement disorders include:
   A. patient support groups at the national level and local chapters for the patient and family
   B. foundation newsletters
   C. the primary care physician, neurologist, and non-physician team members
   D. Internet websites
   E. all of the above

ANSWERS

1. D
2. B
3. B
4. D
5. E
6. A
7. C
8. C
9. E
10. E
11. D
12. E
13. B
14. D
15. B
16. E
17. A

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Chapter 9 – Neck and Back Pain

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General Concepts

Musculoskeletal neck and back pain are common complaints with a prevalence of 60 percent to 90 percent in the general population. Differentiating benign musculoskeletal pathology from a more serious neurologic problem is fairly logical when the differential diagnosis is approached systematically.
Musculoskeletal neck and back pain generally is high and midline, experienced in the upper neck and back muscles. Radicular pain tends to occur medial to the scapula or in the buttock with eventual radiation down the arm or leg. Because sitting increases the intraspinal pressure, radiculopathies are classically much worse with sitting but improved with standing or walking. Also, as a general rule, the pain is maximal proximally, whereas paresthesia and numbness are more prominent distally.

The American Academy of Physical Medicine & Rehabilitation (Click on Conditions and Treatment Section)

Cervical spondylitic myelopathy and lumbar spinal stenosis belong in a special category because neither present with arm or leg pain. Both syndromes can be easily overlooked if not specifically considered during the history and physical exam.

Spondylolysis (Figure 1) is a weak line that occurs between the inferior and superior portions of the facet joint, creating a break in part of the lamina and allowing slippage of one vertebra forward on the vertebral body below. This slippage is called spondylolisthesis. Commonly a cause of back pain after athletic activities in a young patient, this is one cause of back pain, which has a characteristic radiologic appearance.
Figure 1: Schematic drawing of an oblique roentgenogram of the lumbar spine, showing the characteristic "Scotty dog" look of its posterior elements. Note that the defect in the pars interarticularis appears to be a collar around the dog's neck.

The most commonly used grading system for spondylolisthesis is the one proposed by Meyerding in 1947. The degree of slippage is measured as the percentage of the distance the anterior vertebral body has moved forward relative to the vertebral body below.

- Grade 1: 1 percent-25 percent slippage
- Grade 2: 26 percent-50 percent slippage
- Grade 3: 51 percent-75 percent slippage
- Grade 4: 76 percent-100 percent slippage
- Grade 5: Greater than 100 percent slippage
Cervical myelopathy can be produced by chronic compression of the cervical spinal cord and often presents primarily as a gait disorder, though moderate neck pain and hand atrophy from chronic root involvement are often found on exam.

Lumbar spinal stenosis can produce significant leg and back pain but is often present on exertion and relieved by sitting, and the physical examination is usually entirely normal.

"Look-alike" pathology in the shoulder and hip are actually not at all uncommon and can lead to significant diagnostic confusion. Shoulder joint pathology often causes radiation of pain into the upper arm. Unlike radiculopathy, however, the pain originates from a point anterior to the shoulder joint rather than posteriorly beneath the scapular wing, and movement of the arm at the shoulder usually exacerbates the pain.

Hip pain generally radiates into the groin and the anterior thigh rather than the buttock and calf. Generally hip maneuvers will reproduce the pain. Occasionally diagnostic cortisone injections into the hip are required to differentiate hip pain from radicular pain in patients with generalized arthritis in both the hip and the back.

Musculoskeletal neck pain associated with median and ulnar neuropathy is sometimes confused for cervical radiculopathy, and the occasional patient with left arm radiculopathy can have symptoms which mimic angina.

Spinal cord and nerve root symptoms and signs are logically ordered according to specific neurologic levels. It is usually possible to predict the location of the lesion responsible within the neuraxis by evaluating a few key muscle groups and reflexes.

**Cervical Pathology**

**Neck Pain:** Generally presents in the paraspinal muscles high and bilateral rather than presenting beneath the scapular wing and radiating into the arm which is classic for cervical radiculopathy.

**Cervical Radiculopathy:**

Examination of the upper extremity, with careful attention to the motor and reflex abnormalities, generally allows localization of the cervical nerve root affected. In less completely expressed radiculopathies, occasionally, just the history alone of radiating pain and the description of the location of the paresthesia will be enough to localize the nerve root involved. This is done primarily to ensure that the lesion is a benign radiculopathy that can be expected to resolve spontaneously with conservative management.

Treatment is typically the passage of time and physical therapy coupled with nonsteroidal anti-inflammatory medications. Patients can be taught simple exercises; in addition, use of "over-the-door traction" on a daily basis may be helpful. Some physical therapists use mechanical traction as well, but this modality should be used cautiously. Short-term use
of narcotics at night is usually necessary, as a fully expressed cervical radiculopathy can be exquisitely painful. Use of epidural corticosteroid and oral steroids are reserved for patients with intractable symptoms. Prednisone 20 mg taken 4 tabs q day X 3 days, 3 tabs Q day X 3 days, 2 tabs q day X 3 days and 1 tab for 3 days (#30 tabs) is often the last conservative treatment prior to the consideration of surgery.

Five to ten percent of the time patients will fail conservative management and will have progressive, unrelenting pain, progressive motor weakness and reflex loss in the distribution of one cervical nerve root. If this is matched by a convincing disc abnormality, with clear neural impingement at the appropriate level, these patients will often need neurosurgical consultation for cervical laminotomy and discectomy.

Radiculopathies, in general, are reliably worsened with laughing, crying, sneezing or any other variant of the Valsalva maneuver, due to an increase in intraspinal pressure. Sitting usually makes the pain worse while standing relieves the discomfort. A patient with an active radiculopathy may actually walk the floor at night to get relief from pain. Cervical 5 (Figures 2 and 3).

![Figure 2](image)

**Figure 2:** An easy way to remember that the biceps reflex is innervated by C5 is to associate five fingers with neurologic level C5.
Figure 3: Neurologic level C5.

The deltoid and the biceps muscles are the two most important C5 muscles. The biceps reflex is the predominant indicator of C5 involvement; because this muscle also has C6 innervation, however, a comparatively small amount of hyporeflexia may indicate significant nerve root pathology. Sensation testing is unreliable for radicular sensory loss. Rather than test sensation, a careful sensory history will often be most useful, if you encourage the patient to be precise, i.e., "If you had to choose which finger is most involved, which one would you pick?"

Cervical 6

This nerve root is compressed by a disc at C5-6 and is the most common site of disc herniation. Both the bicep and wrist extensor muscles have C6 innervation, but the brachioradialis reflex is the preferred C6 reflex (see Figure 4). Sensory history or examination will generally demonstrate involvement of the thumb and first finger (see Figure 5).
Figure 4: Neurologic level C6.
Cervical 7

A disc at C 6-7 will compress the C7 nerve root. The motor function of the triceps muscle and the wrist flexors are the most accurate for defining a C7 radiculopathy. The triceps reflex is usually hypoactive and there is involvement of the middle finger with paresthesias or numbness (see Figure 6).

Figure 5: An easy way to remember the sensory distribution of C6.

Figure 6: A herniated disc between vertebrae C6 and C7 involves the C7 root.
**Cervical 8**

A disc at C7-T1 produces a C8 nerve root impingement. Finger flexors are often involved but there is no reflex abnormality and the sensory distortion involves the medial surface of the upper arm. Isolated C8 radiculopathy is quite uncommon in clinical practice, possibly because of the stabilization of the ribcage (see Figure 7).

![Figure 7: A herniated disc between vertebrae C7 and T1 involves the C8 root.](image)

**Cervical Spondylytic Myelopathy**

Unlike cervical radiculopathies described above, cervical spondylytic myelopathy has a much more subtle clinical presentation. The cervical spinal cord becomes slowly compressed over time by generalized arthritis so that the patient often presents with a slowly progressive gait disorder without neck or arm pain, often obscuring the real nature of the diagnosis.

Degenerative changes in the intervertebral discs are a natural process that occurs with age, often accelerated in patients with a significant history of trauma. As the discs desiccate and the vertebral bodies move more closely together, the posterior longitudinal ligaments lift away from the posterior aspect of the vertebral body allowing "disc-spur complexes" to form. Thickening of the facet joints and growth of the ligaments all combine to produce circumferential narrowing of the spinal canal with compression of the spinal cord as well as selected nerve roots (produced by foraminal stenosis). The most common sites for this spondylytic change are at the most concave portions of the spinal axis at C4-5 and C5-6 (and at L3-4, producing lumbar spinal stenosis See page 258-259. Some patients also are born with a congenitally small spinal canal from foreshortened
pedicles. The average depth of the canal in the cervical spine is 17 mm. Cord compression rarely occurs until the diameter is reduced below 10 mm.

Patients may present with a gait disorder of months to years duration. Because the posterior columns are the most affected, decreased joint position sense and vibratory loss are common, producing a stiff-legged gait with a tendency to fall backwards or to have exaggeration of gait instability in the dark when visual cues are absent. Bowel and bladder involvement are common, with urinary retention or constipation. On examination, patients have decreased range of motion of the neck with atrophy and weakness in the hands (from chronic nerve root compression) accompanied by spasticity and exaggerated reflexes in the legs, bilateral Babinski signs and a positive Romberg. Wide surgical decompression of the cervical spine by multiple level laminectomies often prevents worsening, though often does not significantly improve symptoms.

**Syringomyelia**

With the advent of MRI scanning, the diagnosis of syringomyelia is more common. A syrinx, expansion of the central canal of the spinal cord by fluid under pressure, is a unique structure that can extend many levels up and down the spinal cord, sometimes reaching all the way to the brainstem. Patients describe a severe ripping, burning discomfort which often presents in both shoulders and arms, sometimes extending up the back of the head in a "cape-like" distribution. Reflexes are often diffusely absent in the arms and weakness can be profound, extending beyond the territory of a single cervical nerve. This disorder is treated with a shunt placed within the distended sac, drained to the lumbar space. Even with surgery, this disorder generally produces chronic neurologic problems. Syringomyelia should be considered in any patient who persistently complains of a peculiar bilateral shoulder and arm pain. MRI of the cervical spine will often show the syrinx as a clear CSF filled structure on sagittal T2 weighted images.

**Shoulder Pathology**

Shoulder joint pathology and cervical radiculopathy are frequently confused, perhaps because patients with shoulder problems often describe the pain in a way that can sound like radicular radiation. Differentiation is relatively easy with careful history and examination. Radicular pain generally radiates beneath the scapular wing before moving on to radiate down the arm, while shoulder pain is usually maximal anteriorly over the point of the shoulder. Movements of the arm at the shoulder exacerbate joint, but not radicular pain. Rolling the bicipital tendon beneath the thumb will often reproduce the pain for patient's with bicipital tenosynovitis, while head turning or compression testing (pushing down strongly on the vertex of the head to see if radicular pain is worsened) reproduce radicular pain. Occasionally steroid injections in the shoulder are used to identify which area is most symptomatic in patients with a clinical picture that suggests both cervical osteoarthritis and shoulder pathology.

**Median neuropathy**

Compression of the median nerve at the wrist, or carpal tunnel syndrome, is extremely common. However, it is not always appreciated that carpal tunnel syndrome can present in an atypical fashion, mimicking the symptoms of a cervical radiculopathy. Carpal
tunnel syndrome must be considered whenever a patient complains of hand or wrist pain that is worse at night. This strong nocturnal predilection is sometimes not clear unless patients are asked directly. Most patients have maximal symptoms in their dominant hand, but bilateral involvement is common. Fingers that feel stiff, tight and swollen (like "sausage casings") in the morning or awaken the person at night is the typical complaint. Shaking the hands, holding them above the head or thrusting them into ice-cold water often brings relief. When only some fingers are involved, it is usually the thumb and first finger, though many patients believe the sensory symptoms involve the whole hand. After some time weakness begins to progress, particularly in the abductor pollicis brevis, or thumb muscle, which in turn produces flattening, or atrophy, of that muscle group with weakness of the pincer grip. Tasks such as using a nail clipper, turning a key in a lock, or opening a jar become difficult. Because the pain in carpal tunnel often radiates up the arm to the shoulder and the sensory symptoms are in the first two fingers, a C6 or C7 radiculopathy might be suspected.

**Tinel's sign** (electrical dysesthesia in the hand produced by tapping over the median nerve in the wrist with a reflex hammer) and **Phalen's sign** (reproduction of symptoms in the hand with forced compression) are often present, but their absence does not exclude a diagnosis of carpal tunnel. Nerve conduction studies (NCS) are more cost-effective than a cervical MRI and therefore need to be considered in cases with mixed symptomatology. Surgical decompression of the median nerve is usually not necessary unless slowing of conduction velocity in the motor portion of the nerve is evident on NCV (nerve conduction velocity) testing or the patient remains symptomatic after a 4 to 6 week trial of wrist splinting.

**Ulnar Neuropathy**
Compression of the ulnar nerve at the elbow can be confused with a C7 or T1 radiculopathy based on sensory symptoms in the fingers. Ulnar neuropathy is much less prevalent than median neuropathy and has a less stereotyped presentation. Sensory complaints are present in the fourth and fifth fingers and are not more common during nighttime hours. When weakness is present, the fourth and fifth fingers sometimes develop a characteristic arched appearance so that the hand cannot easily lie flat on a surface. Treatment is simply avoidance of overuse of the arm at the elbow and elbow pads. Surgery requires transposition of the ulnar nerve at the elbow rather than simple decompression and is, therefore, performed less often. In some cases a fibrous band in the cubital tunnel may compress the ulnar nerve. Lack of improvement by conservative treatment may warrant further investigation with MRI since surgical lysis of the band is beneficial.

**Thoracic Pathology**
Because of the stabilization provided by the ribcage, herniation of thoracic discs, while possible, is not common. Thoracic radiculopathy is, however, seen in diabetic patients who suffer from peripheral neuropathy. The pain is quite intense, described as burning, shooting or tingling and generally in the distribution of one thoracic nerve root involving the back and radiating to one half of the chest wall. Unless this diagnosis is entertained in a diabetic patient, the pain can often be confused with pain from an abdominal or cardiac...
source. Herpes sine zoster can also produce severe neuropathic pain which can be quite puzzling in the few days prior to the outbreak of the characteristic vesicles.

**Malignant Cord Compression**
Hematogenous spread of cancer to vertebral bodies occurs more commonly in the thoracic spine because the amount of bone marrow is greatest due to the size and number of vertebral bodies. While benign musculoskeletal pain is common in the neck and back, it is relatively uncommon in the thoracic area. *Therefore, any worsening pain localized to the thoracic area must be assumed to be cancer-related until proven otherwise.* Typically, pain precedes the development of neurologic signs and symptoms by weeks to months. The pain is often encircling and can be misunderstood as visceral pain. Often, unlike benign disc pathology, the pain worsens at night. Most often the malignant process grows from the marrow bearing space in the vertebral body itself, breaking out backwards to compress the spinal cord. Breast, lung, renal cell and prostate carcinoma are the most common sources for malignant cord compression.

The spinocerebellar tracts and the posterior columns are often involved first, creating an ataxic gait from poor position sense. Antigravity muscles are then selectively affected leading to weakness in the iliopsoas muscles and dorsiflexors of the feet. Bowel and bladder function are affected relatively late in the course leading to complaints of constipation and urinary retention. If pain is the only presenting complaint, an elective MRI of the spinal column can be ordered the following day.

It is important to remember:

- To specify the spinal level of concern
- The lesion is often 2-3 vertebral bodies above the sensory or motor level seen on examination
- Emergency study is indicated for any patient with rapidly advancing motor/sensory or bowel and bladder complaints.

Once the spinal cord compression creates infarction of the anterior spinal artery, the patient becomes permanently paralyzed without return of neurologic function. Dexamethasone 4-24 mg qid given urgently can provide almost complete relief of pain and allow testing to proceed while edema is treated, thereby reducing the risk of abrupt neurologic decline.

**Lumbar Pathology- Low Back Pain**
Musculoskeletal low back pain is one of the most common causes of missed work and disability. Most such pain is benign, self-limited and self-correcting. Generally best treated with activity and exercise, there is now little justification for prolonged bed rest. Lumbar x-rays are not routinely necessary in the first four weeks of symptoms and should only be performed in the presence of "red flags" or warning signs that the pain is due to something other than benign pathology. Fever, history of intravenous drug use, immunosuppression or prolonged steroid use, cancer or unexplained weight loss,
significant trauma, or bowel and bladder complaints are warning signs that should prompt earlier additional testing.

Nonsteroidal anti-inflammatory drugs and physical therapy are the best first-line treatments for low back pain. Muscle relaxants may be used at night to decrease spasm and promote sleep but should not be used for more than four weeks because of risks of habituation. Chiropractic manipulation may be somewhat beneficial acutely, though there is nothing to support its use after the first four weeks of symptoms. Lumbar bracing and lumbar traction have no demonstrated benefit and should not be used.

**Lumbar Radiculopathy**
Radicular pain generally radiates from the buttock near the sciatic notch down the back or side of the leg to the foot. This pain, created by neural impingement from a disc herniation or osteophyte, is generally made worse by sitting and relieved by standing or lying. Generally the pain is worse proximally, in the back and buttock, while the sensory symptoms are more intense distally, in the tips of the toes or bottom of foot. Paraspinal muscular spasm commonly accompanies lumbar disc herniation with limitation of range of motion on forward bending.

Lumbar root pathology can be localized to one level with the careful application of sensory, motor and reflex testing. In general, surgery for lumbar root compression from simple disc herniation should not be entertained unless:

- The patient has failed 6 to 8 weeks of conservative therapy
- Has worsening intractable pain
- Has signs on exam confined to the distribution of one nerve root (which must match the sight of neural impingement on MRI or myelogram/post myelogram CT testing)

Although L3 can be involved, the most commonly involved nerve roots are **L4, L5 and S1**. The pain in all cases will radiate down the leg posteriorly from the buttock; on occasion, L4 pathology produces pain that radiates into the anterior aspect of the thigh before radiating into the foot. Sensory testing is the least useful or reliable part of the examination, though a sensory history of involvement of the sole of the foot (versus the dorsum) can be a reliable indicator of S1 impingement (see Figure 8).
Figure 8: The sensory dermatomes (A) and (B) a practical method of testing sensation across the dorsum of the foot.

L4 Root Level (Figure 9)
Figure 9: A herniated disc between vertebrae L3 and L4 involves the L4 nerve root.

Having the patient attempt to walk on the heels can also test for early foot drop. Remember that the knee reflex can also be absent if the patient has had knee surgery and, therefore, in the presence of this history, the importance of an absent knee jerk is diminished as a localizing sign.

L5 Root Level (Figure 10)
Figure 10: A herniated disc between vertebrae L4 and L5 involves the L5 nerve root. This is the second most common level of disc herniation in the lumbar spine.

Lumbar 5-root pathology can be difficult to distinguish from L4 unless you remember that there is no reflex abnormality caused by compression of the L5 nerve root. Even in its most fully expressed form, the patient will have weakness of the extensor of the great toe and some tingling or numbness on the top of the foot.

S1 Root Level (Figure 11)
Figure 11: A herniated disc between vertebrae L5 and S1 involves the S1 nerve root.
This is the most common level of disc herniation in the lumbar spine.

The most commonly involved nerve root is S1. This typically produces a diminished, or absent, ankle jerk. The motor involvement is not usually obvious unless the nerve root compression is very advanced, and best tested by having the patient try to walk on the toes. If the heel cannot be kept off the ground there is likely involvement of the gastrocnemius muscle that is innervated by S1.

Lumbar Spinal Stenosis

This disorder is quite common and yet often overlooked as a source for back and leg pain because the physical examination is often completely normal. The diagnosis must be suspected on the basis of the history alone. Spinal stenosis is created from circumferential narrowing of the diameter of the spinal canal caused by facet hypertrophy and thickening of the posterior longitudinal ligament, processes which occur naturally with aging. Some people are also born with a congenitally narrow spinal canal from foreshortened pedicles, which predisposes them to the development of this disorder.

Patients with lumbar spinal stenosis sometimes do not complain of back pain at all, but instead describe intense aching or cramping in the thighs and calves. This pain is reliably induced by walking and relieved by sitting. Typically patients will tell you, when asked, that the symptoms come on more quickly when attempting to walk uphill than when walking on level ground. Often they will find that bending the torso forward will decrease discomfort. This allows them to go grocery shopping bent over a cart, but unable to walk the same distance around the store upright, without the cart. Likewise, they may be unable to walk for 20 minutes, but can easily sit on an exercise bike and pedal for the same amount of time without pain. This discomfort is best termed "pseudoclaudication" as it is identical to the complaint of patients with significant arterial compromise to the legs. Commonly these patients are sent first for vascular
studies or to a vascular surgeon before referral to a neurologist or neurosurgeon. MRI of the lumbar spine is the best way to look for spinal stenosis. Surgical treatment is necessary with a generous posterior decompressive laminectomy to remove the bony compression of the cauda equina. In patients who are sedentary and quite comfortable to spend much of their time sitting, surgery may not be necessary. Short-term relief of symptoms can often be achieved with lumbar epidural corticosteroid injections. Because the compression is bony, physical therapy is not helpful. Hyperextension exercises may also exacerbate the pain.

**Cauda Equina Syndrome**

Compression of all of the lumbar nerve roots after they leave the spinal cord (which ends at vertebral level L1) produces a cauda equina ("horse's tail") syndrome. This produces a characteristic clinical syndrome of weakness, numbness, tingling and lack of deep tendon reflexes symmetrically in the legs. This syndrome can be seen with far advanced lumbar spinal stenosis (see above) but, because spinal stenosis is painful, the stenosis is often discovered and treated before a true cauda equina syndrome develops. Tumors are a more common cause of this syndrome, allowing compression of nerve roots to occur from a neurofibroma, meningioma or ependymoma. Metastatic disease to the vertebral bodies can also produce this syndrome, though pain preceding the onset of neurologic symptoms would be expected. Recognition of a patient's bilateral leg weakness as reflective of compression of nerve roots with essentially all of the findings listed for individual nerve roots above (especially L4, L5 and S1) allows targeting of diagnostic studies to the vertebral level L1 and below and prevents a fruitless search for spinal cord pathology.

**Conus Syndrome**

Bowel and bladder fibers travel in the spinal cord. The conus is the tapered end of the spinal cord just before the cauda equina (rostral to caudal). When patients have what appears to be a cauda equina syndrome but with prominent or early involvement of bowel and bladder function, a lesion in the tip of the conus needs to be considered. Because this structure is often at spinal level T11 or T12, it can be missed on routine lumbar MRI studies and certainly on lumbar CT studies which often don't even start the imaging until below L2. Always remember the localization of the problem and make sure the imaging studies show you the involved area as well as one or two vertebral bodies higher in order to ensure that pathology has not been missed.

**Hip Pathology**

Pain from the hip generally radiates into the groin but can also be present into the anterior and lateral surface of the thigh, mimicking an L3 radiculopathy. Hip maneuvers should exacerbate the pain and should be part of the examination of any patient with back and leg pain. Sometimes accurate diagnosis will require hip radiographs and even diagnostic cortisone injections. Patients with generalized arthritis in the back, hips and legs, or those with knee replacements (which render the localizing value of an absent knee jerk useless) are the most likely candidates for this group of problems. Hip pain is also more likely to be present with weight bearing while radicular pain tends to be better with standing and worse with sitting.
It is important to remember that the lumbosacral plexus travels through the pelvis after exiting the lumbar spine.

**On occasion hemorrhage into the psoas muscle in patients taking anticoagulants, or neoplastic spread from pelvic tumors (prostate cancer for example), can compress lumbar nerve roots in the pelvis. A pelvic CT scan needs to be ordered. A pelvic CT scan needs to be ordered for patients with clear involvement of high lumbar nerve roots and an unremarkable lumbar MRI scan.**

**Peripheral Neuropathy**  
Peripheral neuropathy is fiber-length dependant. Axonal loss occurs in the spinal cord and the longest fibers "die-back" first. This produces a symmetrical complaint of numbness in the tips of the toes that spreads slowly up the leg like a knee sock (not a complaint of sole numbness, which would be characteristic of an S1 nerve root compression). Neuropathies can be pure sensory, pure motor or mixed sensorimotor. Bilateral foot drop generally does not occur until the sensory involvement is fairly pronounced. A severe mixed sensorimotor axonal polyneuropathy, therefore, could easily mimic lumbar spinal stenosis with compression of nerve roots as both could produce absent ankle jerks and sensory loss below the knees. Searching for a history of exertional claudication in the legs should serve to separate the two entities, as peripheral neuropathy should not produce back and leg pain. In addition, because of the fiber length dependant features of neuropathy, when a patient is affected in the legs so that sensory loss extends to the knees, careful search for numbness in the tips of the fingers and hands should allow diagnosis of a more widespread problem. Axonal polyneuropathy is generally produced by a systemic illness such as diabetes. Demyelinating neuropathy, where the major site of tissue destruction is the myelin sheath, is often immune mediated and potentially treatable. The most common example of a demyelinating neuropathy is Guillian-Barré syndrome. Vitamin B12 testing, RPR, serum protein electrophoresis (myeloma), and thyroid function studies should be part of the routine evaluation of patients with neuropathy.

Separating neuropathies into axonal versus demyelinating becomes important as one type is treatable and the other is largely untreatable. Symptom onset is fairly slow for the axonal variety and more fulminant for the demyelinating type. The best method to distinguish them from each other, however, is electromyography and nerve conduction studies. Demyelination, which occurs randomly through the plexus and nerve root, produces areas of complete conduction block and very slow conduction times. Axonal pathology produces more modest changes in conduction velocities, allowing the electrophysiologist to tell the clinician which variety of neuropathy is likely. Nerve biopsies and extensive evaluation for the cause of severe neuropathies should be left to tertiary care subspecialty centers.

**Meralgia Paresthetica**  
Meralgia paresthetica, or compression of the lateral cutaneous nerve of the thigh can produce symptoms that overlap with symptoms caused by compression of nerve roots in the back. Patients have a very characteristic complaint of tingling dysesthesias in the...
lateral aspect of the thigh. The discomfort is in a rounded area in the upper lateral thigh and does not involve the leg below the knee. The discomfort is often maximal at night so that the patient awakens rubbing or slapping the thigh to relieve the pain.

The lateral femoral cutaneous nerve enters the leg after diving beneath the inguinal ligament. This nerve is often compressed by excessive weight such as in pregnancy or with morbid obesity. The nerve can also be compressed from tight clothing or activities that involve hyperextension of the leg at the hip such as cross-country skiing or walking with an excessively long stride. The typical patient to be affected with meralgia paresthetica, therefore, would be an overweight truck driver who sits for long hours in a pair of tight jeans wearing a thick billfold in the back pocket on his affected side.

The pain can be quite intense but generally is not affected by positioning. On examination, these patients generally have no abnormalities with the exception of a very small area of numbness within the dysesthetic area. Careful evaluation of iliopsoas strength and presence of knee jerks should serve to differentiate this condition from a high lumbar disc. Treatment is often education to remove precipitating factors though, occasionally, corticosteroid block of the nerve in the groin is necessary for the patient to obtain relief.

References


Self-Assessment Questions

1. Which of the following presenting symptoms is most likely to represent a cervical radiculopathy?
   A. anterior shoulder pain made worse with arm movement
   B. high, midline bilateral cervical pain
   C. elbow and forearm discomfort made worse with sitting and straining
   D. hand tingling which is maximal at night
2. Which of the following presenting symptoms is most likely to represent a lumbar radiculopathy?
   A. groin pain made worse by walking
   B. buttock pain made worse by sitting
   C. bilateral calf and thigh pain made worse by walking
   D. tingling paresthesias in the lateral thigh

3. What signs on physical examination are most often seen in patients with lumbar spinal stenosis?
   A. absent deep tendon reflexes at the knees
   B. weakness of the dorsiflexors of one foot
   C. difficulty walking on the toes
   D. none

4. What signs on physical examination are most often seen in patients with cervical spondylytic myelopathy?
   A. spasticity and hyperreflexia in the legs
   B. Horner's syndrome
   C. diminished deep tendon reflexes at the ankles
   D. down going toes (or a plantar response which is flexor)

Provide the most likely radicular level or other diagnoses for the following patients:

5. A hairdresser who awakens reliably at night with right hand pain and tingling in the thumb and first two fingers. Examination shows some blunting of sensation in the involved fingers without weakness or reflex asymmetry.
   A. C6
   B. Compression of the median nerve at the wrist
   C. C7
   D. C8

6. An elderly man with left buttock pain made worse by sitting. On exam he is unable to rise up on the toes of the left foot and has an absent deep tendon reflex at the left ankle.
   A. L5
   B. L4
   C. S1
   D. lumbar spinal stenosis

7. An elderly woman complains of progressively severe thoracic discomfort that worsens at night. Examination reveals proximal leg weakness manifested by difficulty arising from a low stool.
   A. malignant cord compression
   B. right L5-S1 disc herniation
   C. syringomyelia
   D. lumbar spinal stenosis

8. A young woman presents with urinary retention and constipation with tingling sensations in the soles of both feet. On exam she has only back pain and absent ankle jerks.
   A. polyneuropathy
B. spondylolisthesis of L4 on L5  
C. cauda equina syndrome  
D. conus syndrome

9. A woman complains of numbness and tingling bilaterally from the knees down. The most reliable way to distinguish polyneuropathy from lumbar spinal stenosis by examination is:
   A. absent ankle jerks  
   B. symmetric sensory loss to pinprick testing  
   C. absent knee jerks  
   D. sensory involvement in the hands

10. When carpal tunnel syndrome is the working diagnosis, the most important muscle to test for weakness is:
   A. abductor digiti minimi  
   B. abductor pollicis brevis  
   C. finger flexors  
   D. finger extensors

ANSWERS

1. C  
2. B  
3. D  
4. A  
5. B  
6. C  
7. A  
8. D  
9. D  
10. B

Navigation

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Chapter 10 – Common Neurologic Emergencies

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This chapter will address common neurologic emergencies: coma, stroke, and status epilepticus. These are time sensitive situations in which effective therapy may lessen or completely reverse a potentially catastrophic insult to the central nervous system.

Coma may be anticipated as an integral component of the terminal event of all fatal human illnesses. However, coma, which represents failure of the brain's alerting system, may be completely reversible. The earlier the process inciting the comatose state is treated, the greater the likelihood of a more rapid complete recovery. The differential diagnoses of the causes of coma are numerous and varied. While proceeding towards the correct diagnosis with a directed history, physical examination, and prioritized laboratory investigations, therapies that may be antidotes to the cause of the coma are administered. A systematic approach is described which ensures reaching the definitive diagnosis promptly.

Ischemic stroke, the most common form of stroke, has one therapeutic intervention, which increases the likelihood of a complete or near-complete recovery without increasing morbidity or mortality. The thrombolytic agent, tissue plasminogen activator (tPA), must be administered within 3 hours of stroke onset; the sooner after stroke onset tPA is given, the greater its therapeutic efficacy. However, tPA administration is associated with a definite risk. Thus, the selection of eligible patients requires an extremely rapid response system and strict adherence to inclusion and exclusion criteria. A user-friendly checklist is provided.

Convulsive Status Epilepticus (continuous generalized tonic-clonic seizure activity) needs to be aborted in less than 60 minutes which, depending on the etiology of the seizures, improves the chances of a good outcome. A step-by-step annotated timeline is described below.

COMA
The comatose patient manifests a depressed level of consciousness. To be conscious, the patient has to be both awake and aware. Patients with severe anoxic cortical damage, with brainstem sparing, exhibit wakefulness and sleep but are not aware and are, therefore,
unconscious. This is the hallmark of vegetative state. Once awareness is impaired, the level of consciousness is described as depressed or altered. Terms like lethargy, obtundation, stupor, and coma are used to indicate varying degrees of depression of normal physiologic alertness. The term 'coma' means a deep depression in the state of 'altered level of consciousness.' Coma is characterized by the patient's arousal response to verbal or painful stimuli. The degree of decrease in level of consciousness correlates with the severity of the disease process and dictates urgency of response and type of treatment. The altered level of consciousness may indicate a primary effect on the brain or it may be a sign of other serious illness such as septic shock.

Alertness or arousal depends on an intact reticular formation or reticular activating system (RAS) running through the brainstem from which it then projects to the thalami and on to both cortical cerebral hemispheres. Thus, alteration in the level of consciousness, including coma, can be functionally localized to two areas. There are only two types of coma, brainstem or bilateral hemisphere. One or both areas can incur a chemical or structural insult resulting in an altered level of consciousness. A unilateral lesion does not itself cause an alteration in the level of consciousness, unless by mass effect it also causes significant distortion of the brainstem, which affects the functioning of the RAS in the brainstem.

For example, if there are signs of brainstem coma, such as certain abnormal eye movements or a dilated pupil due to pressure on the III cranial nerve adjacent to the brainstem, then the patient may be herniating and the situation represents a possible neurosurgical emergency. CT scanning may be needed immediately while measures to reduce increased intracranial pressure are being instituted. If these brainstem signs are absent, then the coma is probably due to nonstructural effects on the RAS or bilateral hemisphere disease suggesting a totally different course of action for diagnosis and treatment.

Case Report: Part 1
A 50-year-old man is found unconscious in a downtown park. 911 is called and the patient is transported to the emergency department. The paramedics report that the patient is comatose with a Glasgow Coma Scale of 7 (no eye opening = 1; unintelligible sounds = 2; nonspecific withdrawal movements = 4). His breathing was noisy, but improved with a jaw thrust maneuver. He has been placed on a backboard with spine precautions. His C-spine has been immobilized. Vital signs are 140/90, 90 pulse, 24 respiratory rate, pulsoximetry 94 percent. Oxygen at 6L/min by nasal cannula has been applied. An IV line is initiated. Serum glucose level is 80. Cardiac monitor shows sinus rhythm. There was no response to intravenous naloxone. There is a nearly empty bottle of Thunderbird wine in his jacket along with a full bottle of (phenytoin) Dilantin® capsules dated two weeks earlier. The patient smells of alcohol and his pants are urine stained. There are numerous healed scars about the head with encrusted sutures along his right parieto-occipital scalp. His right pupil is 6 mm and does not appear to react, while the left is 3 mm reactive. According to his buddies, he had been drinking more than usual recently to alleviate a headache. He has been lying on the ground for several hours.
Although the patient is a known alcoholic and appears to be in an alcoholic stupor or perhaps in a postictal state, the history and physical examination point to a more urgent situation. The pupil asymmetry (presumably not due to a previous insult) suggests that coma is due to brainstem compromise with herniation. Because acute or chronic intracranial hematoma is the likely cause, the trauma team is notified.

A careful history, along with timely and appropriate interventions is necessary in the management of patients presenting with an altered level of consciousness. Examination, differential diagnosis, and treatment options are discussed below.

**History**

Obtain history from witnesses, friends, and family keeping in mind that certain interventions (see below) must be performed while gathering information. Is there any history of trauma, seizures, diabetes, allergies or other medical problem? How long has the patient been unconscious? Were there any bottles or medication containers at the scene? Is the patient taking prescribed medications? Is there anything special about the environment in which the patient was found? Indoors or outdoors? Any unusual odors? Any others in the vicinity in a similar state? Is the patient wearing a Medical Alert bracelet?

Examine clothes pockets for identification, suicide notes, or drug bottles. If possible, initiate an immediate search through any previous medical records. They will help to confirm information gathered from witnesses, family and friends, and may add vitally important data. For example, it would be unfortunate to load a patient with phenytoin who has a previous history of a Stevens-Johnson allergic reaction to the medication.

**Interventions**

*Always assume there is a C-spine fracture.* The unconscious patient may have suffered a head injury and simultaneous cervical spine injury as the initial event or during the fall when becoming unconscious. *Ensure a patent airway maintaining C-spine precautions.*

If respirations are inadequate, a jaw-thrust or chin-lift maneuver may assist respirations initially. A nasopharyngeal airway or an oropharyngeal airway may keep the airway patent prior to intubation. The comatose patient cannot protect the airway and needs to be intubated. This is obviously the case for the patient with an absent gag reflex. The patient may vomit at anytime resulting in an increase in morbidity and mortality associated with aspiration pneumonia. The comatose patient may have a seizure at anytime, further complicating the situation.

- Oxygen ? Initially high-flow oxygen by nasal cannula or mask. Note response.
- Repeat and monitor vital signs including temperature. If the patient is hyperthermic or hypothermic, institute appropriate management.

Intravenous line—Normal Saline at a rate to maintain euvoolemia is used initially if the blood pressure is normal. If blood pressure is low due to hypovolemia, then appropriate fluid replacement should be instituted. Hypertension may be secondary to elevated...
intracranial pressure, which should be treated before aggressive use of anti-hypertensive medications is undertaken. Bloods are sent for electrolyte and other analyses.

ECG monitor—The rhythm should be observed throughout and treated as needed. Obtain an electrocardiogram.

Thiamine—Wernicke's encephalopathy may present as coma; the treatment is thiamine. Giving glucose to a patient who appears malnourished and thiamine depleted, as occurs in alcoholics, may precipitate Wernicke's encephalopathy. In such patients, administer 100 mg of thiamine by intravenous injection before giving glucose. Note response.

Glucose—If the patient is hypoglycemic, administer 50 cc D50W intravenously. In children give 2 cc/kg of D25W. If the patient is not hypoglycemic, giving a glucose load to a patient with a stroke or other brain injury may aggravate the brain damage. Note

Naloxone—Give 2 mg intravenously. Be prepared for the patient who is a narcotic overdose individual to awaken in response to the naloxone and to become combative and resist further medical evaluation. Note response.

Flumazenil—If pure benzodiazepine overdose is definite, administer 0.2mg/min up to a maximum of 1mg IV. If the patient ingested other drugs, flumazenil may induce seizures. Note response.

- Review responses to glucose, thiamine, naloxone, flumazenil and oxygen.
- With the airway protected, an orogastric tube for gastric lavage is inserted and activated charcoal is instilled when there is a possibility of a toxic ingestion.
- A Foley catheter is inserted for obtaining urine for laboratory tests and monitoring urine output.

Observe for status epilepticus. A rhythmical twitching of some of the digits of either hand or a rhythmical small amplitude horizontal jerking of the eyes may be the only clue that the patient is in status epilepticus. If the patient is having seizures, treat accordingly (see Chapter 7: Episodic Disorders).

If meningitis is suspected, perform a lumbar puncture. If there are signs of increased intracranial pressure or focality on examination, the LP may be temporarily withheld pending results of a CT scan. Appropriate antibiotics should be initiated prior to LP if there is going to be any delay in obtaining the CT scan in patients suspected of having bacterial meningitis.

If a unilaterally dilated pupil (sluggish or unresponsive to light) is present, suggesting uncal cerebral herniation, the patient is hyperventilated to a pCO2 of about 35mmHg and given mannitol IV at 1 gram/kg as a temporizing measure for the increased intracranial pressure. Obtain a head CT scan while neurosurgery consultation is requested emergently.
Physical Examination
What is the patient's level of consciousness? What are the size of the pupils and their response to light? Is there evidence of trauma?

1. Confirm the comatose state. Voice, touch or noxious stimuli (pressure to sternum or to nailbed of middle finger of each hand, and to the supraorbital nerve) should be used to arouse the patient. Observe and record response.
2. Use the **Glasgow Coma Scale** to assess the degree of coma prior to intubation and the use of paralytic or sedative agents. Compare the Glasgow Coma Scale scores.

<table>
<thead>
<tr>
<th>Glasgow Coma Scale</th>
<th>Eye opening</th>
</tr>
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<tbody>
<tr>
<td>Spontaneously</td>
<td>4</td>
</tr>
<tr>
<td>To verbal command</td>
<td>3</td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
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**Best motor response**

<p>| | |</p>
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<th></th>
<th></th>
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<tbody>
<tr>
<td>Obeys commands</td>
<td>6</td>
</tr>
<tr>
<td>Localizes to pain</td>
<td>5</td>
</tr>
<tr>
<td>Withdraws to pain</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion</td>
<td>3</td>
</tr>
<tr>
<td>Abnormal extension</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
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</table>

**Best verbal response**

<p>| | |</p>
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<th></th>
<th></th>
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<tbody>
<tr>
<td>Oriented converses</td>
<td>5</td>
</tr>
<tr>
<td>Disoriented</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>1</td>
</tr>
</tbody>
</table>

The worst score obtainable is not 0, but 3. Note that score for the motor response is based on the best response so that a hemiplegia on one side with a normal contralateral side receives a motor score of 6. A patient with quadriplegia from a spinal cord injury receives a motor score of 1. The Glasgow Coma Scale provides a useful standard for comparison to help determine if there is deterioration, improvement, or no change in the patient's level of consciousness.

Components of the Physical Examination

Vital Signs
**Blood pressure:** Presence of hypotension requires immediate management. Hypertension with diastolic pressure of at least 140 may indicate hypertensive encephalopathy. Consider eclampsia at a lower blood pressure in the pregnant patient. Cushing's triad of hypertension, bradycardia, and bradypnea is seen in acute marked increased intracranial pressure. Cerebral perfusion pressure (CPP = mean arterial pressure minus intracranial pressure) should be maintained at a minimum of 60 mm Hg.

**Respirations:** Observe the pattern. Hyperventilation may indicate metabolic acidosis. Cheynes-Stokes (crescendo-decrescendo followed by apnea), ataxic (irregular rate and depth), or apneustic (pause at inspiration) breathing may be present indicating different CNS levels of dysfunction. **Temperature:** Fever may be associated with CNS or systemic infection. Fever may also be a symptom of CNS hemorrhage or status epilepticus. Consider heat stroke, environmental causes, as well as thyroid disease in hyper/hypothermia.

**Head**

**Skull palpation:** Look for hemotympanum. Battle sign (post-auricular ecchymosis) and raccoon eyes are signs of basal skull fracture, which take hours to develop.

**Inspect mouth:** Note any toxic/metabolic odors on breath. Tongue laceration may indicate a seizure disorder.

**Neck**

**Look for meningismus:** When the C-spine has been cleared, examine for nuchal rigidity, Brudzinski's or Kernig's sign. If present, a lumbar puncture should be performed looking for meningitis or subarachnoid hemorrhage. A CT scan should be obtained prior to LP in the presence of increased intracranial pressure, papilledema, a history of head trauma, or suspicion of a CNS lesion causing focal lateralizing neurologic signs such as hemiparesis. Begin antibiotic therapy for meningitis and re-evaluate after CT scan. In the comatose patient meningismus (nuchal rigidity) may disappear.

**Eyes (see special section on Pupils and Extraocular Movements below)**

**Pupil size, symmetry, reactivity:** After ABCs (airway, breathing and circulation) and spine immobilization, the pupils are checked. Tiny pinpoint pupils are commonly caused by opiates. Pontine lesions may also cause pinpoint pupils, but are associated with other brainstem cranial nerve signs. Cholinesterase inhibitor, organophosphate insecticide poisoning and clonidine overdose also cause miotic pupils. Notice eyelid fluttering or the presence of tone with voluntary eyelid control in psychogenic coma.

**Extraocular movements:** Instruct all patients who appear comatose to open their eyes and look up. These voluntary movements may be all that patients with locked-in syndrome due to brainstem ischemic or hemorrhagic stroke may be capable of performing. These patients are sometimes erroneously diagnosed as comatose, but are fully awake and may only be able to communicate with eye blinking or eye motion. After opening the eyelids, the resting position of the eyes is noted. **Conjugate tonically deviated**
eyes usually indicate a large ipsilateral hemisphere lesion. Nystagmoid unidirectional jerks may be the only sign of ongoing seizure activity.

**Funduscopic exam:** Subhyaloid hemorrhages indicate subarachnoid bleeding. Papilledema takes 12 to 24 hours to develop after acute increase in intracranial pressure.

**Motor System**
Look for spontaneous movements and response to noxious stimuli as well as asymmetrical movements, which may indicate a hemiparesis. Finger twitching may be only residual of ongoing seizure activity. Observe for decorticate and decerebrate posturing.

**Skin**
Look for petechia, ecchymoses, presence or absence of sweating, skin changes, or needle marks.

**Lungs, Cardiac, Abdomen**
Auscultate and palpate looking for systemic illnesses and secondary effects of CNS insults, e.g., neurogenic pulmonary edema.

**Extremities**
Observe position of limbs; an out-turned leg may be due to hemiparesis or a hip fracture.

**Special Section: Pupils and Extraocular Movements**
The brainstem is small and compact; it imparts the pupillary light reflex, houses the extraocular muscle nuclei and their connections, and the reticular activating system (RAS).

The size of the pupils is maintained by a balance between the parasympathetic and sympathetic autonomic nervous systems. Normal pupils are equal in size within one millimeter and equally change in response to light or dark. The light stimulus to either eye travels via the optic nerve, chiasm and tract to the midbrain Edinger-Westphal nucleus from which the information travels along the parasympathetic fibers running on the outside of the III (oculomotor) cranial nerve to the pupil. The III nerve also innervates the levator palpebrae muscle and the medial rectus, inferior rectus, superior rectus, and inferior oblique extraocular muscles. Anything pressing on the III nerve causes ipsilateral pupillary dilatation in addition to ptosis and eye movement disorder. This is why the unilateral dilated unreactive pupil is such a valuable sign of cerebral herniation of the uncus of the temporal lobe over the edge of the tentorium where the III nerve is running along side on the way from the brainstem to the globe.

The sympathetic fibers also affect pupillary size. The sympathetic fibers innervate the tarsal muscles in the upper and lower eyelids and lesions can then cause the appearance of ptosis by narrowing the palpebral fissure. *Horner's syndrome*, which is a sign of sympathetic fiber interruption, consists of the triad of ipsilateral ptosis, meiosis, and anhidrosis. Pupil asymmetry may also be the result of direct eye trauma, surgery, Adie's
tonic pupil, or accidental or intentional instillation of a mydriatic anticholinergic drug like scopolamine or cholinergic substances like pilocarpine.

Normally, both eyes move conjugately to maintain binocular fixation of objects. This control is mediated through the medial longitudinal fasciculus (MLF) in the brainstem, which connects the ipsilateral III nerve nucleus with the contralateral VI (abducens) nerve nucleus. The MLF ensures that movement of the ipsilateral medial rectus muscle is yoked to the contralateral lateral rectus muscle. This neurologic observation provides the basis for the vestibular-induced oculocephalic (doll's eyes) and caloric testing of the eye movements. The cervical spine is protected in the comatose patient and doll's eyes maneuvers can be performed when there is no suspicion of cervical spine injury. Ice water calorics provide a much more powerful and reliable stimulus than doll's eyes maneuvers for testing the eye movement system. The eyes may be dysconjugate in sleep or with a depressed level of consciousness, but in response to an alerting stimulus or to caloric testing they become conjugate if there is no pathology of the extraocular movement system.

Case Report: Part 2
On arrival at the emergency department, the rescue squad's findings were confirmed. The patient was comatose with a nonreactive 6mm right pupil. In response to noxious stimuli, his left side moved much less than the right. Immediately, the C-spine was examined radiologically and the patient was intubated, slightly hyperventilated, and placed on a ventilator with 100 percent oxygen. Mannitol 100 grams was given intravenously and a CT of the head obtained. The neurosurgeon was at the bedside and the operating room staff were notified of possible emergent surgery. Preoperative laboratory and X-ray studies were performed (see Diagnostic Adjuncts below).

Differential Diagnosis
The problem of patients presenting in coma is common. It may appear to be an overwhelming task to properly evaluate and manage these patients since just about everything in a textbook of medicine can result in decreased level of consciousness and coma. Regardless of the cause, the approach to these patients requires rapid assessment while instituting therapeutic and diagnostic measures, which identify and correct or amend any processes, which might lead to progressive and irreversible damage. The proper evaluation and management of these patients relies on the history, physical examination, and ancillary tests. An organized approach will nearly always give the correct diagnosis and provide the proper management sequence.

The preliminary differential diagnosis addresses the question, "Is the coma due to a primary central nervous system disease or the consequence of a systemic illness?"

This differentiation is primarily based on the presence or absence of focality (localization of a specific anatomical deficit) on the neurological examination. Focal findings strongly suggest the presence of a specific lesion. Systemic problems, such as a lack of nutrients (glucose, oxygen) or metabolic problems (sodium, calcium) or an accumulation of toxins (carbon dioxide, carbon monoxide, alcohol) cause diffuse central nervous system...
dysfunction. Occasionally hyponatremia, hepatic coma, or nonketotic hyperosmolar coma can present with focal neurologic signs. When there is focality on examination, a structural lesion is sought.

The first 10 items in the differential diagnosis list below are the most life- and function-threatening. Measures for therapy are instituted while emergent diagnostic techniques are undertaken to identify the cause of coma.

1. Shock or Hypertensive encephalopathy: decreased cardiac output, myocardial infarction, congestive heart failure, and pulmonary embolus
2. CO2 Narcosis or Hypoxia: pulmonary disease, hypoventilation
3. Hyperthermia or Hypothermia
4. Hypoglycemia (insulin overdose)
5. Wernicke's encephalopathy (thiamine deficiency)
6. Exogenous toxins (e.g., opiates, carbon monoxide, cyanide, barbiturates, benzodiazepines, antidepressants, antihistamines, atropine, organic phosphates, bromides, anticholinergics, ethanol, methanol, ethylene glycol, hallucinogens, ammonium chloride, heavy metals, over-the-counter drugs including salicylates)
7. Stroke (ischemic)
8. Intracranial hemorrhage (with or without trauma): subarachnoid hemorrhage, intracerebral hematoma, epidural hematoma, subdural hematoma
9. Meningitis: bacterial, syphilis, fungal, carcinomatous Encephalitis: Herpes simplex
10. Reye's syndrome (pediatric)
11. Trauma: diffuse axonal injury to the brain without significant intracranial hemorrhage
12. Tumor: CNS meningioma, glioma, and remote effects (e.g., lung cancer)
15. CNS Infections: progressive multifocal leukoencephalopathy, Creutzfeldt-Jakob disease
16. Seizures: status epilepticus, including non-convulsive; prolonged postictal state
17. Blood: anemia, sickle cell disease
18. Vascular: systemic lupus erythematosus (SLE)
19. Metabolic: hypercalcemia, uremic encephalopathy, hepatic encephalopathy, hyperosmolar state, thyrotoxicosis or myxedema coma, Cushing's disease, pituitary apoplexy, porphyria
20. Psychiatric: especially depression; hysterical conversion reaction
21. Other: migraine, basilar (especially in children) intussusception in children

The popular mnemonic TIPPS on the VOWELS lists the frequent causes of coma.

A-alcohol
E-epilepsy
I-insulin
O-opiates
U-urea(metabolic)
T-trauma
I-infection
P-poisoning
P-psychogenic
S-shock, stroke

Diagnostic Adjuncts

The sequence for ordering of the laboratory tests depends on the history and physical examination. If there is a history of head trauma, the important laboratory test is the CT scan. A patient with a head injury may have had a precipitating event that caused a fall that resulted in the head injury. A diabetic patient may have been hypoglycemic; an elderly patient may have had a myocardial infarction or an arrhythmia; and a single car motor vehicle accident may have been a suicide attempt after taking a toxic ingestion.

Laboratory Evaluation

CBC, differential, platelets
Serum glucose, electrolytes, calcium, magnesium, phosphorus
Alcohol level
Renal function tests
Hepatic function tests
Arterial blood gases; carboxyhemoglobin level
Urine for urinalysis and toxicology studies, myoglobin and porphobilinogen
EKG
CT/MRI scan
Thyroid function studies
Lumbar puncture for CSF
—cells, protein, sugar, India ink prep, fungal cultures, and extra tubes as needed
EEG (immediately if suspect status epilepticus)

Case Report: Part 3

The CT scan showed a large right parieto-occipital chronic subdural hematoma, which probably explains the patient's recent headaches. There was fresh blood within the chronic subdural. This recent bleeding probably resulted in the patient's acute decompensation. The patient was taken immediately to the operating room to have the subdural hematoma evacuated.

Special Conditions

Coma In Children
Head injuries in children differ in several ways from those in adults. Children in
traumatic coma usually do not have a surgically correctable lesion, though one should always be sought. A relatively minor injury can have an apparent initial recovery, followed by several hours of decreased level of consciousness with waxing and waning signs, then complete recovery (post-traumatic stupor and delayed non-hemorrhagic encephalopathy).

**Seizures.** The postictal state in children can occasionally be prolonged and last two to three days.

**Reye's syndrome.** This post viral illness tends to be associated with salicylate ingestion and presents with decreased level of consciousness and elevated ammonia levels. Due to a decrease in use of aspirin for fever in children, it is now less common.

**Coma in the elderly**
Ischemic stroke is more common in the elderly. Basilar artery thrombosis impairs brainstem perfusion and can cause coma at onset. Large hemisphere ischemic strokes may develop massive cerebral edema and result in compression of the brainstem over days from onset. Cerebellar hemisphere strokes (ischemic or hemorrhagic) can result in coma over hours to days.

- Chronic subdural hematomas present much more commonly in the elderly and about half the time a history of head trauma, which may be very minor, is obtained.
- Hypothyroidism must always be considered in the elderly.
- The elderly patient can be very sensitive to medications including sedative hypnotic medications.
- The elderly may accidentally, or intentionally, take an overdose of drugs.
- The postictal state following seizures may be prolonged in the elderly patient.

**Narcotics**
Naloxone will reverse the coma, respiratory depression and meiosis of opiates. The presence of pinpoint pupils, skin track marks, and a history of intravenous drug abuse all point to opiate overdose. Even in the absence of meiosis, check for accidental overdose. A child may have gotten into the parent's medication or an elderly person may have taken too much acetaminophen with codeine. The narcotic overdose patient will awaken in response to naloxone, and possibly become combative and resist further medical evaluation. Remember that the naloxone duration of action is one hour and the opiate taken may have a much longer half-life (methadone or propoxyphene). Patients may, consequently, lapse back into coma. Do not forget the need for evaluation of possible complications, which occurred during the comatose state (e.g. aspiration which could lead to pneumonia).

**Alcohol**
Patients who are in coma due to alcohol intoxication need to be observed and monitored until they fully recover their normal state. The problem of alcoholism should be addressed prior to discharge, preferably by a social worker.
**Insulin**

Patients presenting in coma due to a hypoglycemic reaction secondary to an insulin overdose, who have returned to their normal mental state, do not require hospitalization. However, their diabetes management must be re-evaluated so they can avoid a recurrence. Patients that have taken long-acting oral hypoglycemic agents may relapse and need to be observed.

**Psychogenic**

Psychogenic coma does occur, but is uncommon. Usually it resolves with patience and support. Psychogenic seizures, which can be difficult to diagnose by even the most astute neurologists, are probably the most common form of hysterical coma. Clues to the diagnosis are the presence of eyelid fluttering, Bell's phenomenon (elevation of the globes when eyelid opening is resisted by the patient), and the absence of a postictal phase after generalized seizures. Spontaneous crossing of the legs is not a reliable sign of pseudocoma. The neurological exam is otherwise normal.

In hysterical coma, ice water caloric gives normal ipsilateral deviation with fast phase nystagmus in the opposite direction. If you suspect hysterical coma, caloric's should be used only as a last resort, and preferably with a neurologist present. Often times opening the eyelids, noting the normal tone, and bringing your face or a mirror close up to the patient's eyes, results in the patient's looking around or away, confirming that they are indeed awake. Bizarre behavior mimicking psychiatric illness can be seen in individuals under the influence of drugs and alcohol, and those who are postictal, hypoglycemic, or have suffered a head injury or a subarachnoid hemorrhage. In any patient presenting in coma, if the diagnosis is unclear or the patient is not responding as expected, obtain prompt neurologic expert consultation.

**Referral**

Transfer should be considered when the patient is stable enough to be transferred and definitive care exists which your facility does not offer. Referral or consultation should be considered if there is uncertainty regarding the diagnosis or management, if the clinician does not have privileges to provide the type of care needed (e.g., surgery), the clinician is ethically opposed to providing care (e.g., hospice care, or the opposite, definitive care at the patient's/ family's request when it would be futile). Referral or consultation can also be considered when there is a conflict (e.g., personality conflict or the patient is a close friend or family member) and the clinician feels they cannot be objective. Consultation as a second opinion may be wise when the diagnosis is unexpected (e.g., young person with severe injury), serious, the prognosis is grim or the patient is not getting better. It should also be considered if the patient requests a consultation. The first sign that the patient desires a consultation may be provided by the family (i.e., the patient does not want to challenge or doubt the doctor/patient relationship).

Specific examples of consultation for neurologic emergencies include: all neurologic emergencies requiring surgery, status epilepticus requiring general anesthesia, and for rehabilitation for neurological emergencies with sequelae if the clinician is not...
comfortable. Consider transfer when there is inadequate equipment (e.g., no dialysis, CT or EEG) or facilities (e.g., limited ICU) in your hospital. There is some evidence that specialized stroke and closed-head injury units have better outcomes than routine ICU's. If a specialized unit is not available, special staff training for managing victims of stroke or closed-head injury may be beneficial (e.g., monitoring mean arterial pressure, post-thrombolytic monitoring, etc.)

**Psychosocial Impact**

Surviving a neurological emergency can be very stressful for the patient and/or family members. This is especially true if the etiology is recurrent. Although a discussion of stress is beyond the scope of this book, long-term stress can cause physiologic and psychological signs and symptoms, for individuals or families, resulting in family disruption, depression, etc. It can also be associated with medical illnesses, and if coping skills are not developed, with a poor prognosis. Individuals and families should be monitored closely and counseled or treated as necessary. However, long-term stress is not always harmful. At least part of the stress can have positive results if the individual or family is motivated to obtain future care in a timely manner. Long-term stress may also motivate planning for emergencies, even resulting in patients moving to another town or location to be near adequate facilities. Planning can also include such decisions as who will make medical and financial decisions in the event that the outcome from a future emergency is not good.

Survivors of neurologic emergencies with risk of recurrence go through many of the same stages of any patient receiving bad news: denial, anger, bargaining, possibly depression and eventually resolution. Active listening by the clinician may be an important management tool. Often the clinician will observe these stages if they take the time to listen to the patient or family.

Otherwise, the psychological impact of a neurological emergency is dependent upon the cause, especially coma, and whether it is an acute situation, a treatable/preventable situation (e.g., seizures) or potentially a chronic, recurrent and/or disabling situation. The impact from status epilepticus has already been discussed in the chapter on Episodic Disorders (Seizures). The impact from stroke has been partially discussed in the chapter on Weakness.

If coma (and for that matter, stroke or seizure) is secondary to a medical condition and the condition is entirely correctable, the patient and family members may only need reassurance. The patient and family should be prepared for the same psychological impact they could expect from any acute, serious illness. They should also be observed for sequelae related to an intensive care admission (e.g., ICU delirium, post-traumatic stress syndrome, etc.) and a brief recovery.

If the cause of coma is trauma (e.g., closed head injury), or any other cause requiring a prolonged recovery and rehabilitation, patients are at risk for long-term sequelae, a loss of self-dependence, self-confidence, and self-esteem. Support groups as listed below are often helpful.
If we do a good job as clinicians, the psychological impact from an ischemic stroke should be identical to that of a patient newly diagnosed with coronary artery disease following an event. The management is often very similar. In fact, the most common cause for death following an ischemic stroke is a myocardial infarction. After the patient/family absorbs this information, they should also be informed that current prognosis has never been better, especially due to new medications and therapies. Adherence to medical regimens will be very important. The patient and family should be observed for any evidence of the psychological defense known as denial, especially regarding necessary lifestyle changes to prevent recurrences.

The psychological impact on the family for any of these emergencies that result in a disability increases the risk of "caregiver burnout," especially if there is one primary caregiver. Depending on severity of the disability, issues of placement, finances, scheduling/ coordinating care, or even activities of daily living may all be dependent upon the caregiver. Caregiver burnout has been well described in the literature, including risk for anxiety, depression, and other major medical illnesses. With severely disabled patients, many geriatricians suggest that the caregiver be considered the primary patient rather than the disabled patient because the caregiver may be at greater health risk. Support groups and community resources as listed below are very valuable when attempting to avoid or manage caregiver burnout.

**Community Resources**

For patients with status epilepticus or weakness following a stroke, community resources are listed in the chapters on Episodic Disorders (seizures) and Weakness. For additional clinician or patient questions, for patient or family education, recent advances in treatment, or a listing of support groups for stroke or coma, several resources are listed below. It is important to recommend these resources to patients or family members with serious or chronic illnesses. Support groups are often vital for recognizing and preventing caregiver burnout.

**References**


After evacuation of the subdural hematoma, the patient had an uneventful course and recovered completely.

ISCHEMIC STROKE
Stroke is a major health problem and the third leading cause of death in the United States. Unfortunately symptoms are not as readily recognized by the general public as are those for myocardial infarction. A major health initiative is currently underway to educate the public about the symptoms of stroke. Readers are referred to the AAFP patient education web site familydoctor.org, "Stroke: Warning Signs and Tips on Prevention." Use of the term "brain attack" has been promulgated to achieve public recognition equivalent to "heart attack". This initiative is of paramount importance because of the recent development in treating stroke with tissue plasminogen activator (t-PA). If administered in a timely and appropriate fashion, tPA increases the likelihood of a complete or near-complete recovery.

At this time the reader should review the clinical symptoms associated with stroke as outlined in the Episodic Disorders chapter. Familiarity with these symptoms assures that patients are appropriately selected for t-PA therapy.

Case Report
You have just completed your morning rounds at the hospital, and are informed that a long-time patient has notified your office that her husband (a 65-year-old man who has always been in excellent health and on no medications) is en route to the Emergency Department (ED). You go directly to the ED where the paramedics arrive at 8 a.m. They report that the patient's wife called 911 when she noticed upon awakening at 7:30 a.m. her husband was having difficulty speaking, his face was crooked and his right arm was limp at his side. They had established an intravenous line, obtained a blood glucose measurement of 120 mg/dL, and placed the patient on low-flow oxygen by nasal canulae. Blood pressure in the field was 200/100 mm Hg, and it was the same in the ED, heart rate was 82 and regular, with a respiratory rate of 18. The patient's temperature was recorded along with the initial vital signs in the ED as 37°C. You examine the patient and the key findings are neurologic. There is no speech output but he seems to follow some simple commands (close your eyes, lift up your arm), There is right facial asymmetry, a right field cut to threat, a flaccid right arm with no withdrawal to a painful stimulus to the nailbed digits of the right hand, and spontaneous weak movement of the right leg compared to the left. You join the Emergency Physician in providing care.
Question 1

Your initial management includes:

1. Sublingual nifedipine
2. Chewable aspirin
3. Obtain an emergency head computerized tomography (CT) scan
4. All of the above

Question 2

Your management now includes:

1. Ordering tissue plasminogen activator (t-PA) at 0.9 mg/kg estimated weight
2. Ordering a heparin infusion at 10 units/kg/hour
3. Performing a lumbar puncture before either 1 or 2
4. None of the above

None of the above. You may order and even prepare t-PA but do not administer it since the time of stroke onset is not known in a patient who awakens with stroke symptoms. The ischemic stroke may have occurred just before awaking or any time since known to be last neurologically intact (e.g., before going to sleep). In the United States, the manufacturer has established a no-charge pharmacy resupply program for any t-PA, which is opened but not used. Although heparin is often used as therapy for acute ischemic stroke, heparin has not been proven to be beneficial and may increase risk of intracerebral hemorrhage in large hemispheric stroke, which this patient manifests. Lumbar puncture is indicated to help diagnose subarachnoid hemorrhage or meningitis. Neither is suggested in this patient and would be a contraindication for immediate thrombolysis or anticoagulation if those became treatment options.

Minutes later the patient's wife arrives. She states that she and her husband had arisen early that morning, awakening in time to catch a beautiful sunrise. At that time her husband was perfectly normal. They returned to bed at 6:30 a.m., and when they awoke at 7:30 a.m., he was noted to have the neurologic deficit. She knows he's having a stroke and is asking that you do something. You re-evaluate the patient. He's neurologically the same. The radiologist states the CT scan shows no hemorrhage and there are no early infarct signs. The nurse provides you with the blood test results from clinical laboratory. A complete blood count including platelets, glucose, electrolytes, renal function tests, protime and partial thromboplastin time are all within normal limits.

Question 3

Your management now includes:

1. Ordering t-PA at 0.9 mg/kg, 10 percent initial bolus, and the remainder over an hour because the patient has a greater likelihood of functionally independent
recovery with minimal or no disability than without t-PA therapy, despite a 6 percent increase in the likelihood of a symptomatic intracerebral hemorrhage.

2. Ordering tenectaplaste as a single weight-based IV bolus dose since no IV infusion is needed.
3. Withholding thrombolytic therapy for the acute ischemic stroke since the patient cannot give informed consent
4. Withholding thrombolytic therapy for acute ischemic stroke until the patient's private physician arrives since it is now only just over 2 hours from stroke onset and the patient may still be suffering only a transient ischemic attack

The best choice is 1. The dosage of t-PA in acute stroke is lower than in acute myocardial infarction with a maximum dose of 90 mg. Although tenectaplaste (TNK) has been shown to be beneficial for thrombolysis in acute myocardial infarction, TNK has not been shown to improve outcome in acute ischemic stroke, though such trials are being conducted. Patient understanding of risks and benefits of any therapy physicians provide is important. However, when patients are unable to participate in the decision-making, physicians are responsible for providing the best possible medical care. In this case, the patient's spouse can provide any needed informed consent. However, if a legally authorized representative is unavailable, therapy should not be withheld. The rationale for treatment should be documented in the medical record, as well as discussions with appropriate individuals. As for concern that the patient's symptoms may still only be the manifestations of a transient ischemic attack, in the NINDS t-PA stroke trials report, only 2 percent of patients in the placebo group had normal National Institutes of Health Stroke Scale (NIHSS) scores at 24 hours. As in this report, patients who show rapid improvement prior to receiving medication are excluded since they may be experiencing a TIA. However, if a significant deficit persists, these improving patients may benefit from IV t-PA in reducing the likelihood of a poor outcome, best reviewed with physicians experienced with the use of t-PA for stroke.

Your management is based on your understanding of the NINDS t-PA acute stroke trial published in the New England Journal of Medicine December 14, 1995, the subsequent Food and Drug Administration approval in the US in June 1996, and the FDA equivalent in Canada in February 1999. Attention to inclusion and exclusion criteria as organized below is important to replicate the results of the NINDS trial.

Checklist for t-PA For Acute Ischemic Stroke
Inclusion Criteria

1. Ischemic stroke with a defined onset of less than three hours from time t-PA is to be started. Ascertain last time patient known to be awake and deficit-free.
2. Measurable deficit on NIH Stroke Scale. Neurologic deficit minimal weakness, isolated ataxia, isolated sensory deficit, or isolated dysarthria.
3. CT scan shows no evidence of intracranial hemorrhage. If early signs of new major hemisphere infarct are present (e.g., edema, mass effect, sulcal effacement), reassess time of onset. The presence of these CT findings are associated with an increased risk of hemorrhage.
Exclusion Criteria

History:
1. Stroke or serious head trauma within past 3 months.
2. Major surgery or serious trauma within past 14 days.
3. History of intracranial hemorrhage, AVM, or aneurysm.
4. GI or urinary tract hemorrhage within previous 21 days.
5. Arterial puncture at a noncompressible site OR lumbar puncture within previous 7 days.

Clinical:
1. Rapidly improving neurologic signs or minor symptoms.
2. Systolic blood pressure > 185 mm Hg OR Diastolic blood pressure > 110 mm Hg OR aggressive (IV) treatment required to reduce patient's blood pressure to specified limits.
3. Seizure at onset.
4. Symptoms suggestive of subarachnoid hemorrhage.
5. Recent myocardial infarction (post-MI) pericarditis.

Laboratory:
1. Patient taking anticoagulants AND prothrombin time (PT) greater than 15 seconds (International Normalized Ratio [INR] > 1.7).
2. Patient has received heparin within 48 hours preceding stroke onset AND has an elevated partial-thromboplastin time (PTT).
3. Platelet count below 100,000 per mm3.
4. Glucose concentration below 50 mg/dl (2.7 mmol/liter) OR above 400 mg/dl (22.2 mmol/liter)
5. Patient of childbearing age who has a positive pregnancy test

*Discuss the risks and benefits of thrombolytic therapy with the patient and family (if possible) and document the discussion in the medical record*

Prior To Administering t-PA:

Review checklist to confirm inclusion and exclusion criteria. Confirm patient is not showing spontaneous improvement.

Treatment and Patient Management:

1. t-PA 0.9 mg/kg total or maximum 90 mg.
2. Administer 10 percent of t-PA dose as a bolus.
3. Administer remaining 90 percent of t-PA as a constant infusion for 1 hour.
4. DO NOT give anticoagulants for 24 hours from start of t-PA administration.
5. DO NOT give antiplatelet agents for 24 hours from start of t-PA administration.
6. Admit to Intensive Care Area OR Acute Stroke Unit.
7. Maintainsystolic blood pressure **UNDER**180 diastolic blood pressure **UNDER**105
8. Restrict central venous line placement **OR** arterial puncture for 24 hours.
9. **DO NOT** insert indwelling bladder catheter for > 30 minutes after t-PA administration.
10. **AVOID** insertion of nasogastric tube for 24 hours after t-PA administration.

Blood Pressure Management

1. Monitor BP for 24 hours after starting t-PA infusion every 15 minutes for 2 hours; every 30 minutes for 6 hours; then hourly for next 16 hours.
2. If systolic BP 180-230 **OR** diastolic BP 105-120, **THEN** repeat in 5 to 10 minutes. If elevated on both readings:
   - **ADMINSTER** labetalol 10mg IV over 1-2 minutes.
   - **MONITOR** every 15 minutes.
   - **REPEAT** 10mg or 20mg every 10-20 minutes as needed up to 150 mg.
   - **AVOID** hypotension.
3. If systolic BP >230 **OR** diastolic BP 121-140, **THEN** use labetalol as above, repeating every 10 minutes.
   - **If response inadequate, use IV nitroprusside.**
4. If diastolic BP >140, **THEN** use IV nitroprusside (0.5 to 10 mcg/kg/minute).
   - Monitor closely, avoid hypotension. **USE WITH CAUTION!**

If a sudden major rise in BP occurs, consider intracerebral hemorrhage, stopping t-PA infusion, and obtaining emergency CT scan.

STATUS EPILEPTICUS

The reader is advised to review the material on seizures in the Episodic Disorders chapter.

Definition: Patient does not recover to a normal alert state between two or more tonic-clonic seizures or duration of seizures greater than 20 minutes. Although most epileptic seizures are self-limited, some go on for prolonged periods, whereas others recur so rapidly that the condition is referred to as status epilepticus. The most serious form of this disorder is generalized convulsive status epilepticus, in which convulsive seizures are repeated without return of consciousness in between.

Goals of Treatment

1. Terminate seizure activity as soon as possible, preferably within 30 minutes of onset.
2. Prevent recurrence of seizures.
3. Ensure adequate cardiorespiratory function and brain oxygenation by establishment and maintenance of an adequate airway and support of blood pressure.
4. Correct any precipitating factors (e.g., hypoglycemia, hyponatremia, hypocalcemia, or fever).
5. Prevent or correct any systemic complications, especially hyperpyrexia, which may exacerbate neuronal damage caused by the continuous seizure activity.
6. Evaluate and treat possible causes of the episode of status epilepticus.

**Treatment of Generalized Status Epilepticus**

**Immediate Action:**
Obtain vital signs including temperature: If hypertensive, consider hypertensive encephalopathy. If febrile, use appropriate antipyretic measures vigorously.

Maintain airway orally or nasally. Monitor respirations, cardiac monitor and BP monitor.
Draw glucose, lyses, BUN, Ca, Mg, P, CBC with differential, creatinine and CK.

Accucheck-Treat hypoglycemia with 50 cc D5OW. Pediatrics 1cc/kg D25W. Thiamine 100 mg IV to prevent possible precipitation of Wernicke-Korsakoff syndrome in malnourished patients (eg, alcohol and other drug abuse patients).

If IV unavailable, consider glucagon 2mg IM to treat hypoglycemia.

Obtain antiepileptic drug levels and arterial blood gas levels, if indicated. It is not necessary to treat status-induced metabolic acidosis if there is a good airway and seizures stop. If acidosis persists, consider other causes.

Save blood for toxicology screen. Consider theophylline, tricyclic antidepressants or other overdose. Consider amphetamine or cocaine use.

Obtain urine. In addition to urine toxicology screen when appropriate, check for myoglobinuria.

Obtain allergy history, particularly to phenytoin

**At 5 minutes:**
IV NS to maintain euvoolemia. If an IV cannot be obtained by a peripheral line, consider intraosseous infusion, cutdown or central line placement. Consider endotracheal, rectal, IM or gastric administration of needed medication. Recognize your own limitations and obtain consultation for drug route, dosage, concentration, precautions, and complications.

**Lorazepam** no faster than 2 mg/min IV up to 0.1 mg/kg. Give in increments of 2 mg. Repeat increments no more often than every 2 minutes. **Diazepam** 2 mg/min up to 20 mg in 5 mg increments may be used, but lorazepam may be more effective for immediate control of status epilepticus. For pediatrics diazepam may be used up to 0.25 mg/kg in 4 divided doses and it may be equally effective as lorazepam in children. These benzodiazepines may be administered rectally. Do not exceed dosage of benzodiazepines if already given in prehospital care. Stop benzodiazepine when clinical seizures stop.
Clinical seizures may have subtle features such as nystagmoid jerking of eyes, small rhythmic finger movements, or twitching of the corner of the mouth.

Observe for respiratory depression. Have flumazenil available. Place call for neurology consult.

**At 15 minutes:**
Proceed to load phenytoin at 20 mg/kg in NS at 50 mg/min by infusion pump with close monitoring. If BP drops, cease phenytoin infusion, wait for BP to return, then resume infusion at 25 mg/min and continue monitoring. Phosphenytoin may be infused at 100mg phenytoin equivalents/min with similar precautions. If seizures stop and reoccur, resume benzodiazepine until maximum dose is reached. Arrange for admission to ICU.

Arrange for emergency EEG, if overt convulsive activity has stopped but patient is not improving in level of consciousness. Even when seizures are clinically no longer apparent, patient may be in electrographic status.

If status persists, intubate patient if not previously necessitated to maintain airway. Use short-acting neuromuscular agents so that clinical response can be assessed when paralytic drugs wear off.

**At 30 minutes:**
Repeat glucose accucheck and temperature. Review laboratory results.

If still in status, additional phenytoin at 5 mg/kg until cessation. Repeat again if necessary.

Obtain phenytoin level 30–60 minutes after completion of infusion.

**At 60 minutes:**
Arrange for general anesthesia with sodium pentothal or consider other antiepileptic anesthetic drugs. When status has been stopped, evaluate and treat patient for the precipitating cause. Head CT scan or MRI scan are performed to delineate structural brain lesions such as brain tumor or subarachnoid hemorrhage. Lumbar puncture should be performed if meningitis, encephalitis, or subarachnoid hemorrhages are suspected.

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Chapter 11 – Family Medicine Perspective

Section 1

CHANGES IN BEHAVIOR

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PART I: THE 15-MINUTE NEUROBEHAVIORAL EVALUATION

It is 3:30 on Friday afternoon. The front desk buzzes your nurse, announcing the arrival, without an appointment, of a 35-year-old woman accompanying her 83-year-old father. Four other patients are waiting for examining rooms. You are with a four-year-old girl whose asthma is worsening.

"What's the problem?" you overhear your nurse ask the receptionist, her tone conveying the slightest hint of skepticism. "Oh," she says. "I see," she says. "For how long?" she asks. She sighs. Hearing that sigh, you know you're going to be seeing them.

This section will attempt to outline the 15-minute neurobehavioral assessment. Today's pace of practice has accelerated from the epoch of luxurious 45-minute health promotion discussions to an unsettling "Beat the Clock" of frenetic juggling of priorities, hoping, in that circus act, not to drop any patient's ball. A high proportion of primary care visits involve behavioral problems, requiring us to quickly and confidently distinguish between medical/neurological causes and primary psychiatric conditions. So it is essential that we devise realistic strategies for walking into the examining room in total ignorance of the diagnosis and walking out 15 minutes later with a plan. Naturally, we need flexibility. Some things simply demand more time, perhaps not as much for diagnosis as for negotiating the exchange of human information in ways that strengthen the bond between healer and patient. But the burden, increasingly and perhaps absurdly, is now on primary care physicians to attempt to offer an attending's experienced care with an intern's time schedule. Hence, we will be practical. Since the pleasure in practice is often proportional
to the sense of mastery, we hope this plan for rapid neurobehavioral evaluation will make that Friday afternoon a better day, granting the reward of confidence in our practical approach.

We will organize the Neurobehavior Evaluation in ways that aid triage, by following the conventional sequence of history, examination, and laboratory evaluation. However, we recognize that there is actually a continuous evolution of diagnostic hypotheses, a solution to a jigsaw puzzle of biological cause and behavioral effect with every interlocking piece contributing to the next step in the strategy, rather than a linear observation of clinical facts. Given this, we will present the Neurobehavior Evaluation as a series of decisions that progressively narrow the focus of etiology and intervention. This chapter will focus on the following issues for adults:

- Delirium (confusional state)
- Dementia
- Discrete problems of thinking (e.g., amnesia, aphasia, apraxia)
- Psychiatric syndromes having identifiable neurobehavioral/medical causes (see Table 1).

Table 1: Adult Neurobehavioral Syndromes

Delirium (a.k.a. Confusional state) = altered mental status in an apparently awake or somewhat lethargic person (but not sleeping or comatose), usually acute or subacute in onset, with impairment in level of responsiveness or attentiveness to the environment. Example: hepatic encephalopathy.

Key points:
- Awake or lethargic
- Acute or subacute
- Impaired attention

Dementia = acquired impairment in cognition sufficient to interfere with the conduct of waking life, not due to impaired arousal, usually with subacute or chronic presentation, usually impairing multiple aspects of thinking. Example: dementia of the Alzheimer type.

Key points:
- Impacts on awake activities
- Subacute or chronic
- Intact attention

Discrete problems of thinking:
- Amnesia = impaired learning
- Aphasia = impaired language
• **Agnosia** = impaired recognition of sensory stimuli
• **Apraxia** = impaired functional motor skills with intact strength and coordination
• **Executive function impairment** = e.g., altered planning, self-monitoring, idea analysis, or idea generation

**Psychiatric syndromes that have identifiable neurobehavioral/medical causes:**

• Depression
• Mania
• Psychosis
• Anxiety

You enter the room. The elderly man sits, slightly slumped in a vinyl chair. He looks up slowly when you enter, not quite making eye contact.

We adopt the "every picture tells a story" stance in neurobehavioral assessment (Figure 1). From the first glance, you already know that this man has enough lower extremity motor function to make it to the examining room, and enough interactiveness with his daughter to be guided there with neither the support of a wheelchair nor the swaddling of restraints. This already favors a fairly well functioning spinal cord and brainstem for both motor processes and arousal and decreases the odds of a large stroke, subarachnoid hemorrhage (SAH), or meningitis. You know he has enough intact peripheral sensory organ function and enough intact transfer of sensation to sensory cortex to note your entry into the room, so it's likely that much of the visual pathway from eye to occipital lobe is working. You know that the sensory information of your coming, by parallel processing, has also successfully reached his brainstem arousal system and parts of the limbic/emotional response system that provide motivation to respond to your presence. You know that there is working give-and-take of electrochemical discourse between these systems and the frontal cortex that is necessary to organize a motor response to your entrance. And you know that this man can manage the transfer of commands from prefrontal cortex (for planning) to primary motor cortex (for doing) and from motor cortex passing all the way down to anterior motor horn cells to activate a symphony of muscle contraction to lift his head to give you that half-glance. So you know that at least some of the cortical-to-cortical connections and the long cortex-to-spinal cord connections work fine. And, if you happened to notice that his eyes moved together, roughly in your direction, then you know that the cortical eyefields can still send signals to the brainstem, which can still coordinate the third and sixth cranial nerves for purposeful conjugate gaze. In a second, you already know a lot about this man's brain.

But he does not observe the niceties of social intercourse. Is he lethargic? Deaf? Depressed? Assuming that his vital signs are reasonably reassuring, the second step after the first glance is history.

What are the priorities? **Tables 2A, 2B, and 2C** outline key elements of our assessment, suggesting a few high priority items in the history and examination. The rapid neurobehavioral assessment is a matter of triage; not a lock-step progression, but a
hierarchical test of the acuity of the condition ruling out emergency, then urgency, then more benign or chronic states. As in pediatrics, our history taking now becomes a delicate balancing of information you may get from the caregiver, who can be an ally with varying sophistication and agendas, and from the patient, whose very responses to historical questions instantly become part of the exam.

Tables 2A, 2B, 2C
KEY ELEMENTS OF THE RAPID NEUROBEHAVIORAL EVALUATION
Table 2A. History of the Present Illness and Past Medical History
History of Present Illness
How much? How quickly? What's changed?
Items of special concern:

- T: Recent trauma?
- H: Headache?
- I: Incontinence?
- S: Sleep disturbance?

- I: Irritability?
- S: Sensory change, including numbness, or special senses such as vision and hearing?

- M: Motor changes, such as slowing or tremor?
- A: Appetite loss?
- D: Delusions?
- D: Depression?

Past Medical History
Items of special concern:

1. Lifetime mental health interventions
2. Lifetime drug/alcohol history, especially anticonvulsants or psychotropics
3. Lifetime traumatic brain injury, stroke, TIA, MI, tumor, renal or kidney disease

Table 2B. Examination
Mental status vital signs: responsiveness, orientation, agitation
Aphasia screen:

1. Say "dog"
2. "What part of my shoe is this?"
3. 4. 5. "Please raise your right hand. Okay, put your left hand on your right shoulder. Good, now first put your right hand on your left knee, then your left hand on your right ear."

6. "What's the difference between a car and a boat?"
Working memory and mental control:

1. Recall "tuna, Paris, strength" after 3–5 m.
2. Month's backwards

Self-reported mood, delusions, hallucinations

Features of the physical and elementary neurological examination of special relevance to the assessment of behavior

Table 2C. Decisions in the Laboratory Evaluation

Electrolytes (any major change can cause delirium; low sodium particularly lowers the seizure threshold)

Blood count (e.g., megaloblastic anemia hints at B12 deficiency; hematocrit <24 may contribute to delirium)

Liver function tests (e.g., for hepatic encephalopathy)

Ca, Ph, Mg (deficits lower the seizure threshold; parathyroid disease produces dementia)

Thyroid function tests (to rule out the most common endocrine dementia)

B12 (to rule out subacute combined degeneration)

Serum VDRL (helps rule out neurosyphilis; positives generally require CSF exam)

EKG (cardiac dysfunction may compromise brain perfusion or hint at metabolic disorders)

Neuroimaging (rule out, e.g., strokes, tumors, hydrocephalus)

Lumbar puncture (in acute delirium to rule out infection or subarachnoid blood; in dementia usually only when syphilis serology is +)

EEG (when seizures, metabolic encephalopathy, herpes, or Creutzfeldt-Jakob are suspected)

THE CHIEF COMPLAINT AND HISTORY OF PRESENT ILLNESS

"What seems to be the problem?" you might say. The answers come from the daughter. The patient doesn't look up. That in itself is quite telling.

Key points:

- How much?
- How long?
- What's changed?

These are the three questions you want immediate answers to in assessing altered mental status (AMS). While we present them in a certain order, there is no strict sequence to getting this information; it's really a matter of assembling a gestalt.

These are the three questions you want immediate answers to in assessing altered mental status (AMS). While we present them in a certain order, there is no strict sequence to getting this information; it's really a matter of assembling a gestalt.
How Much Has Behavior Changed?

Has the patient gone from a vigorous, sociable retirement to a tragically contracted, nearly "vegetative" state? From a sensory deprived developmentally delayed nearly mute resident of a group home to a not-feeding-himself sensory deprived developmentally delayed nearly mute resident of a group home? The magnitude of the shift from baseline in the overall interactiveness and independence level is the first cue to acuity. However, it tells us less about brain locale than we might wish. The first scenario from retirement to catastrophe suggests a global dysfunction that is sometimes assumed to be due to diffuse or multifocal brain injury. But this picture of profound "global" decline might be produced by even a modest interruption in the millimeter-range brainstem arousal systems - such as that caused by systemic infection, a slower than expected metabolism of digoxin or metoclopramide, or a tiny critically-placed stroke (e.g., in brainstem or thalamus).

The second scenario is more the house-of-cards effect, where, in a patient whose behavior depends on a tenuous balance of marginally functioning systems, even a slight shift in one system may produce marked decline. Another example might be an emphysematous patient with mild CHF who has just dropped his PO2 from 65 to 55. Perhaps the most important thing about "how much", is that it hints a bit at the plan. Large amplitude changes are much more likely to warrant prompt work-up, but even a slight drop in independence may compel dramatic rearrangement in the care giving duties.

How Long Has This Problem Taken to Develop?

Has the patient been dwindling for three years? Or is this a case of, "he was good when he went to bed last night, but this morning we found..." Rapid onset is usually assumed to imply some sudden physiological shift, such as acute infection, toxic ingestion, stroke, subarachnoid hemorrhage (SAH), or seizure. And, very roughly speaking, the more rapid the change, the more urgent the need for diagnosis and intervention. This is particularly true now that we can provide improved intervention during the first several hours after a "brain attack" (acute nonhemorrhagic stroke), and many brain attacks present only with behavioral symptoms. However, neurologic conditions are notoriously susceptible to threshold effects, so that even a chronic problem may present acutely. For example, a slow growing brain tumor may be symptomless until the edema reaches a critical threshold, then numbness, weakness, or lethargy can appear in minutes. Again, the main advantage of knowing "how long" is a matter of the urgency of the plan: Stat labs? Scan? Hospitalize? All of these may be appropriate in acute confusional states of unknown cause. On the other hand, if vital signs are benign and the level of consciousness has been the same for three weeks, urgent laboratory tests and hospitalization are less likely to be required this Friday evening. Table 3 lists conditions organized in terms of rapidity of onset.

Table 3: Rate of behavioral change and causes*
* In rough order of frequency. Note that some conditions span different rates of onset, but are more likely to appear in one category than in another

**Very Rapid onset, seconds to minutes**

- Acute intoxication
- TIA, stroke
- Syncope
- Seizure
- Subarachnoid hemorrhage
- Epidural hematoma
- Critical decompensation of mass (herniation, hemorrhage)
- Panic attack
- Intermittent explosive disorder (episodic dyscontrol)

**Rapid onset, hours to days**

- Toxic/metabolic encephalopathies, including withdrawals
- Bacterial or viral infection
- Stroke
- Subdural hematoma
- Increased intracranial pressure

**Subacute onset, days to 1 month**

- Toxic/metabolic encephalopathies
- Brain tumor
- HIV-associated syndromes (e.g., AIDS-dementia complex, CNS lymphoma, CNS toxoplasmosis)
- Fungal meningitis
- Tuberculous meningitis
- Carcinomatous meningitis
- Increased intracranial pressure
- Subdural hematoma
- Neuroleptic malignant syndrome
- Major depressive episode
- Post-partum depression
- Stroke

**Insidious onset, months to years**

- Neurodegenerative diseases (e.g., Alzheimer's, Parkinson's)
- Cerebrovascular dementia
- Toxic/metabolic encephalopathies
- Brain tumor
- HIV-associated syndromes
- Neurosyphilis
- Normal Pressure Hydrocephalus
• Subdural hematoma
• Major depressive episode, Dysthymia

Fluctuating course

• TIAs
• Seizures
• Syncope
• Cardiac arrhythmias, esp. intermittent atrial fibrillation
• Dementia with Lewy bodies
• Neurocyticercosis

As rapidly as we would like to narrow our focus on the acute versus chronic, we shouldn't be misled by two types of chronological confounds. First, and most frequent, is the "false acute" history. Especially in dementias, it is common for a family member to suddenly notice a behavior change that has really been developing for years but suddenly becomes obvious because a minor illness has robbed the patient's tenuous cognitive reserve. This has sometimes been called a beclouded dementia, but the essential idea is simply that a new mental or physical stress brings out the previously hidden symptoms of dementia in a patient who has been getting by on the edge of normal functioning. For instance, a person with mild Alzheimer's disease or hypothyroidism may not have exhibited obvious dementia until they get the flu, or their CHF decompensates, or they are given an antihistamine or anticholinergic agent. The same thing can happen when a novel life challenge pushes the patient beyond their reserve: "He was perfectly fine," you are told, "until we took him to that new symphony hall for his birthday, and he just got all turned around in the parking garage." A visiting relative, a trip to Las Vegas, a driver's license renewal exam, any such novelty may stress a brain that functions well in a routine life, uncovering a chronic cognitive impairment.

Second, there is the less frequent "false chronic" history, when family members suggest that the new problem is long-term, since today's condition doesn't seem much different from the last year. This is most common among those with prior behavior problems in whom change is harder to detect—a developmentally delayed child or adult who becomes subtly toxic on their anticonvulsant, or a schizophrenic who develops a tumor-induced aphasia in the last three weeks about whom it's remarked, "Oh, he's always said things that were hard to follow."

What's Changed?

Note, even though we will eventually address the CNS locale, this is not the neurology attending's medical-student-tormenting question, "Where's the lesion?" This is the simple question, "What's different?" The following questions may facilitate a focused review of systems, recalled with the useful mnemonic :THIS IS MADD! (see Table 2A).

The advantage of reviewing these issues is self-evident; we are searching for the bounds of the problem, and any hint we can get of etiology or localization. For instance, asking
about recent trauma, even if it was assumed to spare the head ("Well, he did get into the fender bender two months ago.") may actually uncover previously unsuspected traumatic brain injury. Headaches that have increased in frequency or severity from the patient's formerly infrequent and mild headaches might hint at hydrocephalus, a space-occupying lesion, escalating hypertension, or metabolic disorders such as hypoglycemic episodes. Poor sleep not only occurs in many mood and thought disorders, but may hint at sleep apnea, a frequently missed cause of otherwise unexplained mildly impaired cognition, especially in middle-aged men.

The daughter's answer, "Yes, he's really slowed down," may not seem to help in identifying the problem, but it actually can be quite useful because this is not the usual answer in a hemispheric stroke or tumor, which would be a little more likely to produce a hemiparesis the daughter would note, and it is more consistent with diffuse or multifocal processes such as toxic, metabolic, infectious, or neurodegenerative disorders. Unfortunately, general slowness might also be due to increased intracranial pressure that diffuses the effect of a focal mass, or due to focal disorders of the basal ganglia producing a Parkinson's-like slowing (bradykinesia).

Of course, the answer, "You know, he keeps falling to the left," or any such hint of asymmetry leads to the "Ah hah!" that rapidly focuses our inquiry on focal processes such as stroke or mass lesion or trauma. However, we must also beware of the phenomenon of "red-herring localization": a diabetic may experience a drop in glucose level—a systemic problem—and present with right-sided weakness and aphasia because of some unpredictable asymmetric reserve capacity of his cortical neurons. A hyperlipidemic patient with mild basilar artery stenosis, altogether neurologically asymptomatic until today, may have a visual hallucination. This may occur because one visual field is briefly blinded due to global cerebral hypoperfusion that disproportionately affects the area served by the stenotic vessel, but it's actually caused by transient cardiac arrhythmia—best treated as a heart more than brain problem.

So, the first goal is simply to get an accurate fix on "what about this man's behavior inspired this Friday clinic visit?" The net result of the "how much"; "how long"; and "what", questions might simply be: "A 35-year-old woman states that her 83-year-old father is "just different", really slowed down, and has been for a month." Such a seemingly indeterminate characterization is potentially loaded with diagnostic information. Some conclusions are obvious: it's less likely to be SAH because we don't hear about sudden change or head pain. It's less likely to be a bacterial or viral meningitis, which are also usually more precipitous. However, despite the "one-month" history, we must still consider problems that you'd ordinarily expect to cause a sudden change, such as a stroke or traumatic brain injury, but escape detection because they've also impaired the patient's ability to complain. "He never said anything," an informant accurately reports about a history of head trauma, because after standing up under the open kitchen cabinet door and bumping his or her head three months ago, the patient shrugged it off as just another of life's little traumas as their subdural hematoma was forming due to the increased bleeding tendency caused by the Coumadin they take for their atrial fibrillation, and today the resulting amnesia prevents their even recalling the
trauma. "No, he/she hasn't complained of weakness or numbness," the informant accurately reports because the patient's stroke two weeks ago not only damaged the right frontal lobe causing a mild left hemiparesis, but also the right parietal cortex, causing anosognosia - denial of their own hemiparesis. Obviously, still open to consideration in this case are toxic or metabolic disorders, systemic infections, chronic CNS infections, or neurodegenerative diseases.

The present history, of course, could be considerably elaborated if we are rigorous and go into recent travel, exposures to others with illness, exposure to chemicals, nutritional changes, etc. But, in the parsimony of our 15-minute assessment, the most commonly missed pertinent parts of the history and the two general medical questions we must really ask are, 1) "Any infectious symptoms (UTI's or URI's)?", 2) "What drugs or medicines has he been taking?" This last question has probably yielded more specific neurobehavioral diagnoses than any, and notoriously uncovers iatrogenic disorders. Stimulants, depressants, drugs with CNS toxicities, and illicit drugs including alcohol account for 35 percent to 60 percent of cases of new-onset confusional syndromes.

Table 4 lists some drug causes of altered mental status (AMS). In addition, particularly in cases of suspected dementia, we may need to work a little to establish the onset.

"I understand your Dad has been different for the last month, but, in the last few years, was he just the same fellow as he was twenty years ago?" "Pretty much," she answers, "although he hasn't been gardening so much in the last few years."

This change in activities might be due to arthritis, weather, or a myriad of other reasons, but such an innocuous answer might also be the first hint we get that the present illness may actually have been long in coming on. We might proceed to ask a very open-ended question that sometimes gets to the depth of the problem:

"What worries you most about this?" She ponders a moment. "He's just...not my Dad." Absently, she drags her sleeve across her eye.

There is obviously no exact formula, no turn of phrase or tone of voice that will reliably elicit key answers, and every family physician will creatively find their own way. But answers such as this, vague as they may seem, can alert us. This is not a minor matter; the daughter senses that Mr. Johnson is in serious trouble.

Table 4: Drug Causes of Altered Mental Status

- **Sedative hypnotics and opioid analgesics** such as benzodiazepines, neuroleptics (e.g., haloperidol (Haldol®), prochlorperazine (Compazine®), metochlopramide (Reglan®), promethazine (Phenergan®), meperidine (Demerol®), pentazocine (Talwin®), other opiates.
- **Antihistamines**, particularly diphenhydramine (Benadryl®).
- **Anticholinergic agents** such as benztropine mesylate (Cogentin®), trihexphenidyl (Artane®), and tricyclic antidepressants.
• **Histamine blockers**, especially cimetidine (Tagamet®).

• **Cardiovascular agents**, including beta blockers, amiodarone (Cordarone®), calcium channel blockers, digitalis preparations, doxazocin, disopyramide phosphate (Norpace®), methyldopate HCl (Aldomet®).

• **Selective serotonin reuptake inhibitors (SSRIs)** such as fluoxetine (Prozac®), sertraline (Zoloft®), paroxetine (Paxil®).

• **Anti-inflammatory drugs** such as corticosteroids and nonsteroidal anti-inflammatory drugs (including aspirin).

• **Drugs with stimulant or sympathomimetic properties** such as aminophylline, theophyllin, ephedrine, phenylephrine and phenylpropanolamine and herbal ephedra.

• **Muscle relaxants** such as baclofen (Lioresal®), or carisprodol (in Soma®).

• **Antimicrobials** such as sulfamethoxasole, aminoglycosides, tetracycline, ticarcillin.

• **Antineoplastic drugs** including aminoglutethimide, asparginase, 5-Flurouracil, methotrexate, vinca alkaloids.

• **Cholesterol-lowering agents**

• **Drugs of abuse** including alcohol, nicotine, cocaine, amphetamines, caffeine, hallucinogens, phenycyclidine, barbiturates, opiates, inhalants

### Past Medical History

Perhaps the easiest question to ask, and occasionally worth repeating, from the HPI, is: "Has anything like this ever happened before?" High proportions of patients seen for neurobehavior assessment have chronic problems with recurrent episodes of AMS, from major depression to transient ischemic attacks (TIAs). Although it may sound redundant, repeating this question occasionally elicits answers such as, "Oh, you mean like that time back in Iowa when they had to do that thing to his brain?"

Otherwise, areas for special attention in the past medical history include:

1. **Any lifetime mental health interventions**
2. **Any use of drugs, prescribed or not** (A useful helpful question is, "Did he ever in his life take medicine for seizures, or his mood?")
3. **Any history of head trauma** (Including youthful boxing, or incarceration, which may only suggest increased risk for unreported head trauma but also possibly hints at temperament, addictive traits or intermittent explosive behavior.)
4. **Any vascular disease** (increased risk of TIAs and stroke)
5. **Any solid tumor** (increased risk of brain metastasis or paraneoplastic syndromes)
6. **Any renal or liver disease** (risk of encephalopathy)
7. **Any HIV risk factors** (including blood transfusions in the early 1980s)

*Mr. Johnson denies any of the index medical problems. He only recalls taking occasional acetaminophen. His daughter wisely dumps the contents of his medicine cabinet on the examining table. There are full bottles of a calcium channel blocker, a diuretic, with prescription from another physician two years ago, and an over-the-counter cough*
suppressant-decongestant-antihistamine syrup, and a half-empty container of bismuth subsalicylate (Pepto-bismol®) and another of acetaminophen.

**THE NEUROBEHAVIORAL EXAMINATION**

It has been estimated that 70 percent of medical diagnoses are made on the basis of history. The additional information, culled from a few minutes of informal observation in peripheral vision, may add a great deal, particularly in behavioral disorders. But, let us assume you have 5 minutes left to undertake the formal neurobehavioral examination. Again, it is understood that some factors, level of consciousness, cooperation, and language barriers, may frustrate any such artificially imposed schedule, and that a full assessment really takes longer. Nonetheless, we offer the following only in the interests of suggesting ways to efficiently negotiate the largest branches of the decision tree (see Tables 2A, 2B, 2C).

It is conventional to describe this examination in terms of cognitive domains, e.g., attention, mood, language, memory, but in practice, every moment provides opportunities to examine multiple domains. For instance, we extend our hand to greet the patient. Their response in the next two seconds may partly reveal level of consciousness, social appropriateness, affect, vision, presence of dominant sided bradykinesia or dysmetria or paresis. In addition, as we attempt to strategize, our first goal is not so much to systematically assess cognitive domains as to rapidly get a sense for the acuity of the situation. We need to establish, if possible in the first few minutes, whether or not we are dealing with an acute confusional state (delirium) that is more likely to require immediate action. (Note: the terms "delirium" and "confusional state" are used interchangeably. Neither one is ideal because each has misleading connotations from colloquial use. "Delirium" popularly connotes a striking behavior change, but it actually means a broad spectrum of AMS including very subtle changes. "Confusion" is rather vague, since popular use applies it to everything from error to psychosis. In the neurobehavior evaluation, by a delirium, we specifically mean AMS with diminished attention, assayed in terms of coherence and responsiveness). So we need to assess the "vital signs of behavior," the keys to severity, acuity, and need for prompt intervention.

The Vital Signs of Behavior

- The Vital Signs of Behavior
- Level of responsiveness
- Orientation
- Degree of agitation

*We approach the 83-year-old man and extend our hand, introducing ourselves. He looks at the hand, looks up at us, mutely smiles, and accurately reaches to offer a firm handshake.*

This is not normal. Social adepts will watch your hand in their peripheral vision as you begin reaching toward them, beginning their own arm movement before you have even
fully extended yours, and will say something pleasantly appropriate. So we already suspect AMS. But at least his level of responsiveness is sufficient to respond to this cue, if too slowly, and there is no overt anger, suspiciousness, sadness, or agitation. Not to belabor the point, but our examination is really conducted in this way, painting a pointillist portrait by inference from every fleck of behavior.

**Level of responsiveness** simply refers to what the patient does in response to what we do, and whether that is normal. At lower response levels, this is the basis of the Glasgow Coma Scale (GCS). Coma is addressed elsewhere in this volume, but overlaps with this neurobehavioral examination since delirium is on a continuum with coma (while dementia isn't) and delirious patients may lose a point or two on the GCS for failing to move or verbalize appropriately. In delirious patients, level of responsiveness might be quickly assessed by the rate and appropriateness of responses to soft voice, then, if necessary, loud voice, then, if necessary, some form of touching to trigger an alerting response. If the patient appears awake, but does not respond until we touch them, we still cannot assume encephalopathy is present, since deafness, uncooperativeness, paralysis, or (quite rare) catatonia may produce the same lack of response. Language barriers or aphasia, however, do not really compromise this test, since the examiner's voice itself should surely elicit an alerting response. (Imagine yourself ill in a foreign hospital). Mr. Johnson superficially seems to have a normal level of responsiveness.

"Would you please look up for a moment?" may be among the best first questions we can ask. Ability to follow a one-step midline body command tests the most basic level of comprehension, something we learned to do at 18 months old. Even a quadriplegic patient on a respirator or a locked-in patient with no motor control below the brainstem can look up. Patients who have been mistakenly assumed to be aphasic, stuporous, or "vegetative" will be extremely grateful that you ask this initial question, giving them a chance to demonstrate their intact cognition. In addition, it tests hearing, an essential prerequisite for the validity of the entire examination. We ask this question. After a pause, Mr. Johnson looks up at his daughter a bit quizzically. It might have been an appropriate response, but other patients promptly look up at the ceiling. The response delay and direction makes us wonder about a slight deficit in Mr. Johnson's level of responsiveness. We reserve judgment.

**Orientation**, so called, is a reasonable place to proceed with the direct verbal questioning of the patient. Again, these "who, where, when" questions actually assess multiple domains, including alertness, recent memory, and general knowledge, but we are asking in order to see whether the patient has been able to maintain sensory receptiveness, conscious awareness, and a coherent stream of ideas for the last several hours or so. The "why are you here?" question often provides telling information about not only alertness, but also insight, judgment, thought content, mood, personality, and degree of irritability.

By the time we've checked orientation, which may have taken less than a minute in many cases, it is quite likely that we will have a fair idea of whether the patient is delirious and whether they are so agitated as to require a higher level of vigilance, if not sedation or restraint. As a rough rule, if the patient can hear, seems to be trying to cooperate,
your language, and isn't aphasic, they will give prompt (if wrong) answers to these questions, proving that they have an acceptable level of responsiveness. If they do not do so, it is very likely that they are in a confusional or encephalopathic state, upping the ante for prompt intervention.

Perhaps the most difficult exception to this rule is the differential diagnosis of receptive (Wernicke's) aphasia versus confusion. Both problems lead to abnormal verbal responses. The Wernicke's patient is somewhat more likely to produce jargon, and nonsensical speech, with clear enunciation, while the delirious patient is more likely to produce grammatically correct, if inappropriate, statements, with some degree of slurring and/or decreased arousal or wandering attention. Another exception is severe mood disorder, e.g., the profoundly depressed patient with psychomotor retardation (who in fact is encephalopathic as shown by global hypometabolism on brain PET scans), or severe thought disorder (psychosis), e.g., in schizophrenia, and also seen in severe depression or mania. Both of these may mimic a medical and/or neurologic confused state.

If we reach the conclusion that level of responsiveness is depressed, it increases the likelihood of certain diagnoses, such as toxic or metabolic encephalopathy (including drug withdrawal), neuroinfection or systemic infection (especially with fever), hypoxia, increased intracranial pressure (IICP) with or without mass, large stroke, epilepsy-associated phenomena, or CNS vasculitis. Since the mortality rate for delirium is quite high, (15 percent–65 percent of admissions), a suspicion of any of these problems again obliges us to consider jumping ahead: stat labs? scan? hospitalize?

On the other hand, if the patient evinces a satisfactory level of responsiveness, it shifts the diagnostic balance somewhat more in favor of small stroke, tumor without mass effect, neurodegenerative disease, or "primary" psychiatric disease. (For the purposes of this discussion, we will accept the conventional dichotomy between "primary" ["idiopathic"] and "secondary" [due to medical/neurologic conditions] psychiatric disorders, understanding that it is a rather arbitrary rule of thumb created by our slowness to unravel the pathophysiology of a subset of brain-based behavioral disturbances).

So far, 70 seconds into the examination, we have shaken our patient's hand and he has responded to one command and five questions. "John Johnson. It's Tuesday, isn't it?" "Where are we?" "Oh, I don't keep up with that kind of thing." "Why are you here?" "Well, I'm here, aren't I?" He chuckles, punching you lightly on the arm, "and so are you!"

There is no slurring, but the responses come out like the pouring of lumpy soup: a bit slow, then suddenly too fast. His eyes are a bit wider than you'd ordinarily expect, searching, and a little red, as if sleep has eluded him. The uncertainty of the day of the week in itself is not abnormal. He seemed to understand the questions and produce fluent speech, making aphasia less likely. But the emptiness of the other responses indicates definite cognitive disturbance. In addition, while level of responsiveness is fairly good, the odd pacing of his verbal output leaves us uncertain: is this just cognitive impairment
(as in dementias like Alzheimer's), or is there also a confusional state (delirium), with impaired attention to the world around him?

**After the Mental Status Vital Signs - Focusing the Examination**

Ideally, at this point we would perform a complete assessment of affect, mood, thought content, thought process, attention, memory, language, calculations, abstraction, right/left orientation, judgment, insight, praxis, and constructions. We will not. Instead, the press of time often favors focusing the examination on issues we've become particularly concerned about and deferring other parts of the examination until later. How do we focus? We've already substantially narrowed the differential diagnosis based on the rate of onset, degree of change from baseline, type of dysfunction, and presence or absence of a confusional syndrome. This guides the next few minutes of the examination. For instance, an insidious onset causing a mild change without confusion frees us to test complex cognitive functions; we are thinking of neurodegenerative diseases, slow-growing tumors, and the like. Any overt depression or psychosis obliges us to give extra attention to affect and thought processes; whether primary or secondary, we are thinking of psychiatric distress. A rapid onset, large change with confusion suggests that we'd perhaps serve the patient better by rushing to the neurologic examination and laboratory evaluation; we are concerned about an acute and possibly emergently treatable encephalopathy.

If time permits (meaning the apparent absence of an acute confusional state), we can proceed to screen for "higher cortical functions."

[Note: Cognitive functions that seem to us to be more phylogenetically advanced than arousal, less directly tied to autonomic response than emotions, and separate from psychotic thought processes are sometimes called "higher cortical functions." This phrase usually refers to processes such as memory, praxis, or self-monitoring. These were called "higher cortical functions" because of early theories that such functions were mediated by the late-evolving heteromodal association cortex, that is, cortex such as the inferior parietal lobule or prefrontal lobe that integrates multiple subcortical pathways, and it has sometimes been assumed that impairment of those behaviors only occurs following damage to those cortical areas. However, clinical experience shows that subcortical injuries may produce indistinguishable syndromes. For this reason, a more accurate phrase might be "cortical/subcortical cross-modal integrative cognitive functions." But that's a mouthful.]

Many clinicians use the 30 point Mini-Mental State Examination (MMSE) in these circumstances (Folstein et al, 1975 see Appendix A). On the one hand, we must recognize the limits of using the MMSE or any uniform cognitive screening instrument. The MMSE was not intended to provide a diagnosis. An Alzheimer's patient can score 0 or 30. An aphasis patient can score 0 and be completely alert, achieving the same score as a patient in deep coma. A severely psychotic patient may score 30 while a cognitively intact but uncooperative patient may score 5. On the other hand, such a uniform set of queries has four advantages: 1) it touches on a number of cognitive domains and takes
just five minutes in a cooperative patient; 2) it is widely used and the normative value of a near-perfect score has been well established; 3) specific items sometimes reveal specific problems; and 4) although definitive health outcomes research is needed on this subject, the presence of decline on successive tests may reveal an otherwise occult dementia, so we suggest doing the MMSE as a routine part of health screening for adults over 55.

Whether or not we perform the MMSE, at this point in almost every evaluation a high priority is to test that the remainder of interaction with the patient involves meaningful communication. We should quickly screen for aphasia.

THE ONE-MINUTE APHASIA SCREEN

1. "This may sound a little silly, but could you please say 'dog'?")
2. "Thanks, now, what part of my shoe is this?" (Indicate the heel).
3. 4.5. "Good. Please raise your right hand. Okay, put your left hand on your right shoulder. Good, now first put your right hand on your left knee, then your left hand on your right ear."

1. "This may sound a little silly, but could you please say 'dog'?" —Simple repetition tests hearing, Wernicke's area, the arcuate fasciculus (white matter tract from temporal to prefrontal cortex), Broca's area, the transfer of impulses from Broca's area to the motor speech cortex, and the transfer from motor cortex down to brainstem neurons controlling the muscles of articulation.

2. "Thanks, now, what part of my shoe is this?" (Indicate the heel). Naming is not well localized in the brain, but asking for the name of a medium-frequency target (e.g., heel, sleeve, cuff) is a good general screen for dominant hemisphere function. High-frequency words like 'pen' are so well ingrained that they may be named despite an aphasia; low-frequency objects like 'stem' or 'lapel' may be too education-dependent to fairly test language.

3, 4, 5. "Good. Please raise your right hand. Okay, put your left hand on your right shoulder. Good, now first put your right hand on your left knee, then your left hand on your right ear." Having established basic functionality of the left hemisphere, we return to receptive language. By quickly marching up through levels of complexity, from a one-step unilateral command to a two-step cross-body appendicular (extremity) command, we can rapidly get a rough estimate of degree of comprehension. Alert adults can usually manage a three-step sequence. Pointing at one, then two, then three things around the room is an alternative and tells more about environmental awareness but less about comprehension. Note again that it is challenging to distinguish between Wernicke's aphasia and confusion, but confused patients are more likely to have wandering or fluctuating attention. In addition, apraxia can manifest as failure to follow cross-body commands. But the apraxic patient can usually still point to things about the room.

6. "Thank you. Now, I know this may sound a little funny, but what's the difference between a car and a boat?" The exact question we ask to stimulate fluent conversation is
not as important as its evocative effect. We don't want to ask something that can be answered with "Yes", or with a monosyllabic answer like "Sure." We want to hear the patient assemble a fluent string of words, regardless of content, correctly sequencing subject, predicate, and object. So, "Tell me the things you'd buy for a picnic?" is better than, "Do you think the Cubs have a shot this year?" Though our goal is to test for a productive (Broca's) aphasia, odd answers may also help us discover interesting things about the patient's ideas. See Figure 2.

Mr. Johnson shrugs and cooperates, speaks fluently, and follows two-step, but not three-step, commands. He is easily distracted as the nurse walks by the door, and twice, you have to repeat questions. "Well, a car is, like, for out here, but boats you gotta', you know, get to someplace with 'em."

As fluent as this is in a grammatical sense, it is sorely lacking in depth and meaning. This aphasia screen may have required a minute or two, depending on whether we've been able to draw conclusions from casual observations of the patient's verbal interactions even before any formal testing. Reading, writing, or repetition of nonsense phrases all might be useful to test, but we have already assessed most language functions and the memory capacities required to answer orientation questions.

For the purposes of our rapid evaluation, it is rarely urgent to specify the type of aphasia. It is enough, in most cases, to note that language performance is abnormal, assume that the dominant hemisphere is probably affected, then look for an etiology. However, if we wish to go into slightly greater depth, and understanding that the classic syndromes do not typically appear in pure form, nor are they strictly localizable, several rough rules of thumb help to characterize brain/language relationships:

**Broca's aphasia** = productive aphasia: impaired rate and fluency of speech output; stereotyped speech ("I am; I am"); poor generation of word lists; poor writing; and poor repetition, classically due to posterior-inferior frontal lobe dysfunction.

**Wernicke's aphasia** = receptive aphasia: impaired comprehension, often affecting both spoken and written material; poor repetition; sometimes "word salad", paraphasic errors, or nonsense words despite some recognizable grammar (e.g., "We aren't what to going that the fordun is, is it?"), classically due to posterior-superior temporal lobe or adjacent parietal lobe dysfunction.

**Transcortical motor aphasia** is similar to Broca's but repetition is relatively spared, classically due to subcortical prefrontal lobe lesions.

**Transcortical sensory aphasia** is similar to Wernicke's but repetition is relatively spared, classically due to subcortical parietal lobe lesions.

**Conduction aphasia** is relatively worse repetition than production or comprehension, classically due to interruption in the arcuate fasciculus, the subcortical tract running between Wernicke's and Broca's regions.
Mixed aphasia combines features of productive and receptive impairment, either due to patchy dominant hemisphere cortical dysfunction or subcortical lesions that affect both motor and sensory tracts. When severe, this is a global aphasia.

Next we should test two facets of thought that are necessary for a coherent stream of consciousness and to assure that what we say to the patient is at least briefly retained: working memory and mental control.

**Working memory**, a type of short-term memory, refers to *the temporary storage of information that is available for review or mental manipulation*. Intact working memory depends not only on the medial temporal lobe memory system but also on the activity of several mid-prefrontal lobe regions. See Figure 2.

It is beyond the purpose of this chapter to cover the neurobiology of memory, but recent advances are so intriguing that a very brief review might interest the reader: short term memory seems to be based on temporary changes in patterns of synaptic responsiveness. Longer-term memory seems to depend on new protein synthesis and resulting lasting structural changes in synapses. The electrochemical phenomenon of long-term potentiation (LTP), by which a series of stimuli leads to a change in subsequent neural response, may be the physiological underpinning of learning.

Learning probably involves:

1. The **medial temporal lobe memory system** (entorhinal cortex, hippocampus, parahippocampal gyrus and amygdala) and
2. The **prefrontal lobe working memory system**.

The **medial temporal lobe memory system** allows us to incorporate information into a lasting memory trace. This system is activated by the excitatory amino acid neurotransmitter glutamate, but it also requires the presence of acetylcholine (the profound lack of which correlates with memory loss in dementia of the Alzheimer type). The amygdala seems to have a special role, contributing emotional weighting to the memory process. The **working memory system** is a sort of memory buffer in which stimuli and ideas may be manipulated, both during learning and recollection. Recent evidence from functional MRI experiments suggests that especially complex memories require more superior and dorsolateral prefrontal cortical activation.

A simple test of working memory is to ask the patient to repeat and remember three words. Three visual objects are often used, ("apple, table, penny"), but the presence of a table in the room gives the patient a cue, and very common visual things may be stored more easily than abstract concepts. One strategy might be to use one visual object not currently in sight, one somewhat less easily visual word, and one abstract word, e.g., "tuna, Paris, strength." Make sure the patient repeats all three, (registration or immediate memory), to confirm that they've activated the prefrontal lobe working memory store.

*Our 83-year-old patient repeats the words accurately, if bemusedly, after two attempts.*
No matter when we test working memory in the course of the examination, the important thing is that there be three to five minutes of distraction before asking the patient to recall the words. Roughly speaking, spontaneous recall of zero or only one word is abnormal. Mr. Johnson says, "Tuna, terrace, and you know...the other one." Clearly something was retained, and, because he had repeated "Paris" at the registration stage, we know that his phonemic substitution (terrace, rhyming with Paris) is not just from hearing loss.

We may then give the patient hints about the words, (e.g., either category cues, "one of them was a city," or the more generous multiple choice cues, "was the city Rome, Paris, or London?") to see what it takes to jog their memory. In theory, if the patient doesn't remember any of the words, even with cues, it suggests a severe amnesia, a learning problem, often involving medial temporal cortex. However, if they benefit from cues, it indicates that learning is intact, but that there is a retrieval problem, sometimes due to a subcortical dysfunction such as Parkinson's disease. In practice, no such localization distinction should be assumed on the basis of our brief test; we are just getting a sense for the severity of the memory problem. Nor can we assume that memory impairment uncovered by this quick test identifies a particular condition. Digitalis toxicity, Alzheimer's disease, or anxiety may lead to the same results. But at least we have a better idea of the patient's ability to maintain a brief lock on a mental reservoir. Mr. Johnson chooses from the multiple-choice list, "Paris, of course! Didn't I say that?" We conclude that cues help him a bit, but his memory is definitely impaired. What's more, he may even be having trouble monitoring his own behavior from just seconds earlier, which may be another sign of possible prefrontal dysfunction and a hint of inattention (beyond a short-term memory deficit), somewhat suggesting that there might be confusion rather than simple dementia.

**Mental control**, sometimes called "executive function", is the ability to adaptively manipulate information in working memory. This capacity is also referred to with the overlapping concepts of "executive" or "frontal lobe" function; although the prefrontal cortex is only part of the multiregional system invoked. Spelling a word backwards, counting backwards by 7's or 3's, naming every third letter of the alphabet, or reciting the months of the year in reverse all require more than just memory. There are the additional elements of 1) undertaking and maintaining focus on a task in the midst of external or internal distractions - requiring brainstem arousal, midline frontal lobe and limbic motivational systems, and prefrontal attentional systems—as well as, 2) correctly planning and sequencing the production of the answer—requiring working dorsolateral prefrontal lobes.

*We ask Mr. Johnson to recite the months backward. "Sure. January, February..." he starts rapidly forward. We remind him of the task. "Oh, December...ah... September, November, December! And I want my shoes!" He grins.*

As his daughter has intuited, Mr. Johnson is in trouble. Not only does he show signs of disorientation, memory impairment, and mental dyscontrol, but he has also made a couple of odd comments that were not direct responses to our questions. This is a tough case. We still don't know for certain whether this is a dementia or a new onset...
confusional state, since he has not demonstrated overt lethargy. But his fluctuating rate of speech, slight response delays, distractibility, apparent immediate forgetfulness of his own statements and spontaneous behavioral detours make us concerned about mild confusion.

If we were less concerned about quickly assessing Mr. Johnson, or had more time, or noted odd interactions or movements that still required explanation, we might screen for several classic syndromes of cross-modal integrative cognitive function:

**Ideomotor apraxia:** The patient fails to do on command motor acts that they apparently have the strength and coordination to perform. We ask the patient "Show me how you would hammer a nail" or "salute" or "comb your hair" or "how does a boxer hold his hands?" or "blow a kiss" and we see a slow, awkward, befuddled attempt to comply. Dysfunction of the dominant hemisphere with or without paresis or aphasia can produce this apraxia. The rare neurodegenerative condition corticobasal-ganglionic degeneration may also produce this.

**Ideational apraxia:** The patient fails to generate or mime a sequence of actions that one would commonly need to perform to complete some common activity of daily living. We ask the patient "Show me how you would prepare a bowl of cereal" or "write, seal, stamp and mail a letter" and the patient fails to some degree. This problem occurs in both dementia's and confusional syndromes.

**Constructional apraxia:** difficulty copying two or three-dimensional figures. It is sometimes assumed that this indicates right cortical dysfunction. In fact, almost any CNS dysfunction may interfere with copying a figure, from infarcts that affect motor function to impairments anywhere in the visual system. However, setting aside localizing value, constructional difficulty may be quite sensitive to confusional states or dementias, where drawing is often disorganized, as opposed to psychosis or mood disorder, where drawing is usually preserved.

**Angular gyrus syndrome:** a surprisingly well-localized tetrad of impairments, including difficulties with right/left discrimination, identifying fingers, performing calculations, and writing, classically due to dysfunction at the intersection of the posterior temporal lobe and the inferior parietal lobe.

**Neglect:** primarily seen as lack of attention to one side of the environment, most often after right parietal injury, producing inattention to the left hemi-world. The patient may shave half of their face or eat the food on half of their tray.

**Anosagnosia:** impairment in recognizing the presence of an illness, including motor or sensory problems, often accompanied by neglect. For instance, the patient may deny having left hemiparesis, saying "Nothing's wrong with me," as she lifts her plegic left arm, "but could you get this dog out of my bed?" This is common with right hemisphere strokes, especially those involving both frontal and parietal lobes.
Prosopagnosia: failure to recognize faces. This may take the form of inability to recognize relatives, or difficulty identifying pictures of celebrities. It is most often due to bitemporo-occipital lesions.

All of these syndromes are most frequently reported after strokes, since these unfortunate experiments of nature often selectively damage isolated brain regions. However, any process that can affect the relevant parts of the brain may present with these complex cognitive syndromes. Tumors, traumatic brain injury, or neuroinfections may all produce these impairments.

We still need a quick screen for psychiatric symptoms such as depression, psychosis, and anxiety. Mania is possible, but less common and usually apparent from the early moments of the visit in the rapid speech and hyperactivity of the patient. In Mr. Johnson's case, we've already gotten an impression of his apparent lack of extreme depression, agitation, or fearfulness in the face of a clear impairment of cognition. Nonetheless, a couple specific questions are worthwhile as a loose seine to catch mood or thought disorders.

Section 2

1. "Are you feeling sad or depressed?" The more straightforward, the better. "Naw, I don't feel bad." He snaps his fingers. "I'm good." Had his mood (what he reports) or affect (what we observe) been depressed, we might explore this more fully.

2. "Do you have any scary thoughts? Like, people are out to get you?" An extensive series of questions may be necessary to probe for delusions - fixed false ideas - but even one simple query like this gives the patient a chance to ventilate about things that they may have been reluctant to bring up before. "What do ya' mean?" our patient says. No one wants to bother me."

3. "Do you see things that no one else can see? Or hear things like voices when there's no one around?" Again, we're only doing a quick screen for a subset of hallucinations. As blunt and awkward as these questions may sound, psychosis may be hidden until they're asked. "What, do you think I'm crazy?" It's the first time he bristles. You make some apology and carry on. He shrugs, quickly placated. But he turns to his daughter, "Now you take a pie to Fred, all right?" Spontaneous behaviors like this may be more revealing than any of our formal questions. There's no apparent reason for this
skewing of his attention. Unless there is a subtext that we've missed, this man has just demonstrated again his tenuous connection to the circumstances he finds himself in.

A final issue to be considered—not so much as a specific point of examination but as a general question with every patient—is the possibility that the symptoms are psychosomatic, either unconscious somatoform problems (inappropriately called hysteria), or conscious malingering. Many articles have been written proposing tricks of history or examination to uncover such cases. However, as the late D. Frank Benson, M.D. of UCLA put it, "All hysterics die of organic disease." In fact, there is evidence that the signs relied upon to discriminate psychosomatic conditions are often positive in patients with organic illness. Also, a high proportion of patients discharged with an initial diagnosis of hysteria are soon re-examined and found to have an organic problem. We would much rather pursue organicity in the face of doubts than unwittingly dismiss a sick patient.

This is perhaps the essence of the neurobehavioral evaluation: we try to rapidly estimate the likelihood of delirium and to rule out severe mood or thought disorders. That's it. More extensive assessment will certainly improve our diagnostic accuracy, but the practical goal is to narrow the differential and assess the urgency of intervention. By this point we have asked about 20 questions and gotten a sense for the rate of onset and degree of change. We may not have a specific diagnosis, but we know our patient needs further attention today. We check with the nurse regarding our other patients, listen to our asthmatic's lungs, answer a phone call, look at some labs, and return to Mr. Johnson's room to proceed with a quick physical and elementary neurological examination.

**FEATURES OF THE PHYSICAL AND ELEMENTARY NEUROLOGICAL EXAMINATION OF SPECIAL RELEVANCE TO THE ASSESSMENT OF BEHAVIOR**

The components of the physical/neurological examination are well known and covered extensively elsewhere. In this section we will simply focus on several features of the examination that may speed diagnosis.

It is often remarked that an examination is focal or nonfocal. This is somewhat misleading, particularly when "nonfocal" is used as a substitute for "normal." Patients in status epilepticus or coma may have "nonfocal" examinations, so this designation hardly helps specify the diagnosis or the medical acuity. We suggest not using this designation, and instead cataloguing the presence or absence of certain distinguishing features, which help to construct a simple algorithm for narrowing the differential diagnosis. See Figure 3.

1. **Is there any brainstem dysfunction?** The presence of nystagmus, dysconjugate gaze, or altered pupillary responsiveness are easy-to-check hard signs that the patient's problem involves the CNS. Visual field deficits may be the only sign of temporal, parietal or occipital lobe lesions. We got an idea of hearing very early in the assessment, so formal testing is less urgent. We've also long since noted slurred speech or other dysarthria,
which would strongly support a CNS localization, although we can't be sure that slurring specifically means brainstem dysfunction since cerebellar, basal gangliar, or even hemispheric injury may alter speech. Any brainstem signs strongly increase suspicion of a medical/ neurological cause of AMS.

2. Is there any motor dysfunction? Asymmetric strength is obviously suggestive of asymmetric CNS injury—whether ipsilateral or contralateral. But general slowing also narrows the diagnosis, suggesting decreased brainstem/arousal (as in toxic/metabolic encephalopathies), decreased midline frontal/motivation (e.g., frontal convexity meningioma, hydrocephalus, or depression), or impaired basal ganglia function (e.g., Parkinson's). Incoordination on the finger-to-nose test draws attention to the cerebellum, but may actually result from brainstem dysfunction due to toxic CNS depression, or increased intracranial pressure (IICP). Any motor deficit is a potent hint that there is a medical/neurological cause of AMS.

3. Is there any gait dysfunction? Even a ten second look at the patient's gait can be extremely revealing. Schizophrenics who do not have a superimposed neurological problem will walk well. Alzheimer's patients walk well until late in the course. In contrast, most processes that affect the brainstem, cerebellum, motor strip, basal ganglia, intracranial pressure, proprioceptive regions, or spinal cord may show up as slow or awkward gait.

4. Can the patient feel their feet? Peripheral neuropathy may be a quick hint at the presence of several problems causing AMS, such as diabetes or B12 deficiency. A detailed sensory examination can take a great deal of frustrating time in confused patients, but their awareness that you've moved a toe takes a few seconds and serves as an adequate screen.

Mr. Johnson has questionable bilateral gaze-evoked nystagmus. His gait is slightly stooped but he walks faster than we do, grinning at his own performance and not quite tipping on his excessively quick turn.

PART II: DIFFERENTIAL DIAGNOSIS OF CONFUSION AND DEMENTIA

At this point, we might review the spectrum of etiologies to be considered when a patient presents with a poorly defined, but clearly abnormal mental status. As the case we are considering illustrates, it is sometimes hard to distinguish between confusion (or delirium) and dementia. But, for the sake of organization, we will consider these as distinct, if overlapping, syndromes.

Dementias

Classifying dementias. Dementia is defined in the American Academy of Neurology Practice Handbook (1995) as "A clinical state characterized by significant loss of function in multiple cognitive domains, that is not due to an impaired level of arousal." The Handbook further states, "The presence of dementia does not necessarily imply..."
irreversibility, a progressive course, or any specific cause." Note that it is difficult to provide a precise definition. The root meaning of dementia is simply a decline in mind. If we strictly applied the root meaning of the word, dementia would include any confusional state and any circumscribed deficit. For practical purposes, we exclude from the diagnosis of dementia individuals with either confusional state (delirium) or restricted deficits (e.g., aphasia). It is more controversial whether to exclude those with cognitive deficits accompanying psychiatric disorders. That is, some authorities regard the impaired cognition in severe depression as a "pseudodementia," others note that, whether or not it is reversible, it has all the features of dementia and should be called the "dementia of depression."

A straightforward way to classify dementias is as brain-related versus general medical disorder-related. For instance, the neurodegenerative dementias of Alzheimer's or Parkinson's disease, as well as other conditions such as brain tumors or normal pressure hydrocephalus are brain-related, relatively sparing other organ systems. In contrast, disorders such as hypothyroidism or vitamin B12 deficiency might be considered primarily systemic, due to a general medical disorder with significant effects beyond the cerebrum. This distinction breaks down a bit with vascular disease, since strokes can produce a dementia that is primarily brain related, but most stroke patients have widespread vascular disease and, in fact, most stroke survivors die of heart attacks.

Two other ways of classifying dementias used to be quite popular but have lost some luster with advancing research. One is the distinction between cortical versus subcortical dementias. Of course, some dementias exhibit most of their cell loss in the cortex of the brain (e.g., Alzheimer's disease) while others exhibit cell loss mostly from the deep subcortical structures, such as the midbrain in Parkinson's disease or the deep white matter in some vascular conditions. Theoretically, cortical dementias are more likely to produce symptoms of aphasia and amnesia; subcortical dementias are more likely to produce motor slowing with preserved ability to remember with cues. While motor signs are quite important since they will influence treatment, the so-called cortical and subcortical cognitive signs overlap so much that this distinction rarely offers practical help.

Similarly, there is an old tradition of classifying dementias as treatable versus untreatable; for example, older textbooks often classified syphilis or B12 deficiency as treatable and Alzheimer's disease as untreatable. The doctor's express goal in working up dementia was to "rule out treatable causes." This is history. Today, there is meaningful treatment for cognitive and psychiatric features of all the common neurodegenerative dementias, and, in fact, we can probably produce a greater change in the natural history of Alzheimer's disease than we can in the two "treatable" disorders mentioned.

Mild cognitive impairment (MCI; formerly referred to as age-associated memory impairment (AAMI) or age-related cognitive decline) is a phrase used to refer to cognitive decline that is less global and severe than dementia, and less likely to interfere with daily functioning. Some authorities consider this as normal-for-age impairment; others believe that MCI is a transitional state en route to Alzheimer's. However, it is
controversial whether these patients truly represent a homogenous group. When followed for several years, some MCI patients decline much more than others do. Therefore, it is most likely that some people who meet criteria for MCI will go on to exhibit some version of neurodegeneration, while others will remain in the category of "normal aging."

**The most common dementias.** The most common types of dementia, in order of frequency, are

- Dementia of the Alzheimer's Type (DAT)
- Dementia with Lewy Bodies (DLB) (described below)
- Vascular Dementia (VaD)
- Mixed dementias

Despite tremendous strides in unraveling the pathophysiology of dementias in the last decade, each of these syndromes and the boundaries between them remain controversial. (See Table 5 and Appendix B)

**Table 5: Causes of Dementia and Confusion**

(Please see Appendix B for full list)

- **Common Brain-related Syndromes**
  - e.g., Dementia of the Alzheimer's Type (DAT)
- **Common General Medical Causes**
  - e.g., Hypothyroidism
- **Less Common Brain-related Syndromes**
  - e.g., Frontotemporal lobar dementia
- **Less Common General Medical Causes**
  - e.g., Hyperthyroidism
- **II. Confusion/Delirium**
- **More Common Brain-related Causes**
  - e.g., Sleep deprivation
- **More Common General Medical Causes**
  - e.g., Drug toxicity or withdrawal (see Table 4)
- **Less Common Brain-related Causes**
  - e.g., Epidural hematoma
- **Less Common General Medical Causes**
  - e.g., Porphyria

The term "Alzheimer's disease" (AD), for instance, is often used to encompass two groups of conditions:

1. Several specific genetic diseases with related clinical and neuropathological features - chiefly the occurrence of excessive amyloid deposition, neuritic plaques and neurofibrillary tangles containing hyperphosphorylated microtubule-associated protein tau.
2. A broad spectrum of neurodegeneration without known genetic causes that is associated with some degree of decline in mind, but varies considerably in age of onset, rate of progression, and behavioral features, and overlaps to a poorly-defined extent with the clinical and pathological features of normal aging and the genetic Alzheimer's diseases.

In fact, it is unclear at this point what constitutes "normal aging," and whether to consider the various neurodegenerative conditions, including so-called Alzheimer's, as a collection of distinct "diseases" or as a spectrum of overlapping changes expected in the human aging process. Therefore, it is probably imprecise to label the above two spectrums as a single "disease". It may be more precise to reserve the term AD for the four related amyloid-excess genetic diseases (about 10 percent of cases), and to refer to the much larger second group as exhibiting Alzheimer's-type aging, Alzheimer's syndrome, dementia of the Alzheimer's type (DAT) (about 90-95 percent of cases). The actual pathogenesis of DAT is unknown, and the relationship to so-called "normal aging" is unclear: there is probably a multifactorial spectrum between "normal" neurodegeneration (slower) and abnormal neurodegeneration (faster). The most common associated brain changes of DAT are 1) greater-than-expected for age neuronal loss, especially in the hippocampus and the basal forebrain; 2) greater-than-expected for age occurrence of neuritic plaques, excessive amyloid deposition in plaques and blood vessels, and neurofibrillary tangles with hyperphosphorylated tau protein; 3) greater-than-expected for age synaptic loss; and 4) greater-than-expected for age decline in cholinergic innervation.

A typical case of DAT will begin with gradual onset of forgetfulness, word finding difficulty, or both. However, there is great variation in initial symptomatology. Most patients will have a disproportionate problem with short term memory versus long-term, but others will have trouble even with old memories. Most patients have a subtle aphasia similar to a "transcortical sensory aphasia" with more trouble comprehending than speaking and preserved repetition, but any language problem may occur, and language may predominate (primary progressive aphasia). Most patients will have preserved perception, but a few will have a marked loss of ability to interpret what they see (posterior cortical dysfunction). Noncognitive behavior changes may be subtle, or may dominate the clinical picture, especially with depression early in the course and agitation or psychosis further along.

One popular set of criteria for DAT is offered in the Diagnostic and Statistical Manual of Mental Disorders (1994). Again, one of the major conundrums of neurobehavior is that we have yet to figure out how to draw a conceptually meaningful line between DAT and normal aging. But for practical purposes, we see a group of patients with somewhat greater-than-expected for age cognitive decline rapidly increasing in frequency after age 65: about 5 percent are affected at age 70, 15 percent at age 75, 25 percent at age 80, and 35–50 percent at age 85. DAT is the most common cause of dementia, accounting for about 40-70 percent of cases. Apart from the pure genetic forms, risk factors for DAT include age, Apolipoprotein e4 genotype, traumatic brain injury, and family history of DAT. About 6–8 years on average elapse between diagnosis and death. Death is usually from infectious complications, especially pulmonary disease. DAT is currently the fourth
most common cause of adult death, after heart disease, cancer, and stroke. However, the prevalence of DAT is increasing rapidly with the aging of the U.S. population. About 4 million people have DAT now, and the disease is estimated to cost the U.S. 100 billion dollars a year. As many as 17 million may be diagnosable by the year 2030, at which point it may even become the leading cause of death.

We clinically diagnose DAT when there is a dementia without any other apparent cause. That is, despite the emerging availability of somewhat specific markers via functional neuroimaging and CSF (and soon serum), in practice DAT remains a diagnosis of exclusion. Note that apolipoprotein E4 genotype is not recommended as either a screen for risk of DAT or a diagnostic test, since it is neither sensitive nor specific.

There is a great deal of interest in prevention of DAT. Estrogen replacement therapy decreases the risk of DAT in postmenopausal women and there is preliminary evidence that estrogen-based oral contraceptives do the same. Nonsteroidal anti-inflammatories also cut the risk, but carry their own risk of death due to gastrointestinal bleeding. High-dose vitamin E (2000 IU/D) has been shown to decrease DAT symptoms, but the long-term hemorrhagic risk of this dose is currently unclear, and the more conventional 200–400 I.U./d may be sufficient for prophylaxis.

Management of DAT is three-pronged: 1) ameliorate the cognitive disorder, 2) treat the noncognitive behavioral features, and 3) address the distress of the caregiver and the impact on the social milieu. The cholinesterase inhibitor tacrine (Cognex®) definitely has some efficacy in slowing the rate of decline in mild to moderate DAT, but the newer agent Aricept® is easier to use because it is a once-a-day drug with minimal liver toxicity. A host of cholinergic and other agents are on the verge of FDA approval. The noncognitive behavioral features include depression in 10 to 30 percent, agitation in 10 to 40 percent, and psychosis in 5 to 25 percent. There is recent evidence that DAT-associated depression responds to antidepressants. Treatment of agitation is often a trial-and-error process, balancing cognitive and sedative side effects against efficacy. While haloperidol and similar high-potency, low-dose neuroleptics have been very commonly used with a slight to moderate benefit, there is encouraging evidence that carbamazepine may be equally helpful with less side effects. When cholinesterase inhibitor treatment is used for treatment of cognition, some patients exhibit more and some less agitation. Psychosis may respond to neuroleptics, although, again, drugs such as haloperidol are preferable to drugs such as chlorpromazine due to the lessened anticholinergic side effects.

The impact of DAT on the family is enormous. In fact, the patient may be increasingly oblivious to the situation, as the caregivers are increasingly distressed. Referral to educational and support groups, contact with the Alzheimer's association, social work consultation, legal advice regarding assets and durable powers of attorney, and careful discussion of either temporary respite care or lasting institutionalization are necessary as the disease progresses. The cost of institutional care, about $40,000/year, is double that of care at home, which is a compelling argument for therapies that can prolong the period of
relative independence prior to placement, for expanding home-based medical support systems for patients and caregivers, and possibly for long-term care insurance.

**Dementia with Lewy Bodies (DLB)** has recently come to be considered a frequent cause of dementia because about 25 to 33 percent of DAT brains are found to have some cortical Lewy Bodies—oval intraneuronal inclusions. (Actually, using the term "Lewy bodies" is controversial because the inclusions seen in cortical neurons in DLB don't look exactly like the classic Lewy bodies found in the brainstem of Parkinson's patients). In an effort to shed light on the controversy concerning DAT, Parkinson's disease, and DLB, McKeith et al published a consensus report in 1996. DLB is thought to be clinically distinguishable from DAT by:

1. Earlier and more disabling parkinsonian extrapyramidal symptoms, such as rigidity, bradykinesia, and tremor.
3. High frequency of visual hallucinations.

DLB is clearly similar to Parkinson's disease with dementia, but Parkinson's patients usually exhibit extrapyramidal signs at least several years before dementia. DLB probably constitutes the second-most prevalent cause of dementia, accounting for about 10–25 percent of cases.

Treatment of DLB is controversial. When this condition is suspected, the best approach is probably a combination of symptomatic treatment of extrapyramidal features with anti-parkinsonian medications and cholinergic therapy for the cognitive dysfunction. However, since the risk of psychosis is high, and is increased with the very dopaminergic agents that might help the parkinsonian symptoms, there is a need for carefully balancing dopamine-blocking neuroleptics with the anti-parkinsonian medications.

**Parkinson's disease (PD)** involves a loss of dopamine-producing neurons in the substantia nigra in the midbrain. There is recent evidence that people born with a deficiency of mitochondrial complex I have a higher risk of developing PD. There is also evidence that exposure to pesticides may increase the risk of PD, and that drinking coffee is perhaps associated with a reduced risk. PD is conventionally expected to be associated with dementia in about 40 percent of cases, usually after at least several years of progressive motor changes. However, some authorities have suggested that dementia occurs in virtually *all* persons with Parkinson's disease, if followed through the advanced stages. The classical presentation is one of so-called subcortical dementias, with less aphasia and more psychomotor retardation. Yet, in practice, there is a good deal of overlap between the clinical features of dementia in PD and in DAT. Dopaminergic agents may somewhat delay or ameliorate the dementia, but pose the risks of 1) fluctuating mental status as the drugs cycle through peak and trough effects, and 2) delirium with psychotic features due to dopamine excess. New options to treat PD include several types of ablative surgery, or the transplantation of fetal dopamine-producing cells.
**Vascular disease** can affect the brain in many ways, from chronic reduced perfusion due to stenotic carotid arteries to microangiopathy of intracranial vessels related to hypertension or diabetes. The definition for vascular dementia (VaD) is debatable; AMS may be associated with large or small strokes, one or many strokes, subcortical white matter changes attributed to ischemia, or a combination of these conditions. AMS may occur acutely in SAH, or may evolve over decades with the cumulative impact of ischemia. Further complicating the differentiation of vascular dementia from DAT: 1) changes in blood vessels significantly contribute to the clinical picture of DAT, and 2) DAT-type pathological changes correlate with (and may determine) the occurrence of dementia in cerebrovascular disease. Thus, there is an important overlap between so-called DAT and so-called VaD, and the current definitions of VaD are operational. For practical purposes, VaD is diagnosed when:

1. Dementia is present
2. Cerebrovascular pathology is present in areas of the brain thought to be important to cognition (e.g., the hemispheres of the brain, the basal ganglia, and the thalamus), as detected by history, neurological signs, and/or laboratory tests.
3. There is evidence of a relationship between the onset or progression of dementia and the occurrence of cerebrovascular pathology.

This last is the most difficult criterion to fulfill. We are often confronted with a well-established dementia and signs of past strokes. It is of course speculative to attribute the dementia to the past strokes, since we cannot rule out the co-occurrence of DAT-type brain pathology, or determine how much of the AMS is caused by one or the other. A "step-wise progression" has sometimes been considered a hallmark of VaD, but DAT also frequently progresses with drops in cognition followed by apparent plateaus. Also, the introduction of MRI scanning has revealed a high frequency of subcortical white matter changes in elderly patients, with or without dementia. It was formerly popular to use such instruments as the Hachinski scale to diagnose VaD (a scale assigning a point value to various risk factors), reasoning that increased stroke risk factors could be diagnostic. But there is only a rough correlation between such risk factors and a definitive accounting for the etiology of cognitive loss in a given patient, so that many patients have probably been inappropriately diagnosed with VaD using such scales. There seems to be a threshold effect, such that cumulative microvascular changes actually have little impact on cognition until they are quite extensive, whereas a single small stroke in a strategic place can produce immediate dementia. In practical terms, therefore, *VaD* should be diagnosed when cerebrovascular disease predominates in the clinical picture and can be meaningfully temporally related to the course of the dementia. *Mixed dementia* (DAT/VaD) is diagnosed when cerebrovascular disease is apparently related to AMS, but does not fully account for the AMS. (For example, a patient has a stroke followed by marked decline, then some recovery, then a much slower, gradual decline, suggesting the superposition of DAT on VaD).

**Management of VaD** is, at present, largely directed to preventing further cerebrovascular disease by controlling blood pressure and glucose intolerance, judicious choice of antiplatelet or anticoagulant medications, and selective endarterectomy for high
grade carotid stenosis. It is important to note that an element of DAT may underlie the deterioration in some patients diagnosed with VaD, and since new treatments for DAT are usually well tolerated, it may be appropriate to offer this option to VaD patients. There is preliminary evidence that cell transplant therapy may be beneficial after stroke, which raises the possibility that such therapy might also reduce the symptoms of VaD.

Less Common Dementias

Other neurodegenerative diseases. Pick's disease is a focal atrophy of the prefrontal and temporal cortex with disproportionate behavioral changes, especially a depressed, apathetic or disinhibited mental status. Diagnosis is sometimes aided by the presence on brain scanning of gyri so thin they resemble the blade of a knife ("knife-edge atrophy"). Frontotemporal lobar dementia (FTLD) is coming to be recognized as a better term that encompasses the spectrum of neurodegenerative conditions (including Pick's) in which the main problem is a loss of structure and/or function of the frontal and temporal lobes (unlike Alzheimer's, in which the major problem is temporoparietal dysfunction). Although there remains some controversy about whether FTLD truly represents a distinct entity, new consensus criteria were published in 1998. These criteria recognize three types of FTLD: 1) "frontotemporal dementia," marked by a deterioration in social conduct, 2) "progressive nonfluent aphasia," with a decline in verbal production, and 3) "semantic aphasia with associative agnosia," marked by fluent but empty speech and impaired recognition of objects. One hint FTLD represents a unique entity is the discovery of familial forms linked to mutations on Chromosome 17, and perhaps to Chromosome 3. Huntington's disease (HD) occurs both as an autosomal dominant inherited condition and as a sporadic mutation. HD is one form of a large group of problems due to abnormal lengthening of repeating sequences of trinucleotides in the genome. HD is specifically due to expansion of CAG repeats on Chromosome 4. Clinically we expected the writhing movement disorder of choreoathetosis mixed with various degrees of cognitive impairment, irritability, depression and psychosis. Neuroleptics may provide limited relief.

Metabolic disorders. Hypothyroidism is most common cause of progressive metabolic dementia, and may not be accompanied by obvious changes on the physical examination such as goiter, skin changes, or deep tendon reflex abnormalities. However, there is almost always some psychomotor retardation. Diagnosis is usually made by the thyroid function tests, but borderline abnormalities are of uncertain significance. Restoration of the euthyroid state often reduces cognitive impairments. Hypoglycemia is usually considered in the acute setting as the most common metabolic cause of delirium, but there is evidence that hypoglycemic episodes contribute to long-term cognitive loss—yet another reason for careful glucose control.

Vitamin abnormalities. B12 deficiency can appear as the full syndrome of subacute combined degeneration with both pyramidal signs and loss of posterior column function expressed as decreased proprioception and vibration sense in the feet. It can also appear as isolated dementia with minimal neurologic changes. We cannot assume that megaloblastic anemia will occur in all cases. Treatment is 1000 microgram IM per month
of B12, and ameliorates the dementia in some cases. Folate deficiency is drawing increased attention as a possible cause of dementia. Thiamine deficiency causing a persistent Korsakoff's syndrome with marked amnesia, agitation, and sometimes psychosis is a possible result of alcohol abuse. The increased popularity of megadose vitamins has led to increased frequency of vitamin A toxicity, with AMS with or without an accompanying syndrome of "benign" intracranial hypertension.

Normal pressure hydrocephalus (NPH), consists of disproportionate ventriculomegaly as compared with hemispheric atrophy, and the clinical triad of dementia, incontinence, and slowed gait. NPH is something of a misnomer, since there are in fact waves of IICP. diagnosis is pursued when the classic clinical pattern is accompanied by a persuasive CT or MR scans, and usually consists of introducing radio-opaque dye into the lumbar subarachnoid space and watch to see over 48 hours whether it is taken up over the convexity (normal) or hung up in the ventrical (abnormal). A trial of removing CSF may also help diagnostically. Management may consist of ventriculoperitoneal shunting, although the selection criteria for surgical cases is controversial. The use of acetozolamide to reduce CSF production is also unproven.

Traumatic brain injury, especially involving subdural hematoma, can present insidiously with no report of head trauma. Diagnosis is usually made by neuroimaging. Neurosurgical consultation may help decide the risk/benefit ratio of evacuation. Slow spontaneous resorption over months may lead to reduced symptoms.

Obstructive sleep apnea occurs in about 4 percent of men and 2 percent of women between the age of 30 and 60. Nighttime snoring, morning headache, excessive daytime drowsiness, and subtle cognitive decline are markers. Newly approved minor surgical techniques may relive the symptoms.

The AIDS-dementia complex can occur with or without other signs of opportunistic infectious or neoplastic CNS involvement. Varying degrees of progressive cognitive impairment, sometimes admixed with a mild confusional state, may be recognized. There is some controversy about the efficacy of triple drug therapy, including protease inhibitors, for reducing the symptoms once they have become overt.

Neurosyphilis has increased in frequency with the emergence of HIV infections, as an opportunistic infection. The serum VDRL and RPR may produce more false positive results than the MHATP. Any positive serology mandates CSF examination for VDRL—a sign of active infection. Penicillin treatment is necessary to arrest neurovascular progression, but may or may not help the cognitive state.

Creutzfeldt-Jakob disease is apparently due to an infectious protein called a prion, and is related to or perhaps equivalent to bovine encephalitis (mad cow disease). It was recently found that an abnormal prion protein may start a cascade in the brain, serving as a template to convert other prion proteins to the abnormal form that makes neurons vulnerable to oxidative damage. Transmission is usually associated with direct contact with the virus, i.e., in neuropathologists or recipients of corneal transplants or infected
growth hormone, but the agent apparently can also be transmitted by ingestion of infected meat. This rare dementia is associated with rapidly progressive AMS, myoclonic jerks, periodic complexes on EEG, with death in less than two years. There is no treatment.

The Diagnostic Work-Up for Dementia
Diagnostic work-up for dementia includes neurologic history and examination, complete blood count, serum electrolytes (including calcium), glucose, BUN/creatinine, liver function tests, thyroid function tests (FTI and TSH), serum vitamin B12 level and syphilis serology. In some clinical circumstances it may also be helpful to order a serum folate level, HIV testing, chest x-ray, urinalysis, 24-hour urine for heavy metals, toxicology screen, or a neuroimaging study.

Structural neuroimaging using either a noncontrast CT or MR scan is recommended in the routine initial evaluation of dementia patients according to the current AAN practice parameters. There is evidence (Chui and Zhang, 1997) that without a scan, a certain number of cases will be misdiagnosed as DAT who have subdural hematomas, tumors, infections, hydrocephalus, or stroke. This obliges the physician to develop a threshold for when to order these tests. In general, the presence of atypical symptoms, headache, fluctuating or rapidly progressive course, elementary neurological signs, or risk factors for tumor, stroke, or infection should lower the threshold for ordering such a scan. MRI scans have an advantage, since 1) they are more sensitive to any cerebrovascular process (excepting SAH), 2) they will show brainstem lesions invisible on CT, and 3) many MR scanners can get a simultaneous MR angiogram at a modest additional cost. However, patients with AMS may fail to tolerate the 35 minutes supine in a tunnel, giving CT's some advantage. As fast MR's become more widely used, this will be less of an issue.

Neuropsychological testing is optional. It is mostly useful when attempting to detect subtle changes, to discriminate between depression and dementia, and in cases with a preexisting cognitive deficit, e.g., developmental delay. It may also help for ascertaining level of disability, confirming capacity to participate in decisions, or designing rehabilitation for reversible dementias.

Lumbar puncture is not necessary as a routine part of the dementia work-up. However, it should be performed when new AMS accompanies fever, or (as per AAN practice parameters) in cases of metastatic cancer, suspicion of CNS infection, reactive syphilis serology, communicating hydrocephalus, dementia under age 55, rapid or atypical progression, immunosuppression or suspicion of CNS vasculitis.

The principle advantages of EEG are to help distinguish confusion from dementia in equivocal cases, to assist when seizure is known or suspected, and to help rule out the uncommon Creutzfeldt-Jakob disease. EEG is more useful in the diagnosis of confusion than dementia, and will be considered below.

DELIRIUM: DIFFERENTIAL DIAGNOSIS
Approaching the diagnosis of an acute or subacute confusional state (delirium) is often a matter of familiarity with the odds. Drugs effects and metabolic disorders - including hypoxia - are most common. Traumatic brain injury, systemic or neuroinfections, space-occupying lesions, cardio- or cerebrovascular disorders, and epilepsy are also frequent.

**Drugs and Confusion**

Simply in terms of frequency, drug intoxication and drug withdrawal may be the most frequent cause of acute or subacute AMS, followed closely by metabolic disorders. The number of prescribed and nonprescribed drugs that can cause confusion, either in therapeutic or toxic amounts, is dazzling (see Table 4 for a partial list). We will discuss the most commonly offending agents roughly in order of frequency, and mention several interesting and possibly insufficiently recognized syndromes.

All sedative hypnotics and opioid analgesics can produce delirium, with the most common offenders being benzodiazepines prescribed for anxiety or insomnia; benzodiazepine withdrawal can also produce an encephalopathy related, in part, to sleep disturbance. Benadryl (and other sedating antihistamines) is very commonly prescribed as a sleep aid, and may be a frequent cause of delirium or exacerbation of DAT due to its anticholinergic effects. Haloperidol is the most commonly prescribed neuroleptic, but it may also be the most commonly prescribed sedative in the elderly. This drug is a very common cause of delirium as well as parkinsonian motor impairments and, less commonly, tardive dyskinesia (to which elderly women seem especially vulnerable.) Similarly, compazine or metochlopramide may be prescribed for GI indications, but their neuroleptic and anticholinergic impacts make them common culprits producing AMS. Phenergan® (promethazine) is a weaker dopamine blocker, but is still a frequent cause of confusion (see neuroleptic malignant syndrome, below). A particular concern among the analgesics is meperidine HCl (Demerol®), which is associated with convulsions. This drug should never be combined with monoamine oxidase inhibitors since the combination greatly increases the chance of convulsions or death.

It is obvious that anticholinergic agents directly mimic and exacerbate the cholinergic deficit of DAT, but is less obvious that the tricyclic antidepressants imipramine (Tofranil®) and amitriptyline (Elavil®) are notoriously common causes of confusion due to their potent anticholinergic side effects. In this era when so many less toxic, equally effective agents are available, there is little reason to prescribe the most toxic agent, amitriptyline, to any patient. Nortriptyline is perhaps the best tricyclic choice, but the serotonin reuptake inhibitors are even less toxic and are probably better choices for treating depression, especially in the elderly.

Cimetidine - one of the most commonly prescribed gastrointestinal agents - causes confusion in roughly 10 percent of elderly patients. Other H2 receptor antagonists may have less CNS toxicity.

Among the cardiovascular agents, perhaps the most common offenders are the lipophilic beta-blockers such as propranolol, which produce depression - sometimes
quite profound—in about 5 to 10 percent of patients. Amiodarone (Cordarone®) is well known for its potentially fatal pulmonary toxicities, but it also very commonly produces neurological changes (in up to 40 percent of patients) including confusion, involuntary movements, and gait disturbances. Calcium channel blockers, especially nifedipine, produce nervousness in about 5 to 8 percent of patients, and abnormal dreams or psychosis in about 1 percent. Digitalis preparations, of course, may cause confusion, psychosis, or apathy even at borderline elevated levels; this syndrome is sometimes anticipated by a yellowing of vision. The alpha-1-selective adrenergic blocker doxazosin can produce somnolence. Less well known are the anticholinergic effects producing confusion in patients taking the type 1 antiarrythmic disopyramide phosphate (Norpace® Methyldopate HCl (Aldomet®), is an infrequently used antihypertensive these days, in part because it can produce depression, psychosis, agitation, or confusion, sometimes associated with parkinsonism.

Among the most prescribed drugs are selective serotonin reuptake inhibitors (SSRIs). SRIs, especially those with shorter half-lives such as sertraline, but also the long-half life fluoxetine, have recently been shown to produce a withdrawal syndrome if stopped abruptly, with anxiety, agitation, or confusion as well as dizziness. SRIs have also recently been associated with the syndrome of inappropriate ADH secretion (SIADH), in which hyponatremia often leads to AMS and seizures.

Anti-inflammatory drugs, especially corticosteroids, are well known to produce AMS, but the common expectation of mania is incorrect. Depression with various degrees of delirium and psychosis is more common. With the increasing over-the-counter use of nonsteroidal anti-inflammatories such as ibuprofen, there have been increasing reports of AMS, although it is not clear to what extent these are idiosyncratic reactions to therapeutic dose as opposed to toxic encephalopathies. Paradoxically, NSAIDs may help to prevent DAT and many people might be self-prescribing them for this reason, which could increase the frequency of reported AMS. Aspirin toxicity, of course, can cause tinnitus and delirium.

Drugs with stimulant or sympathomimetic properties such as aminophylline and theophylline notoriously case confusion at toxic levels, less frequently in the therapeutic range. Ephedrine, phenylephrine and phenylpropanolamine are popular components of over-the-counter cold remedies that also can cause marked behavioral change in susceptible people. Ephedra-containing Chinese herbal preparations are an increasing cause of concern for the same reason.

The muscle relaxant baclofen (Lioresal®) is a frequent cause of severe encephalopathy. Either by increasing the dose too rapidly, or by precipitous withdrawal, this agent can produce confusion or even coma, accompanied by autonomic instability that sometimes requires ICU monitoring. Carisprodol (found in Soma Compound® is another muscle relaxant causing confusion.

Among frequently prescribed antimicrobials, sulfamethoxasole occasionally produces delirium or even a picture of aseptic meningitis; change in mental status also
accompanies the occasionally induced toxic epidermal necrolysis or hepatic necrosis. In addition to their well-known ototoxicity, aminoglycosides can produce an encephalopathy. Tetracycline occasionally causes symptomatic increased intracranial pressure. Ticarcillin can produce convulsions, especially in patients with reduced renal clearance.

**Antineoplastic drugs** can cause various syndromes of AMS. Aminogluthethimide causes drowsiness in about one third of patients. Asparginase can cause not only depression or confusion directly, but can produce a hyperglycemic hyperosmolar state with attendant encephalopathy. 5-Flourouracil is often associated with an acute syndrome of cerebellar dysfunction that may masquerade as intoxication. Methotrexate, even when used systemically for rheumatoid arthritis, can produce either a transient delirium or a toxic and persistent leukoencephalopathy (white matter degeneration). While the vinca alkaloids are best known for producing neuropathy, they can also cause depression.

A problem of unclear dimensions that is likely to increase in the near future is the psychological impact of *cholesterol-lowering agents*. Treatment with these drugs has been tentatively associated with increased aggression and possibly with suicide.

The *neuroleptic malignant syndrome*, consisting of subacute delirium associated with fever, tremor, and increased CPK, is most frequently associated with high dose neuroleptic prescription—or rapid increase in dose. However, this problem has actually been reported in patients after a single low dose. The diagnosis is frequently delayed because the syndrome goes unrecognized, or is misinterpreted as increased agitation in a psychotic patient, leading to the counterproductive escalation in neuroleptic dose.

**Drugs of abuse** are also obvious causes of encephalopathy, either as a toxic or withdrawal effect. The risk of delirium tremens probably peaks about 48 hours after alcohol withdrawal, and may be preceded by the more benign minor withdrawal syndrome of nervousness, tremor, and confusion. Stimulants such as cocaine, amphetamines, and even (rarely) caffeine can cause irritability, agitation, mania, psychosis, or delirium. Hallucinogens may cause not only hallucinations, but also a general delirium. Phencyclidine is known for the dramatic agitated psychoses it sometimes produces, but it's more likely to simply produce delirium, possibly with autonomic instability. Inhalants including glues and nitrous oxide can produce profound confusion and may not be identified by a toxicology screen.

**General Medical Causes of Confusion**

In the general medical realm, **fever** by itself is perhaps one of the most common causes of confusion. **Sepsis** invariably alters mental status, even with no evidence of CNS infection, although the reason for this is unclear. Delirium occurs with any process that decreases delivery of oxygenated blood to the brain. A wide spectrum of conditions may produce this effect. Hypoxemia or hypoperfusion, low-output cardiac failure or valvular abnormalities, vertebrobasilar insufficiency, anemia sufficient to lower the oxygen carriage capacity (Hct<24), COPD, emphysema, pneumonia or reactive airway disease
that lowers the PO2, or carbon monoxide exposure - all can cause delirium. Hypoglycemia is one of the most common causes of delirium, especially among diabetics, who are also vulnerable to hyperosmolar hyperglycemic encephalopathy. Specific neurotoxicity is produced in uremic and hepatic encephalopathies, which sometimes present with less than markedly abnormal blood chemistries. Even dehydration itself, particularly in the elderly, can cause AMS apparently out of proportion to its severity as measured by the BUN/creatinine ratio. Hyponatremia causes encephalopathy depending to some extent on the rate of change, but almost all patients with NA of 120 or less will have some cognitive changes. SIADH is one well known cause of hyponatremia, but water intoxication- simply due to excessive drinking of water in demented or psychotic patients - is another cause that sometimes adds delirium to the underlying process. Endocrinopathies other than diabetes may also cause delirium. The effects of hypothyroidism (and less often hyperthyroidism) may appear as a gradual onset dementia-like syndrome, but may also cause acute delirium, especially on the case of thyrotoxicosis. Either adrenal insufficiency or hyperactivity may produce delirium.

Less common medical causes of delirium include hypokalemia, hypercalcemia, and hypomagnesemia. Parathyroid abnormalities, especially elevated PTH, may be one cause of so-called dialysis dementia. Another cause, now rare, is aluminum intoxication. More often, dialysis dementia is a multifactorial syndrome related to rapid shifts of both fluid and many electrolytes. Extracranial cancers may produce paraneoplastic encephalopathies by generating antibodies to cerebral tissue, such as anti-Purkinje cell antibodies, by producing carcinomatous meningitis (most often associated with small cell lung cancer) or via limbic encephalitis—a rare inflammation of the brainstem and medial temporal tissue.

Neuropsychiatric Causes of Confusion

Specific neuropsychiatric syndromes that commonly cause confusion include simple sleep deprivation (with or without sleep apnea), as well as other REM and non-REM sleep disorders. These are described in more detail in the chapter on sleep. Migraine headache, thiamine deficiency causing Wernicke's encephalopathy, subdural hematoma, and neuroinfection are other frequent causes of confusion. Diagnosis of subdural hematoma is often unfortunately delayed because the head trauma was not reported—or even recalled—by the patient, and no neuroimage was obtained. Similarly, Wernicke's encephalopathy is sometimes missed unless the full syndrome appears: delirium, gait disorder, and abnormal eye movements.

While bacterial meningitis is often quickly suspected due to fever or characteristic skin changes, perhaps the most frequently delayed diagnosis of a treatable condition among neuroinfections is herpetic encephalitis. There may be no fever, no history of exposure, and a benign neuroimage. This diagnosis requires a high index of suspicion in an otherwise unexplained confusion. The EEG may show distinctive periodic complexes, but it is much better to go right to the CSF examination and initiate acyclovir treatment as soon as this condition is clinically suspected. Other infectious encephalitides include tuberculosis, especially to be suspected in inner-city dwellers and recent immigrants from.
endemic areas, and fungal and protozoal infections. All of these may escape detection by not causing fever, and, again, CSF examination is more or less essential if confusion has not been diagnosed by blood tests or a neuroimage.

**Cerebrovascular disease** may appear first as confusion. Hypertensive encephalopathy may be suspected early on the basis of vital signs. But the patient with SAH may have already lost the ability to report the headache that preceded their current agitated, staggering state. Hypertensive hemorrhage in the pons may show obvious brainstem signs, but in the thalamus or basal ganglia may be tough to localize on examination, particularly because the patient’s confusion complicates careful testing. Stroke-in-evolution, or completed strokes in the right frontal lobe or occipital-parietal-temporal junction area may show little on neurologic examination but much on mental status testing. As we noted previously, given the rapid improvement in immediate post-stroke care, the faster we suspect this diagnosis and scan the patient, the better the outcome may be.

**Traumatic brain injury** is an obvious explanation for delirium when there has been a known loss of consciousness or superficial signs of injury are apparent. However, even mild trauma without loss of consciousness and indirect trauma, as in whiplash, can produce confusion for variable periods of time, and the related brain injury may be undetectable by CT or MR. (Note that 85 percent of those cases in which MR reveals abnormalities immediately after head trauma show no abnormality on CT). Children are often traumatized in bicycle accidents; the elderly often hit their heads in falls. Neither group will necessarily report the injury. Perhaps the best measure of traumatic brain injury severity is not the structural injury, or even the duration of unconsciousness, but the length of time it takes the patient to recover their continuous stream of consciousness, with no difficulty with orientation. This is called the duration of the post-traumatic amnesia (PTA), and requires careful sequential testing of mental status, even when the patient superficially seems recovered. Even minor trauma may cause deposition of beta-amyloid, so the transient delirium seen in traumatic brain injury may be followed, many years later, by an increased risk of dementia.

Any cause of increased intracranial pressure, in particular space-occupying lesions or hydrocephalus, may cause delirium. While tumors may be suspected due to asymmetry in the elementary examination, masses in certain areas (especially the right frontal lobe) may be clinically silent apart from confusion. Hydrocephalus may develop insidiously, e.g., following SAH when the patient seems to be doing well, and during the following week develops AMS because the re-uptake of CSF has been impared by the blood remaining in the cranium. Similarly, a patient with neurocysticercosis, rapidly increasing in the US due to the influx of central and South American residents, may develop a ball-valve effect with intermittent AMS due to hydrocephalus above a cyst that obstructs the third ventricle.

Rarely, unrecognized complex partial or petit mal status epilepticus can cause delirium. While many cases will exhibit suggestive signs, such as purposeless movements or staring, others seem to be conscious. More commonly, an unrecognized postictal state...
after an unwitnessed seizure produces lasting confusion. In either case, an EEG is extremely helpful diagnostically.

**Primary psychiatric conditions** can produce a disorganization of thinking that appears indistinguishable from delirium. In fact, functional neuroimaging supports the hypothesis that severe psychiatric disturbances in fact disrupt brain blood flow and metabolism just as medical encephalopathies might. Depression with psychomotor retardation, mania with psychosis, and exacerbations of schizophrenia may give this appearance. Sometimes, the simple procedure of asking the patient to copy a figure can help distinguish these conditions; delirious patients often fail. Psychotic patients often succeed.

**The Laboratory Work-Up of Confusion**

The laboratory tests that may quickly help to diagnose a delirium are about the same as those proposed for the dementia evaluation. In fact, the major reason for most of the blood tests previously listed is to rule out toxic and metabolic causes of confusion. Given the higher stakes of prompt diagnosis, there are several tests we may be more eager to order in a confusional state. For instance, if the general medical examination hints at hypoxia or conditions that might alter acid/base balance, we are more likely to obtain a chest x-ray and an arterial blood gas. With the slightest suspicion, or especially when there is no suspicion, a toxicology screen should be ordered. In the same way, because the consequences of delayed diagnosis are grave, we are much more likely to perform a lumbar puncture. However, concern about precipitating herniation in a patient with IICP necessitates a CT scan before the LP. (Note: the risk of this complication is higher in children). EEG has limited utility in dementia assessment; however, it can be key in proving the presence of delirium. Most alterations in level of responsiveness will appear as slowing and disorganization of the EEG background; almost all acute neuroinfections and most drug-induced confusion alter the EEG. In contrast, most dementias show little EEG change until advanced stages, and most primary psychiatric conditions, including somatoform illness, will produce a largely normal EEG.

**Returning to the Examining Room**

Our examination of Mr. Johnson is done. We don't have a diagnosis, but we have a plan. Our 83-year-old patient, and any patient with hints of an acute or subacute onset of confusion (with or without evidence of CNS dysfunction on the elementary examination) needs a laboratory work-up right away. Looking at Table 5 (see expanded version in Appendix B), we might check off the processes that are more or less likely to produce this syndrome (e.g., large hemispheric stroke is less likely given the absence of motor asymmetry, neurodegenerative disease is more likely given the global cognitive dysfunction). But we need not feel forced to commit to a diagnosis at this point, since the differential remains huge in cases that tread the border between delirium and dementia, and most clinical settings offer access to extraordinarily valuable and relatively cost-efficient laboratory screening. We order some stat labs.
Forty minutes later, we have written prescriptions for our young asthmatic, seen two other patients briefly, and are somewhat more confident that we know what is going on: Mr. Johnson's sodium came back at 114 mEq/l. All the other tests are normal.

*We ask his daughter, "By chance, have you noticed whether he's been drinking a lot of water?" She hasn't noticed. But the patient overhears the question, "Yeah, so what's it to you?" He's not really irritable; he says it with a smile. "You gotta', you know, you gotta wash out the poisons, know what I mean?"

We still aren't certain. But here's one scenario that could account for this clinical picture: an insidious loss of cognitive ability perhaps led Mr. Johnson to abandon his favorite pastime of gardening several years ago. A garrulous fellow, competent in his own environment, he can talk a good game in casual conversation. So, like most early Alzheimer's patients, he hasn't seemed demented to his family on their weekly visits. Not until his Alzheimer's progressed to the point where he exaggerated his lifelong habit of drinking two glasses of water a day—to "wash out the poisons"—has his dementia become overt: forgetting that he already drank his quota, he's been repeating the procedure six times a day. His resulting water intoxication tips him over the edge into overt cognitive impairment with some features of dementia and some of delirium - a typical "beclouded" dementia. We'll admit him. It's 5:30. We also call home, to slightly rearrange the evening.

**Appendix A: Mini-Mental State Examination (MMSE)**

**Orientation = 10 points**

**Time:** Ask for the date, then ask for parts omitted:

1. What year is this?
2. What day of week?
3. What month?
4. What date?
5. What season is it? (correct if within 1 mo.)

**Place:** Ask in turn:

6. Can you tell me the name of this place?
7. What City is this?
8. What State is this?
9. What County is this?
10. What floor are we on?

**Memory = 6 points**

**Registration:** Ask the patient if you may test his memory; then say the names of three unrelated objects. After you have said all three, ask him to repeat them. This first
repetition determines the score, one point for each word correctly repeated, but keep saying them (up to six trials) until he can say all three; e.g.,

11. Apple,
12. Table,
13. and Penny

Recall (Note: the original MMSE does not specify a delay, but we advise a three minute delay): Ask the patient if he can recall the three words you previously asked him to remember; e.g.,

14. Apple
15. Table
16. and Penny

Attention/Concentration = 5 points
Serial 7's, subtracted back from 100. Stop after 5 answers. (One point for each correct subtraction.) Alternatively, spell WORLD backwards (One point for each letter in correct sequence)

= 17-21

Language = 8 points

Naming to confrontation

Show the patient each object and ask him what it is.

23. Watch
24. Pencil

Repetition:

22. Repeat the following: "No ifs, ands, or buts"

Following three-stage command
(Which should be presented before subject touches the paper):

27. Please take this paper in your right hand
28. Fold it in half
29. And put it in your lap
   (Note: the original MMSE specifies the right hand; however, the authors have found that reaching for a proffered object with the dominant hand is an overlearned response; a truer test of comprehension may be to specify the left hand)
Reading

25. Subject is shown a card that states in large print: "Close your eyes;" Subject is asked to "read obey the following."

Writing

26. Write a sentence, (1 point for a complete sentence, even if handwriting and spelling are poor.)

Construction = 1 point

30. Correctly copies a drawing of two interlocking pentagons

Total = 30 points
Typical cut-off for "dementia" = < 24 points, but this is highly education-dependent.


Appendix B: Expanded Table 5. Causes of Dementia and Confusion

Navigation

- Table of Contents
- Section 1
- Section 2
- Section 3

Section 3

1. Dementia

Common Brain-related Syndromes
Dementia of the Alzheimer's Type (DAT)

Dementia with Lewy Bodies (DLB)

Frontotemporal lobar dementia (FTLD)

Vascular Dementia (VaD)

Mixed dementias
Parkinson's disease

Traumatic brain injury

**Common General Medical Causes**

Hypothyroidism

B12 deficiency

Thiamine deficiency (Korsakoff's syndrome)

Sleep apnea

**Less Common Brain-related Syndromes**

Huntington's disease

AIDs-dementia complex

Neurosyphilis

Chronic meningitis

Creutzfeldt-Jakob disease

Normal pressure hydrocephalus

Other hydrocephalus

Space-occupying lesion

**Less Common General Medical Causes**

Hyperthyroidism

Addison's disease

Cushing's disease

Panhypopituitatarism

Hyperparathyroidism

Folate deficiency
Vitamin A, D toxicity

II. Confusion/Delirium

More Common Brain-related Causes

Sleep deprivation

Exacerbation of dementia by intercurrent illness ("Beclouded" dementia)

Migraine

Stroke, especially brainstem, thalamic, right parietal, or bi-occipital

Traumatic brain injury with or without loss of consciousness

Subdural hematoma

Increased intracranial pressure (IICP, e.g. tumor, hydrocephalus)

Herpetic encephalitis

Cysticercosis

Thiamine deficiency causing Wernicke's encephalopathy, Korsakoff's syndrome

Syndrome of inappropriate ADH excretion (SIADH)

Postictal state

Depression with psychomotor retardation

Schizophrenia

More Common General Medical Causes

Drug toxicity or withdrawal (see Table 4)

Fever

Low output cardiac failure

Pulmonary hypertension

Hypertensive encephalopathy
Hypo- or hyperglycemia

Hyponatremia

Hypothyroidism

Anemia (hematocrit <24)

Hepatic encephalopathy

Uremic encephalopathy

Anoxia/hypoxia/pulmonary disease

Serotonin syndrome

Post-operative confusion

**Less Common Brain-related Causes**

Epidural hematoma

Nonherpetic viral encephalitis

Bacterial or fungal meningitis

Carcinomatous meningitis

Limbic encephalitis

Carotid or vertebrobasilar insufficiency without stroke

Creutzfeldt-Jakob disease

Neurosyphilis

Complex partial or petit-mal status epilepticus

Multiple sclerosis

Neuroleptic malignant syndrome

Mania

**Less Common General Medical Causes**

Porphyria
Addison's disease
Cushing's disease
Systemic lupus erythematosus
Temporal arteritis
Hyperthyroidism
Hyperparathyroidism
Hypercalcemia
Panhypopituitarism
Carcinoid syndrome
Post-CABG delirium
Carbon monoxide poisoning
Heavy metal toxicity
Acetylcholinestase inhibitor toxicity (e.g., insecticide)

REFERENCES


**SELF-ASSESSMENT QUESTIONS**
1. Which of the following items in the past medical history is of special concern when assessing a recent change in behavior in an older adult?
   A. Adolescent mental health interventions
   B. Recent ETOH dependence
   C. Current lung tumor
   D. A and B only
   E. A, B, and C

2. Which of the following is true in regard to changes in mental status?
   A. Dementia requires altered level of attention and arousal
   B. A history of rapid decline helps to rule out a chronic process
   C. Delirium has a mortality rate of 15 to 65 percent
   D. The rate of change often guides the urgency of assessment
   E. C and D only
   F. All of the above

3. Poor sleep or insomnia is common in:
   A. Sleep apnea
   B. Mood disorders
   C. Hydrocephalus
   D. Hypoglycemia
   E. A and B only
   F. A, B, and D

4. Unilateral weakness can occur in:
   A. Stroke
   B. CNS tumor
   C. Hypoglycemia
   D. A and B only
   E. A, B, and C

5. New onset confusional syndromes can be attributed to drugs in approximately:
   A. 10 to 15 percent of cases
   B. 15 to 30 percent of cases
   C. 35 to 60 percent of cases
   D. 60 to 75 percent of cases
   E. 75 to 90 percent of cases

6. Drugs commonly reported to cause altered mental status include:
   A. acetaminophen (Tylenol®)
   B. dysopyramide phosphate (Norpace®)
   C. baclofen (Lioresal®)
   D. sulfamethoxazole
   E. C and D only
   F. B, C, and D

7. Which of the following is true about the mental status exam?
   A. The Folstein MMSE score in Alzheimer's disease falls between 0 and 21.
   B. Asking the patient to name the stem of a watch or the lapel of a jacket is usually a good test of dominant hemisphere function.
   C. An acute confusional state is often very similar to a Broca's aphasia
   D. Repeating three words is a test of working memory
E. D only
F. A, C and D only

8. The following statements about neurodegenerative conditions are true:
   A. Stepwise progression is expected in vascular dementia.
   B. Definitive biological markers have been identified which distinguish Alzheimer's disease from normal aging.
   C. The Hachinski Ischemia Scale can be used to diagnose vascular dementia.
   D. A and C only
   E. none of the above

9. The diagnostic workup for dementia must include:
   A. Neuropsychological testing
   B. Neurological examination
   C. MRI scan
   D. Thyroid function tests
   E. B and D only
   F. B, C, and D only

10. If you introduce yourself to the patient in a loud voice and see no response, this could be explained by:
    A. Deafness
    B. Language barrier
    C. Paralysis
    D. Encephalopathy
    E. A, C, and D only
    F. All of the above

11. Abnormal gait can help to diagnose a change in mental status, since it is common in:
    A. Dementia with Lewy Bodies
    B. Increased intracranial pressure
    C. Parkinson's disease
    D. Alzheimer's disease
    E. B and C only
    F. A, B, and C only

12. In regard to Alzheimer's disease:
    A. About 15 percent of adults are affected by age 70
    B. Onset is often rapid
    C. About 35 percent of adults are affected by age 85
    D. Time from diagnosis to death averages four years
    E. A and C only
    F. A, C, and D

ANSWERS

1. E
2. E
3. E
4. E
Family Physicians frequently see people with changes in behavior or they "are not normal." In a Family Physician's practice the major diagnoses we think of are delirium, dementia, and depression. As a family physician you need to have the tools to approach this problem in the midst of a busy office. This article will not cover cerebrovascular disease.

The first step is taking a history. A good place to start is with these crucial questions:

- How long has this been going on?
- How abruptly did this start?
- Are the symptoms progressing?
- If so, how fast?

The chart below helps to differentiate the characteristics of these three common medical problems seen in Family Medicine.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Delirium</th>
<th>Dementia</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Gradual</td>
<td>Mood Changes</td>
</tr>
<tr>
<td>Duration</td>
<td>Acute Illness</td>
<td>Chronic Illness</td>
<td>Sub acute</td>
</tr>
</tbody>
</table>
Delirium has had numerous other names including altered mental status, acute confusional state, reversible dementia, acute organic brain syndrome, and toxic metabolic encephalopathy. It is characterized by disturbance of consciousness, change in cognition, development over a short time, and a consequence of a medical condition. To help make the diagnosis you can use the Confusion Assessment Method which requires the first two items and either the third or fourth item to make the diagnosis of delirium:

- Acute change in mental status and fluctuating course
- Inattention
- Disorganized thinking
- Altered level of consciousness

To help determine the medical source and workup, you can use the following mnemonic:

- Drugs
- Electrolytes
- Lack of Drugs
- Infection
- Reduced sensory
- Intracranial
- Urinary retention
- Myocardial

Appropriate lab work includes CBC, Electrolytes, renal function, UA, blood cultures, chest x-ray, ECG, and liver functions. It is appropriate to order serum drug levels for the patient on chronic drugs. Do not forget about doing a urine drug screen in this population.

Treatment of Delirium is treating the underlying cause. To help the patient recover, avoid sedative use unless absolutely necessary. Remove indwelling devices such as central lines.
and indwelling catheters. Actively treat constipation and urinary retention. To encourage proper sleep hygiene establish a consistent bedtime in a comfortable setting, a soft night light, providing daytime activity, and treating depression and delusions. While avoiding benzodiazepines and antihistamines, you could consider the use of trazodone and zolpidem. In the hospital setting it is important to re-orient the patient. Softly touching these patients can be very effective.

Depression can be mimicked by thyroid disease or any condition that promotes apathy. Dementia has overlapping symptoms with depression in the form of impaired concentration, lack of motivation, psychomotor retardation, and disrupted sleep. Many older people report somatic symptoms and less often report depressed mood. Side effects of drugs may be confusing in the elderly. Do not forget the elderly has the highest rate of successful suicide.

The U.S. Preventive Services Task Force recommends screening adults for depression in clinical practice that have systems in place to assure accurate diagnosis, effective treatment, and follow up. In a busy family medicine office using an efficient screening tool is welcomed to help identify depression. One such method is to use the Five-item Geriatric Depression Scale:

- Are you basically satisfied with your life?
- Do you often get bored?
- Do you often feel helpless?
- Do you prefer to stay home rather than going out and doing new things?
- Do you feel pretty worthless the way you are now?
- If 2 or more answers are positive for depression then a more thorough evaluation for depression is indicated.

Another method is to use the Periodic Health Questionaire-2 (PHQ-2). This is done by asking the patient if during the past month you have often been bothered by:

- Little interest or pleasure in doing things?
- Feeling down, depressed, or hopeless?
- If the answer is no to BOTH questions then the screen is negative
- If EITHER answer is yes, then proceed with a more in-depth evaluation

The Patient Health Questionnaire-9 can be used to further evaluate patients with a positive screen. This has been designed to correspond with the criteria in the DSM-IV for making the diagnosis of major depression. The PHQ-9 can also be used to follow the severity of depressive symptoms and assessing the response of treatment in these patients. The problematic areas assessed by the PHQ-9 are:

- Little interest or pleasure in doing things
- Feeling down, depressed or hopeless
- Trouble falling asleep, staying asleep, or sleeping too much
- Feeling tire or having little energy
• Poor appetite or overeating
• Feeling bad about yourself, feeling that you are a failure, or feeling that you have let yourself or your family down
• Trouble concentrating on things such as reading the newspaper or watching television
• Moving or speaking so slowly that other people could have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual
• Thinking that you would be better off dead or that you want to hurt yourself in some way

Major Depression is a treatable illness. Psychotherapy can include cognitive-behavioral therapy, interpersonal psychotherapy, and problem-solving therapy. Problem-solving therapy helps the patient to identify practical life difficulties and patient-defined solutions. Cognitive-behavioral therapy has been shown to be helpful as the sole treatment of mild and moderate depression and in conjunction with antidepressants in severe depression.

In considering pharmacotherapy, there is no one antidepressant considered superior in treatment. The duration of therapy should be at least 6-12 months. Older patients with major depression will be more likely to require maintenance therapy. The recurrence rate after the first episode of major depression is felt to 50% and 90% after the third episode. The choice of medication can be based on the side effect profile of the medication. The Selective Serotonin-reuptake Inhibitors (SSRIs) are the medication class of first choice because of their favorable side effect profile. Common side effects are gastrointestinal, insomnia, tremor, agitation, hyponatremia, and occasional sedation. Based on the side effect profile, sertraline, citalopram, and escitalopram would be considered the medications of first choice in treating the elderly.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Usual Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>10 mg</td>
<td>20-40 mgm</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>10 mgm</td>
<td>20-40 mgm</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>10 mgm</td>
<td>20-40 mgm</td>
</tr>
<tr>
<td>Paroxetine CR</td>
<td>12.5 mgm</td>
<td>12.5-37.5 mgm</td>
</tr>
<tr>
<td>Sertraline</td>
<td>25 mgm</td>
<td>100-200 mgm</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>10 mgm</td>
<td>10-20 mgm</td>
</tr>
</tbody>
</table>

Tricyclic antidepressants can be used if patients do not respond to SSRIs. Blood levels are available to ensure proper dosing. The prominent side effects are anticholinergic and include drowsiness, constipation, dry mouth, blurry vision, orthostatic hypotension and urinary hesitancy. With these side effects, nortriptyline and desipramine are more appropriate for use in the elderly.

<table>
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<tbody>
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<td>Paroxetine</td>
<td></td>
<td></td>
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<tr>
<td>Paroxetine CR</td>
<td></td>
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<tr>
<td>Sertraline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escitalopram</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Amitriptyline 10-25 mgm hs 25-200 mgm hs
Desipramine 10-25 mgm hs 25-150 mgm hs
Nortriptyline 10-25 mgm hs 25-100 mgm hs

Other antidepressants include bupropion, venlafaxine, duloxetine, and mirtazapine. Bupropion is usually well tolerated and free of sexual side effects. In doses greater than 300 mgm there is a slight risk of seizures. Therefore it is contraindicated in patients with a seizure disorder. Venlafaxine acts as an SSRI at lower doses while inhibiting the reuptake of norepinephrine at higher doses. Side effects include nausea at low dose and hypertension at higher doses. Duloxetine has been approved for treatment of depression and neuropathic pain. This drug is similar to venlafaxine and has been shown to reduce stress incontinence in women. Mirtazapine is given at bedtime because of its sedative properties. This drug is associated with increased appetite and weight gain. This drug is used frequently in the nursing-home residents.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Initial Dose</th>
<th>Usual Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>75 mgm</td>
<td>150-300 mgm</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>37.5 mgm</td>
<td>75-225 mgm</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>20 mgm</td>
<td>30-60 mgm</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>7.5 mgm hs</td>
<td>15-45 mgm hs</td>
</tr>
</tbody>
</table>

Dementia is chronic irreversible cognitive decline. In lay terms it is "brain failure." The real issue is how to detect mild dementia to help maintain the functional state of the patient in the community. There is no blood test or radiographic test to make an early diagnosis of dementia. The traditional history and physical does not detect the early stages of dementia.

There are a number of reliable and valid cognitive screening tools for use in Family Medicine. The Mini-Cog has been validated in the elderly. You ask the patient to remember three items and then have the patient do the clock drawing test. This is simply done by asking the patient to draw a circle and put the numbers in the correct sequence and position. You ask the patient to draw a short and long hand to a designated time such as 11:10. This test is not affected by language skill and education level. After the clock drawing test you ask the patient to recall the previous three items. If this is normal you can be reassured they do not have a major cognitive problem. If either one of these items is abnormal a more thorough evaluation is needed.

The Mini-Mental State Exam is the most widely used cognitive screening tool in the United States. This measures orientation, registration, attention and calculation, recall, language and constructional skill to help detect dementia. Besides being a valid tool for detection it is useful in tracking and quantifying changes over time. The MMSE is easy to administer. A total score of less than 24 out of a maximum of 30 points is suggestive of dementia. Factors other than cognitive function influencing the MMSE are age,
educational level, deficits in language skills, and motor or visual impairment. Therefore the cut level of 24 may be adjusted by the population being tested. It is not sensitive to mild dementia and not specific to Alzheimer's disease. The MMSE can be found here.

When considering dementia a workup would include a complete blood count, a comprehensive metabolic panel, thyroid stimulating hormone, vitamin B12, and neuroimaging. When considering dementia you must consider depression. This workup is done to improve the function of these patients.

The dementia workup brings up a question, what about reversible dementia? The concept of reversible dementia was discussed when certain illness were treated the cognitive function of these patients improved. However, Knopman reported on a review of 560 consecutive patients newly diagnosed with dementia. In this review at the Mayo Clinic no cases of reversible dementia due to normal pressure hydrocephalus, subdural hematoma, vitamin B12 deficiency, hypothyroidism, or neurosyphilis were found. Knopman said, "none of the patients with dementia reverted to normal with treatment of the putative reversible cause." This means reversible dementia is a rare occurrence.

Many preventive measures for dementia have been discussed. These include vitamin E, NSAIDS, gingko biloba. The Alzheimer's disease Anti-inflammatory Prevention Trial was a randomized, double masked study using celecoxib and naproxen compared to placebo. This study showed these medications did not prevent development of dementia. Another study showed gingko biloba did not prevent the onset of dementia. Some studies have suggested physical activity and participation in leisure activities are associated with decreased risk of dementia.

The treatment of patients with dementia can be frustrating for the caregivers. Many times this falls on the shoulders of the spouse or one of the children. It is important to have consistent caregivers, a consistent daily routine, adequate daytime stimulation, adequate levels of light, scheduled toileting, and particularly a familiar safe environment. Sundowning can be a big problem for caregivers and lead to caregiver fatigue. Behavioral approaches for sundowning should include giving diuretics and laxatives early in the day, clean glasses, working hearing aids, providing personal care at the same time, monitor amount of sensory stimulation, regular dosing of medications, and having familiar objects at the bedside. To help caregiver fatigue, consider respite care for the caregiver.

At times these patients become delusional and have hallucinations. In approaching this problem, first determine if these symptoms are having harmful effects for these patients. If there are no harmful effects, no medication is needed but careful observation. If these symptoms are interfering with care and causing potential harm, then medication should be considered. Quetiapine, olanzapine, and Risperidone reduce agitation and behavioral disturbances for people with dementia. The medications and the doses used for these problems are:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>Peak Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>25-50 mg</td>
<td>200 mgm daily</td>
</tr>
</tbody>
</table>
Clozapine 12.5-25 mgm BID 100 mgm daily
Haloperidol 0.25 mgm HS 3-5 mgm daily
Olanzapine 1.25-2.5 mgm HS 5 mgm daily
Risperidone .25-0.5 mgm HS 1-1.5 mgm daily

The above medications are used for delusions and hallucinations, not for wandering and confusion. Haloperidol has a higher incidence of extrapyramidal symptoms and tardive Dyskinesia. Other potential side effects include lethargy, dry mouth, weight gain, and sexual side effects. All of these medications have black box warnings for increased cardiovascular events and death.

Medications are now available for treatment of dementia. These are cholinesterase inhibitors and NMDA receptors. Many of the early studies showed a delay in nursing home placement, an improvement in functional ability, a slight improvement in cognitive ability, and may decrease behavioral problems. Side effects for these meds include nausea, anorexia, vomiting, diarrhea, headache or nightmares. Contraindications include uncontrolled asthma, angle-closure glaucoma, sick sinus syndrome and left bundle branch block.

The medications available and the doses used are listed below:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Interval</th>
<th>Titration</th>
<th>Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil</td>
<td>5-10 mgm Daily</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>8-24 mgm Daily</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Galantamine</td>
<td>1.5-6.0 mgm BID</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Memantine</td>
<td>5-10 mgm BID</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Galantamine Patch</td>
<td>4.6-9.5 mgm Daily</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

We have now have these multiple drug regimens available for treatment of dementia. The real question is what is the evidence? The American College of Physicians and the American Academy of Family Physicians issued guidelines on the use of these meds:

- Clinicians should base the decision to initiate a trial of therapy with a cholinesterase inhibitor or Memantine on individualized assessment.
- Clinicians should base the choice of pharmacologic agents on tolerability, adverse effect profile, ease of use, and cost of medication. The evidence is insufficient to
compare the effectiveness of different pharmacologic agents for the treatment of
dementia.
• There is an urgent need for further research on the clinical effectiveness of
pharmacologic management of dementia.

We have tried to outline an approach for a busy family medicine office to screen for and
approach these problems.

Bibliography:

1. Rinaldi, Patrizia. Validation of the Five-Item Geriatric Depression scale in elderly
2. Thibault JM. Efficient Identification of Adults with Depression and Dementia.
Am Fam Phy September 15, 2004; 70:1101-1110.
3. Depression Screen and PHQ-9 Symptom Checklist
4. Seigerschmidt, Eva. The clock drawing test and questionable dementia: reliability
5. Knoopman D. Incidence and causes of nondegenerative nonvascular dementia.
Arch Neurol 2006; 63:218-221.
6. ADAPT Research Group. Cognitive function over time in the Alzheimer's disease
anti-inflammatory Prevention Trial (ADAPT). Arch of Neurology 2008; 65:E1-
E10
7. KeKosky S. Ginkgo biloba for prevention of dementia a randomized Controlled
Trial. JAMA November 19, 2008; 300:2253-2262.
8. Off Label use of Atypical Antipsychotic Drugs.

References:


• Adelman A. Initial Evaluation of the Patient with suspected Dementia. Am Fam
Phy May 1, 2005; 71:1745-1750

• Kerwin D. How to prevent a delayed Alzheimer's diagnosis. Journal of Family

Links:

• http://www.aafp.org/afp/20050501/1745.html

• [www.aafp.org](http://www.aafp.org)


  
  o Detection of Dementia and Mild Cognitive Impairment
  o Diagnosis of Dementia
  o Management of Dementia
Chapter 12 – Sleep Disorders

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Sleep medicine constitutes a spectrum of disorders, which combines the specialties of neurology, pulmonary medicine, psychiatry, psychology, otolaryngology, and pediatrics. Sleep disorders may be divided based on symptoms into four types: 1) insomnia, or difficulty initiating and maintaining continuous sleep, 2) excessive sleepiness, 3) circadian sleep-wake rhythm disorders, in which the sleep-wake cycle is out of sync with the day-night cycle, and 4) parasomnias, in which undesirable motor, behavioral and autonomic activity occur before, during, or after sleep.

The International Classification of Sleep Disorders, revised in 1997, lists 84 disorders which are divided into four categories: 1) dyssomnias which include causes of insomnia and excessive sleepiness, 2) parasomnias, 3) sleep disorders associated with medical or psychiatric disorders, and 4) proposed sleep disorders, for which there is suggestive, but not unambiguous data, for a sleep disorder. This chapter will review the properties of normal sleep and sleep disorders based on the symptomatic classification.

NORMAL SLEEP

Sleep is more than a respite from consciousness or sensory stimulation. It is a complex and dynamic process. Much of what we now know about the anatomy of sleep is based on lesion studies in animals. The hypothalamus is critical to the organization of sleep. It is involved in a network of brain nuclei that regulate an intrinsic time clock, body temperature, and sleep-wake cycles, while concurrently relying on cues from light as perceived by the eyes and skin. The thalamus is most closely involved in the control of the sleep-wake cycle. Massive bilateral destruction of the thalamus is characteristic of fatal familial insomnia, which results in progressive insomnia and neurologic deterioration leading to death. Both the hypothalamus and thalamus extensively modulate the actions of the brainstem, the primary site of origin for REM sleep. The reticular activating system, raphe nuclei and locus ceruleus, in particular, have key roles in the generation of REM sleep.

The neuropharmacology of sleep is related to the anatomic regulatory centers of sleep. The fact that the raphe nuclei and locus ceruleus are crucial to REM sleep suggests that serotonin and norepinephrine, respectively, play a crucial role in sleep mechanisms. In clinical practice, however, serotonin precursors have conflicting effects on sleep. Drugs which alter the storage, release and re-uptake of serotonin have minimal effects. Acetylcholine may play an important role in REM sleep because of the cholinergic neurons in the brainstem, which regulate REM sleep. The effect of norepinephrine and dopamine on sleep has been extensively studied in patients with Parkinsonism, but no
significant changes have been found. Pharmacologically, we know that stimulants, such as amphetamines, act by increasing brain norepinephrine and dopamine concentrations. The stimulants reduce total sleep and REM sleep times. Hypnotics, such as benzodiazepines, act by enhancing inhibitory GABAergic neurotransmission. Clinically, they promote sleep onset and reduce slow wave and REM sleep.

In normal day-night conditions, the sleep-wake cycle is 24 hours long. With external time cues removed, the sleep-wake cycle lengthens to about 25 hours. The intrinsic cycling of bodily functions, such as the sleep-wake cycle and body temperature, is referred to as the circadian rhythm. It is determined by an internal pacemaker, which for the sleep-wake cycle is located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN has connections to the retina, which regulate the light-dark synthesis and release of melatonin by the pineal gland. Individuals blind from birth, who lack the SCN-retinal connection, do not have a 24-hour sleep-wake cycle. In normal individuals, the internal 24-hour clock is stable; however, it can be reset by external cues, particularly light, as in travel across time lines. Body temperature is the most reliable marker of circadian rhythm in humans and the biological rhythm most closely linked with sleepiness. Low body temperature correlates with sleep onset while rising body temperatures correlate with sleep offset. Body temperature reaches a nadir twice a day: a relatively small drop in mid-afternoon and a more drastic fall in the early hours of the morning, coinciding with REM sleep.

Normal sleep consists of several stages. Each stage is associated with certain physical properties and EEG findings. Drowsiness or light sleep is Stage 1. The subject is relaxed. Slow random eye movements and slow pupillary constriction and dilatation are noted. On EEG, background activity is slow compared to wakefulness. As sleep continues, Stage 2 is entered. In this stage, bursts of EEG activity called sleep spindles, vertex sharp waves and K complexes appear. With continued sleep, during which the subject is harder to awaken, stages 3 and 4 are entered. During these stages, collectively referred to as slow wave sleep, the EEG shows high amplitude slow waves. About 90 minutes after the onset of sleep, the subject enters rapid eye movement (REM) sleep. This stage of sleep is associated with vivid dreams that follow a story line and are accompanied by realistic imagery. Dream recall is more frequent in awakenings from REM sleep than from non-REM (NREM) sleep. There is loss of skeletal muscle tone except for brief twitching and rapid eye movements. Autonomic changes also occur, including elevated blood pressure, irregular heart rate, and irregular respirations. Arrhythmias such ventricular tachycardia, atrial fibrillation, and heart block are more likely to occur during REM sleep. It is suspected that myocardial infarction and strokes that occur during sleep happen during REM sleep because of the associated autonomic changes. Penile erection also occurs during REM sleep. Patients with psychological causes of impotence will have an erection during REM sleep, while patients with organic etiologies do not.

NREM sleep, which consists of stages 1, 2, 3, and 4, usually occupies the first 60 to 90 minutes of sleep, followed by REM sleep. A night of sleep usually consists of four to six NREM-REM cycles. The duration of slow wave sleep is longest during the first half of the night, while REM sleep becomes more prolonged during the second half of the night. Age-related changes in sleep architecture have been reported. During the neonatal period,
most of the day is spent asleep, with half of the sleep time in active sleep, the equivalent of REM sleep. As one ages, the percentage of total sleep that constitutes REM sleep remains fairly constant at 20 percent to 25 percent. During adolescence, there is a peak in the percentage of slow wave sleep after which it declines with aging. Conversely, stage 1 sleep increases with age. Nocturnal sleep efficiency, or the percentage of time in bed spent asleep, is reduced to about 70 percent to 80 percent in the elderly, most likely as a result of increased nocturnal awakenings. Total sleep time, which takes into account daytime napping in addition to nocturnal sleep, is fairly constant between young and old. Thus, it is a myth that old people need less sleep.

The functional importance of individual stages of sleep has been investigated with selective sleep deprivation studies. These studies, which eliminate one or more stages of sleep, most commonly REM sleep and, less frequently, slow wave sleep, find that total sleep time, not selective sleep stage deprivation, is the most important predictor of cognitive performance.

INSOMNIA
Patients with sleep problems are common challenges in primary care offices; at least 40 million Americans have sleep disorders. Less than 20 percent of these people report that they have discussed their problems with their physicians. Sleep problems are often missed, although they have been shown to lead to health risks such as accidents and absenteeism, and, in the case of patients who may have obstructive sleep apnea (OSA), potential cardiovascular complications. Diagnosing sleep problems can be made easier with simple tools for sleep evaluation, including the Epworth Sleep Scale (see below) and the American Academy of Sleep Medicine's self-assessment (see Internet resources below).

With insomnia, finding out whether the patient has trouble falling asleep or staying asleep, or just does not feel rested, can help guide the treatment, or lead to the possibility of diagnosing anxiety or depression. Consider underlying causes: the medical illnesses that may cause pain or sleep disruption; the psychiatric illnesses that may be the source of the problem or co-exist with it; the drugs, caffeine or alcohol that may interfere with sleep. A sleep log kept for two or three weeks is very helpful. It should include the time the patient got into bed, in addition to the time he fell asleep; the timing and duration of naps, meals, and exercise; a description of the sleep environment; and information on what the patient is using to try to get to sleep, since rebound insomnia because of sleep medication use is not uncommon.

Untreated insomnia has significant risks, including increased accidents and psychiatric disorders, but pharmacologic treatment has its risks, too, such as drug dependence and daytime sedation. In primary insomnia especially, the approach that has been shown to work, and keep working, is behavioral. Medications should be used, if behavioral approaches are not successful, for the shortest time possible in the smallest dose possible. Sleep hygiene—avoiding daytime naps, avoiding stimulants close to bedtime, exercising regularly early in the day, having a nighttime routine, using the bed only for sleep or sex,
and getting out of bed if unable to fall asleep after a designated time period, such as thirty minutes—is, as the late Dr. Lee points out, common sense advice.

There are also behavioral therapy techniques. Sleep restriction limits the amount of time spent in bed to the amount of time spent asleep; stimulus control has the patient who cannot fall asleep leave the bed, go to another room until he feels sleepy, and then return to bed. These methods take persistence on the part of the doctor and cooperation on the part of the patient, but do work. They need to be tried because there is no ideal sleep medication. If one is needed, thinking about the timing and duration of the sleep problem helps guide the choice: very short acting if the problem is getting to sleep, longer acting if the problem is early awakening, provided depression or anxiety is not suspected. If insomnia has been present for six months and there is no response to medical, behavioral, or psychiatric treatment, consider a sleep study.

Insomnia has a greater prevalence in the elderly as a result of comorbidities, depression, sleep apnea (which grows more common as women age), and polypharmacy. In a 2003 National Science Foundation (NSF) poll of older adults, the need to go the bathroom was the most common reason for interrupted sleep. Pain, cough, heartburn, and headache were much less prevalent. Medications in the elderly frequently contribute to insomnia. The elderly seem to require the same seven to nine hours of sleep younger adults do, although their sleep architecture changes. Both the 2003 NSF survey and a 2005 Gallup survey found that the better the health of older adults, the more likely they were to sleep well. Poor sleep in the elderly seems to indicate poor overall health.

Children's sleep problems are a challenge because of changes in their sleep patterns as they grow, especially if they are out of the average range of age for expected changes. Many of their sleep problems, including night terrors, sleepwalking, and enuresis, are the result of central nervous system immaturity and require only supportive and protective measures. Obstructive sleep apnea (OSA) is an exception and is diagnosed much like adult OSA. Children, who for whatever reason are sleep deprived, can become hyperactive, have mood and behavior changes, or develop problems learning. They need a consistent schedule, a relaxing bedtime routine, and a dark bedroom without a TV or computer. Social factors (such as families that share living spaces, or the habit of co-sleeping) may make optimum sleep hygiene difficult to achieve.

In the case of the parasomnias, which are undesirable motor or autonomic activity during sleep, the specific parasomnia may point to the need to treat a medical problem: peripheral neuropathy and iron-deficiency anemia are associated with restless leg syndrome (RLS), for example, and a urinary tract infection or spinal cord disease that may lead to (secondary) enuresis. The parasomnias, apart from RLS and periodic limb movements of sleep, which are treated with levodopa compounds, benzodiazepines or opioids, may not require treatment. In one study, 15 percent of women in the third trimester of pregnancy developed RLS; they were often iron or folate deficient. RLS becomes more prevalent with age, and severity can also increase.

The hypersomnic patient who does not have narcolepsy or neurologic illness needs testing in a sleep lab if obstructive sleep apnea (OSA) is suspected, because treatment
depends on the findings of a sleep study. A bed partner, parent or roommate may provide valuable clues, such as apneas or the presence of loud snoring in other positions than supine, to the diagnosis of OSA. Obesity or a thick neck may be tip-offs to OSA.

OSA in the overweight or obese is often helped by weight loss. Appliances or surgery may be helpful in mild to moderate OSA, but continuous positive airway pressure (CPAP) is the usual treatment for moderate or severe OSA.

Finding out about the patient's expectations and beliefs is always helpful, as is asking if the patient or family members are willing to make the changes you recommend. Environments and cultural practices need to be explored. Offer follow-up of sleep problems to find out what works and to offer alternatives.

EXCESSIVE SLEEPINESS

Excessive daytime somnolence is a more common complaint in sleep clinics than insomnia. The major causes of this symptom are sleep apnea, narcolepsy or neurologic illness such as head injury, post-viral infection, myotonic dystrophy, developmental disorders, Parkinson disease, Alzheimer disease and, occasionally, parasomnias. The diagnosis is determined by history, physical exam, and objective testing for daytime sleepiness, such as the [multiple sleep latency test](#) (MSLT), which is almost always preceded by an overnight polysomnogram to document adequate sleep. The history is often best obtained or corroborated by a bed partner or family member who can provide witnessed accounts of daytime somnolence and the patient's nocturnal sleep patterns.

**Obstructive sleep apnea (OSA)** is due to complete or partial obstruction of the upper airway. During sleep, the tone of pharyngeal muscles diminishes. When pharyngeal muscles collapse, resistance to airflow increases and results in elevated negative intrathoracic pressures during inspiration. Complete obstruction of the upper airway results in apnea or cessation of airflow across the nose and mouth, often, but not always, with associated hypoxemia. Partial obstruction causes a **hypopnea**, which is defined as a 50 percent to 90 percent reduction in airflow. At the end of an apnea or hypopnea, a person is often aroused. An arousal or brief awakening stimulates pharyngeal muscle tone and normal inspiratory airflow resumes. Severity of hypoxemia is dependent on baseline oxygenation, lung oxygen stores and apnea duration. For example, a markedly obese patient is likely to have severe OSA-associated hypoxemia because elevated abdominal pressures are compressing the thoracic cavity and reducing lung oxygen stores. There are many causes of upper airway obstruction. Tonsillar hypertrophy is a common cause of OSA in children and adolescents. Craniofacial abnormalities such as retrognathia, micrognathia, and deviated nasal septum, increase upper airway obstruction, as does fatty infiltration of pharyngeal soft tissues from weight gain. Macroglossia, which may be associated with hypothyroidism, acromegaly, amyloidosis, and Down syndrome, usually causes obstruction at the base of the tongue, lower down the pharynx. Neuromuscular disorders, such as myotonic dystrophy, often cause abnormal laxity of pharyngeal muscle tone during sleep.
OSA is common in the general population. The Wisconsin Sleep Cohort, a comprehensive epidemiologic study investigating the prevalence of obstructive sleep apnea in middle-aged adults, found that 4 percent of men and 2 percent of women had obstructive sleep apnea syndrome (OSAS), a diagnosis defined by both clinical criteria and a sleep study. However, 24 percent of men and 9 percent of women had OSA as defined by sleep study results alone. Among commercial truck drivers a high prevalence of OSA is suspected.

A thorough history can provide clues to the diagnosis of OSAS. Apneas or hypopneas during sleep are best confirmed by the patient's family or bed partner. The physiologic effects of apneas and hypopneas are equal. *The most prevalent complaint is fatigue or daytime somnolence, which results from fragmentation of nocturnal sleep by recurrent apnea-associated arousals.* Choking or gasping at the termination of an obstructive apnea is a common observation and can cause self-arousal. The severity of daytime somnolence can be ascertained by the frequency and duration of naps and the likelihood of falling asleep during activities such as reading, watching television, or driving. Sleep deprivation from OSA often has a paradoxical effect on children, who are more likely to present with hyperactivity. Hypoxemia and sleep fragmentation may result in impairment of memory, attention and concentration, changes in mood and personality, loss of libido, and morning headaches. Snoring is a common, but not requisite, symptom in patients with OSA. The intensity of snoring increases with weight gain and reflects increasing upper airway resistance. Loud snoring in all positions of sleep is more likely to be associated with OSA than snoring in just the supine position. Enuresis and nocturia may occur in patients with OSA as respirations against an obstructed upper airway lead to increased intra-abdominal pressure on the bladder. Restless sleep, described as frequent movements of the limbs and trunk, is common in subjects with frequent apnea-associated arousals. Lastly, a family history of OSA can identify individuals who are at risk for OSA, as risk increases with the number of affected family members.

Several factors increase upper airway resistance and thus exacerbate the frequency and duration of apneas. Hypnotics, sedatives, and alcohol, reduce pharyngeal muscle tone during sleep. Inflammation of the nasopharynx and pharyngeal soft tissues from respiratory allergies increase upper airway resistance. Smoking and high altitudes exacerbate apnea-associated hypoxemia.

The physical examination can be used to identify conditions associated with OSA. *Obesity is reported in two-thirds of patients.* A neck circumference of greater than 17 inches in men and greater than 16 inches in women is associated with increased risk for OSA. As previously mentioned, anatomical abnormalities of the head and neck, such as micrognathia, retrognathia, and macroglossia can cause upper airway narrowing. OSA is more prevalent in men compared to women, at ratios reported between 2:1 to 10:1, most likely reflecting gender differences in head and neck anatomy. Prevalence increases for both genders with increasing age.

The diagnosis and treatment of OSAS is important in lieu of its potential hematologic and cardiovascular complications. Polycythemia, from chronic hypoxemia, is relatively
uncommon in patients with OSA. Hypertension, ischemic heart disease, and
cerebrovascular disease occur with higher prevalence in subjects with OSA compared to
the general US population; however, the relationship between OSA and these diseases is
poorly understood. Pulmonary hypertension is a known complication of chronic,
untreated OSA and is strongly associated with severe nocturnal hypoxemia and
hypercapnea. Cardiac arrhythmias are common in patients with severe hypoxemia. The
type of arrhythmias observed include premature ventricular contractions, sinus arrest,
sinus bradycardia, second-degree atrioventricular block, atrial tachycardia, paroxysmal
atrial fibrillation, atrial flutter, and unsustained ventricular tachycardia. These cardiac
arrhythmias are reversible with treatment for OSA.

The differential diagnosis for OSAS includes disorders associated with loud snoring and
daytime somnolence. Primary snoring is characterized by loud snoring only and is not
associated with daytime hyper somnolence. Excessive daytime somnolence may be due
to behavioral or psychophysiologic factors, psychiatric disorders, environmental factors,
drug dependency from hypnotics or stimulants, central sleep apnea syndrome,
parasomnias, disruption in the timing of the sleep-wake cycle such as shift work sleep
disorder, narcolepsy, idiopathic central nervous system hypersonnia, degenerative
central nervous system disorders, and hormone-related conditions such as pregnancy and
menstruation.

The evaluation of a patient with OSAS must include a sleep study. There are two types of
sleep studies: an overnight polysomnogram, performed in a laboratory under the guidance
of a certified sleep technician, and an ambulatory sleep study performed in the patient's
own home. Ambulatory studies tend to monitor a limited number of parameters, i.e.
respiratory effort, airflow, heart rate and oxygen saturation. Polysomnograms also record
electroencephalography to stage sleep and determine total sleep time monitored,
electrooculography and electromyography (EMG) of the chin to determine the onset of
rapid eye movement (REM) sleep, airflow, chest and abdominal wall motion, EMG of the
legs to detect periodic leg movements of sleep, oximetry, and body position (Figure 1).

The major advantages of a laboratory study are the ability of a sleep technician to
intervene when an electrode or monitor is displaced and the reliability and
comprehensiveness of the sleep data obtained. The major advantage of an ambulatory
study is lower cost. In patients suspected of severe OSAS, an ambulatory monitor can
serve as a screening test, although a negative study should be followed up with a
polysomnogram. For most patients with OSAS, a polysomnogram is the preferred study.

A sleep study is scored on several parameters, including sleep efficiency (total sleep time
divided by total time in bed, expressed as a percentage), sleep latency (time it takes to
fall asleep from the beginning of the study), percentage of each stage of sleep relative
to total sleep time, number of apneas, range of apnea duration and oxygen
desaturation, number of arousals, number of periodic leg movements with and
without associated arousals, REM latency (time it takes to enter REM sleep from the
time of sleep onset), and associated cardiac arrhythmias. An apnea is defined as
cessation of airflow for at least 10 seconds. There are three types of apneas: obstructive,
central and mixed.

**Obstructive apneas** imply the absence of airflow in the presence of continued thoracic and abdominal effort (Figure 1). **Central apneas** are often due to dysfunction of regulatory respiratory centers in the central nervous system. Airflow is absent and so, too, is thoracic and abdominal effort. Insomnia, rather than daytime somnolence, is more likely to be the presenting symptom. **Mixed apneas** have features of both obstructive and central apneas. They are often due to upper airway obstruction.

The severity of OSA is determined by the apnea-hypopnea index (AHI), or the frequency of apneas and hypopneas per hour of sleep, the frequency of arousals and awakenings, body position during apneas, oxygen desaturation, and type of cardiac arrhythmias. REM sleep and sleep in the supine position are of particular interest as obstructive apneas tend to be longer in duration and oxygen desaturation more severe. In general, mild OSAS may be characterized by an AHI of less than 15, mild oxygen desaturation, no cardiac arrhythmias, and minimal or no daytime fatigue. Moderate OSAS may be characterized by an AHI of 15–30, moderate oxygen desaturation (i.e., 70 percent to 85 percent), moderate daytime sleepiness, and sometimes premature ventricular contractions. In severe OSAS, the AHI is usually greater than 40 and associated with oxygen desaturations below 70 percent, cardiac arrhythmias, and severe daytime sleepiness. Polysomnogram results should be congruent with the clinical history. If not, the diagnosis of OSAS must be reconsidered. Occasionally, the polysomnogram may reveal frequent unexplained arousals or crescento snoring just before an arousal, but no apneas. In such cases, a repeat polysomnogram with esophageal balloon pressure monitoring of intrathoracic pressures may disclose upper airway resistance syndrome. This condition is treated in the same manner as OSAS.

The treatment of OSAS is dependent on its severity, the presumed cause, and the patient's age. In obese patients with OSA, weight loss or the correction of hormonal abnormalities can improve or eliminate OSA. However, weight loss is an unrealistic goal for most patients. Positional therapy, or conditioning the patient to sleep in the lateral recumbent position, is effective in patients with mild OSA in the supine position. Younger patients and those with craniofacial abnormalities may prefer surgical over medical treatment.

Mild to severe OSAS may be treated with appliances and/or surgical procedures, which maintain patency of the airway. Oral appliances are used in patients with mild OSAS or primary snoring. The basic working principle of oral appliances is that they advance the mandible or pull the base of the tongue forward to enlarge the upper airway. Mandibular advancing devices, look like mouth guards and tongue retainers, hold the tongue in a bulb of negative pressure, which fits between the teeth and lips (Figure 2). They can be bought over the counter as prefabricated devices or are designed from dental impressions made by a dentist.

**CPAP** is the treatment of choice for moderate to severe OSAS. It keeps the airway open during sleep by delivering positive air pressure via a nasal mask (Figure 3) or nasal pillows which fit snugly in the nostrils. CPAP pressures are titrated to eliminate apneas and snoring in a follow-up polysomnogram to the diagnostic study. In about 80 to 90
percent of patients, symptoms and cardiac arrhythmias are improved. However, noncompliance with CPAP is a leading cause of persistent symptoms. Skin breakdown over the bridge of the nose or, rarely, an allergic reaction to the silicone in the mask may prevent continued use of the mask. Some patients find the mask uncomfortable or experience claustrophobia. Several variations of CPAP may circumvent this problem: 1) nasal pillows, 2) a bilevel CPAP device (bi-PAP) which delivers lower positive pressure during expiration than inspiration, and 3) a ramp which gradually increases CPAP pressures over a period of time during which the patient is allowed to fall asleep. A humidifier attachment prevents drying of mucosal membranes and nosebleeds. CPAP will be ineffective if the patient is a mouth-breather, in which case a chin strap is used to prevent pressure loss.

Surgery is considered when CPAP cannot be tolerated or fails to treat OSAS adequately. Surgery is designed to reconstruct the upper airway at a particular site or bypass it altogether. Tracheostomy is the last option considered and rarely performed. In most children with OSAS, tonsillectomy and adenoidectomy is effective treatment, but not so in adults. Uvulopalatopharyngoplasty (UPPP) is the most common upper airway surgery performed in adults with primary snoring. It enlarges the retropalatal airway through a tonsillectomy, excision of the uvula and posterior portion of the palate, and excision of tonsillar fossae mucosa if tonsillectomy has already been performed (Figure 4). Complications from a UPPP are rare, but include nasal reflux of liquids, postoperative bleeding, nasopharyngeal stenosis, voice change, vague foreign body sensation and death secondary to airway obstruction. *While UPPP may initially improve mild OSAS, its success diminishes with time and is thus not considered a reliable treatment option for OSAS.* Laser-assisted uvulopalatopharyngoplasty (LAUP) is indicated for snoring only. A LAUP involves laser-guided resection of the soft palate and uvula (Figure 5), which is less than the amount of tissue resected in a UPPP. This procedure is highly successful for elimination of snoring, but postoperative pain in the area of surgery has caused it to lose favor as a treatment option. Genioglossal advancement (GA) is designed to enlarge the retrolingual airway by pulling the base of the tongue anteriorily (Figure 6). It is often performed after unsuccessful UPPP. The success rate for GA, with or without previous UPPP, is high. Maxillomandibular advancement (MMA) is typically performed after failed GA, except in patients with primary facial skeletal deformities in whom MMA is the treatment of choice. It allows for maximal enlargement of the retrolingual airway, as well as enlargement of the retropalatal space. Maxilla and mandible are advanced simultaneously, thereby advancing the base of the tongue more than GA (Figure 7). The *response rate to MMA is close to 100 percent.* The major complication is transient anesthesia of the cheek and chin. After all surgical procedures, a follow up polysomnogram is indicated to document the success of treatment. Because of the diminishing efficacy of surgery in some patients, serial polysomnograms may be warranted, particularly if the patient complains of recurrent symptoms.

**Narcolepsy** is a chronic disorder of unknown etiology. It usually begins in the second to third decade of life, rarely before age 5 or after age 50. It affects men and women equally. Narcolepsy is characterized by a tetrak of symptoms: 1) excessive daytime somnolence, 2) sleep paralysis, 3) hypnagogic hallucinations, and 4) cataplexy. Only 20 percent to 25
percent of patients experience the full tetrad of symptoms. *The symptoms of narcolepsy reflect the inappropriate intrusion of REM sleep and its properties of atonia and visual hallucinations into wakefulness and other stages of sleep.* For example, sleep paralysis occurs when REM-associated atonia intrudes on the transition between wakefulness and sleep. The patient is consciousness, but unable to move his limbs. **Hypnagogic hallucinations** are vivid, REM-associated dream-like visual hallucinations which occur at sleep onset, while **hypnopompic hallucinations** occur upon awakening. Sleep paralysis, hypnagogic hallucinations and hypnopompic hallucinations can occur in normal people who have a disruption in their normal sleep pattern, as with sleep deprivation.

Cataplexy is unique to narcolepsy, although about 30 percent of patients with narcolepsy do not experience it. REM-associated atonia intruding into wakefulness causes loss of axial and/or appendicular muscle tone for a few seconds, without loss of consciousness. The longer the episode, the more likely it will lead directly into REM sleep. This phenomenon is often precipitated by extremes of emotion, such as anger, fear, excitement, or, most commonly, laughter. It can occur several times daily or rarely. Cataplexy can endanger a person's life if it occurs while driving, bathing or swimming.

Restless sleep is a common complaint among patients with narcolepsy, but not a major cause of daytime sleepiness. Sleep apnea and periodic limb movements of sleep occur with higher frequency in patients with narcolepsy compared to the general population, but the treatment of these conditions does not improve daytime sleepiness.

The cause of narcolepsy has yet to be determined. An immunologic cause has been suggested by the high association of certain class II human leukocyte antigens (HLA) in patients with narcolepsy with cataplexy. Greater than 85 percent of narcoleptic patients with cataplexy, of various ethnic backgrounds, share a specific HLA allele, DQB1*0602 (previously known as DQw1), often occurring concomitantly with HLA DR2, in comparison to 12 to 38 percent of the general population. Other associated HLA antigens have been reported. Nevertheless, class II HLA typing is not a routine diagnostic test as these antigens may be absent in some patients with narcolepsy with cataplexy and present in asymptomatic persons.

*The definitive diagnosis of narcolepsy is based on a polysomnogram that reveals no cause of hypersomnia and a multiple sleep latency test (MSLT).* The MSLT is a daytime study that consists of a series of four to five nap trials. Severity of daytime sleepiness is based on sleep latency, or time it takes a subject to fall asleep, and presence of sleep-onset REM (SOREM), or REM sleep within 10 minutes of sleep onset. A sleep latency of less than 5 minutes is indicative of a pathologically sleepy state, while a sleep latency of 5-10 minutes is only suggestive of it. The laboratory diagnosis of narcolepsy requires an average sleep latency of less than 10 minutes and SOREM in at least two nap trials. As SOREM can occur with REM-sleep deprivation from sleep apnea or drug and alcohol withdrawal, an overnight polysomnogram prior to the MSLT is done to screen out such causes. A two-week period of alcohol or drug abstinence is required before an MSLT. Compliance can be monitored with a drug screen prior to the study.
The treatment of narcolepsy is often difficult. Excessive daytime sleepiness and cataplexy are particularly difficult to treat. The mainstay of treatment is a combination of several planned naps daily and CNS stimulants, such as pemoline, methylphenidate, amphetamine, and modafinil (Provigil®). To avoid medication tolerance, weekly drug vacations for one to two days are recommended. Cataplexy, sleep paralysis and hypnagogic hallucinations are treated with tricyclic antidepressants, namely clomipramine, imipramine, nortriptyline, and protriptyline, and other serotonin reuptake inhibitors such as fluoxetine.

CIRCADIAN SLEEP-WAKE RHYTHM DISORDERS

This group of disorders is characterized by a mismatch between the patient's sleep patterns and the time at which the patient wishes to fall asleep. The most common scenario in which this complaint occurs is with shift work or jet lag. With shift work, rotating shifts are more disruptive to the sleep-wake cycle than fixed evening or night shifts. Patients older than 40 years of age experience greater difficulty in adapting to shift work than younger workers. Jet lag has the same effect on sleep as shift work. Its effect is exacerbated by alcohol and dehydration. In general, east to west travel across several time zones results in sleep disturbances that last about 4–5 days. Travel from west to east can disrupt sleep for up to 10–14 days. Melatonin and benzodiazepines may reduce jet lag in some people, but their use is not recommended because of inadequate data supporting their efficacy. Furthermore, the long-term side effects of melatonin are unknown.

There are three major circadian rhythm sleep disorders: 1) delayed sleep phase syndrome, 2) advanced sleep phase syndrome and 3) non-24 hour sleep-wake syndrome. In delayed sleep phase syndrome, patients usually go to sleep about 6–8 hours later than socially acceptable. Once asleep, however, sleep architecture and duration are normal. Patients complain of nocturnal insomnia and daytime sleepiness. Psychopathology is common. Delayed sleep phase syndrome occasionally coincides with the onset of bipolar disorder or schizophrenia. Lifestyle, mood, personality, family problems and school problems may be contributing factors. Sometimes, delayed sleep phase syndrome begins in childhood and persists throughout life. It can be familial. The success of treatment with hypnotics, melatonin, stimulants, and psychotherapy is highly dependent on patient motivation, but is usually disappointing. Chronotherapy, which involves delaying bed time by one hour every day, until the desired bed time is achieved, is usually not successful. Another way to advance the circadian rhythm is to expose the patient to a bright light of greater than 5000 lux in the early morning, between 5 and 8 a.m. The results are highly dependent on patient motivation.

Advanced sleep phase syndrome is very rare and is thus questioned as a true entity. It is characterized by early evening sleep onset, i.e., 7 p.m. or 8 p.m., and early morning awakening. Sleep duration and architecture are normal. Attempts to delay the time of sleep onset are usually unsuccessful. The sleep patterns of the elderly most closely match the advanced sleep phase syndrome. The major difference is that the total duration of nocturnal sleep in the elderly is shorter and fragmented. Chronotherapy may be
beneficial, as with delayed sleep phase syndrome. For patients with advanced sleep phase syndrome, exposure to bright light between 9 p.m. and 1 a.m. may induce a phase shift in bed time.

The irregular sleep-wake pattern or non-24 hour sleep-wake syndrome reflects a complete loss of circadian rhythm. There is disorganization and tremendous variability in the sleep-wake schedule. Overall sleep in a 24-hour period is reduced and fragmented into short sleep periods. The fragmentation of sleep parallels the random fluctuations in body temperature as well as the irregularity of other lifestyle habits such as meals. Typically, patients complain of daytime sleepiness, fatigue, and insomnia. Alzheimer's dementia may be associated with the irregular sleep-wake pattern, although circadian rhythm of core body temperature is preserved. Behavioral treatment is the mainstay of establishing a normal sleep-wake schedule. A set bedtime is established. The number of naps is restricted. In some Alzheimer patients, bright lights have been used in the early evening with some success in reducing sleep fragmentation and sundowning.

The diagnosis of circadian rhythm disorders is based on history and the examination of detailed sleep diaries. A polysomnogram may be helpful in assessing time at sleep onset, total sleep time, and sleep architecture while the MSLT can be used to determine severity of daytime sleepiness in patients refractory to treatment for the assumed diagnosis.

PARASOMNIAS

Parasomnias collectively refer to undesirable motor or autonomic activity during sleep or upon arousal. They include hypnic jerks, sleep myoclonus, periodic leg movements of sleep, head banging, sleep paralysis, REM sleep behavior disorder, sleepwalking, nightmares, night terrors, bruxism (teeth grinding), and bed-wetting. It is more common in children than adults. They may be associated with: 1) abnormal sleep architecture such as REM behavior disorder, 2) familial predisposition such as sleepwalking or night terrors, 3) transition between sleep stages or a particular stage of sleep, such as head banging and REM behavior disorder, respectively, and 4) multiple factors as in bed wetting. Anxiety, sleep deprivation or changes in sleep habit may exacerbate the frequency or severity of parasomnias in children and adults.

Hypnic jerks or sleep starts are brief jerks of one or more limbs during sleep onset. They are normal. Often, they may be accompanied by a sensation of falling. Exercise, emotional stress or caffeine in the evening are precipitants. No treatment is required.

Sleep myoclonus refers to rhythmic leg jerking, usually involving the tibialis anterior. It is commonly benign, often familial, and increases with age. The diagnosis is based on history provided by the patient's bed partner and the electromyographic appearance of rhythmic leg movements on polysomnogram. Although the etiology is idiopathic, it has been associated with some medical conditions such as uremia and anemia, neurologic disorders such as sensory neuropathy, narcolepsy, and drug treatment with levodopa for Parkinson's disease, clomipramine for depression, and amphetamines for narcolepsy.
Most patients with sleep myoclonus are asymptomatic. Treatment with clonazepam is recommended only when patients complain of insomnia or daytime somnolence.

**Periodic limb movements of sleep (PLS)** are characterized by repetitive, stereotyped, and asymmetrical leg movements during sleep. The leg movements are often, but not always, associated with cyclical arousals or awakenings. The patient is usually unaware of the limb movements or fragmentation of sleep. PLS may present as insomnia or, less commonly, as excessive daytime somnolence. Men and women are equally affected. Prevalence increases with age, but is rare before the age of 30. The etiology is unknown.

PLS frequently occurs in association with restless legs syndrome (RLS). RLS is characterized by an uncomfortable, ill-described sensation involving the calves, which results in an irresistible urge to move the legs. Symptoms are most severe when the legs are at rest. Most patients with RLS have PLS, but the reverse is not true. In patients with RLS, the major identifiable cause is sensory peripheral neuropathy.

The diagnosis of PLS is confirmed by a polysomnogram, which demonstrates a series of periodic bursts of muscle activity over the leg EMG leads. These bursts of muscle activity are often followed by brief arousals or awakenings. Occasionally, PLS is an incidental finding, often associated with no or infrequent arousals. The polysomnogram can also exclude other causes of excessive daytime somnolence associated with frequent nocturnal limb movements, namely sleep apnea and fragmentary myoclonus.

Levodopa, benzodiazepines, and the opioids constitute first-line therapy for PLS and RLS. Long-term treatment with these medications is hindered by tolerance. Pergolide has been shown to be effective alternative therapy, although other antiparkinsonism medications and some antiepileptic medications are only anecdotally reported as promising to date.

**Head banging**, otherwise called rhythmic movement disorder or jactatio capitis nocturna, often involves body rocking. These movements, which are pleasurable to the patient, occur during sleep onset and stages 1 and 2 of sleep. It is usually confined to infancy and early childhood. Predisposing factors are low IQ, immaturity, and maternal neglect. Most children are normal. Trauma is unusual, although subdural hematoma and retinal hemorrhage may occur. Treatment is recommended only if injuries occur. Benzodiazepines reduce, but do not eliminate, this behavior.

**Sleep paralysis** refers to paralysis of skeletal muscles during the transition from wakefulness to sleep or from sleep to wakefulness. The severity of paralysis is variable from patient to patient. Some patients have mild weakness of the limbs, while others cannot open their eyes or speak. It is often described as a terrifying experience. Respiration is unaffected. Sleep paralysis may occur under four different circumstances: 1) an isolated, rare event, 2) familial, in which case it can occur several times nightly and may be associated with excessive daytime sleepiness, 3) as a symptom of narcolepsy, or 4) as result from sleep-onset REM secondary to sleep deprivation or sleep fragmentation.
REM sleep behavior disorder is characterized by retention of muscle tone during REM, a finding confirmed by polysomnogram. Under normal circumstances, REM sleep is characterized by loss of muscle tone and paralysis. Patients with REM sleep behavior disorder are able to enact their dreams, which are usually frightening and combative. Self-injury or injury to bed partners is usually the precipitating reason for medical attention. This condition most commonly occurs in elderly men. Most cases are idiopathic although it may occur in diseases that affect anatomical areas responsible for REM sleep, for example dementia, subarachnoid hemorrhage, stroke, brainstem lesions and multiple sclerosis. Treatment is quite satisfactory in most cases with clonazepam 0.5–1.0 mg at bedtime.

Sleepwalking, night terrors and nightmares are distinguished by the particular sleep stage in which these behaviors occur. Sleepwalking and night terrors occur during slow wave sleep, usually within the first two hours of sleep. They are more common in children and may be familial. Most children are normal, contrary to popular belief, and outgrow these behaviors. Sleep deprivation, anxiety or fever are predisposing factors. Sleepwalking and night terrors are associated with variable degrees of responsiveness. Night terrors are characterized by piercing, inconsolable crying and autonomic hyperactivity, i.e., tachycardia, piloerection, and sweating. If awoken, children are disoriented and cannot recall what has happened. The inability to recall a dream, as well as its occurrence during slow wave sleep is what distinguishes night terrors from nightmares. Most children with nightmares have some recall of content, as it is essentially a terrifying dream during REM sleep.

A regular sleep schedule is usually effective treatment for sleepwalking. When self-injury occurs as a result of sleep walking, diazepam 2–5 mg nightly may be beneficial because it reduces arousals. Tricyclic antidepressants may also help reduce sleep walking although it can also exacerbate it in some patients. Benzodiazepines can be prescribed to treat severe, frequent night terrors.

Bruxism or teeth grinding is relatively uncommon. It may result in abnormal wear of teeth or jaw pain. This behavior usually occurs during the early stages of sleep and is often associated with stress. It is also observed in patients with mental retardation or in comatose states. A tooth guard may prevent undue wear of teeth.

Bed-wetting occurs in all stages of sleep, including REM sleep. It is often familial and slightly more common in boys than girls. The etiology is believed to be a combination of behavioral and psychiatric problems. If bed-wetting occurs after a period of dryness at night, one should consider diseases of the urinary tract or spinal cord. Behavioral therapy may be effective, with positive reinforcement for dry nights and negative reinforcement with a buzzer that goes off when a pad is soaked. Tricyclic antidepressants, such as imipramine 10–25 mg nightly, may also be beneficial because urinary retention is one of the anticholinergic side effects. Hypnotics, however, may worsen bed-wetting.

REFERENCES

SELF-ASSESSMENT QUESTIONS

1. Night terrors are characterized by:
A. Occurrence during slow wave sleep
B. Occurrence during REM sleep
C. A child's ability to recall the content of a terrifying dream
D. Persistence into adulthood
E. Psychopathology

2. Obstructive sleep apnea is:
A. More common in men than women
B. Often associated with snoring
C. Due to obesity
D. All of the above
E. A & B

3. The stage of sleep, which remains relatively constant throughout life, relative to total sleep time, is:
A. Stage I
B. Stage II
C. Stage III
D. Stage IV
E. REM sleep

4. Daytime somnolence and insomnia are most likely to be the presenting complaints of:
A. Delayed sleep phase syndrome
B. Non-24 hour sleep-wake syndrome
C. Primary snoring
D. Sleep walking
E. Advanced sleep phase syndrome

5. Narcolepsy is characterized by:
A. Excessive daytime somnolence
B. Sleep paralysis
C. Periodic limb movements of sleep
6. Sleep deprivation may cause or precipitate all of the following, except:
A. Sleep paralysis
B. Hypnagogic hallucinations
C. Sleepwalking
D. Periodic limb movements of sleep
E. Sleep-onset REM

7. Periodic limb movements of sleep most commonly coexists with:
A. Narcolepsy
B. Obstructive sleep apnea
C. Central sleep apnea
D. Restless leg syndrome
E. Sensory peripheral neuropathy

ANSWERS

1. A. Night terrors occur during slow wave sleep while nightmares occur during REM sleep.
2. E. Obstructive sleep apnea is more common in men than women and is often, but not always, associated with snoring. Obesity, while commonly associated with obstructive sleep apnea, is not the sole cause.
3. E. The percentage of REM sleep, relative to total sleep time, remains fairly constant after the first year of life.
4. B. In non-24 hour sleep-wake syndrome, sleep is reduced and fragmented. Patients complain of daytime sleepiness, fatigue, and insomnia.
5. D. Narcolepsy is characterized by excessive daytime somnolence, hypnagogic hallucinations, sleep paralysis and cataplexy. Periodic limb movements of sleep are not a symptom of narcolepsy although it occurs with higher frequency in patients with narcolepsy than the general population.
6. D. Sleep paralysis, hypnagogic hallucinations, and sleep-onset REM can occur in normal individuals with a disruption in normal sleep pattern. Sleep deprivation may predispose to sleepwalking.
7. D. Restless leg syndrome and periodic limb movements of sleep often coexist and, together, constitute the fourth most common cause of insomnia. Sensory peripheral neuropathy is the most common identifiable cause of restless leg syndrome.
ABNORMAL HEAD SIZE

Introduction

All family practice physicians and pediatricians care for children who have abnormal head size. An organized approach coupled with a few simple tests reveal the diagnosis in many cases. These include serial measurements, developmental assessment and family history, awareness of unusual physical features, and measurement of the parent's head size. Early diagnosis catches potentially treatable medical disorders and optimizes long-term management of the child.

Head size is defined clinically as the occipito-frontal circumference (OFC). OFC >2 standard deviations (SD) above the mean defines macrocephaly; OFC equally far below the mean is microcephaly. Macrocephaly and microcephaly should raise immediate red flags during a child's visit, but the context in which they occur may reveal their relative importance.

Macrocephaly
Mild macrocephaly (+2 to +3 SD) in an older child with normal intelligence, no other symptoms or abnormal neurologic signs, normal velocity of head growth, and a strong family history of isolated macrocephaly usually gives little cause for concern. The macrocephalic child who lacks these reassuring features or displays neurologic signs or symptoms may have underlying intracranial pathology. An infant or young toddler in whom OFC is increasing too fast (crossing lines on standard growth charts), demands further testing regardless of other factors. Macrocephaly in association with neurodevelopmental abnormalities also requires investigation. If either of these factors is present, a positive family history does not eliminate the need for further work-up, including neuroimaging, even though asymptomatic familial macrocephaly and benign infantile extra-axial fluid collection may cause initially accelerated head growth. Other physical features such as unusual facial features, short stature, and pathologic heart murmurs suggest specific non-neurologic evaluations such as chromosomal karyotype, specific genetic or metabolic testing, x-rays, or echocardiogram respectively.

This further work-up is guided by possible causes. Selected causes for macrocephaly are listed in Table 3 and can be further divided into macrocephaly caused by increased spinal fluid (obstructive versus non-obstructive hydrocephalus, pseudotumor cerebri), and increased tissue. Tumors may cause macrocephaly by both mechanisms, whereas children with megalencephaly have large heads simply due to increased brain size. Evaluation of the young child under 2 to 3 years old, in whom increased intracranial pressure results most readily in increased OFC velocity, includes imaging of the brain. Head ultrasound in the neonate, and CT with contrast in the older child allow some assessment of ventricular size and brain parenchyma, as well as extra-axial spaces, but magnetic resonance imaging (MRI) is preferred. MRI allows better visualization of the cortical mantle, white matter abnormalities, small lesions, and abnormalities in the cerebellum and brainstem, including tumors. MRI requires sedation or general anesthesia in young or uncooperative children. Neuroimaging in pseudotumor cerebri, or benign intracranial hypertension, may reveal a "full" appearance to the brain, with smaller than usual ventricles. Diagnosis of pseudotumor cerebri requires lumbar puncture to demonstrate elevation of opening pressure but reveals normal CSF otherwise. Other ancillary tests important in the initial evaluation of the macrocephalic child are listed in Table 4. Otherwise uncharacterized macrocephaly with mental retardation or autism in a male suggests the need for Fragile X type A (FRAXA) DNA testing as well as more routine chromosomal karyotype. Further testing for cytogenetic microrearrangements may be fruitful as well, but the role of testing for specific autism-related genes (PTEN, NLG3, NLG4X) is unclear. This and other secondary testing may accompany referral to a subspecialist such as a child neurologist.

**Table 3: Selected conditions associated with macrocephaly**

- Obstructive, non-communicating, internal hydrocephalus
  - Tumor
  - Congenital infection (especially toxoplasmosis)
  - Posthemorrhagic
  - Aqueductal stenosis
• Chiari II malformation
• Dandy-Walker malformation
• Tuberous sclerosis
• Neurofibromatosis

• Non-obstructive, communicating, external hydrocephalus
  • Tumor (choroid plexus papilloma)
  • Hydranencephaly and other forms of hydrocephalus ex vacuo
  • Subdural hematoma/hyroma, non-accidental trauma
  • Benign increased subdural space in infancy
  • Cerebral malformations
  • Cerebral vein/sinus thrombosis
  • Post-meningitis
  • Vein of Galen malformation/other arteriovenous malformations
  • Chronic right-heart failure

• Pseudotumor cerebri (benign intracranial hypertension)
  • Toxicity—Lead, Vitamin A, Cyclosporin
  • Iron-deficiency anemia
  • Steroid use/withdrawal
  • Hypoparathyroidism
  • Metabolic disease
  • Renal disease
  • Venous sinus thrombosis

• Megalencephaly/increased tissue
  • Tumors
  • Hemimegalencephaly, other brain malformations
  • Fragile X syndrome
  • Neurocutaneous syndromes
  • Overgrowth syndromes (Sotos, Weaver, and Simpson-Golabi syndromes)
  • Leukodystrophies
  • Lysosomal storage diseases
  • Mucopolysaccharidoses
  • Glutaric acidurias
  • Canavan disease
  • Alexander disease
  • Skeletal dysplasias
  • Chromosome abnormalities
  • Autosomal dominant benign familial megalencephaly

Table 4: Selected valuable ancillary studies for macrocephaly

• Wood's lamp examination (Tuberous sclerosis)
• Neuroimaging (MRI scan)
• CBC with RBC indices
• Lead level, iron studies
• Chromosomal karyotype
• Skeletal x-rays (for trauma and/or bone age assessment)
• Evaluation of cardiac function (in young children)
• Lumbar puncture with opening pressure (only after neuroimaging study)
• FRAXA DNA test
• Other specific gene testing when indicated
• Urine for metabolic screen, organic acids
• Lysosomal enzyme panel, other specific metabolic testing when indicated

The cause for the macrocephaly, once identified, dictates management. Obstructive hydrocephalus requires referral to a neurosurgeon for possible ventriculoperitoneal shunt placement, and correction of the underlying anatomic cause if it is amenable to treatment. Brain tumors and many metabolic diseases also require referral for specialized and complex therapy. As previously stated, management of other causes of macrocephaly requires only observation or simple interventions. Non-obstructive hydrocephalus may be due to increased cerebrospinal fluid production, decreased resorption, or loss of brain volume, and sometimes requires surgery. Symptomatic megalencephaly associated with either developmental delay or other unusual physical features, should be evaluated by a medical geneticist experienced in the diagnosis of dysmorphic syndromes. This is important not only for diagnosis, but to identify certain overgrowth syndromes that carry increased risk of malignancy.

Microcephaly

In the overwhelming majority of cases, microcephaly results from failure of the brain to grow at an appropriate rate at some point during development. As the degree of microcephaly increases, so does the probability of mental retardation. A young child with an OFC more than 3 SD below the mean for age has an approximately 50 percent chance of being mentally retarded, although this risk may be modified by OFC growth velocity and family history. It is important always to measure the parents' OFCs when possible. Among individuals with microcephaly and cognitive disability, acquired causes, including fetal alcohol exposure, hypoxic-ischemic injury, congenital infections, and untreated maternal phenylketonuria (MPKU), are more common than inherited disorders. Despite this, there are hundreds of genetic syndromes that cause microcephaly. Genetic mutations associated with non-syndromic microcephaly have now been described and clinical testing likely will be available soon. Specific diagnosis, if possible, may require extensive testing, and referral to a pediatric neurologist or medical geneticist may be valuable. Selected disorders associated with microcephaly are listed in Table 5.

Table 5: Selected conditions associated with microcephaly

• Acquired causes
  o Alcohol-related birth defects
  o Hypoxic-ischemic injury (pre- and postnatal events)
  o Congenital infections (TORCHS, HIV)
  o Untreated Maternal phenylketonuria (MPKU)
  o Postnatal meningoencephalitis (bacterial and viral)
  o Early non-accidental trauma
Devastating conditions such as severe brain malformations and neurodegenerative diseases may cause microcephaly. While CT scan may reveal intracranial calcifications in some congenital infections and a few other conditions, MRI scan allows better assessment of white matter and the cerebral cortex and may show cortical malformations and neuronal heterotopias that may not be evident on a CT scan. Other salient ancillary tests are listed in Table 6.

Table 6: Selected ancillary studies for microcephaly

- Neuroimaging (MRI scan)
- Ophthalmologic examination
- Hearing evaluation
- Neonatal titers for TORCHS infections, HIV
- CBC, chemistry panel (including cholesterol level)
- Thyroid studies
- Chromosomal karyotype, subtelomeric FISH or DNA microarray testing
- Urine for metabolic screen and organic acids
- Serum lactate, pyruvate
- Specific gene testing when indicated
- Specific metabolic testing, including testing of spinal fluid
- Maternal phenylalanine level

In most cases, microcephaly cannot be corrected. Two specific causes, however, represent significant family planning and public health issues. Fetal alcohol exposure may be the most common cause of mental retardation; alcohol-related birth defects occur in 9/1000 children born in the United States. Affected children may not have features sufficient for diagnosis of fetal alcohol syndrome, yet still suffer cognitive disability and have concomitant retardation of brain growth. Likewise phenylketonuria (PKU), a formerly significant cause of mental retardation, has an incidence of 1:12000 and usually is discovered due to abnormal newborn screens.
Unfortunately, some phenylketonuric females of reproductive age do not continue to follow the prescribed dietary restrictions. These females may have only subtle deficits themselves but they (when pregnant) may expose the fetus to high phenylalanine levels in utero. The untreated PKU female therefore has potent teratogenic consequences for the fetus. The risk for a child of an untreated PKU female is proportional to maternal phenylalanine level and approaches 100 percent with maternal levels over 1200 mg/dl. It is estimated that left unchecked maternal PKU will result in the same number of affected infants as did PKU before widespread use of newborn screening and dietary management. Any mother who has a child with microcephaly for which an etiology has not been established and who has not previously had a normal child, should be tested for PKU. This is done not only to prevent future affected children, but also to prevent neuropsychiatric sequelae that occur in adults with PKU who do not maintain their diets.

Conclusion

Macrocephaly and microcephaly are common. Approximately 5 percent of children are either macro- or microcephalic. The primary care physician must be able to identify even subtle cases, and spot emergent causes, and diagnose major and easily treatable causes. Diagnosis in more complex cases is important from therapeutic, family and public health perspectives; a specialist can refine the differential and provide appropriate treatment.

Selected Reading


Questions and Answers

Cranial Abnormalities

1. Advantages of MRI scan over CT scan include all of the following EXCEPT (choose all that apply):
   A. better visualization of the cerebral cortex
   B. better visualization of the posterior fossa
   C. less need for sedation
   D. better visualization of intracranial calcifications

2. Which of these findings is incompatible with a diagnosis of asymptomatic familial megalencephaly?
   A. female gender
   B. OFC +2.5 SD from mean
C. mild mental retardation  
D. brother and father with large heads  
3. In the case of a 10-year-old boy with normal development but an OFC 2.5 SD below the mean for age, what is the most likely additional finding?  
   A. father's OFC –2.5 SD  
   B. intracranial calcifications on CT scan  
   C. coronal and sagittal craniosynostoses  
   D. positive gene test for Rett syndrome  
4. In a 6-month-old infant with macrocephaly, which of the following by itself excludes the need for further evaluation?  
   A. normal development  
   B. normal appetite  
   C. normal head growth velocity  
   D. family history of macrocephaly  
   E. none of the above  
5. In the case of a newborn child with OFC –4SD from mean, which finding below would be least consistent with this head size?  
   A. normal development  
   B. maternal binge drinking during the first trimester of pregnancy  
   C. the child's parents are first cousins  
   D. somatic growth retardation  

Cranial Abnormalities

1. C, D  
2. C  
3. A  
4. E  
5. A  

PAROXYSMAL NON-EPILEPTIC DISORDERS IN CHILDREN

Introduction
Paroxysmal non-epileptic events are frequently encountered in the pediatric patient population and can be mistaken for epileptic seizures. Up to 20 percent–25 percent of patients referred with the diagnosis of seizures may have non-epileptic paroxysmal disorders and it is important to differentiate between them. Age-based classification of these non-epileptic disorders occur is given in table 1 and some of the common non-epileptic events occurring in different age groups are described.

Breath-holding spells (cyanotic infantile syncope)  
Breath holding spells may be cyanotic or pallid. Cyanotic breath holding spells are more common.  
Cyanotic Breath-holding spells  
Cyanotic breath-holding spells are seen in approximately 4.6 percent of children, with a peak incidence between 6 and 18 months. There is a positive family history in 25 percent
to 35 percent of patients. Episodes are commonly precipitated by minor injury, fright or frustration, resulting in vigorous crying. The infant becomes apneic (holds breath in expiration), cyanotic and loses consciousness and muscle tone. When prolonged, it may be associated with stiffening and brief clonic movements and maybe confused for a seizure. Following the breath holding spell, the child rapidly regains consciousness. Rarely a breath-holding spell may actually evolve into a true generalized tonic-clonic seizure, presumably triggered by cerebral anoxia.

It has been proposed that vigorous crying leads to hypocapnic cerebral ischemia, compounded by arterial oxygen desaturation from apnea and reduced cardiac output from raised intrathoracic pressure is the underlying pathophysiology.

**Pallid Breath-holding spells**
These episodes are precipitated by a sudden, unexpected unpleasant stimulus such as a mild injury, usually to the head (without associated crying) followed by collapse with pallor, diaphoresis, bradycardia and loss of consciousness. The patient may be limp, and have posturing and clonic movements. It may progress into a generalized tonic-clonic seizure presumably due to cerebral ischemia.

In these patients, ocular compression often induces prolonged asystole. A hypersensitive vagal mediated cardiac inhibitory reflex with transient cardiac asystole resulting in syncope due to cerebral ischemia is thought to be the underlying pathophysiology.

Breath-holding spells are often mistaken for epileptic seizures and it is important to differentiate the two to avoid unnecessary treatment with anticonvulsants. Breath-holding spells are always preceded by a precipitating event followed by a sequence of crying, apnea and cyanosis and do not occur spontaneously or during sleep. With a seizure, the child stiffens rather than becoming limp and may have clonic movements of the extremities (Table 2). Treatment of breath-holding spells involves parental reassurance that it is a benign and self-limited condition. Atropine and pacemaker implantation have been used in patients with pallid breath-holding spells with variable success.

**Shuddering attacks**
The onset is usually in infancy or early childhood. They are characterized by sudden flexion of head, trunk and elbows, with adduction of elbows and knees associated with rapid tremulous contraction of the musculature and no loss of consciousness. This is similar to a sudden brief shiver that occurs when exposed to cold. Frequency is variable and there may be multiple episodes in a day or there may be periods of several weeks without episodes. Episodes may also occur in clusters, Parents need to be reassured that this is a benign and self limited condition and treatment is not required.

**Stool-withholding activity and constipation**
The child may exhibit episodic, abnormal behavior due to perineal discomfort experienced during stool withholding, usually associated with chronic constipation. It is characterized by sudden interruption of activity with assumption of a motionless posture of slight truncal flexion, occasionally with brief generalized jerks, seen when the child is
experiencing paroxysmal discomfort associated with withholding stool. The behavior resolves with treatment of constipation.

**Self-stimulatory behavior**
These are episodes of genital self-stimulation seen in infants and young children. The behavior is stereotypic, characterized by tightening of thighs with pressure to pubic or suprapubic area. These rocking, rhythmic movements may continue for minutes to hours, and are often accompanied by irregular breathing and flushing. They may be mistaken for episodes of abdominal pain or dystonia, resulting in unnecessary evaluation. Treatment includes parental reassurance.

**Rhythmic behavior disorder (Head banging, Jactatio Capitis Nocturnus, body rocking, Rhythmie du soleil)**
These are stereotypic repetitive movements involving the large muscles of the body (usually head and neck), occurring during transition from wake to sleep, continuing into light sleep. The intensity of the movements can vary from single turns of the head on pillow to involvement of entire body. They are seen in children between one to five years of age, usually starting before 18 months of age. These movements are seen in about 30 percent of children at 1 year, decreasing to only 2 percent at 5 years of age. They are more common in children with mental retardation. Usually, no specific treatment is indicated. The bed should be padded to avoid injury. Clonazepam may be used if the episodes are potentially injurious, or interfere with normal sleep.

**Stereotypies**
These are more complex motor behaviors that are not truly stereotypic and consist of different movements in each episode. The movements themselves are repetitive, rhythmic, coordinated, non-reflexive and seemingly purposeful, most commonly affecting the upper extremities. They are suppressed by distraction and are usually brief, lasting from seconds to less than 15 minutes. They occur several times a day, often in clusters, and are commonly provoked by excitement, stress, fatigue, and boredom. They do not occur during sleep, and daily activities are rarely affected. These complex physiologic motor stereotypies occur in children, usually starting before 3 years of age. They may be seen in children with normal development and intelligence though neurobehavioral problems such as learning disabilities and attention deficit hyperactivity disorder are commonly present. They may also be seen in children with autism, mental retardation and sensory deprivation. The movements are usually chronic, with resolution seen in only a small percentage of patients by 11–12 years. Stereotypies may be mistaken for tics and differences between these two disorders are outlined in Table 3.

**Tics**
Tics are sudden, brief, rapid, repetitive, non-rhythmic, involuntary movements that may be motor, vocal or both. Attempts to suppress these movements only results in an increasing urge to perform them, with relief upon doing so. They are enhanced by emotional excitement and stress and persist during sleep. Motor tics commonly involve face, neck and shoulders. They are divided into simple and complex types. The simple motor tics include sudden, brief, meaningless movements such as blinking, grimaces,
head jerking, shoulder shrugs and arm or leg jerks. Complex motor tics include more purposeful appearing activity such as bruxism, jumping, skipping, touching or smelling objects or self. Vocal tics are also divided into simple and complex, ranging from throat clearing, grunting, and coughing to uttering syllables, phrases and profanities (coprolalia). Tics may be transient or lifelong.

Tourette’s syndrome is an autosomal dominant disorder. It usually begins in childhood between 2 to 13 years of age. It is characterized by multiple motor tics and vocalizations which have been present for at least 12 months. Behavioral abnormalities such as attention deficit hyperactivity disorder and obsessive compulsive disorder are common. Dopamine antagonists (e.g. haloperidol) have been effective in controlling tics. Other drugs such as guanfacine, risperidone, and clonidine are also effective.

Disorders with Paroxysmal dystonia/choreoathetosis

Paroxysmal kinesiogenic choreo-athetosis (PKC)

PKC is characterized by brief episodes of dystonic and choreoathetotic movements induced by movement or fright. They may be unilateral or bilateral and are not associated with unresponsiveness or incontinence. The attacks are brief, lasting from few seconds to minutes. The attacks begin between 5 and 16 years of age. Idiopathic, familial (autosomal dominant and recessive patterns) and symptomatic forms have been described. Symptomatic cases are less common, and have been described in association with multiple sclerosis, head injury, hypoparathyroidism, basal ganglia calcification, and stroke. Even though the attacks are non-epileptic, they do respond to relatively low doses of anticonvulsants such as phenytoin, or carbamazepine.

Paroxysmal nonkinesiogenic dystonic choreoathetosis (PDC) is another paroxysmal disorder with dystonia/choreoathetosis. Differences between these disorders are outlined in Table 4.

Nocturnal Paroxysmal Dystonia

This is an uncommon disorder characterized by brief episodes in sleep of choreoathetoid, dystonic posturing or violent ballistic flailing of extremities lasting less than a minute. These movements are stereotypic, occurring several times each night in NREM (usually stage 2) sleep. These brief episodes are partial seizures arising from the supplementary motor cortex in the mesial frontal region. The EEG however is normal. Patients respond to carbamazepine.

Pseudoseizures

Pseudoseizures are episodic, behavioral spells that mimic true epileptic seizures. The term non-epileptic seizures is preferred, because it is more neutral. They are common, accounting for 5 percent–20 percent of the outpatient epilepsy population. 10 percent–40 percent of patients with pseudoseizures also have epileptic seizures. Majority of the patients are female. Pseudoseizures commonly occur between 15 to 35 years of age, but are also seen in children. Clinical features that differentiate non-epileptic seizures from epileptic seizures are outlined in Table 5. Traumatic and stressful events such as sexual and physical abuse, bereavement, and parental divorce are commonly present. Psychiatric
illness such as depression and dissociative disorders are more commonly seen in adults. Video-EEG is usually needed to make a definitive diagnosis. It is important to convey the diagnosis to the patient in a non-judgmental manner. The patient is referred for psychotherapy, to learn coping skills to deal with the ongoing stressors. Patients may have been mistakenly placed on anticonvulsant therapy for misdiagnosed pseudoseizures. In this case, anticonvulsants should be weaned slowly, and it should be stressed that the patient-physician contact will be maintained so that the patient does not feel abandoned. Family involvement is important for a good outcome. Consultation with a neurologist is helpful in these cases.

**Table 1: Classification of Paroxysmal Non-Epileptiform disorders based on age of onset**

<table>
<thead>
<tr>
<th></th>
<th>Wake</th>
<th>Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>Jitteriness</td>
<td>Benign neonatal sleep myoclonus</td>
</tr>
<tr>
<td>&lt;8wks</td>
<td>Stiff baby/hyperexplexia</td>
<td></td>
</tr>
<tr>
<td>Infants</td>
<td>Breath holding spells</td>
<td>Rhythmic movement disorder</td>
</tr>
<tr>
<td>2months-2years</td>
<td>Shuddering attacks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Spasmus Nutans</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stereotypies</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Self-stimulatory behavior</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stool withholding/constipation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benign myoclonus of early infancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyperexplexia</td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td>Stereotypies</td>
<td>Head banging</td>
</tr>
<tr>
<td>2-12years</td>
<td>Syncope</td>
<td>Parasomnias -Sleep terrors, sleep walking</td>
</tr>
<tr>
<td></td>
<td>Migraine/variants (cyclic vomiting, benign paroxysmal vertigo)</td>
<td>Hypnic jerks</td>
</tr>
<tr>
<td></td>
<td>Tics</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paroxysmal torticollis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paroxysmal choreoathetosis (kinesiogenic, dystonic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux</td>
<td></td>
</tr>
<tr>
<td>Stool withholding/constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-stimulatory behavior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoseizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Munchausen by proxy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents &gt; 12 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syncope</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Narcolepsy—sleep paralysis, hypnagogic hallucinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Migraine and variants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal choreoathetosis (kinesiogenic, dystonic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudoseizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient global amnesia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Differentiation between Breath-holding spells and Epileptic seizures**

<table>
<thead>
<tr>
<th>Breath-holding spells</th>
<th>Epileptic seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigger</td>
<td>Crying, injury</td>
</tr>
<tr>
<td></td>
<td>Spontaneous, fever, sleep deprivation</td>
</tr>
<tr>
<td>Occurrence during sleep</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>May occur during sleep</td>
</tr>
<tr>
<td>Event</td>
<td>Sequence → provocation — apnea, cyanosis / pallor, limpness.</td>
</tr>
<tr>
<td></td>
<td>Associated with stiffening and jerking of extremities</td>
</tr>
<tr>
<td>Postictal state</td>
<td>Usually brief</td>
</tr>
<tr>
<td></td>
<td>Maybe prolonged</td>
</tr>
<tr>
<td>Epileptiform abnormalities on EEG</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>Usually present</td>
</tr>
<tr>
<td>Treatment</td>
<td>Parental reassurance</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant therapy</td>
</tr>
</tbody>
</table>

**Table 3: Differentiation between stereotypies and tics**

<table>
<thead>
<tr>
<th>Stereotypies</th>
<th>Tics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>&lt; 2yrs</td>
</tr>
<tr>
<td>Pattern</td>
<td>School age</td>
</tr>
<tr>
<td>Movements</td>
<td>Patterned, predictable, identical</td>
</tr>
<tr>
<td>Rhythm</td>
<td>Variable, wax &amp; wane</td>
</tr>
<tr>
<td></td>
<td>Flapping, waving arm/hand movements</td>
</tr>
<tr>
<td></td>
<td>Blink, grimace, shrug</td>
</tr>
<tr>
<td></td>
<td>Rhythmic</td>
</tr>
<tr>
<td></td>
<td>Rapid, sudden, random</td>
</tr>
<tr>
<td>Duration</td>
<td>Prolonged, continuous</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Premonitory urge</td>
<td>No</td>
</tr>
<tr>
<td>Trigger</td>
<td>Excitement, stress</td>
</tr>
<tr>
<td>Suppression</td>
<td>Distraction</td>
</tr>
<tr>
<td>Family History</td>
<td>Rarely positive</td>
</tr>
<tr>
<td>Treatment</td>
<td>Poor response</td>
</tr>
</tbody>
</table>

**Table 4: Differentiation between paroxysmal kinesiogenic choreoathetosis (PKC) and paroxysmal nonkinesiogenic dystonic choreoathetosis (PDC)**

<table>
<thead>
<tr>
<th></th>
<th>PKC</th>
<th>PDC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types</td>
<td>Idiopathic</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Familial (AR &gt; AD)</td>
<td>Familial</td>
</tr>
<tr>
<td></td>
<td>Symptomatic (multiple sclerosis, stroke, head injury, hypoparathyroidism)</td>
<td>Symptomatic—uncommon (multiple sclerosis)</td>
</tr>
<tr>
<td>Precipitants</td>
<td>Movement, fright</td>
<td>Fatigue, stress, caffeine, alcohol</td>
</tr>
<tr>
<td>Duration</td>
<td>Seconds to minutes</td>
<td>Several minutes to hours (gradual onset and resolution)</td>
</tr>
<tr>
<td>Daily frequency</td>
<td>Several</td>
<td>Less frequent</td>
</tr>
<tr>
<td>Response to anticonvulsants</td>
<td>Good</td>
<td>Poor</td>
</tr>
</tbody>
</table>

**Table 5: Differentiation between non-epileptic seizures (pseudoseizures) and epileptic seizures**

<table>
<thead>
<tr>
<th></th>
<th>Non-epileptic seizure</th>
<th>Epileptic seizure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>Prolonged (several minutes)</td>
<td>Usually less than 2 to 3 minutes</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Fluctuating features</td>
<td>Stereotypic features</td>
</tr>
<tr>
<td></td>
<td>Usually during wakefulness</td>
<td>May occur in sleep</td>
</tr>
<tr>
<td></td>
<td>Preserved consciousness, avoidance behavior</td>
<td>Altered consciousness</td>
</tr>
<tr>
<td></td>
<td>Side to side head movements</td>
<td>Head unilaterally turned</td>
</tr>
<tr>
<td></td>
<td>Out of phase extremity movements</td>
<td>In phase extremity movements</td>
</tr>
<tr>
<td></td>
<td>Forward pelvic thrusting</td>
<td>Retropelvic thrusting</td>
</tr>
<tr>
<td></td>
<td>Emotional vocalization</td>
<td>Monotonous vocalization</td>
</tr>
<tr>
<td></td>
<td>Pupillary reflex retained</td>
<td>Pupillary reflex absent</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Rare</td>
<td>Present</td>
</tr>
<tr>
<td>Tongue bite</td>
<td>Occasional</td>
<td>Common</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>Postictal changes</td>
<td>None</td>
<td>Usually present</td>
</tr>
<tr>
<td>Affect</td>
<td>La Belle indifference</td>
<td>Concerned</td>
</tr>
</tbody>
</table>

REFERENCES


ATAXIA

Ataxia is incoordination of the muscles during a voluntary movement or that sustain a voluntary posture. Disturbance of coordination is caused by a dysfunction in the cerebellum or its connections (see Chapter 1). Damage to the cerebellar hemisphere causes a tendency to veer in the direction of the affected hemisphere with dystaxia and hypotonia of the ipsilateral limb. Abnormality of the cerebellar vermis results in head bobbing (titubation), gait and truncal ataxia and nystagmus. Involvement of the sensory pathways in the spinal cord and peripheral nerves results in a wide based gait and inability to maintain a standing posture with the eyes closed (Romberg's sign). Based on duration and progression, ataxias can be classified into acute, subacute and chronic onset ataxias. Some of the common causes of acute ataxia are listed in Table 2. Subacute and chronic onset ataxias are often hereditary in nature. Some of these are treatable and should be recognized. Some examples of treatable ataxias in this group include Bassen-Kornzweig or a-beta-lipoproteinemia syndrome and ataxia with vitamin E deficiency (both treatable with vitamin E supplementation), Hartnup disease (niacin supplementation), familial episodic ataxias (treated with acetazolamide), and Refsum disease (responds to dietary restriction of phytanic acid). There are several familial or hereditary ataxias that may have autosomal dominant or recessive inheritance. Friedreich's ataxia and ataxia telangiectasia are inherited in an autosomal recessive manner while spinocerebellar ataxias of several types and dentatorubral-pallidoluysian atrophy (DPRLA) are autosomal dominant.

Friedreich's ataxia
Friedreich's ataxia is one of the more common inherited ataxias in children with an estimated prevalence of –2 per 100,000 in the general population. It generally presents
with progressive gait ataxia in the later half of first decade though the age of onset may be earlier or later in some children. As the disease progresses there is nystagmus, dysarthria, limb and head tremor, and incoordination and ataxia of the upper limbs. Auditory and ophthalmic involvement is common with hearing deficit and optic atrophy. Patients have scoliosis, and often associated pes cavus, and talipes equinovarus. Examination is characterized by absent deep tendon reflexes, Babinski signs, impairment of posterior column functions, and gait and upper limb ataxia. Axonal sensory neuropathy is demonstrable by electrodiagnostic studies. Diabetes mellitus and progressive cardiomyopathy complicate the course of the disease; hypertrophic cardiomyopathy is often the cause of death in these patients. Friedreich's ataxia gene localizes to chromosome 9 and the disease is due to a trinucleotide expansion in the gene (FRDA) for frataxin. Diagnosis can be confirmed by demonstration of abnormally increased GAA trinucleotide repeats in the majority of patients and by point mutation in the gene in a distinct minority of patients when the clinical picture is characteristic. The normal number of GAA repeats is less than 33 while disease causing alleles contain more than 66 GAA repeats. The range of GAA repeats between 34 to 65 is labeled as premutation alleles. Consultation with a geneticist or a genetic counselor is advisable. 

Alpha fetoprotein is often used as an initial screening test for ataxia telangiectasia. Molecular testing also is a available for several of the dominantly inherited spinocerebellar ataxias.

**Acute Ataxias**

Acute ataxia has a rapid onset, reaching maximum severity in a period of hours to several days. The two most common childhood causes are drug intoxication and acute postinfectious cerebellitis. Rarely, bacterial meningitis may present with ataxia. Drugs that are commonly associated with ataxia include barbiturates, phenothiazines, anticonvulsants such as phenytoin and carbamazepine, antihistamines, benzodiazepines, tricyclic antidepressants and alcohol (Table 2). Ataxia is usually associated with some change in personality or sensorium. The parents should be carefully questioned concerning drugs accessible to the child in the home; urine and blood should be screened when intoxication is suspected. Poison control should be notified and appropriate treatment should be administered depending on the drug ingested and its blood levels.

**Acute Postinfectious Ataxia**

Acute ataxia following an infection (viral or bacterial) or immunization may be due to isolated postinfectious cerebellitis, acute demyelinating encephalomyelitis (ADEM), and sometimes ataxia may be the presenting complaint in Guillain-Barré syndrome (specially the Miller Fisher type). The clinical picture is characterized by rapid onset of ataxia usually following a varicella infection, but other viral infections such as measles, mumps, Coxsackie-B, and Epstein-Barr have also been implicated. Postvaricella cerebellitis usually affects preschool and elementary school age children. It begins approximately 2 weeks after the onset of the viral illness, often after the vesicles begin to clear, and evolves rapidly over 2 to 3 days. Rarely, ataxia may be concomitant with or precede a skin rash. Gait is prominently affected and ataxia varies from mild unsteadiness to complete inability to stand or walk; the child is otherwise normal. Other neurologic signs
may be present when ataxia is part of the clinical picture in patients with ADEM and areflexia and a mild degree of ataxia may be present in children with Guillain-Barré syndrome (GBS).

CT scan and MRI of the head are usually normal in isolated acute ataxia. In patients with other neurological abnormalities associated with ataxia (such as in ADEM) the T2 weighted images of the MRI scan may show increased white matter signal. Spinal root enhancement may be seen in patients with Guillain-Barré syndrome. CSF is usually normal except for a possible mild pleocytosis. It is a self-limited disease with excellent prognosis and complete recovery in the vast majority of the children.

Ataxia is a major feature of the Miller-Fisher variant of the GBS syndrome that typically occurs 10 to 15 days following a viral illness. Miller-Fisher syndrome is characterized by areflexia, ataxia and ophthalmoplegia that commonly affects vertical gaze, especially upward gaze. Horizontal gaze is usually preserved. Elevation of CSF protein with mild or no pleocytosis is often present. Other conditions that may mimic the syndrome should be excluded (Table 2).

Paraneoplastic Disorders
A relatively acute onset ataxia associated with opsoclonus (rapid chaotic conjugate eye movements) and myoclonus (violent jerking of the limbs on attempted movements) should suggest the possibility of neuroblastoma. The association of eye and limb jerking has been termed "dancing eyes, dancing feet syndrome." The tumor is often thoracic in location, but may be found in other regions such as the abdomen and pelvis. Diagnosis can be confirmed by CT or MRI of the chest and abdomen, and elevated urinary catecholamines (homovanillic acid—HVA and vanillylmandelic acid—VMA). The neuroblastoma should be surgically removed. Approximately half of these children will have an impairment of motor ability and one-third will have some disturbance in intellectual function. Similar syndromes may be seen following viral infections and may respond to ACTH or steroid treatment.

On rare occasions, posterior fossa tumors, anomalies of the cervico-occipital region such as Chiari I anomaly and hydrocephalus may present with acute ataxia. Thus, neuroimaging is warranted in almost all cases of acute ataxia, even though the yield of imaging in these patients is quite small. Ataxia may be the only manifestation of certain types of seizures such as absence seizures associated with Lennox-Gastaut syndrome, complex partial seizures or nonconvulsive status epilepticus. In these cases, ataxia may be paroxysmal and the child may appear confused and disoriented during the episode. The demonstration of epileptiform discharges on the EEG concurrent with the episodes is diagnostic, in which case appropriate anticonvulsants should be administered. Vascular and metabolic conditions (Table 2) may require appropriate investigations and treatment. When faced with a child who is displaying unsteadiness or incoordination, the first task is to distinguish normal, age appropriate clumsiness from an abnormal examination. Once ataxia is identified and categorized as acute or chronic, appropriate laboratory studies should be ordered to establish the diagnosis. If the diagnosis remains unclear, referral to a specialist such as a child neurologist, neurosurgeon or geneticist may be appropriate.
Table 2: Selected etiologies of acute ataxia

**Intoxication**
Anticonvulsants (barbiturates, phenytoin, carbamazepine, clonazepam)

- antihistamines, benzodiazepines, phenothiazines, tricyclic
- antidepressants, alcohol, Tic paralysis poisoning

**Infections**

- brain stem encephalitis, bacterial meningitis, viral infections (varicella, mumps, measles, Coxsackie, Echo, Epstein-Barr), cerebellar abscess

**Postinfectious**

- acute postinfectious cerebellitis (varicella), Miller-Fisher syndrome, acute demyelinating encephalomyelitis

**Neoplastic and paraneoplastic disorders**

Neuroblastoma, cerebellar tumors

**Traumatic and vascular**

- postconcussion, cerebellar (and brainstem) infarction (ischemia and hemorrhage), posterior fossa hematoma

**Multiple sclerosis**

**Epilepsy**

- nonconvulsive status epilepticus, Lennox-Gastaut syndrome, complex-partial seizures

**Basilar migraine**

**Conversion reaction**

**Metabolic**

Hypoglycemia, intermittent maple syrup urine disease, Familial episodic ataxia, mitochondrial cytopathies

**Selected Reading**

EPILEPSY IN CHILDREN

Incidence
Approximately 9 percent of the United States population will have a seizure sometime during their lives; 3 percent of these have epilepsy. At least 1 percent of children can be expected to have an afebrile seizure by 14 years of age. The risk of recurrent afebrile seizures ranges from 4 to 8.1 per 1000 by age 11. Principles of recognition, classification and treatment are similar in children and adults. Focal or partial seizures are perhaps more common than primary generalized seizures though recognition of focal onset is often difficult in young children. Some epilepsy syndromes are seen uniquely in children. The more common syndromes are described here.

Neonatal Seizures

Neonatal seizures differ from those in older children and adults. They are often fragmentary and generalized seizures are uncommon except in the term infants. Table I lists some of the common etiologies. Neonatal seizures may or may not always be associated with EEG changes. Neonatal seizures most frequently have subtle clinical manifestations, such as sucking, lip smacking or other oral-buccal-lingual movements, bicycling or pedaling movements, rhythmic ocular movements such as horizontal eye deviation and occasionally apneic spells. Other seizure manifestations include focal clonic, tonic and myoclonic seizures. Intracranial infection must be considered and excluded unless some other etiology is apparent. Management includes treatment of the underlying cause, eg, infection, electrolyte or metabolic abnormalities. Phenobarbital is the drug of choice for seizure control in this age group. Phenytoin maybe added if phenobarbital is not sufficient to control the seizures.

West Syndrome (Infantile spasms, Blitz-nick-salaam krampfe)
West syndrome comprises a triad of infantile spasms, arrest of psychomotor development and EEG features of hypsarrhythmia. Several infantile spasms occur in clusters. Spasms maybe flexor, extensor or, more commonly, mixed. Onset peaks between 4 and 7 months of age. West syndrome is divided into two groups: 1) the smaller cryptogenic group comprises 30-40 percent of the patients in whom no known etiology is identified, and 2) the symptomatic group is characterized by the existence of previous brain damage as evidenced by psychomotor retardation, neurological and radiologic signs or by a known etiology. Tuberous sclerosis may present as infantile spasms. Therefore, a careful examination of the skin for cutaneous stigmata of tuberous sclerosis such as adenoma sebaceum and ash-leaf spots is important.
Infantile spasms are treated with adrenocorticotropic hormone (ACTH); early therapy is thought to improve prognosis. Other therapies are less effective and prednisone, valproic acid, topiramate, vigabatrin (not available in the USA) and pyridoxine (vitamin B6) have also been used with variable results. The prognosis is generally poor with 25 percent-50 percent of the cases evolving into Lennox-Gastaut syndrome, with the spasms transforming into other seizure types (tonic, myoclonic and generalized tonic-clonic seizures). There is a high incidence of mental retardation.

**Lennox-Gastaut Syndrome**

This syndrome manifests in children from 1 to 7 years of age, and a significant number of patients have previous history of infantile spasms. Multiple seizure types are common in this syndrome. Most common seizures are tonic, atonic, and atypical absence seizures but myoclonic, generalized tonic-clonic seizures (GTCS) and partial seizures also occur. EEG exhibits slow background activity and generalized isynchronous 1-2 cps (cycles per second) spike and slow wave discharges. The seizures are difficult to control and prognosis is poor with psychomotor retardation. Antiepileptic medications, which are often only partially effective, include valproic acid, lamotrigine, topiramate and levetiracetam. Sedative anticonvulsants should be avoided if possible, because these drugs may increase seizure frequency by decreasing alertness. *These patients are best managed by epilepsy specialists.*

**Febrile Seizure**

Febrile seizures occur in 2 percent to 5 percent of children with a peak between the age of 6 months to 2 years. Most children have a single febrile convulsion; only 0.5 percent have recurrent febrile seizures. The seizures are brief (<1.5 minutes), generalized tonic clonic seizures that usually occur at the onset of a febrile illness in an otherwise healthy child and in the absence of intracranial infection or a defined cause such as severe metabolic disturbance. *Most children have a single episode of febrile convulsion and there is no evidence that these brief events lead to later CNS damage.* Treatment is normally withheld after the initial seizure. For a child with recurrent simple febrile seizures and in situations when parental anxiety is severe, intermittent oral diazepam at the onset of the febrile illness has been advocated by some to prevent recurrence. Rectal Diazipam may be used for prolonged seizures. Antipyretics may not be effective in preventing recurrent febrile seizures. *There is no convincing evidence that therapy will alleviate the possibility of developing future epilepsy.* Children with simple febrile seizures and normal development have only a 1.5 percent chance of developing epilepsy. This increases to 3 percent to 4 percent in the presence of risk factors that include the occurrence of complex febrile seizure (prolonged seizure with focal features and more than one seizure in 24 hours), underlying developmental or neurological abnormalities and family history of nonfebrile seizures. Many physicians do not treat simple febrile seizures. In cases of complex febrile seizures treatment options include phenobarbital and valproic acid. It is important to differentiate febrile seizures from seizures that have been precipitated by fever in epileptic children.
Benign Childhood Epilepsy with Centrotemporal Spikes
Previously known as Benign Rolandic Epilepsy, this syndrome comprises 75 percent of the benign focal childhood epilepsies. It occurs most commonly between 6 and 16 years of age (peak 9 to 10 years), with male predominance and a genetic predisposition. The seizures usually occur during sleep and are brief, simple focal motor seizures characterized by hemifacial grimacing and twitching, inability to speak and salivation. Generalized tonic-clonic seizures are not uncommon. EEG shows high amplitude unilateral or bilateral centro-temporal spikes that are activated by sleep. Prognosis is excellent with approximately 13 percent to 20 percent of patients experiencing only a single seizure. Treatment is usually unnecessary after the first or even the second seizure. Most anticonvulsants have been reported to be successful. Carbamazepine is the drug of choice, but valproic acid is also effective. Antiepileptic medications are maintained up to 14 to 16 years of age at which time seizures spontaneously resolve.

Childhood Absence Epilepsy (Pyknolepsy)
Childhood Absence Epilepsy has a peak age of 6 to 7 years and is more frequent in girls. It is characterized by frequent daily absence seizures; GTCS may occur during adolescence. Family history is often strongly positive. Though development and neurologic examination are normal, school performance may suffer because of frequent interruption of awareness, which may be misinterpreted as daydreaming or attention deficit. EEG reveals paroxysms of generalized bisynchronous high amplitude 3 cps spike and slow wave discharges, which are markedly activated by hyperventilation. Fifty percent of patients with absence seizures become seizure free, 35 percent develop GTCS in adolescence and absences persist in the rest. Absence seizures may be a harbinger of juvenile myoclonic epilepsy, appearing approximately 4.5 years prior to the appearance of the myoclonic seizures and GTCS. Ethosuximide and valproic acid are the drugs of choice. Lamotrigine and clonazepam have also been found to be effective. Ketogenic diet may be effective for intractable cases. Absence seizures are exacerbated by carbamazepine and therefore should be clinically differentiated from complex partial seizures prior to initiation of therapy. Patients whose seizures are refractory to ethosuximide and valproic acid may need management by a neurologist.

Section 2
Juvenile Myoclonic Epilepsy (impulsive petit-mal)
This syndrome usually appears at puberty with equal sex distribution. It is a familial disorder with the gene localized to the short arm of chromosome 6. Early morning myoclonic seizures are characteristic with single or repetitive, irregular myoclonic jerks,
predominantly in the arms, associated with sudden falls and no noticeable disturbance of consciousness. GTCS and absence seizures are less frequent. The seizures frequently occur on awakening and may be exacerbated by sleep deprivation. Patients often do not recognize the seizures but readily give history of morning jitteriness, clumsiness, and propensity to drop objects. EEG shows brief paroxysms of generalized rapid, irregular spike and polyspike and wave discharges that are provoked by photic stimulation. Valproic acid is the drug of choice and is often effective even at low doses. Patients who are refractory to valproic acid should be referred to a neurologist. These seizures tend to relapse on discontinuation of medication and therefore patients require life-long treatment.

**Single Seizure**

Approximately 20,000 children in the United States are seen annually for a first unprovoked seizure. The therapeutic approach in these children remains controversial. Estimates of the risk of recurrence have varied widely. In one prospective study of 237 patients of all ages with first unprovoked seizure, the recurrence rate at follow up was estimated at 14 percent, 28 percent and 36 percent at one, three and five years respectively. *The risk is highest within the first year following the seizure*. The risk of recurrence is low if the patient has a normal neurological examination, a single GTCS with negative family history of epilepsy, a normal neuroimaging study and a normal EEG. Indications for treatment include clear-cut abnormalities on EEG and MRI, abnormal neurological examination suggesting prior CNS dysfunction, ongoing active CNS infection, the first seizure presenting as status-epilepticus, certain seizure types including infantile spasms, Lennox-Gastaut syndrome, focal seizures and unprovoked or asymptomatic seizure with history suggesting a prior occurrence.

**Table 1: Most frequently identified etiologies of neonatal seizures**

<table>
<thead>
<tr>
<th>Hypoxic-ischemic encephalopathy</th>
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<tbody>
<tr>
<td><strong>Intracranial hemorrhage</strong>: intraventricular, intracerebral, subdural, subarachnoid</td>
</tr>
<tr>
<td><strong>Infection</strong>: meningitis, encephalitis, TORCH (toxoplasmosis, other such as HIV, rubella, cytomegalovirus, herpes)</td>
</tr>
<tr>
<td><strong>Cerebral infarction</strong>: arterial, venous, polycythemia</td>
</tr>
<tr>
<td><strong>Metabolic</strong>: hypoglycemia, hypocalcemia, hypomagnesemia</td>
</tr>
<tr>
<td><strong>Neurocutaneous syndromes</strong>: tuberous sclerosis</td>
</tr>
<tr>
<td><strong>Congenital abnormalities</strong>: lissencephaly, holoprosencephaly and other malformations.</td>
</tr>
<tr>
<td><strong>Inborn errors of metabolism</strong>: aminoacidurias, urea cycle defects, organic acidurias, pyridoxine deficiency and dependency</td>
</tr>
<tr>
<td><strong>Genetic</strong>: benign familial neonatal convulsions, chromosomal anomalies</td>
</tr>
<tr>
<td><strong>Maternal drug dependency</strong>: cocaine, narcotics, barbiturates</td>
</tr>
</tbody>
</table>

**Selected Readings**


FLOPPY INFANT

Introduction

A floppy infant is an infant with decreased muscle tone. Muscle tone may be assessed as active or passive. Tone is often defined as resistance to passive movement at a joint. The resistance offered by the muscles may be normal, increased or decreased. Increased muscle tone is either spastic (clasp knife) or rigid (lead pipe) in type. A common example of spastic tone is a child with spastic hemiplegia. A typical example of decreased muscle tone is a child with Down syndrome. Muscle tone alterations may also be inferred from a child's posture. Thus, a child with hemiplegia may keep his arm flexed against his chest and a child with spastic diplegia may keep his knees flexed when standing. A neonate with decreased muscle tone is likely to assume a "frog leg" posture with his legs abducted and at least partially extended at the hips in contrast to a "normal" posture of hip adduction and flexion in a neonate. As a result of decreased muscle tone, floppy infants not only have decreased resistance to passive movements, they also display an increased range of joint mobility and unusual and bizarre postures.

An organized approach is essential when evaluating an infant with decreased muscle tone or hypotonia. Hypotonia may be due to a disease affecting: 1) the motor unit (consisting of the anterior horn cell in the spinal cord, its axon in the peripheral nerve, the neuromuscular junction, and the muscle fibers it supplies); 2) the suprasegmental structures or the "upper motor neuron" (the spinal cord, brainstem, cerebellum, and the cerebral hemispheres); or 3) systemic, generalized disease. In general, presence of decreased muscle strength and diminished deep tendon reflexes distinguishes diseases of the motor unit from the other two categories. It is not always easy to detect muscle weakness in an infant. However the character of cry, withdrawal of limbs to painful stimulus and ability to sustain them against gravity may be useful indicators. It is important to remember that neuromuscular disease may be present in the absence of these characteristics as seen in some myopathies (e.g., congenital myotonic dystrophy) symptomatic in the neonatal period with respiratory and swallowing dysfunction and hypotonia but with ability to hold limbs against gravity. On the other hand, an infant with Prader-Willi syndrome may be nearly immobile. Some of the common conditions from each category are discussed below.
Neuromuscular Diseases

Neuromuscular diseases are characterized by hypotonia, weakness, and decreased deep tendon reflexes and may involve the anterior horn cells, peripheral nerve, neuromuscular junction, or the muscle itself. An organized anatomical approach is the best aid to diagnosis.

Anterior Horn Cell Diseases

Childhood degenerative anterior horn cell diseases are broadly called the spinal muscular atrophies; three types, type I, II, and III are distinguished. Werdnig-Hoffmann disease is the same as type I spinal muscular atrophy (SMA), or the severe infantile variety. SMA type III is the mild variety and is also called the Wolfhart-Kugelberg-Welander disease. SMA type II is the intermediate variety with variable clinical picture and outcome.

SMA Type I, Werdnig-Hoffmann disease

Patients may be weak at birth or even preterm. However, the most common presentation is with normal early development for several weeks or months followed by progressive weakness. Characteristically these infants never learn to sit. Patients are weak and lose milestones, with eventual swallowing and respiratory difficulty because of bulbar and respiratory muscle weakness. Examination reveals hypotonia and absent deep tendon reflexes in addition to weakness. Fasciculations of the tongue may be present and are best seen with the tongue at rest in sleep. Characteristically patients are alert with spared facial muscles. Clinical course is one of relentless progression with death generally within the first year or two.

SMA Types II and III

SMA II usually becomes symptomatic by 18 months of age. Most commonly children learn to sit but are too weak to walk. Intelligence is spared and children learn to speak without difficulty. Parents may complain about finger tremors; fasciculations of the tongue and fingers, and "minipolymyoclonus" may be seen. Severity of the disease is quite variable. The most severely affected children develop respiratory difficulties early, with poor prognosis. Mildly affected patients survive into adolescence and young adulthood.

Patients with SMA III have normal development for the first year or two and learn to walk. These patients usually present with hip weakness. Intelligence is not affected. Patients have a relatively static course with preserved strength and survival into adulthood. There may be deterioration late in life.

Investigations reveal neurogenic abnormalities on electromyogram (EMG) with fibrillations at rest and reduced interference pattern. In chronic cases (types II and III) polyphasic potentials may also be present. Nerve conduction velocity (NCV) is normal.
Muscle biopsy shows neurogenic atrophy but rarely is necessary. Most cases of SMA are caused by mutation of the survival motor neuron gene 1 (SMN1) on chromosome 5. Molecular testing on blood confirms the clinical diagnosis of SMA1 nearly 100 percent of the time. In ninety-five percent of cases this testing shows homozygous deletion of SMN1 exon 7. Additional gene testing is needed rarely.

*Spinal muscular atrophies have autosomal recessive inheritance.* Consultation with a neurologist and geneticist is advisable.

**Peripheral Neuropathies**

Peripheral neuropathies are uncommon in infants. Presence of sensory symptoms and signs in addition to motor abnormalities are characteristic but often difficult to detect in infants. *Hereditary motor sensory neuropathy* (HMSN) type I and II (Charcot-Marie-Tooth disease, demyelinating and axonal type respectively), type III (Dejerine-Sottas disease), and Refsum's disease (previously HMSN IV) are seen in children. Type III is the most severe and presents at an earlier age than types I and II; NCV are slowed. Type I and II are autosomal dominant; type III is probably recessive though other patterns of inheritance have been described. Hypomyelinating neuropathy may present in infancy with hypotonia and weakness. Molecular diagnosis is possible. There is duplication of *PMP22* in CMT 1A (classic Charcot-Marie-Tooth disease); others have either mutation in *PMP22* or others such as *MPZ* (P0), Connexin 32 etc. There is considerable genetic heterogeneity and consultation with a neurologist and geneticist is advisable.

**Diseases of the Neuromuscular Junction**

**Myasthenia gravis** is the prototype disease. Infants usually have the transient form because of transplacental transfer of maternal antibodies. *The condition should be considered in all infants born to mothers with myasthenia gravis.* Infants may appear normal at birth only to develop weakness with feeble cry, and swallowing and respiratory difficulties at several hours of age. Recognition and prompt treatment with neostigmine or similar drugs is necessary. Patients recover completely as maternal antibodies are cleared over several weeks.

**Botulism** may occur in early infancy. Characteristic findings are acute onset of hypotonia, weakness, ptosis, dysphagia, unreactive pupils and constipation. Patients may have respiratory difficulties and require ventilatory support. Electromyographic study shows facilitation of motor potential following repetitive nerve stimulation at high rates. Prompt treatment with antitoxinum toxin may be helpful in addition to supportive treatment.

Several congenital myasthenic syndromes (CMS) have been described, some of which are symptomatic in infancy. CMS are genetically determined and result from presynaptic or postsynaptic defects. Some syndromes remain poorly characterized. Investigation of these patients is complex and referral to a specialist is recommended.

**Muscle Diseases**
Myopathy is a disease of muscle; myositis is an inflammatory myopathy and muscular dystrophy is a genetic, progressive myopathy. Congenital myopathy is a relatively nonprogressive myopathy that may be genetic; however symptoms may not appear until adulthood. Children usually present with hypotonia and clumsiness rather than prominent weakness as a symptom. Table 7 lists common congenital myopathies. EMG may be normal or may reveal myopathic features. Diagnosis is by muscle biopsy.

There are a host of congenital myopathies that may present in infancy or childhood. Most muscular dystrophies such as Duchenne or Becker muscular dystrophy (X-linked) usually present in childhood rather than infancy. CK levels are elevated in the active disease phase and decline in late stages of the disease. Most common presentation of Duchenne muscular dystrophy is progressive weakness of proximal lower extremity muscles in boys who may also have history of delayed walking. Early in the course of the disease there is pseudohypertrophy of the gastrocnemius muscles (and sometimes of the deltoids). With progressive weakness and atrophy of muscles children are wheelchair bound by teenage with death in the third decade with cardiac involvement. Cognition is impaired in some boys. Becker muscular dystrophy is similar but with a slower progression of the disease and much longer lifespan. There is a defect in dystrophin, a major muscle protein, in both of these muscle diseases and hence the term dystrophinopathies is used sometimes. Muscle biopsy stained for dystrophin shows nearly complete absence in Duchenne and spotty staining in Becker muscular dystrophy. Dystrophin is encoded by the DMD gene on the X-chromosome and hence X-linked recessive inheritance. Approximately two-thirds of mothers of affected boys are carriers so genetic counseling is important. Molecular diagnosis is possible with demonstration of a deletion or mutation in the affected gene. Most commonly there is absence of dystrophin protein in Duchenne muscular dystrophy (due to "out of frame" mutation) while in the Becker muscular dystrophy there is a decreased amount of abnormal molecular weight dystrophin ("in frame" deletion). Consultation with a geneticist is advisable for counseling families and for carrier detection.

Other muscular dystrophies, such as the several limb girdle muscular dystrophies, vary in clinical onset of symptoms from early childhood to middle age and have mild to severe clinical course. Many have defects in dystrophin related proteins such a sarcoglycans.

Myotonic dystrophy is of two types (type 1 ? DM1 and type 2 ? DM2). Only DM1 presents in the neonate with respiratory and swallowing difficulties. Although inheritance is autosomal dominant, the mother is most often the affected parent in this type of presentation, and her examination often aids in the diagnosis. DM1 is caused by a CTG trinucleotide repeat expansion in the DM1 gene. Age of onset varies with size of this expansion; congenital cases are associated with large expansions. DM2 is caused by a CCTG repeat expansion in the DM2 gene. Myotonic dystrophy and Emery-Dreifuss dystrophy (X-linked recessive inheritance with emerin deficiency) have associated cardiac dysfunction (usually in late childhood or young adulthood) that may be clinically important. Consultation with a neurologist and a cardiologist is advisable.

Table 7: Selected congenital myopathies
Central core disease
Nemaline myopathy
Centronuclear (myotubular) myopathy
Severe congenital X-linked myotubular myopathy
Congenital fiber-type disproportion
Minicore (multicore) myopathy
Minimal change myopathy

Systemic Diseases

Hypotonia may be seen in a variety of systemic diseases and syndromes. In these conditions weakness is usually not associated with hypotonia. Chromosomal disorders such as Down syndrome are associated with hypotonia. Severely decreased muscle tone is also a central feature of several genetic disorders such as Prader-Willi syndrome, and Zellweger's syndrome. In many connective tissue disorders such as Ehlers-Danlos syndrome joint laxity and joint hypermobility and hyperextensibility is hard to distinguish from decreased muscle tone. Infants with metabolic and endocrine conditions such as hypoglycemia, hypercalcemia, and hypothyroidism may also have hypotonia. Neonates with sepsis and meningoencephalitis often present with decreased tone among other signs and symptoms. Aminoacidurias, organic acidurias, lipidoses, and sometimes mitochondrial cytopathies may be associated with decreased muscle tone. Cerebral palsy may be hypotonic. Children destined to develop kernicterus pass through a hypotonic phase.

Management of these children depends upon accurate identification of the underlying disease process.

Selected Reading