

COMMON PROBLEMS IN PEDIATRIC NEUROLOGY

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EPILEPSY IN CHILDREN

Incidence

Approximately 9% of the United States population will have a seizure sometime during their lives; 3% of these have epilepsy. At least 1% 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 1** 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.

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. 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% 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.

Infantile spasms are treated with adrenocorticotrophic hormone (ACTH); early therapy is thought to improve prognosis. Other therapies are less effective and prednisone, valproic acid and vigabatrin (not available in the USA) have also been used with variable results. The prognosis is generally poor with 25-50% 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 bisynchronous 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 and lamotrigine. 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 to 5% of children with a peak between the age of 6 months to 2 years. Most children have a single febrile convulsion; only 0.5% 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 to prevent recurrence. 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% chance of developing epilepsy. This increases to 3 to 4% 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% 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 to 20% 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 neurological 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% 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, clonazepam and acetazolamide 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.

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. 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%, 28% and 36% 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

<p>Hypoxic-ischemic encephalopathy Intracranial hemorrhage – intraventricular, intracerebral, subdural, subarachnoid Infection: meningitis, encephalitis, Cerebral infarction: arterial, venous, polycythemia Metabolic: hypoglycemia, hypocalcemia, hypomagnesemia Neurocutaneous syndromes: tuberous sclerosis Congenital abnormalities: lissencephaly, holoprosencephaly Inborn errors of metabolism: aminoacidurias, urea cycle defects, organic acidurias, pyridoxine deficiency and dependency Genetic: benign familial neonatal convulsions, chromosomal anomalies Maternal drug dependency: cocaine, narcotics, barbiturates</p>
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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 nerve 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 and chronic ataxias. Some of the common causes of ataxia have been listed in **Table 2**. Acute ataxias will be discussed in detail.

Acute Ataxia

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. 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 Cerebellitis

Acute postinfectious cerebellitis is characterized by rapid onset of ataxia usually following a varicella infection, but other viral infections such as measles, mumps and Coxsackie-B 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.

CT scan and MRI of the head are usually normal in isolated acute ataxia. In patients with other neurological abnormalities associated with ataxia the T2 weighted images of the MRI scan may show increased white matter signal. CSF is 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. Areflexia and a mild degree of ataxia may be present in children with Guillain-Barré syndrome (GBS). 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 and a mild pleocytosis are seen in both disorders. 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.

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), antihistamines, benzodiazepines, phenothiazines, tricyclic antidepressants, alcohol
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Infections	brain stem encephalitis, bacterial meningitis, viral infections, cerebellar abscess
Postinfectious	acute postinfectious cerebellitis (varicella), Miller-Fisher syndrome
Paraneoplastic disorders	neuroblastoma
Traumatic	postconcussion, hematoma
Multiple sclerosis	
Epilepsy	nonconvulsive status epilepticus, Lennox-Gastaut syndrome, complex-partial seizures
Basilar migraine	
Conversion reaction	

ABNORMAL HEAD SIZE

Introduction

All family practice physicians and pediatricians care for children who have abnormal head size. While extensive work-up often requires other specialists, many, if not most diagnoses, are reached using an organized approach and a few initial tests. This includes serial measurements, developmental assessment and family history, awareness of unusual physical features, and measurement of the parent's head size. Early diagnosis is important to catch potentially treatable medical disorders and to optimize 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 give little cause for concern. If these reassuring factors are absent, or if neurologic signs or symptoms are present, the possibility of underlying intracranial pathology increases. 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 developmental delay or neurologic abnormalities also requires investigation. If any of these factors are present, a positive family history does not eliminate the need for further work-up, even though asymptomatic familial macrocephaly and benign infantile extra-axial fluid collection may cause initially accelerated velocity of head growth. Other physical features such as unusual facial features, short stature, and pathologic heart murmurs (in an infant or young toddler) 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) allows better visualization of the cortical mantle, white matter abnormalities, small lesions, and abnormalities in the cerebellum and brainstem, including tumors. Neuroimaging in pseudotumor cerebri, or benign intracranial hypertension, may reveal a “full” appearance to the brain, with smaller than usual ventricles. Diagnosis is by lumbar puncture with elevation of opening pressure and 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) testing.

Table 3: Selected conditions associated with macrocephaly

Obstructive, non-communicating, internal hydrocephalus

- Tumor
- Congenital infection (especially toxoplasmosis)
- Posthemorrhagic
- Aqueductal stenosis
- 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/hygroma, non-accidental trauma
- Benign increased subdural space in infancy
- Cerebral malformations
- Cerebral vein/sinus thrombosis
- Vein of Galen malformation/other arteriovenous malformations
- Chronic right-heart failure

Pseudotumor cerebri (benign intracranial hypertension)

- Toxicity - Lead, Vitamin A
- Iron-deficiency anemia
- Steroid use
- Metabolic disease

Megalencephaly/increased tissue

- Tumors
- Hemimegalencephaly, other brain malformations
- Fragile X syndrome
- Neurocutaneous syndromes
- Overtgrowth 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% 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. 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

- Alcohol-related birth defects
- Hypoxic-ischemic injury (pre- and postnatal events)
- Congenital infections (TORCHS, HIV)
- Untreated Maternal PKU (MPKU)
- Postnatal meningoencephalitis (bacterial and viral)
- Early non-accidental trauma
- Severe malnutrition

Genetic forms

- Nonsyndromic microcephaly (familial and non-familial)
- Chromosome abnormalities
- Aminoacidopathies (e.g., PKU)
- Metabolic disease (neuronal ceroid lipofuscinosis, mitochondrial disorders, carbohydrate-deficient-glycoprotein syndrome)
- Angelman syndrome
- Fanconi anemia
- Miller-Dieker syndrome
- Rubinstein-Taybi syndrome
- Rett syndrome
- Sekel syndrome
- Smith-Lemli-Opitz syndrome
- Williams syndrome

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
- 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 may expose the fetus (when pregnant) 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% 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% 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.

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 (knife clasp variety) 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, the 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 distinguish 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 outcome.

SMA Type I, Werdnig-Hoffmann disease

Patients may be weak at birth or even preterm. However, the most common presentation is normal early development followed by progressive weakness. 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 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) study and show 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. The diagnosis is now possible with gene testing and muscle biopsy is rarely necessary.

Spinal muscular atrophies have autosomal recessive inheritance. Alterations in the survival motor neuron (SMN) gene have been described and form the basis of molecular diagnosis.

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), type III (Dejerine-Sottas disease), and type IV (Refsum's disease) are seen in children. Type III is the most severe and presents at an early age; 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 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 old. Recognition and prompt treatment with neostigmine or similar drugs is necessary.

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. Prompt treatment with antitoxin 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. **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, but may also be present in affected neonates. There is a defect in dystrophin, hence the term dystrophinopathies. Molecular diagnosis is possible. Clinically similar dystrophies but with autosomal recessive inheritance have been described and at least some have defects in adhalin.

Myotonic dystrophy may present 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 the diagnosis. Molecular diagnosis by determining CTG repeat is possible. Myotonic dystrophy and **Emery-Dreifuss dystrophy** (emerin deficiency) have associated cardiac dysfunction (usually in late childhood or young adulthood) that may be clinically important. Consultation with a neurologist may be advisable.

Table 7: Selected congenital myopathies

- Central core disease
- Nemaline myopathy
- Myotubular (centronuclear) 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

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Self-Assessment

Epilepsies In Children

1. Benign Rolandic epilepsy is characterized by all of the following except:
 - A. focal seizures
 - B. poor prognosis
 - C. it occurs at a peak age of 9-10 years
 - D. centro-temporal spikes on EEG
 - E. all of the above
2. The treatment for absence seizures includes all of the following except:
 - A. ethosuximide
 - B. valproic acid
 - C. carbamazepine
 - D. lamotrigine
 - E. ketogenic diet
3. Infantile spasms are associated with all of the following except:
 - A. poor prognosis
 - B. developmental delay
 - C. medically intractable seizures
 - D. normal EEG
 - E. all of the above
4. Absence seizures are characterized by all of the following except:
 - A. unresponsiveness
 - B. aura
 - C. generalized 3 cps spike wave discharges on EEG
 - D. marked activation by hyperventilation
 - E. strong family history
5. The following statements are true about Juvenile Myoclonic Epilepsy (JME) except:
 - A. the seizures are easily controlled with valproic acid
 - B. JME represents a life-long seizure propensity
 - C. EEG shows focal spikes
 - D. it is characterized by myoclonic and less frequently generalized tonic-clonic and absence seizures
 - E. all of the above
6. Which of the following statements is not true about febrile seizures
 - A. children with febrile seizures are at low risk for epilepsy
 - B. a 5-year-old child with febrile seizures beginning on the left side and lasting 30 minutes has lower than ordinary risk for developing epilepsy
 - C. Phenobarbital is the drug of choice for atypical febrile seizures
 - D. most children with simple febrile seizures do not have recurrences

7. Indications for treatment of a first unprovoked seizure include
- A. seizure presenting as a brief generalized tonic-clonic event
 - B. normal EEG and MRI
 - C. focal Seizure
 - D. normal neurologic exam
 - E. negative family history

Ataxia

1. Damage to the cerebellar hemisphere is characterized by
- A. head bobbing
 - B. inability to maintain a standing posture with the eyes closed (Romberg's sign)
 - C. tendency to veer in the direction of the affected hemisphere
 - D. circumduction gait
 - E. hemiparesis of the ipsilateral limb
2. Common causes of acute ataxia include all of the following EXCEPT:
- A. drug intoxication
 - B. ataxia telangiectasia
 - C. acute post-infectious cerebellitis
 - D. neuroblastoma
 - E. hydrocephalus
3. All of the following statements are true about acute post-infectious cerebellitis EXCEPT:
- A. it is characterized by rapid onset of ataxia
 - B. it occurs following viral infections such as mumps, coxsackie B and varicella infections
 - C. CSF is characterized by marked pleocytosis
 - D. it has excellent prognosis
 - E. it usually begins approximately 2 weeks after a viral illness

Cranial Abnormalities

1. All of the following intracranial abnormalities are seen better using MRI scan than with CT scan EXCEPT?
- A. cerebellar hypoplasia
 - B. pituitary tumor
 - C. focal cortical malformation
 - D. intracranial calcification

2. Fragile X syndrome is a common genetic cause of mental retardation. Rank the scenarios below in order of likelihood of a positive DNA test for Fragile X syndrome:
- A. male, microcephaly, short stature, congenital heart disease, mental retardation
 - B. female, OFC 10th percentile, developmental regression, stereotypical hand movements
 - C. male, macrocephaly, autistic features, mental retardation
 - D. male, macrocephaly, 3 café-au-lait spots, learning disabilities
- A: D-C-A-B
 - B: C-D-A-B
 - C: A-C-D-B
 - D: B-A-C-D
3. In the case of a 10-year-old child with normal development but an OFC 2.5 SD below the mean for age, what is the most likely additional finding?
- A. intracranial calcifications on CT scan
 - B. coronal and sagittal craniosynostoses
 - C. mother positive for Fragile X carrier testing
 - D. father's OFC -2.5 SD
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 head growth velocity
 - C. family history of macrocephaly
 - D. prenatal ultrasound showing normal cerebral architecture
 - E. none of the above
5. In the case of a newborn child with microcephaly, which finding below would be least likely to have contributed to the child's condition?
- A. severely elevated maternal phenylalanine level
 - B. maternal binge drinking during the first trimester of pregnancy
 - C. the child's parents are first cousins
 - D. mild maternal diabetes mellitus

Answers

Epilepsies In Children

1. B
2. C
3. D
4. B
5. C
6. B
7. C

Ataxia

1. C
2. B
3. C

Cranial Abnormalities

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