Chapter 7 – Episodic Disorders

Donna C. Bergen, MD
Professor, Department of Neurological Sciences

Thomas A. Madden, MD
Associate Professor of Family Practice and Preventive Medicine (Emeritus)
Section of Community & Social Medicine
Rush University Medical Center
Chicago, IL

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 of 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 Syncopes

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 **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 7-1. Differential features of complex partial and absence seizures

	Complex Partial	Absence
Aura	Sometimes	Never
Duration	0.5–2 minutes	< 15 seconds
Behavior	Motionless or Automatisms	Motionless stare
Postictal	Confused	Alert

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 2–3 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 30–40 percent of cases of focal seizure disorders. Diagnostic sensitivity for absence and myoclonic epilepsies is better, reaching 80–90 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 7-2**.

Table 7-2. Treatments according to seizure type

Simple partial, complex partial, tonic-clonic seizures

carbamazepine (Tegretol XR®, Carbatrol®)* **

gabapentin (Neurontin ®)

lacosamide (vimpat®)

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 7-4**).
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 7-3**), avoiding more than three times per day dosing.

Table 7-3: Average half-lives of common AEDs (hours)

carbamazepine	8
ethosuximide	12
gabapentin	6
lamotrigine	12 used with inducers 20 used with inducer + valproate 70 used with valproate
levetiracetam	16
oxcarbazepine	12
phenytoin	24
pregabalin	8
primidone	6
tiagabine	6
topiramate	10
valproate	8
zonisamide	12

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 7-5**.

Table 7-5.

AED	Dose Related	Idiosyncratic or chronic
carbamazepine oxcarbazepine	diplopia, nausea blurred vision	neutropenia, hyponatremia
phenytoin	ataxia, dizziness,	gingival hyperplasia, acne, hirsutism
lamotrigine	blurred vision, insomnia	severe skin rash
levetiracetam	cognitive changes	weight gain
primidone	drowsiness, libido	
valproic acid	fine tremor	weight gain, alopecia, hepatitis*
gabapentin	drowsiness	weight gain
topiramate	cognitive changes	numb face, hands weight loss, nephrolithiasis
zonisamide	cognitive changes	weight loss, nephrolithiasis
lacosamide	dizziness, diplopia	

*rare, mainly seen in children under 2 years of age on polytherapy

Many epilepsies remit in time. The rate varies between 80–90 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 two 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 American* [*www.efa.org* (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, (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, e.g., 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 5–30 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 intrahemispheral 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 7-6**. When all of the patient's abnormal neurological findings "fit" onto one side of the cerebrum (e.g., 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 (e.g., numbness of the right side of the face and the left side of the body).

Table 7-6: A guide to localization

Carotid circulation	Vertebral-basilar circulation
monocular visual loss ("amaurosis fugax")	diplopia
hemiparesis	vertigo
hemi-sensory loss or numbness	ataxia
homonymous hemianopsia	limb tremor/incoordination
aphasia	dysarthria
apraxia	"crossed" sensorimotor loss*
conjugate eye deviation	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 blood flow 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 50–25 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 2–3 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-organized, 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 hemispheral 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 hemispheral 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 lifesaving 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 1–2 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 include 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