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An overview of antiepileptic drug therapy

Critical issues in the treatment of epilepsy

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Abstract: Classification of seizure types and evaluation and treatment of seizure disorders are discussed.

Once the diagnosis of a seizure is made, the seizure type must be identified; this will help in determining the treatment. In partial seizures, the electrical discharge occurs focally, while generalized seizures involve both cerebral hemispheres simultaneously. Magnetic resonance imaging is the preferred test in the evaluation of patients with seizures, although computed tomography and electroencephalography can also be helpful. Selection of an antiepileptic drug (AED) is based on efficacy, toxicity, and, to a lesser degree, cost. Adverse reactions occur in up to 50% of patients. First-line AEDs include carbamazepine, ethosuximide, phenobarbital, primidone, phenytoin, and valproic acid. Serum AED concentrations can be helpful in managing patients with epilepsy. The serum concentrations required to control seizures or resulting in toxicity may vary among patients. Most seizures are manageable with oral AEDs. Medications of choice in status epilepticus include diazepam, lorazepam, phenytoin, and phenobarbital.

The key to treating epilepsy is correct diagnosis of the seizure type and, when possible, the type of epilepsy. Most patients with epilepsy respond to one of the first-line AEDs; second-line agents may be useful in patients who do not respond to one or a combination of the first-line agents.

Index terms: Anticonvulsants; Blood levels; Epilepsy; Toxicity

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The first priority in evaluating a patient with a suspected seizure disorder is to be as certain as possible that the patient indeed has seizures.[1,2] Many disorders can be confused with seizures, including breath-holding attacks, pallid infantile syncope, night terrors, somnambulism, syncope, rage attacks, migraines, cardiac arrhythmias, pseudoseizures, and movement disorders such as tics and chorea.[2] It is a serious mistake to inappropriately label someone as having epilepsy or seizures, because the social consequences and risks of antiepileptic drug (AED) use are great.[3]

The second task is to determine the seizure type. This is critical, since the type of seizure to a great extent determines the type of evaluation and treatment a patient will receive.

Seizures are divided into two basic groups: partial and generalized.[4] Partial seizures involve only a portion of the brain at onset and can be further divided into those involving unimpaired consciousness (simple partial) and those with impaired consciousness (complex partial). Both types can spread, resulting in generalized tonic-clonic seizures. Generalized seizures are those in which the first clinical changes involve both hemispheres. There is usually impairment of consciousness during generalized seizures, although some of these seizures, such as the myoclonic type, may be so brief that impairment of consciousness cannot be assessed.

Partial seizures

Simple partial seizures. The signs or symptoms of simple partial seizures depend on the focus of the seizure.[5] Seizures involving the motor cortex most commonly consist of rhythmic or semirhythmic clonic activity of the face, arm, or leg. There is usually no difficulty in diagnosing this type of seizure. Seizures with somatosensory, autonomic, and psychic symptoms (hallucinations, illusions, déjà vu) may be more difficult to diagnose.[2] Psychic symptoms usually occur as a component of a complex partial seizure. Simple partial seizures can occur at any age.

Complex partial seizures. Complex partial seizures (CPSs), formerly called temporal lobe or psychomotor seizures, are among the most common seizure types encountered in both children and adults.[2] CPS may be preceded by a simple partial seizure, which may serve as a warning to the patient (i.e., an aura) of more severe seizures. The aura may enable the clinician to determine the cortical area where the seizure is beginning.

By definition, patients have impaired consciousness during CPS; thus, the patient either does not respond to commands or responds in an abnormally slow manner. While CPSs may be characterized by simple staring and

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impaired responsiveness, behavior is usually more complex during the seizure. Automatisms (involuntary motor activity) are common during the period of impaired consciousness in CPS. Automatic behavior is quite variable and may consist of activities such as facial grimacing, gestures, chewing, lip smacking, finger snapping, and repeating phrases; the patient does not recall this activity after the seizure.[6,7] Although duration varies, CPSs usually last from 30 seconds to several minutes, in contrast with absence seizures, described below, which usually last less than 15 seconds.[8] Most patients have some degree of postictal impairment, such as tiredness or confusion.

Generalized seizures

Generalized tonic-clonic seizures. There is rarely any difficulty in correctly diagnosing generalized tonic-clonic (GTC) seizures (formerly called grand mal seizures). The only caution is that toddlers with breath-holding attacks and adults and children with syncope may have brief GTC seizures at the end of the attack[9]; because these seizures are brief, they should not be treated with AEDs.

Some patients may have a simple partial seizure (aura) preceding loss of consciousness. As the seizure spreads in the cortex, it develops into a GTC seizure or, more specifically, a simple partial seizure with secondary generalization.[10] Loss of consciousness usually occurs simultaneously with the onset of a generalized stiffening of flexor or extensor muscles (tonic phase). Following the tonic phase, generalized jerking of the muscles (clonic activity) occurs. A GTC seizure is almost always associated with deep postictal sleep.

Absence seizures. Absence seizures, formerly called petit mal, are usually characterized by an abrupt cessation of activity and a change of facial expression with a blank gaze.[8,11,12] The seizures are short, rarely lasting over 30 seconds, and are never associated with an aura or postictal impairment. Like CPS, absence seizures are frequently associated with automatic behavior.

Absence seizures almost always begin during childhood, typically between three and six years of age. While they occasionally continue into adulthood, they are most prevalent during the first 10 years of life. In most patients with absence seizures, the results of a neurologic examination are normal.

Hyperventilation is a useful diagnostic tool in cases where absence seizures are suspected.[2] Three minutes of hyperventilation in an untreated patient with absence seizures is likely to induce an absence seizure. Hyperventilation in a patient with GTC or myoclonic seizures may occasionally induce a seizure. Partial seizures are rarely precipitated by hyperventilation. Photic stimulation (blinking lights), usually administered during the electroencephalogram (EEG), may also result in a GTC, absence, or myoclonic seizure.

At times it may be difficult to differentiate absence seizures from partial complex seizures, since both are associated with a change in facial expression, staring, and automatic behavior. Table 1 shows the diagnostic features of absence seizures and complex partial seizures.

Clonic seizures. Clonic seizures are similar to GTC seizures, but are characterized by rhythmic or semi-rhythmic contractions of a group of muscles. These contractions can involve any muscle group, although the arms, neck, and facial muscles are most commonly involved. Clonic seizures are much more common in children than adults.

Myoclonic seizures. Myoclonic seizures are characterized by sudden, lightning-like contractions of muscle groups. The contractions, which can occur in any muscle group, are quicker than those seen with clonic seizures. Myoclonic seizures may be dramatic, causing the patient to fall to the ground, or subtle, resembling tremors. Because of the brevity of the seizures, it is not possible to determine whether consciousness is impaired. Myoclonus may occur as a component of an absence seizure or at the beginning of a GTC seizure.

Tonic seizures. Tonic seizures are brief (usually less than 60 seconds) and characterized by the sudden onset of increased tone in the extensor muscles.[13-15] If standing, the patient typically falls to the ground. There is impairment of consciousness during the seizure, although the brevity of the seizure may make this difficult to assess. Tonic seizures are frequently seen in patients with Lennox-Gastaut syndrome, which consists of a mixed seizure disorder, mental retardation, and a slow spike-and-wave EEG pattern.[16-18] The seizures usually occur more frequently at night.

Atonic seizures. Atonic seizures are rare and are usually confined to childhood.[13,14] They are characterized by the sudden loss of muscle tone. These seizures

Table 1.
Comparison of Clinical and EEG Features in Absence and Complex Partial Seizures[a]

Clinical Variable	Absence Seizures	Complex Partial Seizures
Frequency/day	Usually multiple	Rarely >1–2
Duration	Usually <10 sec Rarely >30 sec	Usually >90 sec Rarely <30 sec
Aura	No	Frequent
Automatisms	Common	Frequent
Postictal impairment	No	Frequent
Activation		
Hyperventilation	Frequent	Rare
Photic stimulation	Common	Rare
EEG findings		
Between seizures	Usually normal	Spikes/sharp waves; may be normal
During seizures	Generalized spike-waves	Focal discharges

[a] EEG = electroencephalogram.

are very brief, lasting seconds, and are rarely associated with any significant postictal impairment. If truncal tone is involved, the patient falls to the ground. Most children who suddenly fall during a seizure, however, are experiencing a myoclonic or tonic seizure. If only the neck extensors are involved, the patient's head may drop briefly. During atonic seizures lasting more than a few seconds, consciousness is impaired. Atonic seizures are frequently seen in patients with other seizure types. In addition, there may be an atonic component of absence seizures.

Epileptic syndromes

After identifying the seizure type, the clinician should determine whether the patient has an epileptic syndrome. An epileptic syndrome is a cluster of signs and symptoms customarily occurring together.[2,19] Since certain syndromes are associated with specific genotypes, proper identification may allow the physician to counsel patients as to the genetic risks for their offspring. In addition, identifying a syndrome helps in determining appropriate therapy and prognosis. Although it is beyond the scope of this discussion to cover all epileptic syndromes, a review of one example, juvenile myoclonic epilepsy (JME), demonstrates why syndrome identification is useful.

JME is a familial disorder that typically begins in the second decade of life and is characterized by mild myoclonic seizures, GTC seizures, clonic-tonic-clonic seizures (a variation of GTC seizures in which there is an initial clonic phase), or, occasionally, absence seizures. The interictal EEG in this disorder is easily discerned from those seen with other forms of generalized epilepsies.[20,21] The characteristic EEG features are fast (3.5–6 Hz) spike-and-wave or multiple spike-and-wave complexes. This pattern contrasts with the 3-Hz spike-and-wave complexes seen in classic absence seizures and the slow (1.5–2.5 Hz) spike-and-wave complexes of Lennox-Gastaut syndrome. The epileptiform discharges of JME may be activated by photic stimulation. If JME is suspected and the waking EEG is normal, it is imperative that a sleep-deprived EEG be obtained, since the abnormality may be present only during sleep deprivation.

Identification of this syndrome is important for several reasons. While myoclonic seizures may be associated with degenerative disease, JME is benign. Once the diagnosis of JME is established, the physician does not need to perform neuroimaging procedures such as magnetic resonance imaging (MRI) or computed tomography (CT) or tests for neurodegenerative diseases. JME responds extremely well to treatment with valproic acid, so identification of this syndrome also enables the clinician to prescribe the proper AED. (Although the seizures respond well to valproic acid, the disorder persists throughout the patient's life, and withdrawal of AEDs is usually not possible.) Finally, identification of JME in a large number of patients has enabled investigators to establish hereditary patterns for this syndrome and has led to research linking it to chromosome locus 6p21.3.[22-24]

In summary, identification of a patient's epileptic syndrome often helps the clinician determine the type and extent of the workup required, guides him or her in selecting the proper AED, allows counseling of the patient as to the extent of the genetic risk for his or her offspring, and assists in establishing the prognosis.

Evaluation

The history and neurologic examination remain the cornerstones of neurologic diagnosis. As mentioned above, it is important to determine by history whether the patient has had a seizure and, if so, what type. In general, if there is uncertainty about the diagnosis, it is usually best to withhold treatment and wait for another attack before embarking on an extensive (and expensive) workup and initiation of AED therapy.

After diagnosing a seizure, the clinician must determine its underlying or precipitating cause. The initial workup is partly determined by the patient's condition. The patient who arrives at the emergency room with status epilepticus (continuous seizure activity) or who is comatose or febrile is approached differently from the patient who has totally recovered from the seizure by the time he or she sees the clinician. Methods for evaluating the second type of patient will be discussed here.

Electroencephalography. When appropriately used, the EEG can support the diagnosis of epilepsy, localize onset of the seizures, delineate an epileptic syndrome, suggest prognosis, and even aid in choosing appropriate therapy. Since the routine EEG is noninvasive, safe, and relatively inexpensive compared with other diagnostic studies, all patients with suspected seizures should have one.

Epileptiform patterns are distinct from the background activity appropriate for the patient's age and state, have an electrical field and configuration indicative of cerebral origin, illustrate characteristic morphologic features, and demonstrate predictable effects with activation procedures.[25] Many of the patterns observed in neonates and young children are far different from those seen in adolescents, and the clinician must be aware of these age-specific patterns. Infantile spasms, early infantile epileptic encephalopathy, early myoclonic epileptic encephalopathy, benign rolandic epilepsy, Landau-Kleffner syndrome, and juvenile myoclonic epilepsy are among the epileptic syndromes with distinct EEG signatures.

While the value of an EEG in the evaluation of children with suspected epilepsy is beyond dispute, epileptiform activity on the EEG is rarely diagnostic of epilepsy. In a study population of 6497 nonepileptic patients, 142 (2.2%) had epileptiform discharges on their EEG but only 20 of those patients (14.1%) eventu-

ally developed seizures.[26] In a separate study of 743 normal children, 2.7% showed epileptiform activity on the EEG while awake, versus 8.7% during sleep.[27] Finally, Cavazzuti et al.[28] reported that in a study of 3726 children, 131 (3.5%) had epileptiform activity on the EEG while awake but only 7 of those children (5%) eventually developed seizures.

Conversely, a normal EEG does not rule out the possibility of epilepsy. In a study of 1824 EEGs from 308 patients with known seizures who ranged in age from 1 to 64 years, only 56% had epileptiform activity on the first EEG; subsequently, epileptiform activity was seen in an additional 26% of the patients.[29]

Neuroimaging. MRI and CT are superior to the clinical examination, EEG, and routine skull radiographs in the diagnosis of structural lesions of the central nervous system (CNS).[30-32] Whether all patients with seizures require MRI or CT scans is still a matter of debate. A substantial number of neuroimaging studies show abnormal findings in children and adults with epilepsy. MRI is more sensitive than CT and is now the preferred test in the evaluation of a patient with seizures.[33,34]

MRI and CT are frequently abnormal in children with partial seizures.[35-37] Although most abnormalities will not alter management of the child, in a small but significant percentage an unexpected neoplasm or other treatable lesion will be discovered. In addition, even when the scan does not alter therapeutic management, it may offer the clinician valuable information regarding the cause of the seizures.[35,37] A normal scan also serves to comfort both the physician and family that nothing is being missed. Even with a normal scan, however, the physician should follow the patient closely because the development of neurologic signs would necessitate a repeat study.

Treatment

The first step in the treatment of seizures is to firmly establish the diagnosis. Many nonepileptic conditions resemble seizures. If the diagnosis is uncertain, it is better to withhold characterization of the patient as having epilepsy and initiation of potentially toxic medications.

Since both children and adults who receive medical attention after their first partial or generalized seizure have only a 40% chance of recurrence, many physicians choose not to treat after just the first seizure.[38-42] There is a consensus that patients who have had two or more seizures should be placed on antiepileptic therapy.

Once the diagnosis is established and the physician decides to treat, the next step is to determine which AED to use. This decision is based on efficacy and possible toxicity. Table 2 lists the AEDs used to treat the various seizure types.

Treatment should always be initiated with a single AED and the dosage slowly increased until the seizures are controlled or until clinical toxicity occurs. If the first AED does not work, the drug should be slowly tapered while a second AED is introduced. AEDs should never be stopped abruptly unless a severe adverse effect occurs. Although it is sometimes difficult to avoid polytherapy, the goal should be to have the patient taking a single AED. Monotherapy is likely to result in higher serum drug concentrations, fewer adverse effects, and better control.

Serum drug concentrations are useful guides in assessing therapy.[2] In general, patients have better seizure control when serum concentrations are within the usual therapeutic range than when they are below it. Likewise, patients with serum concentrations exceeding the upper therapeutic range are more likely to experience adverse effects than those with concentrations within the therapeutic range. Phenytoin, phenobarbital, carbamazepine, and primidone concentrations correlate better with seizure control and toxicity than do those of valproic acid, ethosuximide, and clonazepam. It is far more important for the physician to listen to and examine the patient after initiating AED therapy than to guide therapy strictly by the serum concentration. If seizures are continuing and the patient is tolerating the medication well, the dosage should be increased. Conversely, if the patient has persistent adverse effects, the dosage should be reduced.

Once the patient achieves a serum AED concentration that controls seizures without producing adverse

Table 2.
Antiepileptic Drugs (AEDs) of Choice in the Treatment of Epilepsy

	Partial Seizures		Generalized Seizures					
AED	Simple	Complex	GTC[a]	Absence	Myoclonic	Clonic	Tonic	Atonic
First choice	Carbamazepine Phenobarbital Phenytoin Primidone Valproic acid	Carbamazepine Phenobarbital Phenytoin Primidone Valproic acid	Carbamazepine Phenobarbital Phenytoin Primodone Valproic acid	Ethosuximide Phenobarbital Valproic acid	Valproic acid	Valproic acid	Valproic acid	Valproic acid
Second choice	Clonazepam Clorazepate	Clonazepam Clorazepate	Clonazepam Clorazepate	Acetazolamide Clonazepam	Clonazepam	Clonazepam	Carbamazepine Clonazepam Phenytoin	Clonazepam

[a] GTC = generalized tonic-clonic.

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