JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Diagnosis and Management of New Onset Epilepsy

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Abstract

Over the past decade, advances in the diagnosis and treatment of epilepsy have included a new definition of epilepsy as well as the development of new antiepileptic drugs. Several of these drugs are increasingly prescribed to patients with new onset epilepsy. The aim of this review is to provide clinicians with a framework for diagnosing and managing patients with new onset epilepsy, with an emphasis on selection of an appropriate antiepileptic drug. We begin with the new International League Against Epilepsy definition of epilepsy and its basis in the epilepsy literature, followed by a discussion of the initial work-up of epilepsy. The majority of this review discusses the selection of an appropriate antiepileptic drug for adult patients with new onset epilepsy, including a discussion of the SANAD trials and a systematic review of the data supporting the use of newer agents as monotherapy. Finally, we conclude with a discussion of risk assessment and counseling that should be provided to all patients with a new diagnosis of epilepsy.

Keywords

Epilepsy, seizures, focal epilepsy, generalized epilepsy

Introduction

Epilepsy and stroke are the 2 most common neurological disorders: at any one time 7 in 1000 people in the general population have epilepsy. Epilepsy usually begins in childhood, potentially impeding education, employment, social relationships and development of a sense of self-worth. Prompt, accurate diagnosis with appropriate social and medical management will optimize the situation. A family physician, in conjunction with a neurologist, can ascertain (a) if the episodes represent epileptic seizures and (b) if so, which epileptic syndrome they represent. The International League Against Epilepsy (ILAE) revised its definition of epilepsy in 2014 in order to maximize early identification and treatment of patients with epilepsy(1,2).

The ILAE's conceptual definition of epilepsy, first formulated in 2005, is "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures." In practice, this definition corresponded to patients with two or more unprovoked seizures more than 24 hours apart.

Although a major early study suggested that an abnormal neurologic examination was associated with an increased risk of seizure recurrence, a follow-up study from the same group found no increase in risk(3-5). The same follow-up study found that having a sibling with epilepsy increases the risk of recurrence among patients with idiopathic epilepsy, but even among these patients, the recurrence risk is only 46% at 5 years. Thus, neurologic examination findings and family history of epilepsy should be taken into consideration when evaluating a patient with a first seizure, but these features alone are not sufficient to make a diagnosis of epilepsy(5).

Principle Epilepsy Syndrome

The first step in epilepsy management is identification of the syndrome. A syndrome is a constellation of factors that defines each epileptic disorder and influences management. Syndrome determination hinges on seizure description and frequency, age at onset, neurological history and functional enquiry, neurological examination and one or more EEGs. The neurological functional enquiry (review of systems) seeks areas of cognitive and other neurological dysfunctions that may lead to syndrome identification. Neuroimaging may aid in evaluation, but most syndromes are defined by the afore-mentioned means. Most epileptic disorders that a general physician will see will be manifestations of a syndrome. The following describes the most common ones(6).

Characterization of epilepsy type

Determination of the patient's epilepsy type—focal or generalized—at the time of initial diagnosis is important because it helps predict prognosis and guide selection of an appropriate AED. This determination is typically made based on seizure semiology along with magnetic resonance imaging (MRI) and EEG findings. Lateralized motor or sensory symptoms, forced eye deviation or head turn, automatisms, language disturbances, and experiential phenomena suggest focal onset, while bilateral myoclonic jerking or initial bilateral tonic activity suggest generalized onset.

However, semiology alone can be misleading: focal seizures may lack lateralizing features at onset, and more than half of patients with generalized epilepsy have focal seizure symptoms(7). Moreover, three-quarters of patients with focal epilepsy are amnestic for at least some of their seizures, and 30% are amnestic for all seizures. Additionally, up to 60% of patients do not have an aura preceding their seizures(8). These factors make the diagnosis and characterization of epilepsy challenging in many patients.

Most patients with a first seizure should have an MRI, unless there is a contraindication. MRI has a higher yield than computed tomography (CT) for detecting focal epileptogenic lesions. The presence of a focal lesion can confirm a focal onset if the lesion's location corresponds to the patient's semiology. For patients with a clear electroclinical primary generalized epilepsy syndrome, such as juvenile myoclonic epilepsy, neuroimaging may not be required(9)

Seizure type and classification

In 1981, theInternational League against Epilepsy (ILAE) recommended an updated and consistent classification of seizures. In 2010, the ILAE-revised the terminology and concepts for organization of seizures and epilepsy were introduced, and included many epilepsy syndromes and pathophysiologic etiologies. The classifications are shown in fig 1(10). Seizures can be provoked by a variety of influences including severe metabolic disturbance, head trauma, alcohol intake and withdrawal, fever, illness and some medications. Causes of epilepsy are also broad, and include traumatic brain injury, stroke, tumor, central nervous system (CNS) infection such as viral and bacterial meningoencephalitis, inflammation or autoimmune diseases, genetic causes such as SCN1A mutation in Dravet syndrome, and structural brain abnormalities including hippocampal sclerosis, cortical dysplasia and vascular malformation.

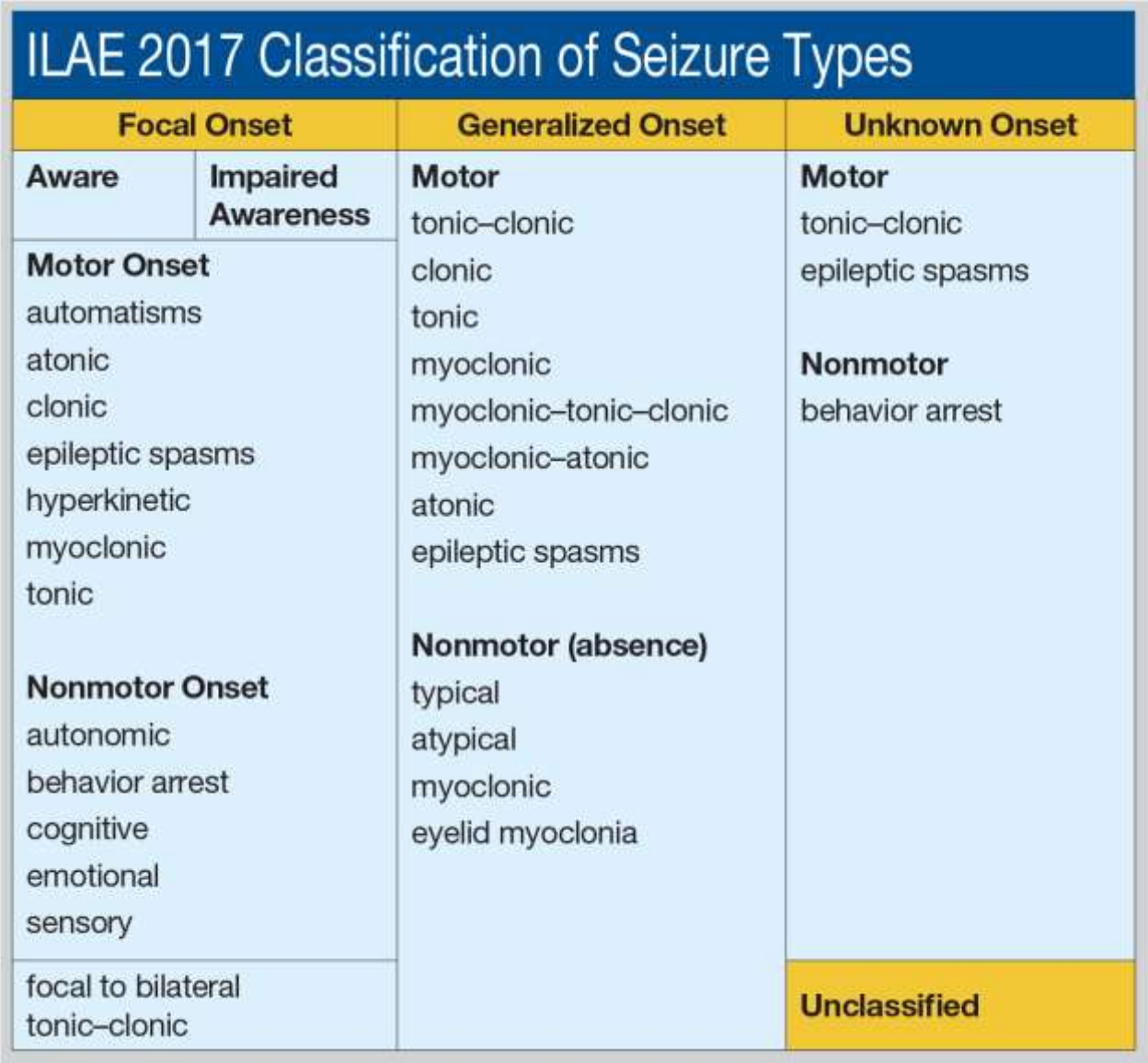

Fig 1 classification of seizures

Absence seizures

Absence seizures begin in childhood or early adolescence, with 5–20-second episodes of sudden arrest of activity, staring straight ahead or upward, occasionally with myoclonic activity of the eyelids, face or upper extremities, and ending abruptly without postictal confusion. Generalized tonic-clonic (GTC; "grand mal") seizures occur in about one-third of such patients, usually in adolescence. Findings from the neurological functional enquiry and examination, including cognition, are normal. Prognosis varies such that "growing out of it" cannot be assured.

Management

The EEG shows sudden bursts of bilaterally synchronous 3-Hz spike-waves, whose quantity usually reflects the frequency of absence seizures.

Complete eradication of absence attacks may require excess medication, and therefore a compromise between adequate dosage and attack frequency may be required. Valproate and lamotrigine act against absence and GTC seizures, whereas ethosuximide, although equally effective, only acts against absence seizures(11).

Drug Treatment.

When neurologists choose medications to treat seizures, they consider the evidence of effectiveness/ efficacy, seizure classification, potential side effects, comorbid conditions, age and gender in order to select an effective medication while minimizing side effects(12).

Vaproic acid has been shown to significantly increase the risk of major fetal malformation in women with childbearing age whereas lamotrigine and levetiracetam are found to more safe choices. Chronic usage of antiepileptic medications can cause bone weakness. Certain hepatic enzyme inducing medications tend to have more drug-drug interactions and potentially become problematic in other co-morbid conditions, requiring anticoagulation, anti-tumoral or anti-HIV treatment. Some of antiepileptic drugs can affect the mood. Levetiracetam has higher risk of causing some irritability, depression and other mood disturbance whereas lamotrigine and valproic acid may have mood stabilizing effects. Certain medications such as topiramate and valproic acid are found to be useful to treat migraine headache(12).

Focal epilepsy of childhood with “rolandic spikes”

This benign focal epilepsy has no identifiable brain lesion. It accounts for 10%–16% of all patients with seizures under the age of 15 years and is 3–4 times more common than childhood absence seizures(13,14) An otherwise healthy child has episodes of a unilateral unusual sensation in the mouth, face or one arm, with hypersalivation. Focal tonic or clonic phenomena involving the mouth, tongue or arm may occur, and speech may arrest. Most of such attacks begin during sleep, awakening the patient. This syndrome may present as nocturnal GTC seizure followed by a brief Todd's paresis and may be the most common cause of an idiopathic nocturnal GTC seizure in children between 5 and 10 years of age.

Management

This benign syndrome cannot be diagnosed without demonstration of typical “rolandic” spikes on an EEG of a nonsedated patient, whether awake or asleep, but 2 EEGs may be required to disclose their presence. Lack of such spikes draws into question this diagnosis and may prompt further evaluation, including imaging. The seizure tendency ends by adolescence in 98% of cases, and medication can then be omitted.

First-line treatment for focal epilepsy

Levetiracetam has performed as well as, or slightly worse than, older AEDs in head-to-head trials, and is a reasonable first-line treatment in patients without a history of psychiatric issues, particularly if seizures are frequent or patients have difficulty with the lamotrigine titration schedule. In patients with psychiatric comorbidities, we recommend lamotrigine as first-line treatment. The pending SANAD II trial will more definitively answer the question of which of these two AEDs is superior with regards to both efficacy and tolerability. Depending on the patient’s comorbidities and side effect tolerance, several of the older AEDs (carbamazepine, oxcarbazepine, topiramate) and newer AEDs (zonisamide, lacosamide, eslicarbazepine) may be reasonable alternatives(15). Brivaracetam, clobazam, perampanel, and cenobamate may be viable options in the future, but there is insufficient evidence at this time. Gabapentin and pregabalin should not be used as first-line treatments.

Temporal lobe seizures

The temporal lobe is the most common site of focal seizures, and the seizures most often begin in childhood or adolescence. Aurae include an epigastric sensation, fear and various types of visual, olfactory or auditory experiential phenomena. Cognition may be impaired during the seizure, manifesting as confusion, a receptive or expressive dysphasia, apraxia, distraction by an experiential phenomenon or amnesia. Thus, the term “dyscognitive” will replace “complex partial” for this seizure type.

Unilateral or bilateral manual automatisms may occur when cognition is impaired. Dystonic posturing should be sought by observation or history-taking, as it almost always occurs in the arm contralateral to seizure origin.

Chewing and swallowing may occur. Ictal speech, even if nonsensical, suggests involvement of the temporal lobe nondominant for language. A GTC seizure may evolve immediately from a dyscognitive one and is often heralded by contralateral head and eye deviation. Alternatively, GTC seizures may appear independently.

Prolonged febrile seizures may have occurred in infancy. Memory may be impaired if the epilepsy and pathology reside in both temporal lobes or principally in the temporal lobe dominant for language. Subtle or overt signs of unilateral motor dysfunction in the face, hand or leg should be sought on neurological examination.

Management

Temporal lobe interictal EEG spikes should be sought to confirm the clinical diagnosis, but more than one EEG may be required. The lack of temporal lobe epileptiform activity on about 3 routine EEGs suggests the need to reassess the diagnosis. MRI scanning is clearly warranted to determine the side and nature of the abnormality and its cause.

Generally favoured medications include carbamazepine, phenytoin, lamotrigine and topiramate(16).

Antiepileptic drug therapy: key points

- Monotherapy suffices for most seizure disorders.
- Twice-daily dosing is most practical except in pregnancy, when dosing 4 times daily prevents a serum level surge and therefore has less effect on the fetus.
- The severity of the seizure disorder, not the laboratory numbers, determines the “therapeutic range.” Whatever serum drug level renders the patient seizure free is adequate for that patient, even if it is below the laboratory range.
- Dual therapy with most antiepileptic drugs at serum levels in the middle of the laboratory range impairs cognition.
- Effectiveness and side effects both depend on dosage. Small changes in dosage can produce dramatic effects.
- Traditional antiepileptic drugs may be as effective as new ones.
- Fatigue is the most common side effect of most antiepileptic drugs.
- Phenytoin is the only antiepileptic drug that can be started at full dose.

Conclusion

Although epilepsy only affects 1-3% of the US population, the economic burden and cumulative fatality are significant. Various diagnostic tools are used to find the etiology, type, and location of epileptic foci. It is important to have an accurate diagnosis and to start appropriate treatment. Despite29 different antiepileptic medications available in the US, one third of patients remain refractory to pharmacologic treatment. In those patients, other treatments should be considered to improve the quality of life and decrease morbidity and mortality.

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