Evaluation of Seizure Etiology From Routine Testing to Genetic Evaluation

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ABSTRACT

PURPOSE OF REVIEW: Recognizing the cause of a first seizure and identifying the etiology of epilepsy are essential for management. A systematic approach to patients who present with a first seizure helps distinguish between an acute symptomatic seizure, a provoked or unprovoked seizure, and potential mimickers. Routine testing with EEG and MRI may reveal a predisposition for further seizures and help to establish the underlying epilepsy syndrome. An acquired etiology can be identified in 30% of patients with established epilepsy. The remaining 70% of patients have a presumably genetic etiology. Particularly in patients with specific epilepsy syndromes or suspicion for an autosomal dominant inheritance, genetic testing and counseling should be considered.

RECENT FINDINGS: Neuroimaging, autoimmune antibodies, and genetic testing have revolutionized our ability to investigate the etiology of many epilepsies. The new epilepsy classification distinguishes structural, metabolic, genetic, infectious, and immune-mediated etiologies, which often help determine prognosis and treatment.

SUMMARY: There is growing acceptance and demystification of the term epilepsy as the most common cause for recurrent seizures. The new classification of epilepsy does not stop with the recognition of particular epilepsy syndromes but aims to determine the underlying etiology. This can lead to earlier recognition of surgical candidates, a better understanding of many of the genetic epilepsies, and medical treatments aimed at the underlying mechanism causing the disease.

INTRODUCTION

Evaluating the cause of a seizure is essential to inform rational treatment decisions and counseling, beginning with the question of whether a spell is truly epileptic or instead may be related to some other physiologic or psychogenic paroxysmal, transient phenomenon. At the next level, we need to decide whether an epileptic seizure was caused by an acute insult, provoked by other triggers, or related to a predisposition for recurrent, unprovoked seizures, defined as epilepsy.
The term *etiology* is typically reserved for the cause of the underlying epilepsy itself. Before deciding which tests are indicated in the evaluation of a patient’s epilepsy etiology, it is useful to classify the suspected seizure type(s) and to determine the type of epilepsy, either generalized or focal. Particularly when considering a genetic evaluation, it is helpful to recognize if the patient is presenting with a distinct epilepsy syndrome.

The most recent classification of the epilepsies emphasizes the importance of searching for the underlying etiology which can be divided into structural, metabolic, genetic, infectious, immune, or unknown categories (FIGURE 2-1). For a comprehensive evaluation of epilepsy, a number of comorbidities and complications should be addressed (TABLE 2-1). Unfortunately, in many patients, the steps to understand the cause of the seizure and the etiology of the epilepsy are insufficient for specific categorization of the etiology, and patients end up as yet another “seizure disorder.”

This article discusses the basic workup of patients presenting with a new-onset seizure to determine the cause of the first seizure and whether the patient has epilepsy. In patients with epilepsy, a comprehensive epilepsy evaluation is needed to determine the underlying etiology. We will then discuss which patients may benefit from advanced testing, including a genetic evaluation.

**NEW-ONSET SEIZURE**

The initial question when a patient presents with a first transient paroxysmal episode is whether the event was likely epileptic or not, based on the patient’s recollection and witnesses’ reports (FIGURE 2-2). Risk factors for provoked seizures, such as sleep deprivation and alcohol or illicit drug exposure, need to be
explored. In approximately 20% of cases, patients may already reveal a history of absence, myoclonic, or subtle focal aware seizures that were previously unrecognized as signifying a new-onset epilepsy syndrome. **CASE 2-1** exemplifies the different aspects of a seizure history and the common pitfalls, such as missing a history of prior auras or overlooking a subtle lesion on brain MRI.

The extended history and examination should determine whether the patient has evidence of an acute symptomatic seizure (eg, a persistent focal deficit, prolonged altered consciousness or fever) requiring urgent workup including brain imaging, blood work, and lumbar puncture to look for infectious causes. The examination should assess potential injuries from a convulsive seizure, such as tongue bites, lacerations, back pain from a compression fracture, or shoulder pain from a subluxation.

Recent developments in the definition and classification of epilepsy align the diagnosis of epilepsy with the indication for treatment.3,4 Patients with a first seizure, who have an epileptogenic structural abnormality on brain imaging and/or interictal epileptiform activity on EEG, have a greater than 60% risk of recurrence after a first unprovoked seizure and are considered as having

### TABLE 2-1

**Epilepsy Evaluation**

**Epilepsy Type: Focal or Generalized**
- Presence of a specific epilepsy syndrome
- Focal: determine if frontal, temporal, or parietooccipital onset; laterality

**Seizure Type**
- Seizure description (patient and witness reports; descriptive seizure classification)
- EEG findings (interictal, ictal)
- International League Against Epilepsy seizure type (basic, advanced classification)
- Frequency, triggers, timing, awareness of events, risk factors

**Etiology**
- Structural
- Metabolic
- Genetic
- Infectious
- Immune
- Unknown

**Comorbidities**
- Nonepileptic seizures
- Depression, anxiety, attention deficit hyperactivity disorder
- Migraine
- Cognitive impairment
- Mortality, sudden unexpected death in epilepsy (SUDEP)

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EEG = electroencephalogram.
epilepsy. Those patients typically benefit from antiepileptic medication, which is also considered for patients after a first nocturnal convulsion.5

Patients with a provoked seizure are typically not treated but are counseled about lifestyle modifications and, if necessary, referred for drug and/or alcohol rehabilitation. Acute symptomatic seizures are often treated with temporary antiepileptic coverage for a variable amount of time, depending on how quickly the underlying process resolves or the acute trigger can be corrected. Acute brain insults can have a risk of leading to late seizures in up to 20% of patients and do not warrant prolonged seizure prophylaxis, even if the injury was associated with early seizures or status. Exceptions are possibly a penetrating head trauma and herpes encephalitis, which are associated with a 50% risk of developing epilepsy.

Brain Imaging
Patients with a first seizure should undergo neuroimaging. Urgent imaging should be performed in any patients with a new neurologic deficit, persistent altered mental status, recent trauma, or prolonged headache. CT scan is often used as the first imaging modality because of its ease of access and should be considered for

**KEY POINTS**

- Laboratory testing after a first seizure should include a complete blood cell count; blood chemistry, including calcium, magnesium, and phosphate; thyroid-stimulating hormone; and urine toxicology. A 12-lead ECG should also be considered.

- Acute brain insults can have a risk of leading to late seizures in up to 20% of patients and do not warrant prolonged seizure prophylaxis, even if the injury was associated with early seizures or status. Exceptions are possibly a penetrating head trauma and herpes encephalitis, which are associated with a 50% risk of developing epilepsy.

**FIGURE 2-2**
Systematic approach to patients with new-onset seizure.
CT = computed tomography; EEG = electroencephalogram; MRI = magnetic resonance imaging.
Modified with permission from Gavvala JR, Schuele SU, JAMA.© 2016 American Medical Association.
A 41-year-old right-handed woman presented for evaluation at an epilepsy center. Three weeks earlier she had collapsed and convulsed on a soccer field during a hot summer day. She remembered being at the field watching her son play, walking toward the other side of the field, and then losing consciousness. She was unaware of what happened when she arrived in the emergency department. There was no witness report, and she was thought to have had a syncopal event given the circumstances as well as the results of the normal EEG and brain CT in the emergency department.

During follow-up in an epilepsy center, it was revealed that the patient had asked a witness who had seen the event, who described how the patient collapsed to the ground, became rigid, and then started convulsing for more than a minute. Afterward, the patient appeared confused and incoherent.

The patient remembered on further questioning that she had a really weird feeling of sudden, strong fear for about 10 seconds right before she passed out. The patient had this sudden, distinct fear sensation a few times before, 1 to 2 times per year, over the last 4 years. She was typically able to calm herself down with a few deep breaths, usually lasting for a minute or less. During some of these episodes, she had told her husband that she felt weird, and when he checked on her, she seemed to always be able to respond. This had happened while running but also when resting.

Brain MRI had been done in the interim and was initially interpreted as normal. On further review, her brain MRI was found to demonstrate a 6-mm ovoid signal abnormality in the right middle temporal gyrus (FIGURE 2-3). Within the subcortical white matter of the right middle temporal gyrus there was a region of T2/fluid-attenuated inversion recovery (FLAIR) hyperintense signal that had a smaller cystic component with a hypointense rim. This likely represented a focal cortical dysplasia or glioneuronal tumor. Subsequent 36-hour ambulatory EEG was read as normal.

The patient’s epilepsy was classified as right temporal lobe epilepsy with the symptomatology of psychic aura preceding a bilateral tonic-clonic seizure. According to the International League Against Epilepsy, this would be classified as a focal aware emotional seizure progressing to a bilateral tonic-clonic seizure. The frequency was one to two auras per year with an isolated convulsion. The etiology was identified as right middle temporal focal cortical dysplasia versus low-grade tumor, and there were no comorbidities.

There were no further events, and the seizures were controlled with levetiracetam. The patient underwent resective surgery to confirm the etiology and ensure the underlying lesion was not a malignant tumor. Intraoperative electrocorticography found spikes anterior to the lesion. Surgical pathology demonstrated a ganglioglioma with surrounding tissue showing focal cortical dysplasia type IIIb. The patient remained seizure free on medication.
This case illustrates the different aspects of a seizure history and common pitfalls, such as missing a history of prior auras or overlooking a subtle lesion on brain MRI and the option for early surgery to understand the etiology and distinguish benign versus potentially malignant underlying pathology in selected candidates.
patients with new-onset seizures seen in the emergency department to assess for an acute brain insult, such as a stroke, bleed, or traumatic injury, often followed by a more accurate brain MRI performed with and without contrast.\textsuperscript{6,7} CT scans and standard MRI protocols often fail to detect the lesions associated with chronic epilepsy; for this reason, an MRI should be performed using an epilepsy-specific protocol. These lesions typically do not require acute interventions and are arguably better evaluated during subsequent follow-up. The use of an epilepsy-protocol MRI, with communication to the reader of the suspected seizure focus before reading of the study, and review of the imaging results by an expert neuroradiologist doubles the sensitivity in detecting the often subtle abnormalities that may be amenable to epilepsy surgery.\textsuperscript{8,9}

Electroencephalogram
Emergency EEG is indicated for patients who do not have a timely recovery after a seizure, have fluctuating mental status changes, or show a neurologic deficit that is not explained by the imaging findings. A routine EEG is insufficient to

CASE 2-2

A 36-year-old right-handed woman found to have an incidental hypophyseal brain aneurysm underwent elective clipping via left pterional craniotomy. She was awake and alert postoperatively, and the next day, she was witnessed to have staring episodes and confusion. Her brain CT demonstrated a small parenchymal hemorrhage in the posterior inferior left frontal lobe and a small amount of subarachnoid blood. The patient was started on levetiracetam. Video-EEG was initiated, which showed evidence of left hemispheric dysfunction and moderate encephalopathy during the first 2 recording days. On the third day, four electrographic seizures arising from the left temporal area were seen without a clear clinical correlate. Lacosamide was added, the seizure activity subsided, and the patient improved quickly. Left temporal sharp waves were noted, often in a semiperiodic pattern (FIGURE 2-4). The left temporal sharp wave activity persisted during the subsequent 3 recording days, although with diminishing frequency, and the patient was discharged.

The patient was seen in the epilepsy clinic 4 weeks later; she was seizure free and still taking both medications. An EEG was performed at that time, which showed resolution of the epileptiform activity. Both seizure medications were sequentially tapered over a period of 2 months, first by withdrawing levetiracetam, then lacosamide. The patient was seen in follow-up 7 months postoperatively and has remained seizure free.

The patient’s condition was classified as acute symptomatic seizures with the symptomatology of an altered awareness/responsiveness seizure. According to the International League Against Epilepsy, this would be classified as a focal impaired awareness seizure. The frequency was several per day, but after postoperative day 3, the patient was seizure free. The etiology was identified as post–left pterional craniotomy for aneurysm clipping and a small left inferior frontal hemorrhage with subarachnoid blood, and there were no comorbidities.
detect subclinical seizure activity, which is captured within the first 30 minutes in only one-fourth of patients found to have subclinical seizures on long-term monitoring and in the first 2 hours in one-half of those patients. The yield increases to greater than 90% with 24- to 36-hour continuous recordings. **CASE 2-2** illustrates the need for prolonged monitoring to capture subclinical seizures in a patient with an acute symptomatic seizure after brain surgery, but also emphasizes that the initial EEG may not be appropriate to assess the long-term risk for subsequent development of epilepsy.

EEG recording after a new-onset seizure can show interictal epileptiform activity and help determine the potential seizure type and recurrence risk after a first event. Of patients with new-onset seizures, 29% will have epileptiform abnormalities on EEG. An initial EEG is particularly valuable for patients with a predisposition for generalized seizures. Those patients tend to have a higher frequency of epileptiform discharges compared with focal epilepsies and a typical response to activation with hyperventilation and photic stimulation. The EEG in generalized epilepsies may normalize with appropriate treatment, and it

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**FIGURE 2-4**

EEGs of the patient in **CASE 2-2**. **A**, EEG on postoperative day 4 with prominent left temporal sharp waves and spikes, often in semiperiodic runs, during stage II sleep. **B**, EEG 1 month after surgery. Asymmetry and continuous slow over the left temporal region as sequelae of the surgery during stage I sleep; no epileptiform abnormalities are seen.

This case illustrates the need for prolonged monitoring to capture subclinical seizures in a patient with an acute symptomatic seizure after brain surgery. It also emphasizes that EEGs in the early phase may not be appropriate to assess the long-term risk of epilepsy. The patient remained seizure free after discontinuing medication despite periodic focal sharp waves in the acute seizure setting.
is important to obtain a pretreatment study. There does appear to be a slightly higher yield of epileptiform abnormalities on EEGs performed in patients within 24 to 48 hours of a new-onset seizure. However, acute EEG changes may reflect the sequelae of the acute insult to the brain or aftermath of the seizure and may not necessarily be predictive of the risk of late seizure recurrence (CASE 2-2). Patients presenting with a provoked seizure should get at least an EEG and a brain imaging study because not infrequently they are found to have a remote structural abnormality or an EEG indicating a predisposition for generalized seizures.

**EPILEPSY EVALUATION**
The evaluation in a patient with established epilepsy differs in many aspects from that of a first seizure. In particular, chances to have a reliable witness report for the events are higher, and the yield of EEG to capture interictal epileptiform abnormalities increases. In patients with frequent events, video-EEG recording can be considered, and brain imaging needs to focus on structural abnormalities amenable to surgery.

**Seizure Evaluation**
Patients with established epilepsy may have several seizure types. The interview should provide guidance for the patient to describe the seizures in his or her own words, to characterize different seizure types associated with specific epilepsy syndromes, or recognize that focal seizures often evolve from an aura to loss of awareness and sometimes convulsions. A variety of sources for witness reports may be available, and the patient or family may have already recorded an event on video. It may also become apparent when speaking to family members and other witnesses that the patient is not aware of some seizures. For patients with epilepsy who continue to have seizures, we want to know if the seizure was caused by some trigger or nonadherence to medication or is indicative of an incomplete medication response requiring medication adjustment. Seizures may be seen mostly during certain times of the day or triggered by specific situations, suggesting a form of rare reflex epilepsy.

The physician should use a systematic descriptive vocabulary to capture the essential components of the clinical seizure and its evolution (FIGURE 2-5). Many epilepsy centers use this vocabulary to create a seizure classification based purely on the clinical symptoms and observed behavioral signs, which is helpful to localize the seizure onset and to capture all essential components of a seizure and its evolution. This independence from other tests allows a seizure description without having to know the EEG onset pattern, which is often more practical. CASES 2-1 and 2-2 demonstrate the use of a systematic descriptive classification in parallel with the International League Against Epilepsy (ILAE) classification.

The ILAE seizure classification was revised in 2017. The terms for each seizure type indicate the suspected or confirmed EEG onset (focal versus generalized) followed by a brief descriptor of the patient’s symptoms, creating an electroclinical entity. The basic version divides focal aware seizures and focal impaired awareness seizures (FIGURE 2-6). Focal and generalized seizures can be classified as motor and nonmotor. A more extended version allows additional descriptors.

Approximately 70% to 80% of patients with chronic focal epilepsies eventually develop interictal epileptiform discharges. The yield is noticeably
higher in long-standing focal epilepsies compared with first-time seizures. The yield to capture the presence of discharges depends on the duration of the recording. Today, most patients and physicians prefer the convenience of an ambulatory EEG and the ability to request interpretation by an expert reader over repeat routine EEGs. In a study by Faulkner and colleagues\textsuperscript{14} in patients with epilepsy found to have interictal epileptiform abnormalities during 4 days of EEG recordings, interictal epileptiform discharges were recorded in 44% of patients within 4 hours, 58% within 8 hours, 85% within 24 hours, and 95% within 48 hours of recording. Recording for the full 96-hour period revealed only 5% new interictal epileptiform discharges. The median latency to the first discharge was significantly shorter in patients with generalized epilepsies (43 minutes) compared with focal epilepsies (512 minutes for extratemporal and 590 minutes for temporal lobe epilepsies), indicating a 2-day recording length as most adequate for looking for interictal epileptiform activity and a potentially shorter recording length in suspected generalized epilepsies.

**FIGURE 2-5**
Glossary of descriptive terminology for ictal symptomatology.
\textsuperscript{10}Autonomic symptoms can be verifiable for the observer (eg, tachycardia, goosebumps).
Data from Blume WT, et al, Epilepsia.\textsuperscript{10}

**FIGURE 2-6**
International League Against Epilepsy classification of seizure types.

**KEY POINTS**
- Typical MRI lesions associated with surgically amenable epilepsy, such as glioneuronal tumors, low-grade gliomas, hippocampal sclerosis, small cavernous malformations, and subtle malformations of cortical development (eg, cortical dysplasia or isolated periventricular nodular heterotopia), are not seen on brain CT scans and often missed on standard MRIs.
- An epilepsy-protocol brain MRI differs from a typical MRI in that it includes thin 1- to 3-mm slices without interslice gap and coronal fluid-attenuated inversion recovery sequences, which offer additional sensitivity over standard-protocol MRIs.
- A brain CT and an EEG should be considered even in the presence of an alternative etiology for a provoked seizure.
### TABLE 2-2 Electroclinical Syndromes Arranged by Age at Onset

<table>
<thead>
<tr>
<th>Age at Onset</th>
<th>Syndromes</th>
</tr>
</thead>
</table>
| **Neonatal Period** | - Benign familial neonatal epilepsy  
- Early myoclonic encephalopathy  
- Ohtahara syndrome |
| **Infancy** | - Epilepsy of infancy with migrating focal seizures  
- West syndrome  
- Myoclonic epilepsy in infancy  
- Benign infantile epilepsy  
- Benign familial infantile epilepsy  
- Dravet syndrome  
- Myoclonic encephalopathy in nonprogressive disorders |
| **Childhood** | - Febrile seizures plus (can start in infancy)  
- Panayiotopoulos syndrome  
- Epilepsy with myoclonic atonic (previously “astatic”) seizures  
- Self-limiting epilepsy with centrotemporal spikes  
- Autosomal dominant nocturnal frontal lobe epilepsy  
- Late-onset childhood occipital epilepsy (Gastaut type)  
- Epilepsy with myoclonic absences  
- Lennox-Gastaut syndrome  
- Epileptic encephalopathy with continuous spike-and-wave during sleep  
- Landau-Kleffner syndrome  
- Childhood absence epilepsy |
| **Adolescence to Adulthood** | - Juvenile absence epilepsy  
- Juvenile myoclonic epilepsy  
- Epilepsy with generalized tonic-clonic seizures alone  
- Progressive myoclonic epilepsies  
- Autosomal dominant epilepsy with auditory features  
- Other familial temporal lobe epilepsies |
| **Less Specific Age Relationship** | - Familial focal epilepsy with variable foci (childhood to adult)  
- Reflex epilepsies |

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In most patients, particularly if they respond to medical therapy and remain seizure free, a confirmation of the seizure and epilepsy type through symptomatology and interictal EEG is sufficient for management. However, in patients whose seizures remain resistant to medication after 1 year, an evaluation in the epilepsy monitoring unit is recommended to understand the actual cause of the seizures. Approximately 25% of patients considered intractable are found to have nonepileptic seizures, and 10% to 20% of patients with epilepsy also have nonepileptic events. Some patients with generalized epilepsies will not be recognized unless they are monitored off medication for several days. Last but not least, there is the considerable number of patients with focal epilepsy who are candidates for epilepsy surgery who benefit from a presurgical evaluation in the epilepsy-monitoring unit.

**Epilepsy Type**

The next step in the evaluation is to determine the type of epilepsy: focal, generalized, or unknown. In the ILAE classification, the seizure type and epilepsy type largely overlap with each other; however, there is recognition of a subgroup of patients (eg, those with Lennox-Gastaut syndrome or Dravet syndrome) who can have focal and generalized onset seizures and present with a combined generalized and focal epilepsy. In focal epilepsies, the epilepsy type should be further divided into the anatomic region of suspected seizure origin based on seizure description, imaging, and interictal EEG investigations or confirmed by ictal video-EEG–recorded seizures and accordingly classified as left or right, temporal, frontal, or parietooccipital lobe epilepsy.

**Epilepsy Syndrome**

A variety of distinct epilepsy syndromes have been described, many with onset in childhood or adolescence (TABLE 2-2). The recognition of these syndromes is not only important for treatment and prognosis, it also guides genetic evaluations because many of the established epilepsy syndromes have a likely genetic etiology.

**Etiology of Epilepsy**

The etiology of epilepsy can be divided into six different categories: structural, metabolic, genetic, infectious, immune, and unknown. The etiologies are not mutually exclusive, allowing a structural-genetic cause for patients with tuberous sclerosis or a metabolic-genetic cause for patients with epilepsy associated with inborn errors of metabolism. Genetic generalized epilepsies include four epilepsy syndromes still referred to as idiopathic generalized epilepsies: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and sporadic generalized tonic-clonic seizures alone. Genetic generalized epilepsies also include the group of patients with epileptic encephalopathies, which are often due to a specific genetic cause.

**STRUCTURAL.** Most patients with epilepsy require a high-resolution epilepsy-protocol brain MRI to assess the possibility of a structural etiology. An exception can be made in patients with a convincing history and classical EEG findings of an idiopathic generalized epilepsy. The presence of a resectable, epileptogenic lesion should trigger a surgical evaluation in patients with medication-resistant epilepsy.
epilepsy. In patients with intractable focal epilepsy and a normal MRI, a fludeoxyglucose positron emission tomography (FDG-PET) scan is useful in looking for a hypometabolic region.

**METABOLIC.** Epilepsy associated with inborn errors of metabolism usually has the features of an epileptic encephalopathy with seizures arising at an early age, often refractory to antiepileptic drugs, and associated with severe cognitive, sensory, and/or motor impairment. Most metabolic epilepsies have a presumed genetic basis. They are typically categorized according to the biochemical pathway involved and the age of onset. The presence of other neurologic abnormalities, such as movement disorders and ataxia, systemic involvement, parental consanguinity, and a positive family history of a similar illness, can be clues. The general examination should look for dysmorphic features and an abnormal head circumference. Skin and hair abnormalities can point toward Menkes syndrome or a biotinidase deficiency. A formal ophthalmologic evaluation is essential in identifying signs of pigmentary retinopathy (neuronal ceroid lipofuscinosis, mitochondrial disorders), macular cherry-red spots (gangliosidosis, Niemann-Pick disease), lens dislocation (sulfite oxidase deficiency), and cataracts (serine biosynthesis defects). A selected number of inborn errors of metabolism can present in adolescence and adulthood (TABLE 2-3) and require a systematic evaluation for biochemical abnormalities and genetic causes (FIGURE 2-7).

**TABLE 2-3**

<table>
<thead>
<tr>
<th>Metabolic Epilepsies Presenting in Adolescence or Adulthood</th>
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<tbody>
<tr>
<td><strong>Progressive Myoclonic Epilepsies</strong></td>
</tr>
<tr>
<td>◆ Ceroid lipofuscinosis</td>
</tr>
<tr>
<td>◆ Sialidosis type I</td>
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<tr>
<td>◆ Gaucher disease type III</td>
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<tr>
<td>◆ Mitochondrial cytopathies</td>
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<tr>
<td>◆ Lafora disease</td>
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<tr>
<td>◆ Unverricht-Lundborg disease</td>
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<tr>
<td><strong>With Intellectual Disability</strong></td>
</tr>
<tr>
<td>◆ Disorders of creatine metabolism</td>
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<tr>
<td>◆ Mitochondrial disorders</td>
</tr>
<tr>
<td>◆ Glucose transporter type 1 deficiency</td>
</tr>
<tr>
<td>◆ Urea cycle defects</td>
</tr>
<tr>
<td>◆ Organic acidemias</td>
</tr>
<tr>
<td>◆ Succinic semialdehyde dehydrogenase deficiency</td>
</tr>
<tr>
<td>◆ Lysosomal storage disorders (juvenile Niemann-Pick disease type C)</td>
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<tr>
<td><strong>Without Intellectual Impairment</strong></td>
</tr>
<tr>
<td>◆ Wilson disease</td>
</tr>
<tr>
<td>◆ Porphyria</td>
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</table>
INFECTIOUS. Infections trigger not only acute symptomatic seizures during the initial infection but may also lead to late seizures remote from the initial infection onset and its resolution that are instead consistent with epilepsy. Infectious etiologies include neurocysticercosis, viral encephalitis, bacterial meningitis, fungal infection, tuberculosis, toxoplasmosis, malaria, and HIV.

Neurocysticercosis is more prevalent in developing countries and is often the leading cause of epilepsy in those countries. Seizures can occur in any stage of the cyst formation. Seizures in the acute phase of a bacterial meningitis are an ominous sign and associated with increased mortality. Late epilepsy is seen in approximately 5% to 10% of survivors after bacterial meningitis. Viral encephalitis–related epilepsy is most commonly seen with herpes simplex type 1, which develops in 50% of patients. Acute seizures are a presenting symptom of herpes simplex type 1 in a similar proportion. Cytomegalovirus is the most common fetal viral infection and can cause malformations of cortical development and calcifications, with seizures typically presenting in the first month of life. Subacute sclerosing panencephalitis is a chronic, progressive disorder associated with an initial measles infection before the age of 2 years.

Acute symptomatic seizures are seen in influenza B, varicella, measles, mumps, rubella, and West Nile virus, but there is limited information about how often the acute viral encephalitis leads to late seizures. Approximately 50% of congenital Zika virus cases are associated with epilepsy, typically presenting in the first...
months of life. Tuberculous vasculitis and also cortical tuberculomas can lead to epilepsy. Seizures in cerebral toxoplasmosis are typically associated with the reactivation of a latent infection in immunocompromised individuals.

**INFLAMMATORY.** Increasingly, autoimmune antibody syndromes are recognized as a cause of epilepsy. The majority of these antibodies are directed against neuronal cell surface antigens, including synaptic neurotransmitter receptors, ion channels, or related proteins (TABLE 2-4). A second group has antibodies specific for intraneuronal nuclear or cytoplasmic antigens. Both groups have an association with cancer risk, which is as high as 90% in the patients with nuclear or cytoplasmic antibodies. Thyroid antibodies seen in patients with steroid-responsive encephalopathy and patients with high levels of glutamic acid decarboxylase 65 antibodies can present with immune-mediated epilepsy.

Patients with autoimmune epilepsy often present with a high frequency of seizures and/or treatment-refractory status epilepticus, which is discussed in “Epilepsy Emergencies: Status Epilepticus, Acute Repetitive Seizures, and Autoimmune Encephalitis” by Stephen VanHaerents, MD, and Elizabeth E. Gerard, MD, in this issue of *Continuum.* Aside from high seizure frequency and treatment resistance, patients often show progressive mental status change, neuropsychiatric symptoms, autonomic dysfunction, a viral prodrome, and

### TABLE 2-4

**Autoimmune Antibodies Associated With Epilepsy**

**Antinuclear and Cytoplasmic Antibodies**

- Antineuronal nuclear antibody type 1 (ANNA-1) (anti-Hu)
- Antineuronal nuclear antibody type 2 (ANNA-2) (anti-Ri)
- Antineuronal nuclear antibody type 3 (ANNA-3)
- Antiglial neuronal antibody type 1 (AGNA) (SOX1)
- Purkinje cell antigen type 1 (PCA-1) (anti-Yo)
- Purkinje cell antigen type 2 (PCA-2)
- Purkinje cell antigen type Tr (PCA-Tr)
- Collapsin response mediator protein-5 (CRMP-5) (anti-CV2)
- Amphiphysin
- Glutamic acid decarboxylase 65 (GAD65)

**Plasma Membrane Antibodies**

- N-methyl-d-aspartate (NMDA) receptor
- Voltage-gated potassium channel (VGKC) complex
- Leucine-rich glioma inactivated 1 (LGI1)
- Contactin-associated protein-like 2 (Caspr2)
- α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor
- γ-Aminobutyric acid (GABA)-B receptor
- P/Q and N-type calcium channel
- Neuronal ganglionic AChR
- IgLON5 neuronal cell surface protein
sometimes facial or faciobrachial dyskinesias. Testing may show CSF findings consistent with inflammation, increased signal in the mesial temporal lobe on T2-weighted images, and associated malignancies on screening. In patients with longer-standing epilepsy who may not have initially presented as an emergency, the yield of a positive antibody test result can be predicted through an Antibody Prevalence in Epilepsy (APE) score of greater than 4, which has a sensitivity of 82.6% and a specificity of 82.0%. The score was validated in a large cohort of patients with epilepsy and had a sensitivity of 97.7% in patients with epilepsy of unknown etiology to predict the presence of an autoimmune antibody, which was seen in 43 of 87 patients.

**GENETIC.** Only approximately 30% of epilepsies are acquired, and the remaining 70% are likely caused by one or more genetic factors. The genetics of epilepsies follow a complex pattern, and most genetically determined epilepsies have a polygenic basis with several susceptibility genes contributing to the disease. Next-generation sequencing technology has revolutionized gene discovery in epilepsy and many other disorders.

Comparative genomic hybridization microarray (FIGURE 2-8) is typically the first test for patients presenting with epilepsy and developmental delay, intellectual impairment, and/or dysmorphic features. In patients with genetic generalized epilepsy and intellectual disability, genomic hybridization microarray is able to detect a copy number variant in 28%. Copy number variants have been identified in approximately 1% of the idiopathic generalized epilepsies. Phenotypic and genetic variability is seen in most genetic epilepsies, and single-gene testing has been largely replaced by gene panels and whole exome

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**FIGURE 2-8**

Genetic testing. Comparative genomic hybridization microarray is typically the first test for patients presenting with epilepsy and developmental delay. Single-gene testing has been largely replaced by gene panels and whole exome sequencing. Gene panels are either targeted for a specific phenotype, eg, a progressive myoclonic epilepsy, or offered as a comprehensive epilepsy gene panel. Whole exome sequencing and whole genome sequencing are usually performed within the setting of a genetic clinic.

Courtesy Gemma Carvill, PhD, Northwestern University.
sequencing. Gene panels are either targeted for a specific phenotype, eg, a progressive myoclonic epilepsy, or offered as a comprehensive epilepsy gene panel. Whole exome sequencing and whole genome sequencing are usually performed within the setting of a genetic clinic and research program with access to genetic counseling and the ability to interpret variants of unknown significance.

Dravet syndrome is the best-known epileptic encephalopathy with a distinct clinical presentation associated with a pathogenic variant in the \textit{SCN1A} gene in 80% of patients. Dravet syndrome typically presents with early, prolonged febrile seizures, which are often provoked by modest hyperthermia. Generalized tonic-clonic, tonic, and hemiconvulsive seizures are most common. Myoclonic seizures develop later in the course. Patients often show cognitive dysfunction, ataxia, and psychomotor regression and demonstrate attention deficit hyperactivity disorder–like behavior. However, variable penetrance and phenotypic severity make clinical characterization challenging. Interestingly, 10% of families with generalized epilepsies with febrile seizures plus (GEFS⁺) are positive for \textit{SCN1A}, and family members are at risk of presenting with more severe epilepsies, such as myoclonic-astatic seizures or Dravet syndrome. A variety of other genes have been reported to cause Dravet syndrome–like disorders, including \textit{SCN2A}, \textit{SCN8A}, \textit{SCN9A}, \textit{SCN1B}, \textit{PCDH19}, \textit{GABRA1}, \textit{GABRG2}, \textit{STXBP1}, \textit{HCN1}, \textit{CHD2}, and \textit{KCNA2}, requiring gene panel testing or whole exome sequencing. Epileptic encephalopathies other than Dravet syndrome have been associated with mutations in \textit{CDKL5}, \textit{STXBP1}, \textit{SCN2A}, \textit{SCN8A}, \textit{KCNA2} genes; most are de novo mutations. Recessive or mitochondrial or more complex inheritance is rare and includes X-linked \textit{PCDH19} encephalopathy in girls with normal male carriers.

The clinical neurologist should be familiar with a small group of genetic epilepsies that present with a rather distinct clinical phenotype and if clinically indicated can be evaluated with commercially available gene panels. Notable genetic epilepsies include the autosomal dominant focal epilepsies:

- **Autosomal dominant temporal lobe epilepsy**
- **Autosomal dominant nocturnal frontal lobe epilepsy**
- **Familial focal epilepsy with variable foci**

Autosomal dominant temporal lobe epilepsy is associated with mutations in the \textit{LGI1} (30%) and \textit{RELN} gene and has a 55% to 78% penetrance. Patients present with distinct auditory auras or receptive aphasia that may progress to tonic-clonic seizures. Onset is typically in adolescence or early adulthood, and patients typically have normal intellect and good antiepileptic drug responses. Autosomal dominant nocturnal frontal lobe epilepsy is associated with neuronal nicotinic acetylcholine receptor mutations, which are seen in 20% of patients with this disorder. A more severe form with intellectual disability is associated with \textit{KCNT1} mutation. Penetration is approximately 70%, and seizures typically present in childhood to adolescence, characterized by clusters of nocturnal seizures, which can be tonic, dystonic, or hypermotor, with 70% preceded by nonspecific aura. The diagnosis is clinical, and the EEG often obscured or normal. Patients respond well to carbamazepine and zonisamide, but 30% are drug resistant. Familial focal epilepsy with variable foci is associated with mutations in the \textit{DEPDC5}, \textit{NPRL2}, and \textit{NPRL3} genes, all part of the guanosine triphosphatase (GTPase)–activating protein activity toward Rag (GATOR)
complex, accounting for at least 10% of familial frontal lobe epilepsies. Patients show variable foci and a 50% to 80% penetrance. Onset is variable from 1 month to 51 years of age with an average of 12 years. Long periods of remission in the teen/adult years are noted.

It is worthwhile to be familiar with glucose transporter type 1 (GLUT1) deficiency syndromes associated with SLC2A1 gene mutation given the excellent response to dietary treatment and the recent discovery of milder, later-onset variants.39 The typical presentation is in the first months of life. Children often present with seizure clusters and status epilepticus during fasting (eg, before breakfast). Associated features are often severe psychomotor retardation, dystonia, ataxia, and acquired microcephaly. The syndrome can present as early-onset absence epilepsy and myoclonic-astatic epilepsy. A diagnostic clue is a low fasting CSF glucose level. Excellent responses to ketogenic diet are seen.

Periventricular nodular heterotopia associated with a filamin A mutation is important to recognize given the implication for prenatal counseling in this X-linked dominant disorder. It affects female patients who typically show normal or borderline intelligence and presents with seizures in close to 90%. Forty-nine percent of classic bilateral periventricular nodular heterotopia cases are associated with X-linked filamen A mutations, which are perinatally lethal in affected males. As a consequence, half of male offspring perish, and half of female offspring are affected.

Understanding the genetic etiology of an individual with epilepsy has a number of clinical implications. A genetic diagnosis provides closure and can avoid unnecessary testing or lead to important screening for known complications or malignancies. There is the hereditary aspect for some genetic epilepsies, which affects prognosis and counseling. Mitochondrial disorders presenting with epilepsy may not be recognized until adulthood and the diagnosis has a direct impact on treatment and counseling of the patient and family members.30

Discovering a specific gene abnormality can also open the door for precision medicine. A gene abnormality may not only cause the disease but also be associated with a specific mechanism leading to seizures amenable to specific treatment. SCN1A-associated Dravet syndrome responds well to medications such as clobazam and valproate and can worsen with sodium channel blockers, whereas SCN8A-associated Dravet syndrome may benefit from sodium channel blockers and PCDH19-related Dravet syndrome may respond well to steroids.31 The mammalian target of rapamycin (mTOR) signaling pathways affect regulation of cell growth and proliferation. Mutations in the mTOR pathway can lead to a spectrum of malformations of cortical development ranging from focal cortical dysplasia to hemimegalencephaly and megalencephaly, or can cause multisystem disorders such as tuberous sclerosis complex or hamartoma syndromes including Cowden and Lhermitte-Duclos disease.32 Several mTOR regulatory genes, DEPDC5, MTOR, NPRL3, PI3KCA, and PTEN, are associated with hemimegalencephaly and lesional and nonlesional focal cortical dysplasia and can present as germline or somatic mutations in the brain. In polyhydramnios, megalencephaly, and symptomatic epilepsy syndrome (PMSE), an autosomal-recessive disorder associated with mutations in the STRADA gene, treatment with the mTOR inhibitor rapamycin prevents the occurrence of seizures. In tuberous sclerosis complex, seizure control with everolimus, a synthetic mTOR inhibitor, has been more variable, suggesting that treatment before seizure onset may be crucial for prevention of the epilepsy.32
Physicians treating patients with epilepsy are frequently asked about the inheritance risk of epilepsy. In the absence of a family history or evidence of a specific genetic syndrome, the epilepsy risk for the general population is estimated at approximately 1%; for a child of a mother with epilepsy, 2.8% to 8.7%; for a child of a father with epilepsy, 1.0% to 3.6%. It increases if the parent’s epilepsy started before the age of 20 years. Genetic counseling for a specific epilepsy syndrome can be straightforward in patients with a 100% penetrant syndrome but complicated in situations of incomplete penetrance and de novo mutations (eg, Dravet syndrome) and should be performed with the help of a genetic counselor.

COMORBIDITIES. Epilepsy presents with a bidirectional relationship with other neurologic (eg, stroke, migraine, dementia, traumatic brain injury) and psychiatric (eg, depression and anxiety) comorbidities. Several diseases, including depression, anxiety, dementia, migraine, heart disease, peptic ulcers, and arthritis, are up to 8 times more common in people with epilepsy than in the general population. The prevalence of comorbidities persists even in patients in seizure remission, and patients with inactive epilepsy remain at risk of premature mortality, suggesting a systemic component involved in the etiology of epilepsy. This component may be mediated by basic pathophysiologic processes and/or genetic factors. To have a comprehensive understanding of the etiology of epilepsy, these comorbidities and systemic vulnerability should be taken into account and adequately treated.

CONCLUSION
Evaluating the etiology of seizures has noticeably changed over the past decade. There is a greater emphasis to distinguish acute symptomatic and provoked seizures (requiring treatment of the underlying condition) from an unprovoked seizure, which may already represent epilepsy. There is growing acceptance and demystification of the term epilepsy as the most common cause of recurrent seizures. The new classification of epilepsy does not stop with the recognition of particular epilepsy syndromes but aims to recognize the underlying etiology. This can lead to earlier recognition of surgical candidates, a better understanding of many of the epileptic encephalopathies, and with time, hopefully medical treatments aimed at the underlying mechanism causing the disease.

USEFUL WEBSITES
INTERNATIONAL LEAGUE AGAINST EPILEPSY DIAGNOSTIC MANUAL
The website provides an excellent diagnostic manual for epilepsy diagnosis in clinical practice. Epilepsydiagnosis.org

GENE REVIEW
Peer-reviewed, regularly updated chapters providing clinically relevant information on inherited conditions, covering diagnosis, management, and genetic counseling. www.ncbi.nlm.nih.gov/books/NBK1116/

REFERENCES


