Epilepsy is common but complex

Epilepsy is a complicated neurological condition with variable manifestations, numerous etiologies, and a diverse range of treatments. It is a chronic disease that, in many cases, can be controlled. However, treatment requires accurate clinical evaluation to allow intelligent treatment choices.

Epilepsy has been designed to help you develop these evaluation skills. Expert neurologists have distilled the evidence and combined their experience. They provide practical guidance to:

- The causes and classification of epilepsy
- Working up seizures
- Antiepileptic medications
- Pediatric epilepsy
- Adult epilepsy
- Emergency epilepsy
- Comorbidity and mortality of epilepsy

Clinical in approach, practical in execution, Epilepsy is packed with tricks, tips, and focused advice to help you better manage your patients’ seizures.
Epilepsy
Epilepsy

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Series Foreword

The genesis for this book series started with the proposition that, increasingly, physicians want direct, useful information to help them in clinical care. Textbooks, while comprehensive, are useful primarily as detailed reference works but pose challenges for uses at the point of care. By contrast, more outline-type references often leave out the *hows and why's* – pathophysiology, pharmacology – that form the basis of management decisions. Our goal for this series is to present books, covering most areas of neurology, that provide enough background information to allow the reader to feel comfortable, but not so much as to be overwhelming, and to associate that with practical advice from experts about care, combining the growing evidence base with best practices.

Our series will encompass various aspects of neurology, with topics and the specific content chosen to be accessible and useful.

Chapters cover critical information that will inform the reader of the disease processes and mechanisms as a prelude to treatment planning. Algorithms and guidelines are presented, when appropriate. “Tips and Tricks” boxes provide expert suggestions, while other boxes present cautions and warnings to avoid pitfalls. Finally, we provide “Science Revisited” sections that review the most important and relevant science background material and “Bibliography” sections that guide the reader to additional material.

We welcome feedback. As additional volumes are added to the series, we hope to refine the content and format so that our readers will be best served.

Our thanks, appreciation, and respect go out to our editors and their contributors, who conceived and refined the content for each volume, assuring a high-quality, practical approach to neurological conditions and their treatment.

Our thanks also go to our mentors and students (past, present, and future), who have challenged and delighted us; to our book editors and their contributors, who were willing to take on additional work for an educational goal; and to our publisher, Martin Sugden, for his ideas and support, for wonderful discussions and commiseration over baseball and soccer teams that might not quite have lived up to expectations. We would like to dedicate the series to Marsha, Jake, and Dan; and to Janet, Laura, and David. And also to Steven R. Schwid, MD, our friend and colleague, whose ideas helped to shape this project and whose humor brightened our lives, but he could not complete this goal with us.

Robert A. Gross
Jonathan W. Mink
*Rochester, NY, USA*
Preface

Epilepsy is a common but heterogeneous neurological condition of children and adults, with variable manifestations, numerous etiologies, and diverse treatments. Every clinician frequently encounters this disorder in the emergency room, the hospital, and the outpatient clinic and needs to have a systematic approach for its evaluation and management.

In keeping with the goals of this series, this book summarizes the knowledge and practices of expert epilepsy specialists in a concise, practical pocketbook for everyday use by treating physicians. The main emphasis is on bedside clinical evaluation and treatment. The target audience is neurology residents and fellows, general neurologists, and primary care, ICU, and emergency room providers that frequently encounter seizures and epilepsy in their practices. This book is intended to make all of the major issues of the clinical evaluation and treatment of seizures and epilepsy accessible to the practitioner, and we believe the authors have covered these topics in a way that is useful for everyday clinical decisions.

The book opens with a discussion of the basics of epilepsy, including the definitions of seizures and epilepsy, their classification, and their causes. These concepts are the foundation of a rational approach to diagnosis and workup at the bedside. This is followed by a guide to treatment with antiepileptic drugs, addressing when and how to initiate medical therapy. Choice of antiepileptic medications in clinical practice is determined not only by possible efficacy, but also by issues of adverse effects, safety, drug interactions, and effects on comorbid conditions. Dose adjustments and transitions to alternate antiepileptic medications are also discussed, as are strategies for optimizing medication regimens and considering nonmedical treatments in patients who have drug-resistant epilepsy.

Specific common syndromes and conditions in children and adults are reviewed, with special emphasis on new information on treatable genetic and metabolic disorders. Another topic of great relevance to the practicing clinician is the treatment of acute seizures and status epilepticus in the home, emergency room, and ICU. A hot topic of special interest is the emergence of continuous video-EEG monitoring as a tool for the diagnosis and management of acute seizures in the ICU.

The book closes by reviewing the consequences of chronic epilepsy. Uncontrolled epilepsy has profound effects on the daily life of individuals and is associated with increased risk of injury and mortality. It affects the management of comorbid medical conditions and may have significant effects on mood and cognitions.

The complexities of this malady demand a nuanced and customized approach to diagnosis and management. One size does not fit all. We believe this book distills the most salient information on this protean disorder, which will allow the practitioner to devise a plan to appropriately evaluate and manage each individual patient. Although this book is dense with information, the authors have striven to organize the facts to place them at the fingertips of the busy practitioner, so that the most important points are presented in boxes and tables that jump out of the page. We hope that the readers will agree and that this book will find a favored place on the shelf of staff rooms and physician offices and in the pockets of their white coats.

During the editing of this book, we were saddened to learn of the passing of Autumn Klein, MD, PhD, who was renowned for her expertise and research in epilepsy in pregnant and postpartum women. She will be missed.

John W. Miller
Howard P. Goodkin
Part I

Epilepsy Basics
Recognizing Seizures and Epilepsy: Insights from Pathophysiology

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Introduction

This chapter provides a brief overview of seizures and epilepsy, with emphasis on pathophysiological mechanisms that determine seizure generation and how these differ from the mechanisms underlying paroxysmal neurologic events that are not epileptic in nature. Detailed discussion about the pathophysiology of epilepsy can be found in numerous reviews, so the question arises: why consider this topic in a book that focuses on the practical approach to seizure management? There are two major reasons. First, the choice of antiepileptic drug (AED) is often crucially dependent on the seizure type or epilepsy syndrome, and hence an understanding of the underlying pathophysiology can direct medication choice. Second, burgeoning knowledge of epilepsy genetics is revealing more and more syndromes with specific mutations that determine the seizure phenotype, sometimes suggesting drugs that should or should not be selected. In this chapter, important terms are defined, and some basics of seizure pathophysiology are discussed as an aid for the practicing physician. It is important to recognize that epilepsy is not a singular disease, but is heterogeneous in terms of clinical expression, underlying etiologies, and pathophysiology.

Definitions

A seizure is a temporary disruption of brain function due to the hypersynchronous, abnormal firing of cortical neurons. Sometimes, the term epileptic seizure is used to distinguish it from a nonepileptic seizure such as a psychogenic (“pseudo”) seizure (Chapter 6), which involves abnormal clinical behavior that might resemble an epileptic seizure but is not caused by hypersynchronous neuronal firing. The clinical manifestations of a seizure depend upon the specific region and extent of brain involved and may include an alteration in motor function, sensation, alertness, perception, autonomic function, or some combination of these. Anyone might experience a seizure in the appropriate clinical setting (e.g., meningitis, hypoglycemia, toxin ingestion), attesting to the innate capacity of a “normal” brain to support epileptic activity in certain circumstances. More than 5% of people will experience a seizure at some point during their lifetimes.

Epilepsy is the condition of recurrent, unprovoked seizures (i.e., two or more seizures). Epilepsy occurs when a person is predisposed to seizures because of a chronic pathological state (e.g., brain tumor, cerebral dysgenesis, or post-traumatic scar) or a genetic susceptibility. Approximately 1% of the population suffers from epilepsy, making it the second...
most common neurologic disorder (after stroke), affecting more than two million persons in the United States.

An epilepsy syndrome refers to a group of clinical characteristics that occur together consistently, with seizures as a primary manifestation. Syndrome features might include similar seizure type, age of onset, electroencephalogram (EEG) findings, precipitating factors, etiology, inheritance pattern, natural history, prognosis, and response to AEDs. Examples of epilepsy syndromes are infantile spasms, Lennox–Gastaut syndrome, febrile seizures, childhood absence epilepsy, rolandic epilepsy, and juvenile myoclonic epilepsy. Many of these syndromes are discussed in Chapter 21.

Finally, epileptogenesis refers to the events by which the normal brain becomes capable of producing epileptic seizures, that is, the process by which neural circuits are converted from normal excitability to hyperexcitability. This process may take months or years, and its mechanisms are poorly understood. None of the currently available AEDs have robust antiepileptogenic effects. Clearly, the development of antiepileptogenic therapies is a research priority.

**Classification of seizures and epilepsies**

Epileptic seizures are broadly divided into two groups, depending on their site of origin and pattern of spread. Focal (or partial) seizures arise from a localized region of the brain, and the associated clinical manifestations relate to the function ordinarily mediated by that area. A focal seizure is called “simple” if the patient’s awareness or responsiveness is retained, and “complex” if those functions are impaired during the seizure. Focal discharges can spread locally through synaptic and nonsynaptic mechanisms or distally to subcortical structures, as well as through commissural pathways to involve the whole brain, in a process known as secondary generalization (Figure 1.1). For example, a seizure arising from

![Figure 1.1](image-url)

*Figure 1.1.* Coronal sections of the brain indicating patterns of seizure origination and spread. (A) Primary generalized seizure begins deep in brain (thalamus) with spread to superficial cortical regions (arrows). (B) Focal onset seizure begins in one area of the brain (star) and may spread to nearby or distant brain regions. (C) A focal onset seizure “secondarily generalizes” by spreading first to thalamus (left panel) then to widespread cortical regions (right panel).
the left motor cortex may cause rhythmic jerking movements of the right upper extremity; if the epileptiform discharges subsequently spread to adjacent areas and eventually encompass the entire brain, a secondarily generalized tonic–clonic convolution may ensue.

In contrast, in a generalized seizure, abnormal electrical discharges begin in both hemispheres simultaneously and involve reciprocal thalamocortical connections (Figure 1.1). The EEG signature of a primary generalized seizure is bilateral synchronous spike-wave discharges seen across all scalp electrodes. The manifestations of such widespread epileptiform activity can range from brief impairment of responsiveness (as in an absence seizure) to a full-blown convolution with rhythmic jerking movements of all extremities accompanied by loss of posture and consciousness.

Epilepsy syndromes have been divided historically by etiology (symptomatic vs. idiopathic; the majority of idiopathic epilepsies have a genetic basis) and site of seizure onset (generalized vs. focal or “localization-related”). This classification is being revised based on rapidly accumulating knowledge about the molecular genetic basis of epilepsies and new information gleaned from modern neuroimaging, as well as the realization that many epilepsy syndromes include both focal and generalized seizures. The newer classification scheme (Chapter 2) uses etiologic categories: genetic, structural/metabolic, and unknown. Undoubtedly, this scheme will be refined as further knowledge is gained. From the pathophysiological perspective, some mechanisms are likely to operate across epilepsy categories, and other mechanisms may be specific to certain epilepsy syndromes.

**Pathophysiology**

At the cellular level, the two hallmark features of epileptiform activity are neuronal hyperexcitability and neuronal hypersynchrony. *Hyperexcitability* refers to the heightened response of a neuron to stimulation, so that a cell might fire multiple action potentials rather than single ones in response to a synaptic input. *Hypersynchrony* reflects increased neuron firing within a small or large region of cortex, with cells firing in close temporal and spatial proximity.

While there are differences in the mechanisms that underlie focal versus generalized seizures, at a simplistic level it is still useful to view any seizure activity as a perturbation in the normal balance between inhibition and excitation in a localized region, in multiple discrete areas (seizure “foci”), or throughout the whole brain (Figure 1.2). This imbalance likely involves a combination of increased excitation and decreased inhibition (Table 1.1).

In addition to the traditional concept of excitation/inhibition imbalance, novel pathophysiological mechanisms for the epilepsies are also being discovered. For example, in febrile seizures, release of inflammatory mediators such as cytokines could contribute to neuronal hyperexcitability, an observation that might open new avenues of treatment.

**Seizure mimics**

Many conditions resemble seizures clinically yet have a distinct etiology and therefore warrant treatment other than AEDs. Such seizure mimics are typically paroxysmal and recurrent, like seizures. Representative examples, listed in Table 1.2, illustrate the wide diversity of mechanisms and hence treatment modalities.

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**Tips and Tricks**

Distinguishing epileptic from nonepileptic episodes relies on a detailed clinical history including precipitating triggers; careful description of the patient’s behavior before, during, and after the episode; whether ictal movements can be suppressed manually; and the ability of the patient to recall the spell.

Response of a suspected seizure event to an AED does not necessarily mean that the episode was epileptic, as the ability of AEDs to reduce neuronal excitability are well recognized. Recording such an event on EEG or, preferably, video-EEG is often helpful in differentiating a seizure from a nonepileptic event. However, some epileptic seizures have a subtle or minimal electrophographic correlate, especially if the focus is deep in the brain, such as in the temporal lobe. Therefore, a detailed clinical description should be combined with appropriately selected laboratory investigations in the evaluation of a seizure-like event.
Table 1.1. Examples of pathophysiological processes leading to epilepsy.

<table>
<thead>
<tr>
<th>Level of dysfunction</th>
<th>Disorder</th>
<th>Pathophysiological mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion channels</td>
<td>Benign familial neonatal convulsions</td>
<td>Potassium channel mutations: impaired repolarization</td>
</tr>
<tr>
<td></td>
<td>Dravet syndrome</td>
<td>Sodium channel mutations: enhanced excitability</td>
</tr>
<tr>
<td>Synapse development</td>
<td>Neonatal seizures</td>
<td>Depolarizing action of GABA early in development</td>
</tr>
<tr>
<td>Neurotransmitter receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitatory</td>
<td>Nonketotic hyperglycinemia</td>
<td>Excess glycine leads to over-activation of NMDA receptors</td>
</tr>
<tr>
<td>Inhibitory</td>
<td>Angelman syndrome</td>
<td>Abnormal GABA receptor subunits</td>
</tr>
<tr>
<td>Neurotransmitter synthesis</td>
<td>Pyridoxine (vitamin B6) dependency</td>
<td>Decreased GABA synthesis; B6 is a cofactor of GAD</td>
</tr>
<tr>
<td>Neuron structure</td>
<td>Down syndrome and other disorders with intellectual impairment and seizures</td>
<td>Abnormal structure of dendrites and dendritic spines: altered current flow in neuron</td>
</tr>
<tr>
<td>Neuronal network</td>
<td>Cerebral dysgenesis; post-traumatic scar; mesial temporal sclerosis (in TLE)</td>
<td>Altered neuronal circuits: formation of aberrant excitatory connections (sprouting)</td>
</tr>
</tbody>
</table>

GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; NMDA, N-methyl-d-aspartate; TLE, temporal lobe epilepsy.

Figure 1.2. Simplified scheme indicating that seizure generation results from increased excitation (E), decreased inhibition (I), or both. Examples of intracellular recordings from normal and epileptic neurons are drawn next.
Recognizing Seizures and Epilepsy: Insights from Pathophysiology

Overview of medication mechanisms of action

Knowledge of pathophysiological mechanisms of seizures and epilepsy is helpful in choosing the best AED for a given seizure type or epilepsy syndrome. Many AEDs work at specific cellular or molecular targets (Table 1.3). For instance, agents that enhance γ-aminobutyric acid (GABA) function include benzodiazepines and phenobarbital. Other drugs, such as phenytoin, carbamazepine, and lacosamide, decrease repetitive neuronal firing by altering sodium channel function. Still others (e.g., valproate, topiramate) act at multiple sites, endowing the AED with a broad spectrum of action. In clinical practice, it is optimal to choose an AED that has a specific action in the given epilepsy syndrome, if possible (Chapter 11). For example, ethosuximide is preferable for absence seizures due to its blockade of a calcium channel subtype that underlies the rhythmic, reciprocal epileptic firing between neocortical neurons and thalamic neurons.

Table 1.2. Some common seizure mimics.

<table>
<thead>
<tr>
<th>Seizure mimic</th>
<th>Underlying pathophysiology</th>
<th>Representative treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign paroxysmal position</td>
<td>Labyrinth dysfunction</td>
<td>Head repositioning procedures</td>
</tr>
<tr>
<td>Benign positional vertigo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breath-holding spells</td>
<td>Vasovagal</td>
<td>Reduce precipitant, reassurance</td>
</tr>
<tr>
<td>Migraine</td>
<td>Spreading cortical depression, neurogenic inflammation</td>
<td>Serotonin receptor agonists</td>
</tr>
<tr>
<td>Paroxysmal movement disorders</td>
<td>Multiple types and genetic basis; most are channelopathies</td>
<td>AEDs (e.g., carbamazepine)</td>
</tr>
<tr>
<td>Psychogenic seizure</td>
<td>Unknown; unresolved psychological conflicts</td>
<td>Counseling, behavior therapy</td>
</tr>
<tr>
<td>Sleep disorders</td>
<td>Multiple defects in regulation of arousal</td>
<td>Depends on type: e.g., reassurance for night terrors, arousal-promoting drugs for narcolepsy</td>
</tr>
<tr>
<td>Syncope</td>
<td>Vasovagal</td>
<td>Avoidance of triggers</td>
</tr>
<tr>
<td>Tics</td>
<td>Basal ganglia dysfunction</td>
<td>Dopamine receptor blockade</td>
</tr>
</tbody>
</table>

AED, antiepileptic drug.

CAUTION!

Epileptic seizures and seizure mimics can occur in the same patient, making their differentiation particularly challenging.

TIPS AND TRICKS

The best practice is to use a single agent (monotherapy) to avoid side effects due to multiple AEDs. If it is necessary to treat a patient with more than one AED, drugs with differing mechanisms of action should be chosen to minimize adverse effects and drug–drug interactions.

Two examples illustrate how knowledge of pathophysiological principles informs clinical practice. In neonates, there is a reversed chloride ion gradient across the neuronal membrane, such that binding of the neurotransmitter GABA to its receptor may paradoxically cause excitation rather than inhibition, as occurs in the mature brain. Thus, the clinical consequence of treating neonatal seizures with GABAergic agents (phenobarbital, benzodiazepines) might be to exacerbate seizures, due to increased excitation rather than inhibition. Alternative treatments for neonatal seizures are not yet validated, though bumetanide, a diuretic that speeds up the maturation of GABAergic inhibition, is undergoing clinical trials.

The second example is Dravet syndrome (DS), previously called severe myoclonic epilepsy of infancy. In DS, mutation of sodium channels results
in impaired closure of sodium channel gates and increased neuronal firing. In this disorder, agents that further block sodium channels are best avoided, and in fact, lamotrigine can worsen seizures in children with DS. Many other examples are likely to emerge whereby understanding the underlying epilepsy pathophysiology and pharmacological mechanisms of action will directly impact patient care. In addition, as more epilepsies yield to molecular genetic elucidation, the application of patient-specific pharmacogenetic profiles may guide therapy.

**Conclusion**

This book provides a practical approach to the diagnosis and management of seizures and epilepsy. The principles outlined in this introductory chapter stress the importance of understanding the pathophysiology of seizure generation for optimal management. Details can be found in the references, and many of the concepts introduced here are expanded on in subsequent chapters.

**Bibliography**


**Table 1.3. Mechanisms of commonly prescribed antiepileptic drugs (see also Chapter 19).**

<table>
<thead>
<tr>
<th>AED</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>Activates GABA&lt;sub&gt;A&lt;/sub&gt; receptors</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Blocks Na channels</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Blocks Na channels</td>
</tr>
<tr>
<td>Valproate</td>
<td>Multiple - enhances GABA action, blocks Na and Ca channels</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Blocks T-type Ca channels</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Activate GABA&lt;sub&gt;B&lt;/sub&gt; receptors</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Modulates synaptic vesicle protein SV2A</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Multiple - blocks AMPA-type glutamate receptors and Na channels, enhances GABA action</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Inhibits GABA transaminase</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Multiple - blocks Na and Ca channels, alters neurotransmitter transport</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Blocks Na channels</td>
</tr>
</tbody>
</table>

AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; Ca, calcium; GABA, gamma-aminobutyric acid; Na, sodium; SV, synaptic vesicle.


Classifying Epileptic Seizures and the Epilepsies

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Introduction
The first classification of epileptic seizures was proposed by Henri Gastaut in 1964, with modifications by the Commission on Classification and Terminology of The International League Against Epilepsy (ILAE) in 1981 and 1989. The original purpose of classifying seizures and epilepsy, as stated by Engel, was to “provide a universal vocabulary that not only facilitated communication among clinicians, but also established a taxonomic foundation for performing quantitative clinical and basic research on epilepsy.” The classification was based on expert opinion of the electroclinical features of seizures. Gastaut and colleagues recognized the imperfection of their system due to limited knowledge of the underlying pathophysiology of epilepsy. With advances in neuroimaging, neurophysiology, genetics, and neuroimmunology, classification needed to evolve further.

The International League Against Epilepsy (ILAE) organization of the epilepsies in 2010 was a major update of terminology to incorporate scientific advances. The term organization, rather than classification, was proposed, as the new term enables epilepsies to be organized by different parameters such as seizure type, age at onset, electroencephalogram (EEG), or neuroimaging. This new system, with its limitations, is “a work in progress” that will continue to develop as knowledge of the underlying pathophysiology and etiologies of epilepsies evolves.

Generalized and focal seizures
In all classification schemes, the distinction between focal and generalized seizures is critical, since this distinction determines possible etiologies (Chapter 3) and choice of medical and surgical treatments (Chapters 11 and 27). In the updated nomenclature (2010), generalized seizures (Chapter 24) originate at some point within and rapidly engage bilaterally distributed networks. Such networks can include cortical and subcortical structures but do not necessarily involve the entire cortex. Although individual seizure onsets can appear localized, the location and lateralization are not consistent from one seizure to another. Generalized seizures can be asymmetric.

The subtypes are summarized in Table 2.1, with the main changes from the 1981 classification being the addition of subtypes of absence and myoclonic seizures. Focal seizures originate “at some point within networks limited to one hemisphere. Focal seizures may originate within subcortical structures.” Focal seizures may be classified as focal without...
impairment of consciousness (clonic, autonomic, and hemiconvulsive), focal with subjective sensory or psychic phenomena (aura specific), focal dyscognitive with impairment of consciousness, and focal evolving to a bilateral convulsive seizure.

The terms simple partial, complex partial, and partial seizures with secondary generalization have been embedded in the epilepsy lexicon for decades. There is considerable resistance to letting go of these terms. However, simple (without alteration of awareness) and complex (with altered awareness) are often used incorrectly. Complex partial has been replaced by the term focal dyscognitive, describing seizures with disturbed cognition as the prominent feature. The term secondarily generalized seizure is replaced by focal seizure evolving to a bilateral convulsive seizure.

Neonatal seizures (Chapter 20) are no longer regarded as a separate entity. Seizures in neonates can be classified within the new scheme.

Epileptic spasms (Chapter 21) were not acknowledged in the 1981 classification. Epileptic spasms is preferred to infantile spasms because they may continue or begin after the first year of life. Because there is insufficient knowledge to classify these seizures as focal, generalized, or both, they have been placed in their own group, unknown. In some patients, there is evidence that epileptic spasms can arise from surgically treatable focal brain lesions.

### Generalized and focal epilepsies

Many patients can be classified as having focal or generalized epilepsy based on clinical features (Chapter 5), EEG (Chapter 7), and MRI (Chapter 8). Generalized epilepsies are associated with generalized spike wave discharges on EEG while focal epilepsies are associated with focal slowing or epileptiform discharges and sometimes focal structural abnormalities (Chapters 7 and 24).

However, some patients do not fit exactly into the generalized or focal epilepsy categories and instead have features of both. Children with Dravet syndrome are an example.

### Electroclinical syndromes or epilepsy syndromes

The classification of epilepsy syndromes has great usefulness in clinical practice, as it guides the choice of antiepileptic drugs (Chapter 11) and other treatments. There are no major differences in the classification of epilepsy syndromes between the 2010 nomenclature and the earlier system of 1989 except that several new epilepsy syndromes have been added. These include the very common febrile seizures plus, autosomal dominant frontal lobe epilepsy, and autosomal dominant temporal lobe epilepsy with auditory features due to mutations in the leucine-rich, glioma-inactivated 1 (LGI1) gene.
Table 2.2 presents a partial list of epilepsy syndromes categorized by age at onset. A particular epilepsy syndrome may have a number of possible causes, as exemplified by West syndrome (epileptic spasms and hypsarrhythmia), which may be due to brain malformations, brain injury due to hypoxic-ischemic encephalopathy, infection, hypoglycemia, neurocutaneous disorders, or gene defects (Chapter 3).

Electroclinical syndromes include a range of epileptic encephalopathies (Chapter 21), which begin early in life and are characterized by generalized and/or focal seizures or epileptic spasms, persistent severe EEG abnormalities, and cognitive dysfunction or decline (Table 2.3). The term epileptic encephalopathy refers to the concept that the epileptic activity itself contributes to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone. It is important to identify patients with epileptic encephalopathy because early effective intervention may improve seizure control and developmental outcome in some cases.

Idiopathic focal epilepsies comprise a group of syndromes characterized by focal onset seizures, no detectable brain lesion, and a characteristic EEG signature. These syndromes (Chapter 21) include

Table 2.2. Electroclinical syndromes arranged by age at onset and related conditions.

<table>
<thead>
<tr>
<th>Neonatal period and infancy</th>
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</thead>
<tbody>
<tr>
<td>Benign familial neonatal epilepsy (BFNE)</td>
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<tr>
<td>Early myoclonic encephalopathy (EME)</td>
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<tr>
<td>Ohtahara syndrome</td>
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<table>
<thead>
<tr>
<th>Infancy</th>
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<tbody>
<tr>
<td>Epilepsy of infancy with migrating focal seizures</td>
</tr>
<tr>
<td>West syndrome</td>
</tr>
<tr>
<td>Myoclonic epilepsy in infancy (MEI)</td>
</tr>
<tr>
<td>Benign infantile epilepsy</td>
</tr>
<tr>
<td>Benign familial infantile epilepsy</td>
</tr>
<tr>
<td>Dravet syndrome</td>
</tr>
<tr>
<td>Myoclonic encephalopathy in nonprogressive disorders</td>
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<table>
<thead>
<tr>
<th>Childhood</th>
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<tbody>
<tr>
<td>Febrile seizures plus (FS+)</td>
</tr>
<tr>
<td>Panayiotopoulos syndrome</td>
</tr>
<tr>
<td>Epilepsy with myoclonic-atonic (previously astatic) seizures</td>
</tr>
<tr>
<td>Benign epilepsy of childhood with centrotemporal spikes (BECTS)</td>
</tr>
<tr>
<td>Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)</td>
</tr>
<tr>
<td>Late-onset childhood occipital epilepsy (Gastaut type)</td>
</tr>
<tr>
<td>Epilepsy with myoclonic absences</td>
</tr>
<tr>
<td>Lennox–Gastaut syndrome</td>
</tr>
<tr>
<td>Epileptic encephalopathy with continuous spikes and waves during slow sleep (CSWS)</td>
</tr>
<tr>
<td>Landau-Kleffner syndrome (LKS)</td>
</tr>
<tr>
<td>Childhood absence epilepsy (CAE)</td>
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<table>
<thead>
<tr>
<th>Adolescence and adulthood</th>
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<tbody>
<tr>
<td>Juvenile absence epilepsy (JAE)</td>
</tr>
<tr>
<td>Juvenile myoclonic epilepsy (JME)</td>
</tr>
<tr>
<td>Epilepsy with generalized tonic–clonic seizures alone</td>
</tr>
<tr>
<td>Progressive myoclonic epilepsies (PME)</td>
</tr>
<tr>
<td>Autosomal dominant epilepsy with auditory features (ADEAF)</td>
</tr>
<tr>
<td>Other familial temporal lobe epilepsies</td>
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</table>

<table>
<thead>
<tr>
<th>Less specific age relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial focal epilepsy with variable foci (childhood to adult)</td>
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<tr>
<td>Reflex epilepsies</td>
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Table 2.3. Age-related epileptic encephalopathies.

<table>
<thead>
<tr>
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<tr>
<th>Childhood</th>
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<tr>
<td>Epileptic encephalopathy with continuous spikes and waves during slow sleep (CSWS)</td>
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<tr>
<td>Myoclonic-atonic epilepsy</td>
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<tr>
<th>Other severe epileptic encephalopathies</th>
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</thead>
<tbody>
<tr>
<td>Rasmussen's syndrome</td>
</tr>
<tr>
<td>Fever-induced refractory epileptic encephalopathy</td>
</tr>
<tr>
<td>Hemiconvulsion-hemiplegia epilepsy syndrome</td>
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