Epilepsy in childhood presents a profound challenge

Epilepsy is an unsettling, complex condition. There is no “one size fits all” option. For effective treatment a full understanding of each patient’s situation and clinical history is needed. Recent remarkable improvements in our ability to image brain structures, to define physiological patterns and in treatment options has made the task of care of the child with epilepsy potentially more effective.

Epilepsy in Children and Adolescents provides the contemporary, caring guidance you need to diagnose and manage seizures in a young patient. Beginning with an overview of the classification of epilepsy syndromes, the experienced authors cover:

- Diagnostic evaluation of childhood epilepsies
- Principles of treatment
- Generalized seizures and generalized epilepsy syndromes
- Partial onset seizures and localization-related epilepsy syndromes
- Epilepsies relative to age, etiology or duration
- The full range of treatment options: medical, dietary, surgical

Epilepsy in Children and Adolescents takes a practical approach to a common but complex clinical challenge.
Epilepsy in Children and Adolescents
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## 2 Classification and definition of seizures and epilepsy syndromes in childhood

*Susan E. Combs and Phillip L. Pearl*

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## 3 Initiating and withdrawing medical management

*David T. Hsieh and Bhagwan Indur Moorjani*

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*Dewi Frances T. Depositario-Cabacar, William McClintock, and Tom Reehal*

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Of all the neurological disorders that affect infants, children, and adolescents, epilepsy is a profound challenge for the patients, caregivers, and physicians and demands expertise to evaluate and treat. As with every illness, gathering a clinical history is an important first step in helping define the problem. However, remarkable improvements in our ability to image brain structures, define physiological patterns, and select medications has made the task of caring for the child with epilepsy more effective than in past years. I envision this book to be a resource for all physicians and other professionals taking care of children with seizures or epilepsy. The goal was for each chapter to be succinct, so a physician confronted with a child who has seizures would have an efficient resource for answering questions and designing treatment. I thank the authors for their focus and persistence. I am ever mindful of the patients and their families who bear the challenge of epilepsy with courage. I have learned from them and am keenly aware of our responsibility to do the very best for their care.

James W. Wheless  
Memphis, TN, USA  
June, 2012
Epilepsy is a common illness in childhood, and the epidemiology has been well described. However, epilepsy is also complex and controversial in terms of optimal methods for diagnosis and treatment. Classification schemes for seizures have been refined over the years and improved treatment options have allowed better outcomes for children with epilepsy. Understanding of comorbidity, particularly psychiatric comorbidity, has also improved over recent years, yet in many cases it is difficult to resolve whether psychiatric illness is coincidental or associated with the underlying seizure disorder. This chapter addresses the incidence and prevalence of childhood epilepsy and strategies for identifying and managing common psychiatric comorbidities.

1.1 Epidemiology

An epileptic seizure is defined as the clinical manifestation of abnormal or excessive discharge of neurons in the brain [1]. Epilepsy is defined as recurrent seizures, specifically two or more seizures separated by 24 hours but within 18 months of one another [1,2]. This common consensus is based on observations that children who experience one seizure have
an approximately 50% chance of recurrence within 2 years [3,4]. It is important to note
that febrile seizures are not included in most epidemiological studies of epilepsy.

Population-based studies concerning seizures and epilepsy have been done in numerous
communities around the world. Although many international studies of prevalence are
based on small communities, the results can be extrapolated to reflect wider regions of
the world. In the United States, there are approximately 2.3 million people diagnosed
with epilepsy, which reflects an incidence of approximately 1% of the population [5]. The
pediatric population, however, has a higher prevalence of epilepsy; 4–10% of children
will experience a seizure before the age of 16. Thus, a working knowledge of epilepsy is
very important for primary and specialty clinicians in pediatrics, as well as for pediatric
neurologists [6].

### Terminology review

**Incidence**: The rate at which new cases of disease occur in a population during a
given period of time.

**Prevalence**: The proportion of a population who have a disease during a given time
period.

### 1.2 Incidence and prevalence

In the general population, the incidence of epilepsy is reported at between 40 and 70 cases
per 100,000 [7]. The incidence of childhood epilepsy has been reported to be 82.2 per
100,000 children, markedly higher than that of the overall population [8]. A meta-analysis
of over 40 epidemiological studies found that the highest incidence of epilepsy occurs
in childhood and in the geriatric population. Interestingly, the incidence of epilepsy has
been decreasing over the past 50 years. This decrease in incidence could be explained by
more stringent and/or universally followed diagnostic criteria or perhaps from a decrease
in exposure to epilepsy risk factors [8].

The overall number of children affected by epilepsy, or the prevalence of the disease, is
higher than the incidence because of the chronic nature of epilepsy. A significant variation
in prevalence is found in international epidemiology studies [9–12]. In the United States,
epilepsy prevalence averages 3.83 per 1000 children, while in northern Tanzania, it is
7.39 per 1000 [13,14]. This discrepancy may result from a variety of factors including
possible misclassification of a single seizure as epilepsy. Environmental factors, access to
healthcare, and different methods of reporting may also account for some of the variability.
The prevalence of epilepsy in varying regions across the world is described in Table 1.1.

### 1.3 Gender and age

Studies have consistently found that males are diagnosed with epilepsy more often than
females [18]. While the difference between the genders is slight, this trend holds true for
most populations [13]. Although there are exceptions to this trend, they are rarely statisti-
cally significant in children [10,11]. Analysis of prevalence among children of varying ages
found that epilepsy was most common in children under the age of 5, with a gradual decline
Table 1.1 International epidemiology studies.

<table>
<thead>
<tr>
<th>Location</th>
<th>Years of study</th>
<th>Epilepsy prevalence</th>
<th>Age range</th>
<th>Limits/comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okayama Prefecture, Japan [9]</td>
<td>1999</td>
<td>5.3 per 1000</td>
<td>0–12 years</td>
<td>Removed data resulting from only one seizure</td>
</tr>
<tr>
<td>Kayenta, Shiprock, and Crowpoint Reservations, Navajo Nation, USA [10]</td>
<td>1999–2002</td>
<td>6.46 per 1000</td>
<td>0–19 years</td>
<td>Only those who went to hospital; excluded those who used tribal medicine</td>
</tr>
<tr>
<td>Hordaland count, western Norway [12]</td>
<td>1995</td>
<td>5.13 per 1000</td>
<td>6–12 years</td>
<td>Small sample area, limited age range</td>
</tr>
<tr>
<td>Northern Tanzania (14)</td>
<td>2003–2004</td>
<td>7.39 per 1000</td>
<td>0–19 years</td>
<td>Only villages polled around centralized hospital location</td>
</tr>
<tr>
<td>Estonia [15,16]</td>
<td>1995–1997</td>
<td>3.7 per 1000</td>
<td>0–19 years</td>
<td>Much of data came from one hospital, University of Tartu</td>
</tr>
<tr>
<td>Canada [17]</td>
<td>1994–2001</td>
<td>2.5 per 1000</td>
<td>0–11 years</td>
<td>Utilized national census data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.4 per 1000</td>
<td>12–14 years</td>
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in occurrence in older age groups [15]. Figure 1.1 demonstrates the peak of prevalence at a young age and a gradual decrease in children as they age.

1.4 Classification

When studying the epidemiology of epilepsy, means of classification must be clarified to ensure uniformity in standards. Since 1909, the International League Against Epilepsy

![Graph showing prevalence of epilepsy (per 1000) in children by year from age 1 to 19 [16].](image)
PARTIAL ABSENCE
JAN 1, 1940 JAN 1, 1950 JAN 1, 1960
CENSUS DATE
JAN 1, 1970 JAN 1, 1980
SEIZURE TYPE
PREVALENCE/1000
MYOCLONIC GEN TONIC-CLONIC
OTHER
AGE ADJUSTED 1980 US POPULATION

Figure 1.2  Bar graph of relative prevalence of adolescent seizure etiologies (per 1000) [13].

(ILAE) has worked toward identifying, studying, and classifying all variations of seizure disorders. Epilepsy syndromes can be classified as localization-related or generalized. The syndromes are determined by multiple criteria, with particular emphasis on seizure type as well as associated patient characteristics such as age of onset, comorbidities including neurodevelopmental status, presence of associated family history, and identification of an underlying etiology [1]. Distinguishing characteristics of seizure types can range from loss or modification of consciousness and responsiveness, along with total or partial motor control impairment [2].

A 40-year detailed study done in Rochester, Minnesota, found that partial seizures are the most prevalent, followed by generalized tonic-clonic, absence, and then myoclonic. Details for prevalence are represented in Figure 1.2 [13].

1.5 Febrile seizures

Febrile seizures are a common seizure disorder for children under the age of 3 years. Between 2% and 4% of children will suffer from one febrile seizure, and only one-third of these children will have a second seizure [18]. Most importantly, a febrile seizure will not always lead to epilepsy. Between 2% and 10% of children who experience one febrile seizure will develop epilepsy [19].

1.6 Etiology

Most cases of epilepsy are of unknown etiology [12]. Recent guidelines have identified three main classifications of epilepsy etiologies: Genetic, metabolic/structural, and idiopathic/unknown [2]. Genetic disorders include diseases due to a known genetic defect in which seizures are the main manifestation of the disease. Seizures of metabolic/structural etiology can be those epilepsies attributed to lesions, which are often a result of head trauma, central nervous system (CNS) infection, or tumor [4]. Epilepsy of unknown etiology represents the most common designation for epilepsy in childhood.
1.7 Psychiatric comorbidity

Psychiatric and psychological complications are commonly associated with pediatric epilepsy [20–23]. In pediatrics, the classic Isle of Wight epidemiology study reports psychiatric illness present in 16% of patients with chronic medical illness; however, if that illness happened to be epilepsy, the psychiatric comorbidity was 29% [24]. Subsequent studies have confirmed an overrepresentation of psychiatric illness associated with epilepsy as compared to many other chronic medical illnesses. Some studies report a two- or three-fold greater prevalence of psychiatric illness associated with epilepsy as compared to diabetes or asthma [25,26]. Of particular concern is evidence showing an overrepresentation of epilepsy among children and adolescents hospitalized for suicide attempts [27]. Despite numerous reports confirming high levels of comorbidity, many children and adolescents with epilepsy do not receive treatment for psychiatric illness [28]. In many cases, the psychiatric comorbidity may be more impairing to quality of life for children and families than the seizures themselves [29].

This consistently high level of psychiatric comorbidity suggests that epilepsy is a complicated illness that may have neuropsychiatric symptoms well beyond discrete seizures. However, the etiology of psychiatric comorbidity in children and adolescents with epilepsy is still controversial. Psychiatric illness may be difficult to isolate as an independent disorder in the context of seizure events. Some symptoms may be clearly related to ictal or postictal phenomena, but more often, psychiatric symptoms occur during interictal time periods and may be viewed as only indirectly related to epilepsy pathophysiology [30]. Classic views of forced normalization, in which psychiatric symptoms increase when the epilepsy stabilizes (the EEG “normalizes”), complicate conceptualization of comorbidity in relation to epilepsy pathophysiology [31]. Nevertheless, the frequent occurrence of psychiatric disorder has raised awareness of the need for an interdisciplinary approach to management of epilepsy [32,33]. The existing literature tends to focus upon one of three potential explanations for psychiatric comorbidity: symptoms related to psychosocial stress of chronic disease; symptoms related to medication side effects; and symptoms directly related to epilepsy pathophysiology.

1.8 Psychological and psychosocial stress related to chronic disease

Studies of health-related quality of life consistently report marked psychosocial stress for children and families [34]. Because seizures may involve sudden loss of consciousness and social embarrassment, epilepsy may be expected to carry a higher level of psychosocial sequelae. The disruption to the quality of life may be significant, as is the potential stigmatization of the child suffering publicly witnessed seizures [35]. Social difficulties are commonly reported among children with epilepsy, and lifestyle changes may occur among families, including limitations on activities and hindered development of social independence for the child facing the risk of spontaneous seizures [36]. Classroom teachers have reported discomfort in having a child with epilepsy in the classroom and favored increased restrictions upon the child’s activity [37]. Children with epilepsy have been noted to have lower self-esteem, often associated with a negative attitude toward illness and a lack of a sense of control [38].
Although social stigma and stress related to chronic epilepsy are significant, many groups do not consider that these issues sufficiently account for the marked overrepresentation of psychiatric illness associated with epilepsy. One body of literature that is well developed is the study of “new-onset” epilepsy. By assessing patients early in their treatment course, the impact of psychosocial stress or treatment side effects leading to psychiatric dysfunction would be minimized. Psychiatric illness identified at “baseline” may be plausibly considered to result from underlying neurological disease rather than from the stress or stigma of chronic epilepsy. Well-designed studies with sibling controls identify high levels of anxiety and depression very early in the course of epilepsy [39]. Such anxiety and mood disorder cannot be attributed to a reactive depression resulting from the stress of chronic disease.

1.9 Psychiatric symptoms related to medication side effects

Studies of psychiatric side effects resulting from antiepileptic medication treatment are common, although few focus upon the pediatric population [40]. Although psychiatric and behavioral problems may potentially be associated with any medicine, the risk with some medicines has been more commonly reported. Phenobarbital has been well known to increase the possibility of depression, irritability, and disinhibition [41–43]. Irritability has also been associated with levetiracetam [44]. Impairments in short-term memory, verbal fluency, and cognitive processing speed have been reported with topiramate [45]. However, it should be noted that antiepileptic drugs are commonly used as primary treatments for psychiatric illness; many psychiatric symptoms may be improved by judicious selection of antiepileptic drugs. In some cases, psychiatric symptoms and seizures may be improved simultaneously by the same anticonvulsant medicine [46]. Behavioral symptoms may be misattributed as a side effect instead of representing a comorbid psychiatric illness that would be an appropriate target of anticonvulsant medicine.

Despite the association of some anticonvulsants with psychiatric symptoms, medication side effects may not account for the broad spectrum of psychiatric comorbidity present in children and adolescents with epilepsy. Recent studies in the new-onset population confirm that internalizing behavior problems such as depression or anxiety are commonly found prior to the start of antiepileptic treatment [47].

1.10 Psychiatric comorbidity related to epilepsy pathophysiology

Over the past decade, a paradigm shift has occurred such that epilepsy pathophysiology is considered to play a direct role in comorbid psychiatric illness. Many researchers and clinicians now consider that the impaired neural function related to epilepsy pathophysiology may directly cause behavioral and cognitive difficulties. In this sense, a structural lesion or seizure focus may concurrently cause epilepsy and psychiatric symptoms. It is possible that a transactional process occurs between psychiatric illness and epilepsy, in that one condition may aggravate or even precede exacerbations of the other [48]. Improved characterization of seizures has fueled speculation that specific seizure types or localizations in the brain may present higher risks of psychological or psychiatric complications. Although psychiatric comorbidity is understudied and conclusions are difficult to make given varying
methodology, some specific childhood psychiatric disorders have emerged as particularly associated with epilepsy (Table 1.2).

### Table 1.2 Common psychiatric comorbidities with epilepsy and their associated prevalence.

<table>
<thead>
<tr>
<th>Psychiatric comorbidity</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention-deficit/hyperactivity disorder (ADHD)</td>
<td>20–38% [50,51]</td>
</tr>
<tr>
<td>Anxiety</td>
<td>20–33% [59,60]</td>
</tr>
<tr>
<td>Depression</td>
<td>26–33% [60,61]</td>
</tr>
<tr>
<td>Intellectual and developmental disability (IDD)</td>
<td>10–33% [70,71]</td>
</tr>
</tbody>
</table>

#### 1.11 Attention-deficit/hyperactivity disorder (ADHD)

Attention-deficit/hyperactivity disorder is the most common psychiatric comorbidity associated with pediatric epilepsy; the prevalence ranges from 20% to 38% depending upon assessment methods and samples [49,50]. ADHD is described in terms of subtypes: primarily inattentive, primarily hyperactive or impulsive, and combined type. Symptoms of absence epilepsy may appear similar to ADHD-primarily inattentive subtype, and the latter is a common differential diagnosis for pediatric epileptologists [51]. One recent report suggests a bidirectional relationship such that ADHD increases risk for seizures and that more patients with epilepsy have ADHD [52]. A sizeable literature suggests that EEG spikes are found in children with ADHD though it is unclear whether they go on to develop frank epilepsy [53,54].

#### Case 1

M is an 8-year-old female who presents to her pediatrician after a referral from school. Despite seeming to be bright and capable, teachers note that she is frequently “off task” and inattentive. She occasionally has trouble organizing material and remembering to turn in completed worksheets. Several times a day, she does not respond when teachers call her name and ask her a question, though with prompting she will acknowledge the teacher. She is below grade level on academics despite coming from a highly educated family. She is described as a quiet child who is well-behaved and friendly, but at times seems distant and even confused. One incident was noted by a playground attendant when M stood motionless, almost “frozen” for about 10 seconds when it was time to line up to go back into the classroom. She is successful with many outside activities, including soccer, and she enjoys playing complex, strategy-based computer games. Physical exam was unremarkable.

#### Comment

The case of M illustrates the sometimes difficult differential diagnosis of absence epilepsy and ADHD-inattentive subtype. Sometimes absence seizures may appear as periods of
inattention and are considered to be symptomatic of ADHD. ADHD is characterized by the presence of impairing symptoms in multiple settings, which often having academic and social sequelae. Careful history-taking will correctly place more emphasis upon the playground incident as evidence of disruption of consciousness. M also has interests and periods of intact functioning not characteristic of a child who is chronically inattentive. The astute pediatrician consulted a pediatric neurologist, who ordered an EEG that revealed generalized spike and wave discharges at a rate of 3 per second, consistent with absence epilepsy.

Case 2

J is a 7-year-old male with a 2-year history of partial complex seizures who presents to his pediatric neurologist with a chief complaint of disruptive behavior. He has been seizure free for 8 months on a stable dose of lamotrigine. J is described as always “on the go” from preschool age, and is unable to stay in any one place, including the dinner table, for more than 5 minutes. He will often get up out of his seat in school, and will disturb other students by talking to them or going to their desks while they are trying to complete their assignments. He has performed poorly in school because of not finishing assignments and losing textbooks and materials necessary for class. He is below grade level despite his teachers believing that he is very smart when he is focused. Two separate teachers completed an ADHD rating scale, which was overwhelmingly positive for hyperactivity, impulsivity, and inattention. He is forgetful and does not seem to listen when spoken to directly. His parents report that he is very hyperactive – much more than his two older brothers were at his age. They report trying behavioral strategies and counseling to no avail. Now they are exhausted and need help. Physical and neurological examination is unremarkable.

Comment

The case of J illustrates a typical case of comorbid epilepsy and ADHD. Confidence in the diagnosis of ADHD is paramount to treatment planning, and clinicians should seek corroborating information from several sources. Historically, clinicians have been hesitant to use stimulant medication in children with epilepsy for fear of exacerbating seizures. However, several recent studies report that stimulants are well tolerated and effective for patients with stable epilepsy, defined as less than one seizure per month [55–57]. Given that alternative management strategies have been attempted without success, J was given sustained-release methylphenidate, and within 2 weeks showed marked improvement in attention span and impulse control. The parents are grateful.

1.12 Anxiety

Anxiety is a common feature in pediatric epilepsy. Anticipatory anxiety regarding possible seizure events is often present to some extent though it may not rise to the level of a formal psychiatric illness. Social anxiety symptoms such as isolation and fear of being in public places are often noted. Anxiety is also notable as an experiential phenomenon in patients