Section 1

Epidemiology and classification of childhood epilepsies

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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 statistically 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>
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<tr>
<td></td>
<td></td>
<td>4.4 per 1000</td>
<td>12–14 years</td>
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</table>

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
(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
### 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

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

<table>
<thead>
<tr>
<th>Psychiatric comorbidity</th>
<th>Prevalence</th>
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<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>

Methodology, some specific childhood psychiatric disorders have emerged as particularly associated with epilepsy (Table 1.2).
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...
with temporal lobe seizure foci, especially amygdalar foci. Sensations of fear or anxiety may occur in the context of a seizure aura or throughout the ictal period. Several studies note anxiety disorder prevalence ranging from 20% to 33% by using either structured psychiatric interviews or validated rating scales [58,59].

Case 3
D is 13-year-old female with a history of complex partial seizures and secondary generalization. She has a 5-year history of epilepsy, and has had three seizures over the past 6 months, usually in the context of a viral illness. She has been stable with levetiracetam. She had a generalized seizure in school approximately 6 weeks ago in Physical Education class, and was brought to the emergency room. Her parents have brought her to the pediatric neurologist because since that time she complains of feeling dizzy. She had to come home from school twice last week because of the dizzy feeling. The dizziness does not occur at home or when she visits her grandmother’s house. Physical examination is unremarkable, as is the MRI scan, EKG, and chemical and hematological studies. The parents are worried that this is a medication side effect, and want to switch medications.

Comment
After the neurologist is satisfied that the medical and neurological status is at baseline, consideration of a psychiatric or psychological stressor should occur. Publicly witnessed seizures are stressful for adolescents and may have long-lasting impact upon social function. The neurologist referred D to a clinical social worker for psychotherapy. Within several weeks, the social worker helped her process her anxiety regarding having recurrent seizures, and the dizziness resolved. Treatment focus included helping her discuss epilepsy with close friends. The neurologist provided educational materials to the school nurse, who provides periodic check-ins with the patient during the school day.

1.13 Depression
Depression is a particularly worrisome comorbidity of pediatric epilepsy. Pediatric studies are uncommon, but recent reports found a prevalence of depression ranging from 26% to 33% [58,60]. Suicidal ideation has been reported to be several-fold higher than in patients without epilepsy [61]. Suicide has been reported as responsible for 10% of deaths in adults with epilepsy as compared to 1% in the general population [62]. A recent report suggests that seizures with a temporal lobe focus may lead to a higher risk for depression [63]. Recent precautions from the US Food and Drug Administration (FDA) have raised concern about antiepileptic drugs as a class leading to increased risk of suicidal thoughts and behaviors. However, this risk has not been isolated independent of comorbidity of depression [64,65]. Clinicians are well advised to screen for depression in children and adolescents with epilepsy.
Case 4

R is a 15-year-old male with a history of complex partial seizures with a left temporal lobe focus since age 9. He presents to his pediatric neurologist for a routine follow-up visit. He has been taking topiramate for 3 years with fair result, although he has seizures approximately every 3 months. Over the past 6 months, his parents have noted a significant departure from his usual function. He has lost interest in seeing his friends or participating in organized youth group activities. He often skips meals, and says he just does not feel hungry. His academic performance has worsened and he often skips assignments. He has an unhappy expression on his face, and usually goes to his room and sleeps, often going to bed at 7 pm. A week ago, he told his parents that he had no reason to live. The parents are concerned that this is a medication side effect.

Comment

Depression may have an insidious onset, and often builds very gradually. Some reports state that seizure focus in the temporal lobe yields a higher risk for depression, but results are inconsistent, and pediatric studies are uncommon [66–68]. R demonstrates worrisome symptoms, particularly given his hopelessness and thoughts of death. He is promptly referred to a pediatric psychiatrist, who initiates treatment with fluoxetine. After a few weeks he has more energy and is more engaged socially and academically.

1.14 Intellectual and developmental disabilities (IDD)

The presence of epilepsy in children with IDD ranges from 10% to 30% depending on how the diagnosis of autism is made. Some groups report that complex partial seizures and temporal lobe EEG abnormalities may be particularly common with autism [69,70]. There are some cases of improved behavior and cognition in autistic children treated with antiepileptic drugs [71,72].

1.15 Conclusion

Epilepsy is a complex medical condition that has a high prevalence in pediatrics. Psychiatric comorbidity is very common and in some cases may be more debilitating than the seizure disorder itself. The etiology of psychiatric comorbidity is still difficult to resolve, but interdisciplinary management from both neurology and psychiatry is well indicated for many patients with epilepsy and psychiatric comorbidity. Although the evidence base is limited regarding treatment for the most common comorbidities of ADHD, depression, anxiety, and IDD, strategies are similar to those utilized for patients without epilepsy. Future studies will improve understanding of the relationship between psychiatric illness and specific epilepsy types. Ultimately, treatment outcome studies are needed in order to minimize morbidity related to psychiatric illness and to maximize quality of life for children and adolescents with epilepsy.
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EPIDEMIOLOGY AND COMMON COMORBIDITIES OF EPILEPSY IN CHILDHOOD


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