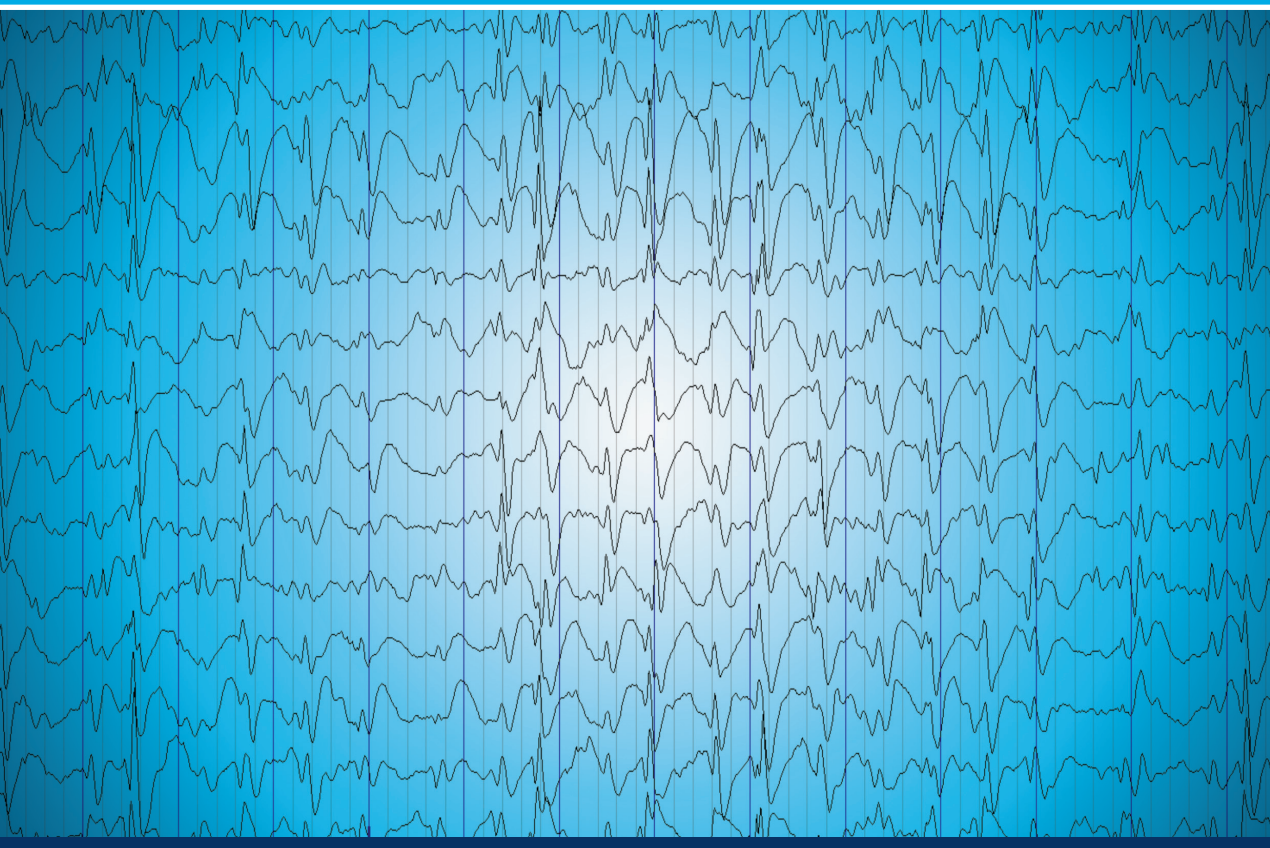
Epilepsy in Children and Adolescents

EDITED BY

James W. Wheless

David F. Clarke, Amy L. McGregor, Phillip L. Pearl and Yu-Tze Ng



WILEY-BLACKWELL

Epilepsy in Children and Adolescents

Epilepsy in Children and Adolescents

Edited by
James W. Wheless, MD
Department of Pediatric Neurology
University of Tennessee Health Science Center
Le Bonheur Comprehensive Epilepsy
Program and Neuroscience Institute
Le Bonheur Children's Hospital
Memphis, TN, USA

WILEY-BLACKWELL
A John Wiley & Sons, Ltd., Publication

Wiley-Blackwell is an imprint of John Wiley & Sons, formed by the merger of Wiley's global Scientific, Technical and Medical business with Blackwell Publishing.

Registered office: John Wiley & Sons, Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

Editorial offices: 9600 Garsington Road, Oxford, OX4 2DQ, UK
The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

For details of our global editorial offices, for customer services and for information about how to apply for permission to reuse the copyright material in this book please see our website at www.wiley.com/wiley-blackwell.

Library of Congress Cataloging-in-Publication Data

Epilepsy in children and adolescents / [edited by] James W. Wheless.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-0-470-74123-8 (cloth)
I. Wheless, James.
[DNLM: 1. Epilepsy. 2. Adolescent. 3. Anticonvulsants–therapeutic use. 4. Child. 5. Epilepsy–therapy. WL 385]
616.85′300835–dc23

2012024368

A catalogue record for this book is available from the British Library.

Wiley also publishes its books in a variety of electronic formats. Some content that appears in print may not be available in electronic books.

Cover image: 4 year old with Lennox-Gastaut Syndrome, slow spike and wave complexes in sleep, courtesy of Dr James W. Wheless.

Set in 10/12pt Times by Aptara Inc., New Delhi, India

First Impression 2013

Contents

List of contributors **xiii**
Preface **xvii**

Section 1 Epidemiology and classification of childhood epilepsies **1**
Section editor: Phillip L. Pearl

1 Epidemiology and common comorbidities of epilepsy in childhood **3**
Jay Salpekar, Matthew Byrne, and Georgann Ferrone

1.1 Epidemiology 3
1.2 Incidence and prevalence 4
1.3 Gender and age 4
1.4 Classification 5
1.5 Febrile seizures 6
1.6 Etiology 6
1.7 Psychiatric comorbidity 7
1.8 Psychological and psychosocial stress related to chronic disease 7
1.9 Psychiatric symptoms related to medication side effects 8
1.10 Psychiatric comorbidity related to epilepsy pathophysiology 8
1.11 Attention-deficit/hyperactivity disorder (ADHD) 9
1.12 Anxiety 10
1.13 Depression 11
1.14 Intellectual and developmental disabilities (IDD) 12
1.15 Conclusion 12
References 13

2 Classification and definition of seizures and epilepsy syndromes in childhood **17**
Susan E. Combs and Phillip L. Pearl

2.1 Introduction 17
2.2 Purpose and goals of definitions and classification 17
2.3 Systems of classification and definitions 18
2.4 Seizures 18
2.5 Generalized seizures 19
2.6 Focal seizures 22
2.7 Syndromes 23
2.8 Specific age-related epilepsy syndromes 25
2.9 Future directions 34
Acknowledgements 34
References 34

3 Initiating and withdrawing medical management **37**
David T. Hsieh and Bhagwan Indur Moorjani

3.1 Initiating medical management 37
3.2 The chances of seizure recurrence after the first unprovoked seizure 39
3.3 Seizure recurrence 42
3.4 The possible adverse effects of seizure recurrence 42
3.5 The risks of initiating antiepileptic drug therapy 44
3.6 The benefits of initiating antiepileptic drug therapy 45
3.7 How to initiate treatment with antiepileptic drugs 45
3.8 Special circumstances 48
3.9 Summary: initiating medical management 48
3.10 Withdrawing medical management 49
3.11 The long-term prognosis of childhood-onset epilepsy 50
3.12 When to consider discontinuing antiepileptic drug therapy 51
3.13 Risk factors for seizure recurrence after discontinuation 51
3.14 The risks of discontinuing antiepileptic drug therapy 54
3.15 The benefits of discontinuing antiepileptic drug therapy 55
3.16 How to discontinue antiepileptic drugs 55
3.17 Special circumstances 55
3.18 Summary: withdrawing medical management 56
3.19 Disclaimer 57
References 57

4 Common genetic and neurocutaneous disorders in childhood epilepsy **59**
Dewi Frances T. Depositario-Cabacar, William McClintock, and Tom Reehal

4.1 Idiopathic epilepsies 60
4.2 Symptomatic epilepsies 63
4.3 Epilepsy in common chromosomal abnormalities 63

4.4 Epilepsy in metabolic and mitochondrial disorders 65
4.5 Epilepsy in malformations of cortical development 66
4.6 Neurocutaneous disorders 67
4.7 Summary 70
References 70

Section 2 Diagnostic evaluation of childhood epilepsies 73
Section editor: David F. Clarke

5 Evaluating the child with seizures 75
Kristen Park and Susan Koh

5.1 Emergent diagnosis and management 76
5.2 Subsequent evaluation 79
5.3 Additional neurodiagnostic evaluation 84
References 87

6 The use of EEG in the diagnosis of childhood epilepsy 90
David F. Clarke

6.1 Technical aspects of the EEG 91
6.2 Methods used to increase EEG yield 91
6.3 When should an EEG be ordered? 92
6.4 EEG findings in epilepsy and epilepsy syndromes 93
6.5 Neonatal EEGs 94
6.6 The EEG in focal epilepsy 96
6.7 The EEG of generalized epilepsy 99
6.8 Specific disease-related epilepsy syndromes 104
6.9 Conclusion 105
References 105

7 Imaging of pediatric epilepsy 107
Asim F. Choudhri

7.1 Introduction 107
7.2 Imaging considerations 107
7.3 Congenital malformations 117
7.4 Neoplasms 124
7.5 Acquired/idiopathic abnormalities 126
References 127

8 Non-epileptic paroxysmal events of childhood 129
Sucheta M. Joshi

8.1 Introduction 129
8.2 Breath-holding spells 130
8.3 Parasomnias 131

8.4 Benign paroxysmal positional vertigo of childhood 133
8.5 Syncope 134
8.6 Paroxymal non-epileptic events (PNEs) with a psychiatric or behavioral basis 134
8.7 Hyperekplexia 136
8.8 Alternating hemiplegia of childhood 136
8.9 Movement disorders 137
8.10 Sandifer syndrome 138
8.11 Conclusion 138
References 139

Section 3 Principles of treatment 143
Section editor: James W. Wheless

9 Pharmacology of antiepileptic drugs 145
James W. Wheless

9.1 Pharmacokinetics 146
9.2 Pharmacogenomics 155
References 157

10 Therapeutic efficacy of antiepileptic drugs 159
James W. Wheless

10.1 Efficacy-based treatment guidelines 160
10.2 Antiepileptic drug selection based on specific pediatric epilepsy syndromes 164
10.3 Influence of comorbidities in children with epilepsy 171
10.4 Conclusions 172
References 172

11 Adverse effects of antiepileptic drugs 175
James W. Wheless

11.1 Introduction 175
11.2 Specific drugs 179
11.3 At-risk profiles and monitoring 189
References 191

12 Vagus nerve stimulation therapy and epilepsy surgery 193
Kate Van Poppel and James W. Wheless

12.1 Vagus nerve stimulation 195
12.2 Epilepsy surgery 203
12.3 Conclusions 215
References 215

13 Dietary therapies to treat epilepsy **219**
James W. Wheless

13.1 History 220
13.2 Efficacy 221
13.3 Mechanism of action 228
13.4 Selection of candidates for the diet 232
13.5 Initiation and maintenance 234
13.6 Complications 236
13.7 The ketogenic diet in the twenty-first century 239
References 239
Resources 240
Websites 241

Section 4 Generalized seizures and generalized epilepsy syndromes **243**
Section editor: Amy L. McGregor

14 Idiopathic generalized epilepsies **245**
Amy L. McGregor

14.1 Clinical features 246
14.2 Natural history 248
14.3 Genetics 248
14.4 Treatment 248
14.5 Classification 249
14.6 Myoclonic epilepsy in infancy 249
14.7 Childhood absence epilepsy (CAE) 250
14.8 Juvenile absence epilepsy (JAE) 252
14.9 Juvenile myoclonic epilepsy (JME) 254
14.10 Epilepsy with generalized tonic-clonic seizures alone (IGE-GTCs) 256
14.11 Epilepsy with myoclonic absence 257
14.12 Epilepsy with myoclonic-atonic seizures/Doose syndrome 258
14.13 Febrile seizures plus (FS+) 259
14.14 Eyelid myoclonia with absences (EMA)/Jeavons syndrome 260
14.15 Summary 262
References 264

15 Cryptogenic and symptomatic generalized epilepsies: epilepsies with encephalopathy **267**
Karen Keough

15.1 Neonatal-onset epilepsies with encephalopathy 268
15.2 Infantile-onset epilepsies with encephalopathy 270
15.3 Epilepsies with encephalopathy with onset later in infancy 275
15.4 Epilepsies with encephalopathy with onset after infancy 277

15.5 Continuous spike wave of sleep (CSWS) and Landau–Kleffner syndrome (LKS) 279
References 280

Section 5 Partial-onset seizures and localization-related epilepsy syndromes 283
Section editor: James W. Wheless

16 Idiopathic partial epilepsies 285
Freedom F. Perkins Jr

16.1 Benign infantile seizures 286
16.2 Benign childhood epilepsy with centrotemporal spikes 287
16.3 Childhood occipital epilepsy (Panayiotopoulos type) 289
16.4 Late-onset childhood occipital epilepsy (Gastaut type) 292
References 294

17 Cryptogenic and symptomatic partial epilepsies 296
Stephen Fulton

17.1 Etiology 296
17.2 Seizure phenomena 297
17.3 Temporal lobe epilepsy 297
17.4 Extratemporal epilepsy 303
17.5 Occipital lobe epilepsy 306
17.6 Parietal lobe epilepsy 307
17.7 Hypothalamic hamartoma 307
17.8 Other localizing and lateralizing signs 308
References 309

Section 6 Epilepsies relative to age, etiology, or duration 311
Section editor: Yu-Tze Ng

18 Neonatal seizures 313
Eric V. Hastriter

18.1 Significance of neonatal seizures 313
18.2 Pathophysiology of neonatal seizures 314
18.3 Classification and clinical features of neonatal seizures 316
18.4 Electrographic seizures 317
18.5 Monitoring and recording 317
18.6 Etiology of neonatal seizures 321
18.7 Metabolic causes for neonatal seizures 323
18.8 Inborn errors of metabolism 323

18.9 Treatment 327
18.10 Chronic postnatal epilepsy and the need for long-term treatment 328
18.11 Potential adverse effects of antiepileptic drugs on the immature CNS 329
18.12 Conclusion 329
References 330

19 Febrile seizures 333
Marie Francisca Grill

19.1 Introduction 333
19.2 Definition 333
19.3 Incidence and prevalence 334
19.4 Pathophysiology 334
19.5 Prognosis 334
19.6 Initial evaluation and management 335
19.7 Long-term management 338
19.8 Management in practice 341
19.9 Genetics 342
19.10 Parent counseling 343
19.11 Conclusion 344
References 344

20 Status epilepticus in childhood 346
Yu-Tze Ng and Rama Maganti

20.1 Definition 346
20.2 Epidemiology 349
20.3 Pathophysiology 349
20.4 Etiology 350
20.5 Diagnosis and investigations 351
20.6 EEG patterns in status epilepticus 352
20.7 Treatment 356
20.8 Prognosis 359
References 359

Index 365

List of contributors

Matthew Byrne, BA
Uniformed Services
University of the Health Sciences
Bethesda, MD
USA

Asim F. Choudhri, MD
Departments of Radiology and Neurosurgery
University of Tennessee Health Science Center
Le Bonheur Children's Hospital
Memphis, TN
USA

David F. Clarke, MBBS, ABPN (Child Neurology and Sleep), ABCN
Dell Children's Comprehensive Epilepsy Program
Dell Children's Medical Center of Central Texas
Austin, TX
USA

Susan E. Combs, MD
Department of Neurology
Children's National Medical Center
The George Washington University School of Medicine
Washington, DC
USA

Dewi Frances T. Depositario-Cabacar, MD
Neurology and Pediatrics
George Washington University Medical Center
Children's National Medical Center
Washington, DC
USA

Georgann Ferrone, MD
Center for Neuroscience and Behavioral Medicine
Children's National Medical Center
Washington, DC
USA

Stephen Fulton, MD
Department of Neurology and Pediatrics
University of Tennessee Health Science Center
LeBonheur Comprehensive Epilepsy Program
Le Bonheur Children's Hospital
Memphis, TN
USA

Marie Francisca Grill, MD
Department of Neurology
University of California San Francisco
San Francisco General Hospital
San Francisco, CA
USA

Eric V. Hastriter, MD
Mayo Clinic Hospital
Phoenix, AZ
USA

David T. Hsieh, MD
San Antonio Military Medical Center
Division of Child Neurology
Wilford Hall Medical Center
Lackland AFB, TX
USA

Sucheta M. Joshi, MD, MS
Pediatrics and Communicable Diseases
Division of Pediatric Neurology
University of Michigan
Ann Arbor, MI
USA

Karen Keough, MD
'Specially For Children'
Austin, TX
USA

Susan Koh, MD
Children's Hospital Colorado
Aurora, CO
USA

Rama Maganti, MD
Department of Neurology
Barrow Neurological Institute
St Joseph's
Hospital and Medical Center
Phoenix, AZ
USA

William McClintock, MD
Neurology and Pediatrics
George Washington University Medical Center
Children's National Medical Center
Washington, DC
USA

Amy L. McGregor, MD
Department of Pediatrics
Division of Child Neurology
Le Bonheur Comprehensive Epilepsy Program
University of Tennessee Health Science Center
Memphis, TN
USA

Bhagwan Indur Moorjani, MD, FAAP, FAAN
Hope Neurologic Center, La Quinta
JFK Memorial Hospital
Indio, CA
USA

Yu-Tze Ng, MD, FRACP
University of Oklahoma
Health Science Center and The Children's Hospital
Pediatric Neurology
Oklahoma city, OK
USA

Kristen Park, MD
Children's Hospital Colorado
Aurora, CO
USA

Phillip L. Pearl, MD
Department of Neurology
Children's National Medical Center
The George Washington University School of Medicine
Washington, DC
USA

Freedom F. Perkins Jr, MD
Seton Healthcare and Dell Children's Hospital
Austin, TX
USA

Tom Reehal, BA
University of Sheffield School of Medicine Dentistry and Health
Sheffield
UK

Jay Salpekar, MD
Center for Neuroscience and Behavioral Medicine
Children's National Medical Center
Washington, DC
USA

Kate Van Poppel, MD
Department of Pediatric Neurology
University of Tennessee Health Science Center
Le Bonheur Comprehensive Epilepsy Program and Neuroscience Institute
Le Bonheur Children's Hospital
Memphis, TN
USA

James W. Wheless, MD, FAAP, FACP, FAAN
Department of Pediatric Neurology
University of Tennessee Health Science Center
Le Bonheur Comprehensive Epilepsy Program and Neuroscience Institute
Le Bonheur Children's Hospital
Memphis, TN
USA

Preface

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 succint, 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

Section 1

Epidemiology and classification of childhood epilepsies

Phillip L. Pearl

1 Epidemiology and common comorbidities of epilepsy in childhood

Jay Salpekar[1], Matthew Byrne[2], and Georgann Ferrone[1]

[1]Center for Neuroscience and Behavioral Medicine, Children's National Medical Center, Washington, DC, USA
[2]Uniformed Services University of the Health Sciences, Bethesda, MD, USA

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

Epilepsy in Children and Adolescents, First Edition. Edited by James W. Wheless.

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.

Location	Years of study	Epilepsy prevalence	Age range	Limits/comments
Okayama Prefecture, Japan [9]	1999	5.3 per 1000	0–12 years	Removed data resulting from only one seizure
Kayenta, Shiprock, and Crowpoint Reservations, Navajo Nation, USA [10]	1999–2002	6.46 per 1000	0–19 years	Only those who went to hospital; excluded those who used tribal medicine
Hordaland count, western Norway [12]	1995	5.13 per 1000	6–12 years	Small sample area, limited age range
Northern Tanzania (14)	2003–2004	7.39 per 1000	0–19 years	Only villages polled around centralized hospital location
Rochester, Minnesota [13]	1950–1980	3.83 per 1000	0–14 years	Very comprehensive
Estonia [15,16]	1995–1997	3.7 per 1000	0–19 years	Much of data came from one hospital, University of Tartu
Canada [17]	1994–2001	2.5 per 1000	0–11 years	Utilized national census data
		4.4 per 1000	12–14 years	

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

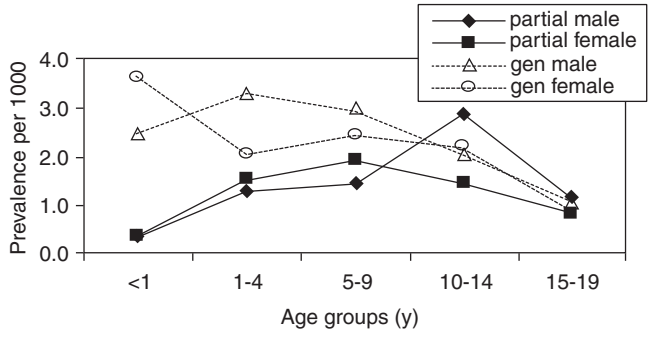


Figure 1.1 Graph showing prevalence of epilepsy (per 1000) in children by year from age 1 to 19 [16].

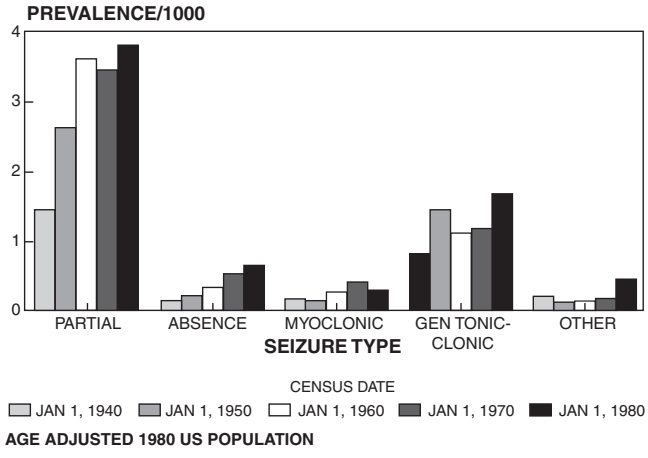


Figure 1.2 Bar graph of relative prevalence of adolescent seizure etiologies (per 1000) [13].

(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

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

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

methodology, some specific childhood psychiatric disorders have emerged as particularly associated with epilepsy (Table 1.2).

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