# Handbook of Pediatric Epilepsy

David C. Dredge
*Editor*

MOREMEDIA

Springer

# Handbook of Pediatric Epilepsy

David C. Dredge
Editor

# Handbook of Pediatric Epilepsy

Springer

*Editor*
David C. Dredge
Division of Pediatric Neurology
Massachusetts General Hospital
Harvard Medical School
Boston, MA, USA

ISBN 978-3-319-08289-9 ISBN 978-3-319-08290-5 (eBook)
https://doi.org/10.1007/978-3-319-08290-5



This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

*This book is dedicated to Dr. Paul Marshall, who helped fan the flames of my interest in the field of pediatric neurology. He is missed but will not be forgotten.*
*David C. Dredge, MD*
*March 30, 2021*

# Preface

Thank you for purchasing this handbook. Our intent was to compile a portable reference that is both easy to digest and expansive enough to cover key points in the diagnosis and management of pediatric epilepsy. Our goal is to provide trainees (students, residents, and fellows) with an up-to-date, convenient reference that can be used on the fly. We also hope information herein is also relevant to seasoned pediatric neurologists and epileptologists.

Where at all possible, we have utilized the best evidence regarding evaluation and treatment. However, there is limited quality evidence-based data in the field of pediatric epilepsy. We have supplemented data where possible with consensus approaches to therapy and the clinical experience of the MGH epilepsy and pediatric neurology staff.

David C. Dredge
Division of Pediatric Neurology
Massachusetts General Hospital
Harvard Medical School
Boston, MA, USA

# Acknowledgments

I owe Catherine Chu, MD, a debt of gratitude for initiating this project and handing it off to me with a solid first draft. I would like to thank the contributors who dedicated their time and effort to the completion of this work. I would like to thank the following physician mentors, who have imparted their epilepsy knowledge to me: Paul Marshall, Herbert Gilmore, Anthony Jackson, Beth Rosen, Elizabeth Thiele, Ron Thibert, and Catherine Chu. Thanks to Ylfa for supporting me through the process of finishing this book, and Edda for the lovely illustrations.

# Contents

# Contributors

**Amy Armstrong-Javors, MD** Division of Pediatric Neurology, Massachusetts General Hospital, Boston, MA, USA

**David C. Dredge, MD** Division of Pediatric Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

**Britt C. Emerton, PhD** Psychology Assessment Center, Massachusetts General Hospital, Boston, MA, USA

**Grace Yoonheekim Gombolay, MD** Pediatric Neuroimmunology and Multiple Sclerosis Clinic, Children's Healthcare of Atlanta, Division of Neurology, Emory University, Atlanta, GA, USA

**Anna M. Larson, MD** Pediatric Epilepsy Program, MassGeneral for Children, Boston, MA, USA

**Yancheng Luo, MD** Division of Pediatric Neurology, Massachusetts General Hospital, Boston, MA, USA

**Albert Misko, MD, PhD** Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

**Amy K. Morgan, PhD** Psychology Assessment Center, Massachusetts General Hospital, Boston, MA, USA

**Ron Thibert, MD** Pediatric Epilepsy, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

**Ronald L. Thibert, DO** Pediatric Epilepsy Program, MassGeneral for Children, Boston, MA, USA

**Elizabeth A. Thiele, MD, PhD** Pediatric Epilepsy Program, MassGeneral for Children, Boston, MA, USA

**Amanda Tourjee, NP** Pediatric Epilepsy, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA

**Melissa A. Walker, MD, PhD** Division of Pediatric Neurology, Massachusetts General Hospital, Boston, MA, USA

**Lila Worden, MD** Ketogenic Diet Program, Division of Pediatric Neurology, Connecticut Children's, Hartford, CT, USA

# Introduction

1

David C. Dredge

## Introduction

To begin, we will start with basic definitions used in pediatric epilepsy, review epidemiology of seizures in childhood, and summarize concepts of pathophysiology. More information regarding seizure subtypes and epilepsy syndromes will follow in forthcoming chapters.

## Definitions

The ILAE (International League Against Epilepsy) defines a seizure as: "a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain" [1]. This definition is quite broad, as is appropriate given the multitude of different clinical expressions we see with different types of seizures (see Chap. 2).

### Epilepsy

Epilepsy is defined as: "a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, and by the neurobiological, cognitive, psychological, and social consequences of this condition" [1]. The definition of epilepsy requires the occurrence of at least one seizure. Historically, the definition of epilepsy required 2 or more unprovoked seizures in a patient's lifetime. "Unprovoked" means that there was no proximal event that triggered the seizure, such as fever,

D. C. Dredge (✉)
Division of Pediatric Neurology, Massachusetts General Hospital,
Harvard Medical School, Boston, MA, USA
e-mail: ddredge@partners.org



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_1

trauma, hypoglycemia, and meningitis. Recent publications have broadened the definition of epilepsy to include a single seizure with any factor that predicts seizure recurrence risk of greater than 60% [1]. Examples include epileptiform EEG patterns highly predictive of seizure recurrence, identification of a specific epilepsy syndrome, or identification of a lesion (acquired or congenital) with a known predilection for generating seizures (i.e., focal cortical dysplasia, hemi-megalencephaly, lissencephaly, perinatal stroke).

Epilepsy can be further divided into symptomatic and idiopathic categories. The symptomatic group includes seizures due to a previous stroke, brain malformation, metabolic disorder, or other lesion. It is important to recognize that symptomatic seizures tend to occur at a time remote from the initial injury, distinguishing this category from provoked seizures. Idiopathic epilepsy is defined as recurrent seizures without a preceding injury, structural abnormality, or other insult. There is a presumption that many cases of idiopathic epilepsy are genetically mediated, and recent advances in genetic testing have revealed numerous genes associated with epilepsy. However, we have not yet uncovered genes associated with many of the most common forms of childhood epilepsy (absence, juvenile myoclonic, childhood epilepsy with centrotemporal spikes). Specific seizure types and epilepsy syndromes will be thoroughly covered in the following chapters.

## Status Epilepticus

Status epilepticus (SE) is defined as a seizure lasting more than 5 minutes (historically 30 minutes) or at least 2 seizures without recovery of consciousness in between [2]. When the American Epilepsy Society endorsed that definition in 1993, they chose the 30-minute cutoff based on animal model data suggesting permanent neuronal injury and death occurred with seizures of that duration [2]. Subsequently, it has been shown that serious metabolic and neuronal derangements occur with seizures of shorter duration [3, 4]. In 2012 the Neurocritical Care Society recommended new guidelines for definitions. They redefined as “5 min or more of continuous clinical and/or electrographic seizure activity or recurrent seizure activity without recovery between seizures” [5]. Seizures lasting more than 5 minutes have a low likelihood of abating on their own. In addition, aggressive early treatment can decrease mortality in status epilepticus.

While there are potentially as many different types of status epilepticus as there are seizures, status epilepticus is classified broadly into 2 categories: convulsive or non-convulsive SE [6]. Nonconvulsive SE (NCSE) is marked by continued seizure activity seen on an EEG without clear clinical symptoms (although some degree of mental status change is typical). NCSE is an increasingly recognized phenomenon and is seen especially in critically ill children or in certain global epilepsy syndromes (Angelman syndrome, Doose syndrome) [7]. Focal status epilepticus is rare but does occur. Epilepsia partialis continua is a type of focal motor SE that typically lasts for hours or days with clonic seizure on one area of the body without spread and with preserved consciousness. This phenomenon is often associated with

Rasmussen's syndrome, a degenerative disorder of unclear etiology that involves one hemisphere. Status epilepticus involving focal eyelid myoclonia has been reported in Jeavons syndrome. (See Chap. 4). Aura continua is a focal sensory status epilepticus that can last for years [8].

## Epidemiology

Seizures and epilepsy are one of the most common presenting complaints in the field of child neurology. A 2015 child neurology clinical workforce survey reported that seizures and epilepsy account for 21–30% of patients in child neurology clinics [9]. On the inpatient side, the proportions of patients admitted for seizures was recorded as 61–70% [9].

Each year, an estimated 150,000–200,000 (around 50/100,000) Americans experience a first seizure; 25,000–40,000 (around 80/100,000) are children below the age of 15 years [10, 11]. The incidence (number of new cases per year) of epilepsy has a wide range, and quite variable in different age categories. In Rochester, MN, the incidence ranges from 102/100,000 in children ages 1–12 months, 50–62/100,000 in age 1–9, and 39/100,000 in 10–14 [12, 13].

Several studies across different nations have collected epidemiological data on pediatric epilepsy. Estimated incidences range from 41/100,000 in Nova Scotia to 187/100,000 in Kenya [14, 15]. A Norwegian study accessing a healthcare database of greater than 100,000 patients demonstrated an overall incidence rate of 70 patients per 100,000 person years. The incidence was highest in the first year of life, with an incidence of 144 patients per 100,000 [18].

Prevalence is defined as the number of people with epilepsy at a given point of time. The prevalence of epilepsy in the population follows a bimodal age distribution, with the greatest number of cases in the elderly and children below the age of 5 years [16]. In the United States, the prevalence is 4.71/1000 [17]. Estimates of prevalence in Europe range from 3.2 to 5.1/1000.

The overall prevalence of pediatric epilepsy in the Norwegians study was 5/1000 [18]. Studies in Turkey and Sweden have demonstrated similar results [19, 20]. Prevalence varies from region to region around the world, including 3.6–10.5/1000 in Arab countries, 7.5–44.3/1000 in Latin America, and 6/1000 in Asia [21–23].

Another Turkish study looked at seizure types and epilepsy syndromes across different age groups [24]. 30% of all patients with an epilepsy diagnosis were identified in the first year of life. Focal seizures were overall more common than generalized, 56.5% vs. 43.5%, respectively. The only age group in which generalized seizures were more common were in the 1-month to 1-year group, where they accounted for 73.5% [24]. The distribution of seizure types was characterized further, as seen in Table 1.1. These seizure types will be discussed in detail in Chap. 2.

In the Turkish study, 482 of 532 patients were identified with specific epilepsy syndromes. 53% of identified syndromes were focal epilepsies. Among idiopathic focal epilepsies, childhood epilepsy with centrotemporal spikes (6.2%) and childhood occipital epilepsy (1.3%) were the most common. Symptomatic focal

**Table 1.1** Frequency of seizure types in epilepsy [24]

| Seizure type | % |
|---|---|
| Focal seizures | 56.5 |
| Simple focal | 4.7 |
| Complex focal | 23.8 |
| With secondary generalization | 28 |
| Gelastic | 0.4 |
| Generalized | 43.1 |
| Absence | 3.4 |
| Atypical absence | 2.3 |
| Myoclonic | 6.3 |
| Clonic | 2.4 |
| Tonic | 6.2 |
| Tonic-clonic | 12.3 |
| Atonic | 1.9 |
| Epileptic spasms | 8.3 |

**Table 1.2** Prevalence of specific childhood epilepsy syndromes [24]

| Idiopathic epilepsy syndromes | % |
|---|---|
| Focal | 53 |
| CECTS | 6.2 |
| Childhood occipital epilepsy | 23.8 |
| Symptomatic | 26.5 |
| Temporal lobe | 6 |
| Generalized | 37 |
| Absence | 10 |
| West syndrome | 8.2 |
| LGS | 3.7 |
| JME | 2.3 |

*CECTS* childhood epilepsy with centrotemporal spikes, *LGS* Lennox-Gastaut syndrome, *JME* Juvenile myoclonic epilepsy

epilepsies accounted for 26.5%, the most common of which was temporal lobe epilepsy (6%). Generalized epilepsy syndromes accounted for 37.1% of syndromes, 9.2% of which were idiopathic. West syndrome (8.2%), Lennox-Gastaut syndrome (3.7%), childhood absence epilepsy (3%), and juvenile myoclonic epilepsy (2.3%) were notable syndromes in this category [24] (Table 1.2).

## Pathophysiology

The incidence of epilepsy has a bi-modal representation in the population, with the 2 highest groups being children and the elderly. Onset of epilepsy in the elderly is usually related to acquired pathology, such as strokes, trauma, neoplasms, etc. There are a number of features in the developing brain that make it more susceptible to seizures and epilepsy. While an exhaustive review is beyond the scope of this text, we will highlight some key contributors to this phenomenon.

**Table 1.3** Factors increasing susceptibility to seizures in the immature brain

| | |
|---|---|
| Excitatory action of γ-aminobutyric acid (GABA) | High synaptic density with over-expression of excitatory synapses |
| High glutamate receptor levels | Delayed development of the substantia nigra pars reticulata anticonvulsant network relative to the pro-convulsant network |
| Altered composition of NMDA and AMPA receptors favor excitation | Prolonged action potentials due to low levels of Na/K ATPase and slower kinetics of delayed rectifier K channels |

In general, we can conceptualize the tendency to have seizures as an imbalance between excitatory and inhibitory factors in the brain. In patients with epilepsy, that balance is tilted toward excitation, which lowers the seizure threshold. Human brain growth and development depends largely on excitatory activity to make and strengthen new connections ("neurons that fire together, wire together"). Thus, the developing brain favors excitation, whereas the mature brain generally has achieved balance between excitation and inhibition.

The physiological factors that confer this tendency to excitation have been studied for the most part in neonates. While this topic will be discussed in further detail in the chapter on neonatal seizures, we will review the highlights here (Table 1.3).

Neurons function by propagating action potentials along axons and dendrites. The action potentials, and their termination, are generated by influx and efflux of cations and anions. In general, inward flow of positive ions, chiefly sodium ($Na^+$) and calcium ($Ca^{++}$), through ion channels causes depolarization of the cell membrane which initiates and then propagates the activating signal. Repolarization occurs with potassium ($K^+$) efflux and chloride ($Cl^-$) influx. The intracellular and extracellular ion gradients are maintained by energy-requiring ion (co)-transporters.

One area that has been explored in recent years is the physiology of GABA receptors and the maintenance of chloride gradients. Barbiturates and benzodiazepines act by modulating the activity of GABA receptors, increasing their open time. The GABA receptor is a ligand-gated chloride ($Cl^-$) channel with non-competitive binding sites for barbiturates and benzodiazepines. In mature neurons, GABA is inhibitory due to the higher extracellular concentration of $Cl^-$ ions. With ligand-induced channel opening, $Cl^-$ flows into the cell, hyperpolarizing the cell membrane and thus inhibiting action potential propagation. In the mature brain, the extracellular chloride gradient is maintained by a potassium chloride cotransporter called KCC2. In immature neurons, GABA receptors are actually *excitatory* [25]. Immature neurons have a much higher predominance of a different ion cotransporter called NKCC1. This cell membrane protein transports sodium, potassium, and chloride into the cell, causing a high intracellular chloride concentration. Consequently, upon channel opening, chloride flows out of the cell through the GABA receptor, causing depolarization [25] (Fig. 1.1).

The concentration of KCC2 begins to rise toward the end of the first month of life, achieving 80% of adult levels by 1 year of age. The percentage of NKCC1

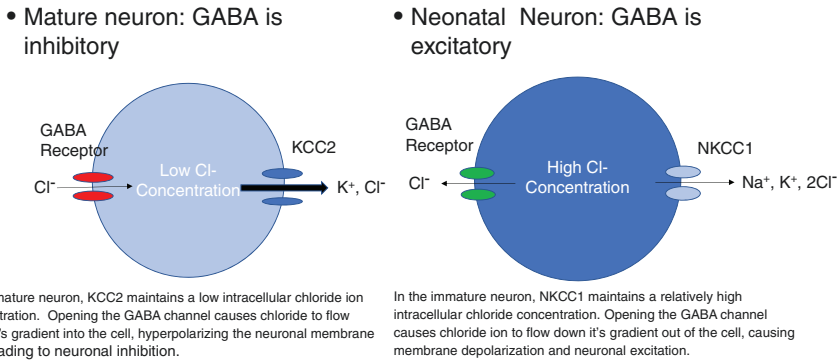



**Fig. 1.1** Excitatory action of GABA receptors in immature neurons

peaks during the third trimester and first weeks of life and decreases to adult levels by 1 year of age [25]. Therefore, the brain of the infant in the first year of life is significantly more excitable than that of older children.

Maturation-dependent differences in composition have also been described in glutamate receptors. There are three forms of glutamate receptors: kainite, N-methyl-D-aspartate (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Most glutamate receptors are ion channels that cause influx of calcium and/or sodium into cells, causing cell depolarization. Glutamate receptors are expressed at higher levels in the immature brain compared to mature nervous systems. Ontologically this makes sense, given the need for excitatory activity to form synapses and networks. In the neonatal period, NMDA receptors are primarily responsible for excitation and synapse formation and are more prevalent than AMPA receptors early in life. AMPA receptors do not have as large of a role in forming new connections [26]. NMDA receptors are more dependent on $Ca^{++}$ gradients than AMPA [27]. Additionally, in AMPA receptors, lower proportions of the GluR2 subunit in immature brains render the AMPA receptor more permeable to calcium ions, increasing depolarization [28].

In terms of potassium physiology, as mentioned above, repolarization of the cell membrane is largely caused by efflux of $K^+$. In addition to repolarization, $K^+$ efflux causes hyperpolarization leading to a refractory period that limits repetitive action potentials. In immature brains, the concentration of intracellular potassium is reduced due to lower levels of the Na/K ATPase, which requires energy to transport $K^+$ into the cells [29]. Therefore, the amount of current generated by potassium channel opening is decreased, leaving the cell in a potentially excitable state. This phenomenon is thought to be the cause of repetitive action potentials in animal models of seizures in immature brains [30].

Sodium gradients do not have significant age-dependent differences, and therefore sodium's role in increased epilepsy risk in childhood is not well understood. We do know that sodium channel mutations are responsible for a number of childhood epilepsy syndromes (See Chap. 4). Interestingly, increased body temperature may increase the probability of sodium channel opening. This may explain the relationship between an increased propensity for febrile seizures, as seen in disorders such as genetic epilepsy with febrile seizures plus (GEFS+), and Dravet syndrome [31].

Beyond ion channels, there may also be maturation-dependent effects on seizure modifying circuits in the brain. The substantia nigra pars reticulata is thought to play a role in controlling the spread of seizure activity in mature brains. In animal models, adult rats have an anterior region of the SNPR that appears to have anticonvulsant effects, while the posterior region may be proconvulsant. These two regions are undifferentiated in the immature brain, and the "proconvulsant" activity appears to dominate [32].

## Structural Pathology

The above discussion focuses on factors that increase seizure susceptibility in normal developing brains. How does brain pathology lead to seizures? There are many different brain lesions that can lead to seizures, from malformations caused by genetic mutations to brain injury such as stroke and trauma (See Chap. 3). In presumed genetic lesions, such as polymicrogyria or grey matter heterotopia, the pathological tissue does not make normal connections to a larger network. There can be spatially displaced projections, excessive excitatory connections, or loss of inhibitory synapses [33]. Cells that have not arrived at their intended location can display spontaneous bursting of action potentials [34]. In the case of polymicrogyria, the primary pathology is caused by failure of neurons to migrate to their intended location in the cortex. Because of this aberrant morphology, abnormal connections are formed, which can be epileptogenic [35]. Additionally, synaptic receptor populations are often abnormally distributed in cells with abnormal networks. Finally, neurons themselves in malformations of cortical development can be dysplastic, often large with abnormal intracellular inclusions and tangled projections [36].

In acquired lesions, such as strokes, damaged tissue is often gliotic, and surviving neurons may form aberrant connections. This phenomenon has been studied in human hippocampal sclerosis. While loss of neurons appears to be the primary pathology, the remaining neurons reorganize and make new connections, often with a different region of the hippocampus than the original links [37]. Neuronal loss appears more common in inhibitory neurons, which also promotes epileptiform activity. Mossy fiber sprouting, which occurs in the setting of neuronal injury, appears to favor neuronal projections that contain increased numbers of glutamate-containing synaptic vesicles. These new connections can by highly excitable [38].

## Genetics

There are numerous genes associated with epilepsy (see Chap. 3). Many of these genes encode ion channels, proteins essential for neuronal migration, or proteins with major organizing roles in brain morphogenesis. Some forms of epilepsy are caused by genetic changes that directly affect brain structure, such as the TSC1 gene in tuberous sclerosis complex. Therefore, there can be a strong interplay of structural and physiological effects of genetic mutations that effect ion channel systems

and cortical organization as outlined above. Specific genes in epilepsy will be explored in subsequent chapters.

## References


1. Fischer RS, Acevedo C, Arzimanoglou A. A practical clinical definition of epilepsy. Epilepsia. 2014;55:475–82.
2. Working Group on Status Epilepticus. Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA. 1993;270(7):854–9.
3. Meldrum BS, Horton RW. Physiology of status epilepticus in primates. Arch Neurol. 1973;28(1):1–9.
4. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol. 2006;5(3):246–56.
5. Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17:3–23.
6. Rona S, Rosenow F, Arnold S, et al. A semiological classification of status epilepticus. Epileptic Disord. 2005;7(1):5–12.
7. Riviello J, Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review) Report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. 2006;67(9):1542–50.
8. Seshia SS, McLachlan RS. Aura Continua [1]. Epilepsia. 2005;46(3):454–5.
9. Kang PB, Bale JF Jr, Mintz M, Joshi SM, Section on Neurology Executive Committee of the American Academy of Pediatrics, and the Board of Directors of the Child Neurology Society. The child neurology clinical workforce in 2015: report of the AAP/CNS Joint Taskforce. Neurology. 2016;87(13):1384–92.
10. Begley CE, Famulari M, Annegers JF, et al. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. Epilepsia. 2000;41(3):342–51. http://www.ncbi.nlm.nih.gov/pubmed/10714408.
11. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first. Neurology. 2000;55:616–23.
12. Hauser WA, Annegers JF, Kurland LT. Incidence of epilpesy and unprovoked seizures in Rochester, MN 1935—1984. Epilepsia. 1993;34:453–68.
13. Wirrell EC, Grassardt BR, Wong-Kisiel LCL, et al. Incidence and classification of new onset epilepsy and epilepsy syndromes in children in Olmsted County, MN from 1980–2004: a population-based study. Epilepsy Res. 2011;95:110–8.
14. Camfield CS, Camfield PR, Gordon K, et al. Incidence of epilepsy in childhood and adolescence: a popluation-based study in Nova Scotia from 1977 to 1985. Epilepsia. 1996;37:19–23.
15. Mung'ala-Odera V, White S, Meehan R, et al. Prevalence, incidence and risk factors of epilepsy in older children in rural Kenya. Seizure. 2008;17:396–404.
16. Theodore WH, Spencer SS, Wiebe S, et al. Epilepsy in North America: a report prepared under the Auspices of the Global Campaign against Epilepsy, the International Bureau for Epilepsy, the International League Against Epilepsy, and the World Health Organization. Epilepsia. 2006;47(10):1700–22.
17. Cowan LD, Bodensteiner JB, Leviton A, Doherty L. Prevalence of the epilepsies in children and adolescents. Epilepsia. 1989;30:389–99.
18. Aaberg KM, Gunnes N, Bakken IJ, et al. Incidence and prevalence of childhood epilepsy: a nationwide cohort study. Pediatrics. 2017;139:1–9.
19. Serdaroglu A, Ozkan S, Aydin K. Prevalence of epilepsy in Turkish children between the ages of 0 and 16 years. J Child Neurol. 2004;19:271–4.

20. Larsson K, Eeg-Olofsson O. A population-based study of epilepsy in children from a Swedish county. Eur J Pediatr Neurol. 2006;10:107–13.
21. Benamer HTS, Grosset DG. A systematic review of the epidemiology of epilepsy in Arab countries. Epilepsia. 2009;50:2301–4.
22. Burneo JG, Tellez-Zenteno J, Wiebe S. Understanding the burden of epilepsy in Latin America: a systematic review of its prevalence and incidence. Epilepsy Res. 2005;66:63–74.
23. Mac TL, Tran DS, Quet F, et al. Epidemiology, aetiology, and clinical management of epilepsy in Asia: a systematic review. Lancet Neurol. 2007;6:533–43.
24. Unver O, Keskin SP, Uysal S, Unver A. The epidemiology of epilepsy in children: a report from a Turkish pediatric neurology clinic. J Child Neurol. 2015;30(6):698–702.
25. Dzhala VI, et al. NKCC1 transporter facilitates seizures in the developing brain. Nat Med. 2005;11(11):1205–13.
26. Tremblay E, Roisin MP, Represa A, et al. Transient increased density of NMDA binding sites in the developing rat hippocampus. Brain Res. 1988;461:393–6.
27. Pellegrini-Giampietro DE, Gorter JA, Bennett MV, et al. The GluR2 hypothesis: $Ca^{2+}$ permeable AMPA receptors in neurological disorders. Trends Neurosci. 1997;20:464–70.
28. Law AJ, Weickert CS, Webster MJ. Expression of NMDA receptor NR1, NR2A,and NR2B subunit mRNAs during development of the human hippocampal formation. Eur J Neurosci. 2003;18:1197–205.
29. Fukuda A, Prince DA. Postnatal development of electrogenic sodium pump activity in rat hippocampal pyramidal neurons. Brain Res. 1992;65:101–14.
30. Heinemann U, Lux HD. Ceiling of stimulus-induced rises in extracellular potassium concentration in the cat. Brain Res. 1977;120:230–49.
31. Spampanato J, Excayg A, Meisler MH, et al. Functional effects of two voltage-gated sodium channel mutations that cause generalized epilepsy with febrile seizures plus type 2. J Neurosci. 2001;21:7481–90.
32. Moshe SL, Brown LL, Kubova H, et al. Maturation and segregation of brain networks that modify seizures. Brain Res. 1994;665:141–6.
33. Paredes M, Pleasure SJ, Baraban SC. Embryonic and early postnatal abnormalities contributing to the development of hippocampal malformations in a rodent model of dysplasia. J Comp Neurol. 2006;495:1133–48.
34. Baraban SC, Schwartzkroin PA. Electrophysiology of CA1 pyramidal neurons in and animal model of neuronal migration disorders: prenatal methylazoxymethanol treatment. Epilepsy Res. 1995;22:145–56.
35. Cepeda C, Andre VM, Levine MS, et al. Epileptogenesis in pediatric cortical dysplasia: the dysmature cerebral developmental hypothesis. Epilepsy Behav. 2006;9:210–35.
36. Vinters HV, Fisher RS, Cornford ME, et al. Morphological substrates of infantile spasms: studies based on surgically resected cerebral tissue. Childs Nerv Syst. 1993;8:8–17.
37. Babb TL, Kupfer WR, Pretorius JK, et al. Synaptic reorganization by mossy fibers in human epileptic fascia dentata. Neuroscience. 1991;42:351–63.
38. Zhang N, Houser CR. Ultrastructural localization of dynorphin in the dentate gyrus in human temporal lobe epilepsy: a study of re-organized mossy fiber synapses. J Comp Neurol. 1999;405:472–90.

# Seizure Classification and Semiology

# 2

Lila Worden

## Introduction

classification of seizures categories has allowed for standardized terminology and improved our ability to study seizures. Correct seizure classification is the first step in diagnosis and can subsequently affect treatment choices. For example, carbamazepine is a good anticonvulsant medication for focal seizures, but can worsen generalized seizures [1]. Additionally, epilepsy that is refractory to medication may be amenable to surgical resection if the seizure focus is localized to non-eloquent cortical regions. Prior to EEG and neuroimaging technology seizure classification was based purely on seizure *semiology*, the outward signs, and symptoms of the seizure [2]. Though advances in brain imaging, EEG monitoring, and genetic testing have affected how we approach diagnosis and management of epilepsy today, seizure semiology is the first clinical information available to the provider. An accurate and clear understanding of what the seizure looked like or what the patient experienced helps to guide further testing, optimize treatment, and localize the seizure focus and proximity to eloquent areas when epilepsy surgery is considered.

In this chapter, we will first discuss the major classification of seizures and describe major seizure types, and then discuss seizure semiology that helps localize or lateralize seizures.

**Supplementary Information** The online version of this chapter (https://doi.org/10.1007/978-3-319-08290-5_2) contains supplementary material, which is available to authorized users.

L. Worden (✉)
Ketogenic Diet Program, Division of Pediatric Neurology, Connecticut Children's, Hartford, CT, USA
e-mail: LWorden@connecticutchildrens.org


D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_2

## Seizure Classification

The most widely used classification system was developed by the International League Against Epilepsy (ILAE). The original schema from 1981 established the organization into generalized and partial seizures, from which originated the terms simple partial (maintained awareness), complex partial (altered awareness), and partial seizures with secondary generalization [3]. These terms remain in frequent use today. However, the most recent revision of the ILAE classification system, published in 2017, updated the major categories to focal (with or without impaired awareness), generalized, and unknown onset, with further subdivision in each category to specify motor or non-motor onset [4]. Focal seizures (synonymous with partial seizures) denote those that originate within networks limited to one hemisphere. Generalized seizures are defined as "originating at some point within, and rapidly engaging, bilaterally distributed networks," often spreading bilaterally within milliseconds [5] (Table 2.1).

Seizure classification schemata continue to shift due to rapidly expanding knowledge in the fields of genetics, basic science, and neuroimaging. It is acknowledged that that there may be overlap across semiological types. For example, many "generalized seizures" are frontal-lobe predominant but affect both hemispheres equally. Others may falsely be labeled as "generalized" due to a focus near the midline that leads to rapid bilateral generalization. Of note, a generalized or focal *seizure* is not the same as generalized or focal *epilepsy*. A child with an epilepsy syndrome like Dravet, which typically manifests multiple types of generalized seizures, can also have focal seizures. This distinction in classification can be a source of confusion for both providers, patients, and their families.

While there is debate about seizure classification, there is shared terminology that is widely accepted for seizure descriptors. Many of the descriptors can be applied to both generalized and focal seizures; e.g., a clonic seizure that is bilateral is likely generalized while a unilateral clonic seizure is focal. Within these categories, there are seizure types that are generally recognized as discrete entities, as outlined below.

**Table 2.1** 2017 ILAE seizure classification system [4]

| Focal onset | | Generalized onset | Unknown onset |
|---|---|---|---|
| Aware | Impaired awareness | | |
| *Motor onset* | | *Motor* | *Motor* |
| Automatisms | | Tonic-clonic | Tonic-clonic |
| Atonic | | Clonic | Epileptic spasms |
| Clonic | | Tonic | *Nonmotor* |
| Epileptic spasms | | Myoclonic | Behavior arrest |
| Hyperkinetic | | Myoclonic-tonic-clonic | |
| Myoclonic | | Myoclonic-atonic | |
| Tonic | | Atonic | |
| *Non-motor onset* | | Epileptic spasms | |
| Autonomic | | *Non-motor* | |
| Behavioral arrest | | Typical absence | |
| Cognitive | | Atypical absence | |
| Emotional | | Myoclonic absence | |
| Sensory | | Absence with eyelid myoclonia | |
| *Focal to bilateral tonic-clonic* | | | |

## Generalized Seizures

### Tonic-Clonic

Generalized tonic-clonic (GTC) seizures historically have also been known as "grand mal" seizures. The tonic phase appears as full body stiffening, typically with the lower extremities extended and the upper extremities either flexed or extended with neck extension. During the tonic phase there can be an ictal cry, which is the sound of forced air expired against a closed glottis due to contraction of the diaphragm and chest muscles. There may also be cyanosis associated with the tonic phase. The tonic phase is subsequently followed by a clonic phase of rhythmic jerking of the extremities. (Video 2.1) Generalized tonic-clonic seizures generally last 1–3 minutes.

Generalized tonic-clonic seizures are often associated with tongue biting, incontinence of urine or stool, and drooling or foaming at the mouth from excessive salivation. They are always accompanied by loss of consciousness. After the seizure, there is a period of recovery called the post-ictal period. The post-ictal period is usually characterized by lethargy, decreased arousal, confusion (which can lead to combativeness), aphasia, fatigue, headaches, and body aches. Post-ictal periods can last from minutes up to a few hours. A prolonged post-ictal period or persistent altered mental status after a seizure should raise concern for an alternative etiology, such as a medication effect or non-convulsive status epilepticus. The EEG pattern during a GTC typically shows diffuse voltage attenuation with low amplitude fast generalized poly-spikes or beta activity during the tonic phase evolving to synchronous spike and wave during the clonic phase. However, the EEG pattern is often obscured due to movement artifact. Following the seizure there is generalized diffuse slowing and background suppression.

### Myoclonic

Myoclonic seizures are characterized by a brief contraction of a muscle or muscle group. The shock-like jerks that occur are very brief (<200 milliseconds) and appear most often in the upper arms and shoulders or upper legs, though they can happen anywhere [2] (Video 2.2). They are typically associated with generalized epilepsy syndromes or diffuse brain dysfunction. Some myoclonic seizures may be focal, and the specific localization and physiology of this seizure type has not been elucidated. There is commonly no definite impairment in consciousness, although it is possible that alteration of consciousness occurs, but it is too brief to be clinically recognized. The EEG during a myoclonic seizure shows a burst of generalized spike- or polyspike-waves (Fig. 2.1). Myoclonic seizures are common features of several epileptic encephalopathies and typically represent significant cerebral dysfunction. One notable exception is juvenile myoclonic epilepsy. In this disorder, myoclonic seizures are a defining feature of the epilepsy syndrome, classically observed in the morning hours. This epilepsy syndrome, described in later chapters, is one that typically is easily treated with medication.

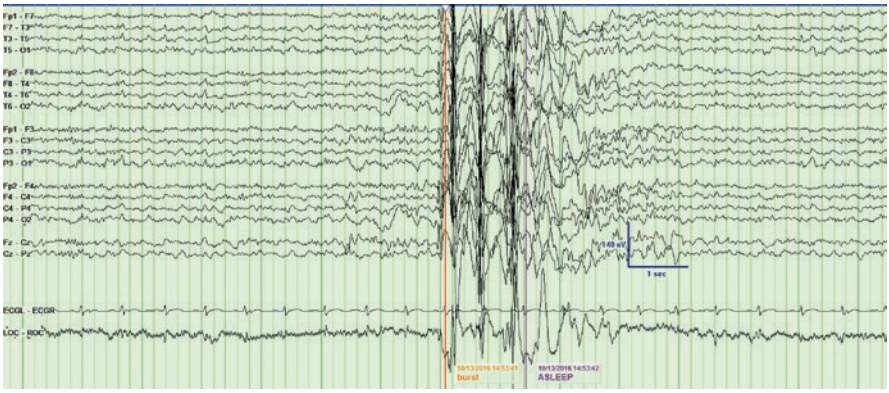



**Fig. 2.1** Myoclonic seizure with generalized spike-wave burst

## Tonic

Tonic seizures are characterized by increased tone (stiffening) of the affected body area. In the case of generalized tonic seizures, children often have flexion or extension of the neck, flexion or extension of the bilateral arms, and extension of the bilateral legs. The movement is often symmetrical, though focal tonic seizures can also occur. Tonic seizures frequently occur in sleep or when the child is emerging from sleep. They can last up to 1 minute, though most are often <20 seconds. A prolonged tonic seizure can develop a tremulous component that can be mistaken for clonic movements. The EEG usually shows generalized, low-voltage, fast polyspikes with diffuse voltage attenuation (Fig. 2.2). Tonic seizures rarely occur in isolation and are frequently seen in children with other neurologic abnormalities or specific epilepsy syndromes such as Lennox-Gastaut syndrome.

## Clonic

Clonic seizures are characterized by rhythmic, repetitive jerks. They can be focal or generalized. The extremities are often flexed. Clonic seizures tend to occur at a frequency of 2–3 Hz and then gradually slow as the seizure ends. Clonic seizures can be focal or generalized.

## Atonic

Atonic seizures are characterized by a brief loss of tone. Atonic seizures are commonly accompanied by impaired consciousness, though these seizures can be so brief that mental status changes may not be detectable. Loss of tone occurs primarily in the trunk, but more subtle forms can manifest as jaw drops or head drops.

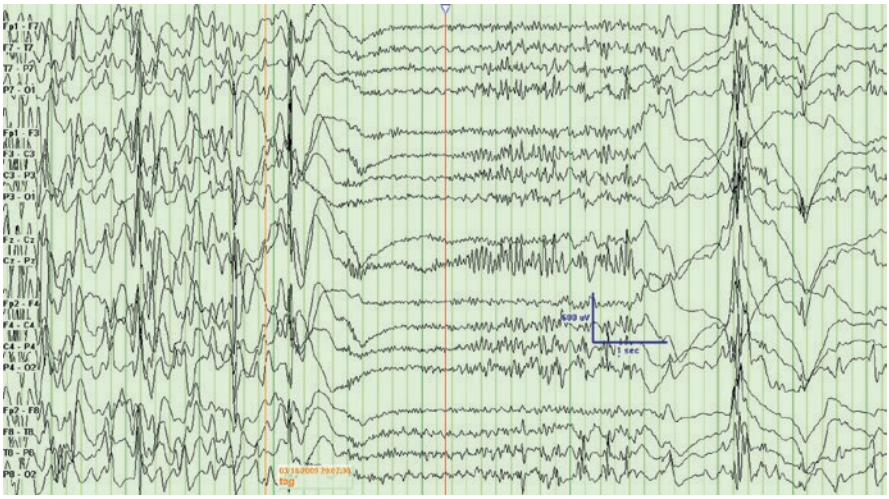


**Fig. 2.2** Tonic seizure. Note the high-voltage slow-wave followed by electrodecrement that evolves into low-voltage fast spikes

Atonic seizures typically last only a few seconds (<2–5 seconds) and rarely up to 1 minute. Atonic seizures often result in a fall if the patient is standing (Video 2.4). Because the patient is not aware and therefore does not protect themselves, atonic seizures can lead to significant injury. The EEG during atonic seizures will show generalized, slow spike-wave or polyspike-wave complexes followed by electrodecrement (flattening of the EEG background).

Of note: astatic – or "drop" – seizures are not synonymous with atonic seizures. Astatic seizures include other seizure types, such as myoclonic or tonic seizures. All three of these seizure types can be associated with abrupt falls. Myotonic-astatic seizures are the hallmark seizures of Doose syndrome, now referred to as epilepsy with myoclonic-atonic seizures in the current classification systems.

## Absence

Absence seizures, previously known as "petit mal" seizures, are brief episodes characterized by behavioral arrest and impaired conscious that externally present as staring spells. The spells are brief, typically lasting only 3–20 seconds. Children may be noted by their teachers or parents to be frequently "daydreaming" or parents may state that they often do not pay attention. Typical absence seizures start and end abruptly and there is immediate resumption of prior activities with no post-ictal period or memory of the event (Video 2.5). Absence seizures can often have associated subtle motor components such as swallowing or chewing movements, lip smacking, or repetitive blinking [6]. Absence seizures are the defining feature of childhood absence epilepsy, where the seizures are present in otherwise

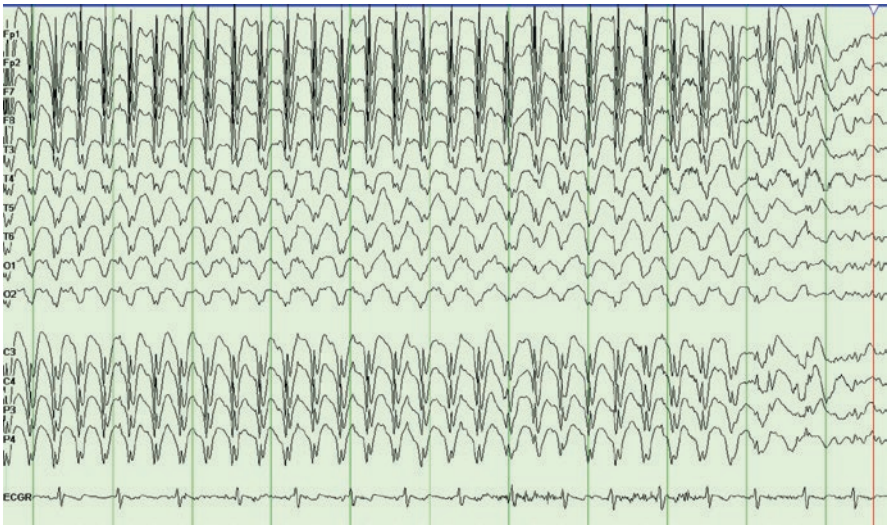



**Fig. 2.3** Childhood absence epilepsy. Note the typical bi-frontally predominant generalized 3 Hz spike-wave discharges

developmentally normal children. In this disorder, seizures occur many times per day. Absence seizures can occur in other generalized epilepsy syndromes as well, including juvenile myoclonic epilepsy or juvenile absence epilepsy. The EEG pattern of absence seizures is a very distinctive 3 Hz generalized, bi-frontally predominant spike-and-wave pattern (Fig. 2.3). Hyperventilation in the office can often induce a typical absence seizure and is a useful diagnostic maneuver.

"Atypical" absence seizures are also marked by a loss of awareness, but the onset and offset of impaired to consciousness is more gradual. In addition, the impairment in consciousness is often incomplete, such that the patient may continue performing an activity but with less attention, coordination, and precision. There can be a gradual loss of truncal tone as well, resulting in slumping but not falls. Unlike typical absence seizures, the spells are not provoked by hyperventilation. The EEG often shows slower spike-wave or polyspike-wave complexes, typically at 1.5–2.5 Hz. Atypical absence seizures occur frequently in children with developmental and cognitive delays and may be hard to distinguish from behavioral inattention. Atypical absence seizures last longer than typical absence seizures and can at times progress into atypical status epilepticus, seen in Angelman syndrome, Lennox-Gastaut syndrome, and other genetic epilepsy conditions.

## Epileptic Spasms

Epileptic spasms are more commonly known as infantile spasms, though more general terminology was adopted since they can occur outside of infancy [7]. Spasms are marked by a sudden change in axial/truncal tone characterized by flexion,

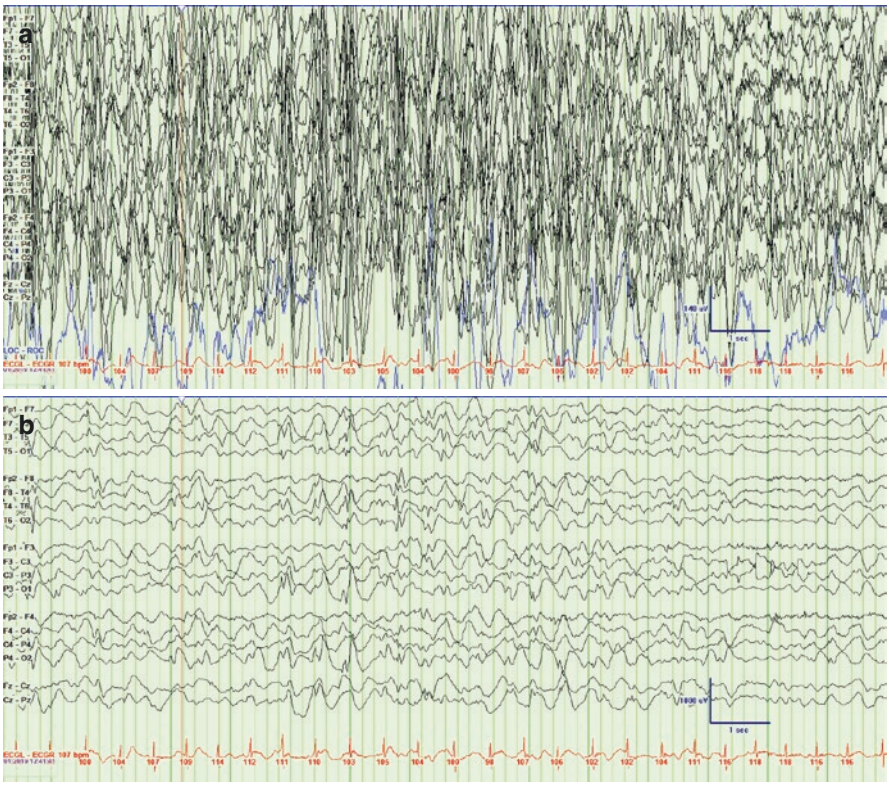



**Fig. 2.4** (**a**) Hypsarrhythmia. This is the EEG at standard recording sensitivity, depicting a very chaotic tracing. (**b**) Hypsarrhythmia. This is the EEG from the same patient as image (**a**), with the sensitivity reduced. Note diffuse, high-voltage slowing, poor organization of the background, and multifocal epileptiform discharges

extension, or mixed flexion-extension posturing. Flexor posturing is the most common manifestation. Raising of the arms or flexing all four extremities is also very common (Video 2.6). The activity can be as subtle as a brief head drop with sustained neck flexion, or can be quite pronounced. Spasms typically involve both sides of the body simultaneously, but they can be unilateral or asymmetric. A spasm lasts 1–2 seconds, in contrast with myoclonus which is extremely brief (<200 milliseconds) or tonic seizures, which tend to last >10 seconds. Spasms often occur in clusters lasting several minutes, frequently upon awakening from sleep. The background EEG in patients with epileptic spasms typically shows a disorganized background, high-voltage activity, and multifocal spikes (Fig. 2.4). This interictal pattern is called hypsarrhythmia. The spasms themselves are represented on EEG by a high-amplitude slow wave followed by electro-decrement (Fig. 2.5). Infantile spasms are the hallmark of West syndrome, the triad of developmental delay, infantile spasms, and hypsarrhythmia.

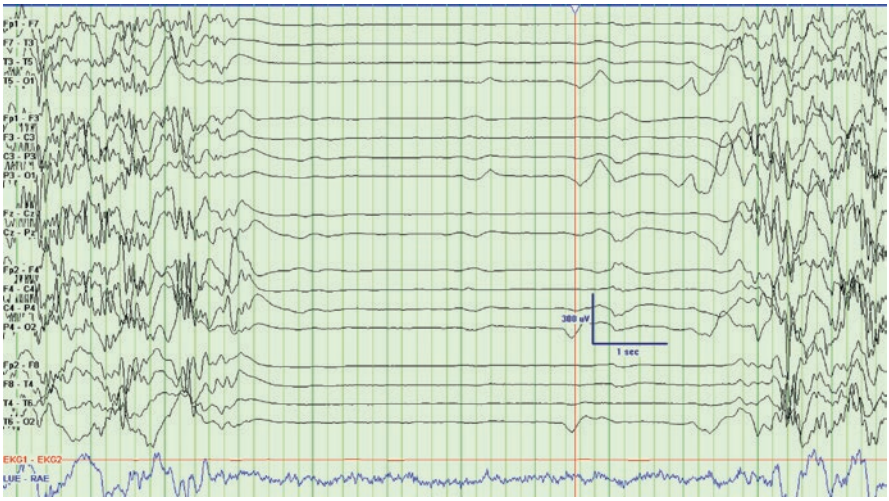


**Fig. 2.5** Epileptic spasm. During the spasm there is diffuse suppression of the background, termed electrodecrement. The hypsarrhythmia pattern is evident before and after the seizure

Epileptic spasms were previously classified as generalized seizures, but multiple well-documented case series have shown that spasms can be due to a unilateral lesion [8–10]. While epileptic seizures can be of focal, generalized, or unknown onset, the majority of epileptic spasms remain generalized in semiology as well as in EEG signature.

## Focal Seizures

Close observation of the semiology of a seizure can be extremely useful to *lateralize* the ictal origin to a hemisphere or *localize* its origin to a brain region. The semiology of seizures is extremely varied, since the external signs of a seizure depend on the cortical area involved [11]. When observing a seizure, it is important to remember that only the *initial* semiology provides information on the seizure origin. Ictal semiology will evolve due to electrical spread of the seizure to adjacent areas or networks. After seizure spread occurs, one may observe signs from the symptomatic zone (clinical symptoms seen by electrical activation of an area of the brain) instead of the epileptogenic zone (origin of seizure) (Fig. 2.6) [12].

Video EEG recording allows us to correlate clinical features with epileptic discharges on the EEG. Because EEG only captures abnormal activity near the cortical surface, localization by surface EEG can be limited. Imaging techniques such as ictal single-photon emission computerized tomography (SPECT) scans and MEG (magnetoencephalogram) can aid with the evaluation of seizure onset, but accurate localization is still limited by insufficient access to deeper structures. Invasive EEG monitoring can add to our precision when localizing epileptic activity. The localizing signs discussed below, while not exhaustive, are meant to touch on the most common and most specific.

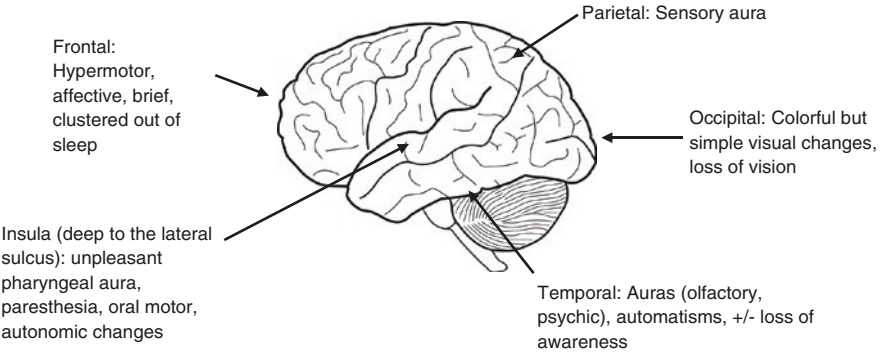



**Fig. 2.6** Seizure semiology by lobe

## Frontal

Focal seizures with onset in the frontal lobe are often marked by a prominent motor component. Frontal seizures tend to look bizarre and can be predominantly or exclusively nocturnal. They can be mistaken for parasomnias at times. Unlike parasomnias, frontal seizures usually occur throughout the night instead of at specified stages in the sleep cycle. They are typically brief (<2 minutes), stereotyped and occur in clusters [13]. Focal clonic or tonic seizures localize to the contralateral primary motor cortex, the most posterior portion of the frontal lobe. The frontal lobe can also give rise to more complex motor movements due to the activation of the supplemental motor and motor association areas. Frontal seizures are often "hypermotor," or hyperkinetic. Movements associated with this seizure type include large, irregular ballistic movements such as thrashing, pedaling, and jumping, or automatisms like pelvic thrusting or genital manipulation [14] (Video 2.6). Hypermotor seizures were once thought to originate from the orbitofrontal or mesiofrontal cortices, but they have recently been shown to originate more diffusely from the dorsolateral frontal cortex, frontal pole, temporal pole, and operculum [15–18].

Seizures originating from the supplementary sensorimotor area (SSMA), located in the frontal lobe anterior to the primary motor cortex, classically cause asymmetric tonic seizures [19], though they can also lead to bilateral *symmetric* tonic posturing with preserved awareness [20]. Asymmetric tonic limb posturing can be in the form of the "fencing posture" when directly stimulated. This posture, also called the M2e sign, consists of tonic abduction of the contralateral arm and external rotation of the shoulder with flexion of the ipsilateral elbow [21] (Fig. 2.7). Seizures from the SSMA can take another form called the figure of 4 sign. This posture is composed of rigid extension of one arm at the elbow, often with the fist clenched and flexed at the wrist, while the opposite extremity is flexed at the elbow (Fig. 2.7). The figure of four sign has value primarily in lateralization, as the extended arm is typically contralateral to the hemisphere of seizure onset [22].

Frontal lobe seizures may also produce motor inactivation and are called hypomotor or hypokinetic seizures. This term is used primarily to describe seizures in

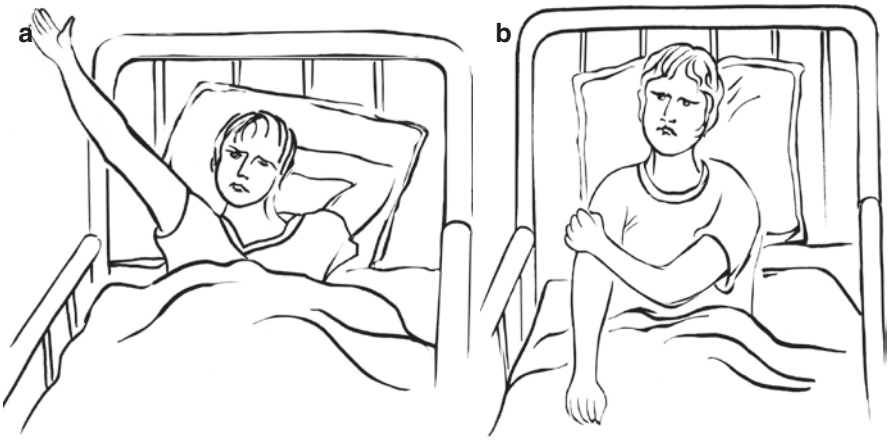



**Fig. 2.7** Semiology of asymmetric tonic limb postures arising from the supplementary sensorimotor area. (**a**) M2e or fencing posture. (**b**) Figure of 4, seen during secondary generalization due to asymmetric activation. (Illustrations by Edda V. Sigurdardottir)

individuals whose consciousness cannot be tested, such as in infants or the severely intellectually disabled [15]. Hypomotor seizures, in which consciousness is retained but the patient is unable to perform a desired movement, localize to the middle and inferior frontal gyri. Masticatory seizures and hypersalivation can localize to the fronto-parietal operculum. Aphasia or dysphasia in a person who is responsive during a seizure may localize to Broca's area [23].

## Temporal

Seizures of temporal lobe onset are classically associated with auras and/or automatisms, and are typically accompanied by impaired awareness [24]. Some seizures are preceded by an aura, a subjectively felt sensory or psychic phenomenon due to ictal activity. When an aura is experienced in isolation, it is considered a focal sensory seizure. Most auras localize to the temporal lobe but are not necessarily lateralizing [25]. Auras can be sensory or experiential. Sensory auras can involve any of the five traditionally recognized senses in addition to less tradition ones, such as an abdominal/epigastric or cephalic aura. An abdominal (also known as epigastric) aura can present as many sensations including nausea, stomach tightness, butterflies, or a sensation of stomach rising as on a roller coaster. A cephalic aura involves sensation in the head like lightheadedness or headache, and can occur in frontal as well as temporal seizures [14]. Experiential auras are also known as psychic auras. They involve the experience of complex feelings such as fear, déjà vu, jamais vu, out of body sensations, or a feeling of religiosity. Vertigo or dizziness are also frequently experienced in temporal lobe seizures, though they are not strictly specific

to the temporal lobe [26]. While olfactory auras occur in many seizure types, they occur most frequently in seizures of mesial temporal lobe origin, previously termed "uncinate" seizures (originating from the uncus) [27]. While some simple auras may originate elsewhere (e.g., visual shapes or colors from the occipital lobe), complex auras such as hallucinations or experiential auras localize to the temporal lobe. Auditory auras are most often non-verbal sounds like buzzing or ringing in the ears. Auditory auras localize to the superior temporal gyrus (Heschell's gyrus), though unilateral auditory hallucinations are not reliably predictive for lateralization of seizure origin [28, 29].

Automatisms are common features of focal seizures, particularly those of temporal lobe onset. An automatism is a repetitive movement, often resembling voluntary or purposeful movements, which happens during altered consciousness. There are numerous types of automatisms. The most common are oro-alimentary (lip smacking, chewing), manual or pedal (fumbling, tapping of hands or feet), gestural, gelastic (laughing, usually described as atonal or "mirthless"), or vocal (repetitive non-word vocalizations such as grunting, rarely words) (Video 2.7). Some specific semiological signs are associated with temporal lobe epilepsy, though there is disagreement about lateralization. Peri-ictal water drinking, ictal hypersalivation (especially mesial temporal), ictal spitting, and ictal vomiting (especially anterior temporal) are most frequently seen in temporal lobe onset seizures, but do not consistently lateralize to the dominant or non-dominant hemisphere [30].

Temporal lobe seizures may have unique features in young children compared to adults. There is a predominance of oro-alimentary automatisms before 6 years old, and hyperkinetic movements can originate from the temporal lobe instead of the frontal lobe in infants and toddlers less than 3 years old [31, 32].

The EEG may show interictal focal spikes in the temporal lobe. Temporal lobe focal seizures are characterized by repetitive epileptiform discharges that may spread to adjacent cortex (Appendix B, Fig. B.9).

## Parietal

Seizures originating in the parietal lobe are rare but often have a strong sensory component due to ictal onset in the primary sensory cortex. Focal paresthesias (typically numbness or tingling) of one body part localize the seizure origin to the contralateral primary sensory cortex [12]. As with motor seizures, the paresthesia can spread along to adjacent areas in the primary sensory cortex analogous to a Jacksonian march. Ictal pain has also been localized to the primary somatosensory cortex and occurs more frequently in parietal lobe seizures [33, 34]. Involvement of secondary sensory areas can result in bilateral paresthesias [35]. Lastly, illusions of size change in a body part (macrosomatognosia or

microsomatognosia) localize to the non-dominant temporo-parieto-occipital junction [36]. There are no predominant motor signs that localize to the parietal lobe and the motor semiology is typically due to ictal spread of the seizure to the frontal regions, though hypermotor activity has been localized to the posterior cingulate cortex [16].

## Occipital

Occipital seizures are characterized by elementary visual hallucinations. Simple visual auras such as geometric shapes (particularly spheres), lights, or loss of vision, i.e., ictal blindness or ictal amaurosis, are localized to the primary visual cortex [37, 38]. In contrast, formed visual hallucinations, or those with movement associated, tend to occur more laterally in the parieto-temporal visual association areas [22]. Hallucinations associated with occipital seizures can be colorful and are often accompanied by "white out" or "black out" of the central vision [37, 38]. Symptoms are often bilateral, but if the visual symptoms are confined to one visual field, the seizure can be localized to the contralateral occipital lobe. Epileptic nystagmus has also been reported to localize to the parieto-occipital junction, where the fast phase of the nystagmus is contralateral to the region of seizure onset. This feature, along with forced eye closure and eyelid fluttering, is not specific or reliable [38, 39]. EEG often shows repetitive occipital spikes (Appendix B, Figs. B.10 and B.11).

## Insula

The insula is a fold of cortex buried beneath the central sulcus that demarcates the temporal from frontal and parietal lobes. Insular semiology has been historically difficult to separate from other lobes due to rapid propagation to frontal or temporal regions. Insular seizures are marked by a typical sequence, starting with an initial unpleasant laryngeal or pharyngeal aura, usually constriction or dyspnea. They then evolve into paresthesia, commonly described as an electrical sensation or warmth, either periorally or diffusely. Most of these seizures are followed by typical focal motor semiology [39]. Motor components of insular seizures tend to be limited to the perioral region in children [41]. While many present with behavioral arrest, awareness is initially preserved until ictal spread to other lobes [39]. The insula is also often thought of as the "visceral sensory cortex." [42] An epigastric aura can be elicited by direct stimulation of the insula. The presence of an abdominal aura does not necessarily localize to the insula, as epigastric auras have also been elicited with stimulation of the mesial temporal lobe, basal ganglia, SSMA, and thalamus [12]. Insular seizures frequently include autonomic features,

particularly palpitations, flushing, sweating, piloerection, and changes in temperature (heat) or pain [36, 40]. Ictal bradycardia or cardiac arrest have been described in insular seizures [41].

## Lateralization of Seizures by Hemisphere

While seizure semiology can suggest frontal, parietal, temporal, or occipital lobe origin, many signs instead help lateralize the seizure focus to one *hemisphere* instead of one lobe (Table 2.2).

**Table 2.2** Lateralizing and localizing features of seizures

| Lateralizing sign | Lateralizing value | Localizing value/note | References |
|---|---|---|---|
| **Sensory** | | | |
| Unilateral sensory aura | 52–96% contralateral | Very reliable if parietal lesion | [43, 44] |
| Hemifield visual aura | 100% contralateral | Occipital | [39] |
| Unilateral piloerection | 84% ipsilateral | | [45] |
| **Motor** | | | |
| Head version<br>*Forced, sustained unnatural turning of head and eyes to one side, with neck extension* | 90–100% contralateral | Easy to mistake for non-versive head turning | [46–51] |
| Unilateral clonic activity | 81–92% contralateral | | [47, 50] |
| Unilateral tonic activity | 80-100% contralateral | Predominately frontal or fronto-temporal | [19, 47, 50] |
| Figure-of-4<br>*Asymmetric tonic limb posturing – extension of one arm with the other arm crossing bent at elbow* | 70–94% contralateral to extended arm | Can be seen in tonic phase of GTC | [49, 52–54] |
| Unilateral dystonic posturing<br>*Sustained, forced, unnatural positioning of an extremity with clear rotational component* | 80–100% contralateral | Temporal > frontal | [48–50, 55, 56] |
| Automatisms with preserved consciousness | 100% non-dominant hemisphere | Temporal | [57–59] |
| Ictal spitting | 75% non-dominant hemisphere | Temporal | [60, 61] |
| Unilateral ictal eye blinking | 83–100% ipsilateral | Frontotemporal.<br>Unreliable in tuberous sclerosis complex patients | [62–66] |

(continued)

**Table 2.2** (continued)

| Lateralizing sign | Lateralizing value | Localizing value/note | References |
|---|---|---|---|
| Asymmetric clonic ending after generalized tonic-clonic<br>*Prolonged clonic movements on one extremity compared to the other; ≠ amplitude difference* | 80–89% ipsilateral | Thought to be due to metabolic burnout or exhaustion of neurotransmitters | [53, 67, 68] |
| Unilateral ictal akinesia<br>*Unilateral limb immobility* | 100% contralateral | Activation of negative motor areas | [49, 69, 70] |
| **Language** | | | |
| Ictal speech<br>*Fluent, conversant speech.*<br>*≠ single verbalizations, or non-word sounds* | 83% non-dominant | | [48, 71] |
| Ictal dysphasia or aphasia | 100% dominant | | [71] |
| **Postictal features** | | | |
| Todd's paralysis<br>*Paralysis or paresis of one limb* | 93–100% contralateral | | [72, 73] |
| Unilateral postictal nose wiping | 86–92% ipsilateral in TLE.<br>PPV 100% if done more than once within 1 min only using 1 hand | More frequently seen in TLE than extra-TLE. Reliable if within 10 seconds of seizure offset and if temporal lobe epilepsy | [74–76] |
| Post-ictal aphasia | 80–100% dominant hemisphere if post-ictal aphasia >60 seconds | May be difficult to separate from post-ictal confusion, requires structured assessment | [68, 71, 77–80] |

*PPV* positive predictive value, *TLE* temporal lobe epilepsy, *GTC* generalized tonic-clonic seizure. Dominant and non-dominant refers to the hemisphere to which speech is lateralized

Many lateralizing signs are thought to be from either neglect or "burn out" of the seizing hemisphere. Post-ictal nose wiping with one hand is a sign that points to an ipsilateral seizure focus to the hand used, as there is post-ictal neglect of the hemisphere affected by the seizure that controls the contralateral hand. Likewise, post-ictal paralysis or weakness (known as Todd's paralysis) indicates that the affected limb was involved during the seizure and represents post-ictal depression of the hemisphere that was seizing.

Head version – *sustained* and *forceful* head and eye turning in one direction accompanied by neck extension – lateralizes contralateral to the direction of head turning [46]. Ictal head turning, which can also be called a versive seizure when it occurs in isolation, is most often due to activation of the frontal eye fields and dorsolateral frontal lobe [47, 81]. This clinical feature is thought to be due to activation of the frontal eye fields, though versive seizures have since been noted in other

**Table 2.3** Predictive power of lateralizing features in focal seizures that secondarily generalize

| Sign | Positive predictive value (%) | Inter-rater agreement |
|---|---|---|
| Version | 97[a] | ++ |
| Unilateral tonic | 96[a] | |
| M2e | 100[a] | ++ |
| Unilateral clonic | 90[a] | |
| Figure-of-4 | 74 | + |
| Dystonia | 67 | |
| Asymmetric clonic ending | 89[a] | ++ |
| Todd's paralysis | 83[a] | + |

[a]Lateralization of the epileptogenic zone has positive predictive value of 100% if 2 or more of these signs support the same side

lobes. When strictly defined, version has strong lateralizing value, but it is difficult at times to distinguish from non-versive head turning, which is non-localizing.

Speech function is lateralized to the dominant hemisphere (the left hemisphere in >80% of people). Therefore ictal or post-ictal aphasia in someone who is otherwise alert and trying to converse suggests a dominant hemisphere seizure. If both speech *and* orientation are unimpaired, then the seizure lateralizes *and* localizes the non-dominant temporal lobe [82]. In contrast, ictal speech, which is fluent conversant speech during a seizure, has been thought to lateralize to the non-dominant hemisphere; however, this can be falsely localizing if misinterpreted since many non-words sounds or single verbalizations have no localizing significance.

If focal seizures progress to a bilateral tonic-clonic semiology (frequently still referred to as "secondary generalization"), it can be difficult to glean any localizing or lateralizing signs if the initial focal semiology was witnessed. In contrast to primary generalized seizures, there is a typical motor sequence of *secondarily* generalized seizures that can assist in lateralization of the seizure onset: versive head turn (contralateral seizure focus), tonic or clonic seizure of the face (contralateral), adoption of fencer position, also known as the M2e sign (contralateral to the raised arm) [22], and subsequently the "figure of 4" characterized by asymmetric limb posturing resembling the number 4 (contralateral to the extended arm) [52]. Many secondarily generalized seizures do not pass through all sequences. If any 2 or more of the lateralizing signs support the same hemisphere of origin, then the positive predictive value for lateralization of the epileptogenic zone is 100% [67] (Table 2.3).

## References

1. Perucca E, Gram L, Avanzini G, Dulac O. Antiepileptic drugs as a cause of worsening seizures. Epilepsia. 1998;39(1):5–17.
2. Blume WT, Lüders HO, Mizrahi E, Tassinari C, Van Emde BW, Engel J. Glossary of descriptive terminology for ictal semiology: report of the ILAE Task Force on classification and terminology. Epilepsia. 2001;42(9):1212–8.
3. Fisher RS, Cross JH, D'Souza C, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia. 2017;58(4):531–42.

4. Fisher RS, Cross H, French JA, Higurashi N, Hirsch E, et al. Operational classification of seizure tyes by the International League against Epilepsy: Position Paper of the ILAE Commission for classification and terminology. Epilepsia. 2017;58(4):522–30.
5. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51(4):676–85.
6. Sadleir LG, Scheffer IE, Smith S, Connolly MB, Farrell K. Automatisms in absence seizures in children with idiopathic generalized epilepsy. ArchNeurol. 2009;66(6):729–34.
7. Goldstein J, Slomski J. Epileptic spasms: a variety of etiologies and associated syndromes. J Child Neurol. 2008;23(4):407–14.
8. Donat JF, Lo WD. Asymmetric hypsarrhythmia and infantile spasms in west syndrome. J Child Neurol. 1994;9(3):290–6.
9. Gaily EK, Shewmon DA, Chugani HT, Curran JG. Asymmetric and asynchronous infantile spasms. Epilepsia. 1995;36(9):873–82.
10. Drury I, Beydoun A, Garofalo EA, Henry TR. Asymmetric hypsarrhythmia: clinical electroencephalographic and radiological findings. Epilepsia. 1995;36(1):41–7.
11. Lüders H, Acharya J, Baumgartner C, et al. Semiological seizure classification. Epilepsia. 1998;39(9):1006–13.
12. Lüders HO, Amina S, Bailey C, et al. Proposal: different types of alteration and loss of consciousness in epilepsy. Epilepsia. 2014;55(8):1140–4.
13. Jan MMS, Girvin JP. Seizure semiology: value in identifying seizure origin. Can J Neurol Sci. 2008;35(September 2015):22–30.
14. Jobst BC, Siegel AM, Thadani VM, Roberts DW, Rhodes HC, Williamson PD. Intractable seizures of frontal lobe origin: clinical characteristics, localizing signs, and results of surgery. Epilepsia. 2000;41(9):1139–52.
15. Tufenkjian K, Lüders HO. Seizure semiology: its value and limitations in localizing the epileptogenic zone. J Clin Neurol. 2012;8(4):243–50.
16. Montavont A, Kahane P, Catenoix H, et al. Hypermotor seizures in lateral and mesial parietal epilepsy. Epilepsy Behav. 2013;28(3):408–12.
17. Wang X, Hu W, Zhang K, et al. The anatomo-electrical network underlying hypermotor seizures. Front Neurol. 2018;9(Apr)
18. Vaugier L, McGonigal A, Lagarde S, et al. Hyperkinetic motor seizures: a common semiology generated by two different cortical seizure origins. Epileptic Disord. 2017;19(3):362–6.
19. Werhahn KJ, Noachtar S, Arnold S, et al. Tonic seizures: their significance for lateralization and frequency in different focal epileptic syndromes. Epilepsia. 2000;41(9):1153–61.
20. Sitthinamsuwan B, Usui N, Tottori T, et al. Seizures with tonic posturing: Semiologic difference between supplementary sensorimotor area (SSMA) origin and extra-SSMA origin. Epilepsia. 2016;57(2):e39–44.
21. Ajmone-Marsan C, Ralston B. The epileptic seizure: its functional morphology and diagnostic Significunce: a clinical-electrographic analysis of metrazol-induced attacks. Springfield: Charles Thomas Publisher; 1957.
22. Loddenkemper T, Kotagal P. Lateralizing signs during seizures in focal epilepsy. Epilepsy Behav. 2005;7(1):1–17.
23. Loesch AM, Steger H, Losher C, et al. Seizure-associated aphasia has good lateralizing but poor localizing significance. Epilepsia. 2017;58(9):1551–5.
24. Vendrame M, Zarowski M, Alexopoulos AV, Wyllie E, Kothare SV, Loddenkemper T. Localization of pediatric seizure semiology. Clin Neurophysiol. 2011;122(10):1924–8.
25. Blair RDG. Temporal lobe epilepsy semiology. Epilepsy Res Treat. 2012;2012:1–10.
26. Kim DW, Sunwoo JS, Lee SK. Incidence and localizing value of vertigo and dizziness in patients with epilepsy: video-EEG monitoring study. Epilepsy Res. 2016;126:102–5.
27. Jackson JH, Steward P. Epileptic attacks with a warning of a crude sensation of smell and with the intelleuctual aura (dreamy state) in a patient who had symptoms pointing to gross organic disease of the right temporo-sphenoidal lobe. Brain. 1899;22(4):534–49.

28. Foldvary N, Acharya V, Luders HO. Auditory auras. In: Luders HO, Noachtar S, editors. Epileptic seizures: pathophysiology and clinical semiology. Philadelphia: Churchill Livingstone; 2000. p. 304–12.
29. Florindo I, Bisulli F, Pittau F, et al. Lateralizing value of the auditory aura in partial seizures. Epilepsia. 2006;47(Suppl 5):68–72.
30. Pietrafusa N, de Palma L, De Benedictis A, et al. Ictal vomiting as a sign of temporal lobe epilepsy confirmed by stereo-EEG and surgical outcome. Epilepsy Behav. 2015;53:112–6.
31. Ray A, Kotagal P. Temporal lobe epilepsy in children: overview of clinical semiology. Epileptic Disord. 2005;7(4):299–307.
32. Gataullina S, Dulac O, Bulteau C. Temporal lobe epilepsy in infants and children. Rev Neurol (Paris). 2015;171(3):252–8.
33. Young GB, Blume WT. Painful epileptic seizures. Brain. 1983;106(3):537–54.
34. Siegel AM, Williamson PD, Roberts DW, Thadani VM, Darcey TM. Localized pain associated with seizures originating in the parietal lobe. Epilepsia. 1999;40(7):845–55.
35. Lüders H, Lesser RP, Dinner DS, Hahn JF, Salanga V, Morris HH. The second sensory area in humans: evoked potential and electrical stimulation studies. Ann Neurol. 1985;17(2):177–84.
36. Foldvary-Schaefer N, Unnwongse K. Localizing and lateralizing features of auras and seizures. Epilepsy Behav. 2011;20(2):160–6. https://doi.org/10.1016/j.yebeh.2010.08.034.
37. Williamson P, Thadani V, Darcey T, Spencer D, Spencer S, Mattson R. Occipital lobe epilepsy: clinical characteristics, seizure spread patterns, and results of surgery. Ann Neurol. 1992;31(1):3–13.
38. Salanova V, Andermann F, Oliver A, Rasmussen T, Quesney LF. Occipital lobe epilepsy: electroclinical manifestations, electrocorticography, cortical stimulation and outcome in 42 patients treated between 1930 and 1991: surgery of occipital lobe epilepsy. Brain. 1992;115(6):1655–80.
39. Isnard J, Guenot M, Sindou M, Mauguiere F. Clinical manifestations of insular lobe seizures: a stereo-electroencephalographic study. Epilepsia. 2004;45(9):1079–90.
40. Freri E, Matricardi S, Gozzo F, Cossu M, Granata T, Tassi L. Perisylvian, including insular, childhood epilepsy: presurgical workup and surgical outcome. Epilepsia. 2017;58(8):1360–9.
41. Lanz M, Oehl B, Brandt A, Schulze-Bohange A. Seizure induced cardiac asystole in epilepsy patients undergoing long term video-EEG monitoring. Seizure. 2011;20(2):167–72.
42. Weil AG, Le NMD, Jayakar P, et al. Medically resistant pediatric insular-opercular/perisylvian epilepsy. Part 2: outcome following resective surgery. J Neurosurg Pediatr. 2016:1–13.
43. Tuxhorn IEB. Somatosensory auras in focal epilepsy: a clinical, video EEG and MRI study. Seizure. 2005;14(4):262–8.
44. MarARSAN CA, GOLDHAMMER L. Clinical ictal patterns and electrographic data in cases of partial seizures of frontal-central-parietal origin. UCLA Forum Med Sci. 1973;17:235–58.
45. Loddenkemper T, Kellinghaus C, Gandjour J, et al. Localising and lateralising value of ictal piloerection. J Neurol Neurosurg Psychiatry. 2004;75(6):879–83.
46. Wyllie E, Lüders H, Morris HH, Lesser RP, Dinner DS. The lateralizing significance of versive head and eye movements during epileptic seizures. Neurology. 1986;36(5):606–11.
47. Janszky J, Fogarasi A, Jokeit H, Ebner A. Lateralizing value of unilateral motor and somatosensory manifestations in frontal lobe seizures. Epilepsy Res. 2001;43(2):125–33.
48. Chee MW, Kotagal P, Van Ness PC, Gragg L, Murphy D, Lüders HO. Lateralizing signs in intractable partial epilepsy: blinded multiple-observer analysis. Neurology. 1993;43(12):2519–25.
49. Bleasel A, Kotagal P, Kankirawatana P, Rybicki L. Lateralizing value and semiology of ictal limb posturing and version in temporal lobe and extratemporal epilepsy. Epilepsia. 1997;38(2):168–74.
50. Bonelli SB, Lurger S, Zimprich F, Stogmann E, Assem-Hilger E, Baumgartner C. Clinical seizure lateralization in frontal lobe epilepsy. Epilepsia. 2007;48(3):517–23.
51. Kernan JC, Devinsky O, Luciano DJ, Vazquez B, Perrine K. Lateralizing significance of head and eye deviation in secondary generalized tonic-clonic seizures. Neurology. 1993;43(7):1308–10.

52. Kotagal P, Bleasel A, Geller E, Kankirawatana P, Moorjani BI, Rybicki L. Lateralizing value of asymmetric tonic limb posturing observed in secondarily generalized tonic-clonic seizures. Epilepsia. 2000;41(4):457–62.
53. Trinka E, Walser G, Unterberger I, et al. Asymmetric termination of secondarily generalized tonic-clonic seizures in temporal lobe epilepsy. Neurology. 2002;59(8):1254–6.
54. Jobst BC, Williamson PD, Neuschwander TB, Darcey TM, Thadani VM, Roberts DW. Secondarily generalized seizures in mesial temporal epilepsy: clinical characteristics, lateralizing signs, and association with sleep-wake cycle. Epilepsia. 2001;42(10):1279–87.
55. Kotagal P, Lüders H, Morris HH, et al. Dystonic posturing in complex partial seizures of temporal lobe onset: a new lateralizing sign. Neurology. 1989;39(2 Pt 1):196–201.
56. Yen D-J, Yu H-Y, Yiu C-H, Shih Y-H, Kwan S-Y, Su M-S. The lateralizing value of upper extremity movements in complex partial seizures of temporal lobe origin: a video-EEG study. J Epilepsy. 1998;11(6):314–8.
57. Park SA, Heo K, Koh R, Chang JW, Lee BI. Ictal automatisms with preserved responsiveness in a patient with left mesial temporal lobe epilepsy. Epilepsia. 2001;42(8):1078–81.
58. Ebner A, Dinner DS, Noachtar S, Lüders H. Automatisms with preserved responsiveness: a lateralizing sign in psychomotor seizures. Neurology. 1995;45(1):61–4.
59. Janszky J, Balogh A, Hollo A, et al. Automatisms with preserved responsiveness and ictal aphasia: contradictory lateralising signs during a dominant temporal lobe seizure. Seizure. 2003;12(3):182–5.
60. Kellinghaus C, Loddenkemper T, Kotagal P. Ictal spitting: clinical and electroencephalographic features. Epilepsia. 2003;44(8):1064–9.
61. Quevedo-Diaz M, Campo AT, Vila-Vidal M, Principe A, Ley M, Rocamora R. Ictal spitting in non-dominant temporal lobe epilepsy: an anatomo-electrophysiological correlation. Epileptic Disord. 2018;20(2):139–45.
62. Kalss G, Leitinger M, Dobesberger J, Granbichler CA, Kuchukhidze G, Trinka E. Ictal unilateral eye blinking and contralateral blink inhibition - a video-EEG study and review of the literature. Epilepsy Behav Case Rep. 2013;1(1):161–5.
63. Jadhav T, Bailey C, Maixner W, Harvey AS. Ictal unilateral blinking is an unreliable lateralizing sign in tuberous sclerosis complex. Epilepsy Res. 2016;125:58–61.
64. Benbadis SR, Kotagal P, Klem GH. Unilateral blinking: a lateralizing sign in partial seizures. Neurology. 1996;46(1):45–8.
65. Henkel A, Winkler PA, Noachtar S. Ipsilateral blinking: a rare lateralizing seizure phenomenon in temporal lobe epilepsy. Epileptic Disord. 1999;1(3):195–7.
66. Wada JA. Unilateral blinking as a lateralizing sign of complex partialseizures of temporal lobe origin. In: Wada JA, Penry JK, editors. Advances in epileptology, Xth epilepsy international symposium. New York: Raven Press; 1980. p. 533.
67. Marashly A, Ewida A, Agarwal R, Younes K, Lüders HO. Ictal motor sequences: lateralization and localization values. Epilepsia. 2016;57(3):369–75.
68. Leutmezer F, Wöginger S, Antoni E, Seidl B, Baumgartner C. Asymmetric ending of secondarily generalized seizures a lateralizing sign in TLE. Neurology. 2002:1252–5.
69. Oestreich LJ, Berg MJ, Bachmann DL, Burchfiel J, Erba G. Ictal contralateral paresis in complex partial seizures. Epilepsia. 1995;36(7):671–5.
70. Noachtar S, Lüders HO. Focal akinetic seizures as documented by electroencephalography and video recordings. Neurology. 1999;53(2):427–9.
71. Gabr M, Lüders H, Dinner D, Morris H, Wyllie E. Speech manifestations in lateralization of temporal lobe seizures. Ann Neurol. 1989;25(1):82–7.
72. Kellinghaus C, Kotagal P. Lateralizing value of Todd's palsy in patients with epilepsy. Neurology. 2004;62(2):289–91.
73. Gallmetzer P, Leutmezer F, Serles W, Assem-Hilger E, Spatt J, Baumgartner C. Postictal paresis in focal epilepsies--incidence, duration, and causes: a video-EEG monitoring study. Neurology. 2004;62(12):2160–4.
74. Geyer JD, Payne TA, Faught E, Drury I. Postictal nose-rubbing in the diagnosis, lateralization, and localization of seizures. Neurology. 1999;52(4):743–5. https://doi.org/10.1212/WNL.52.4.743.

75. Hirsch LJ, Lain AH, Walczak TS. Postictal nosewiping lateralizes and localizes to the ipsilateral temporal lobe. Epilepsia. 1998;39(9):991–7.
76. Leutmezer F, Serles W, Lehrner J, Pataraia E, Zeiler K, Baumgartner C. Postictal nose wiping: a lateralizing sign in temporal lobe complex partial seizures. Neurology. 1998;51(4):1175–7.
77. Koerner M, Laxer KD. Ictal speech, postictal language dysfunction, and seizure lateralization. Neurology. 1988;38(4):634–6.
78. Goldberg-Stern H, Gadoth N, Cahill W, Privitera M. Language dysfunction after frontal lobe partial seizures. Neurology. 2004;62(9):1637–8.
79. Privitera M, Kim KK. Postictal language function. Epilepsy Behav. 2010;19(2):140–5.
80. Fakhoury T, Abou-Khalil B, Peguero E. Differentiating clinical features of right and left temporal lobe seizures. Epilepsia. 1994;35(5):1038–44.
81. Manford M, Fish DR, Shorvon SD. An analysis of clinical seizure patterns and their localizing value in frontal and temporal lobe epilepsies. Brain. 1996;119(Pt 1):17–40.
82. Lux S, Kurthen M, Helmstaedter C, Hartje W, Reuber M, Elger CE. The localizing value of ictal consciousness and its constituent functions: a video-EEG study in patients with focal epilepsy. Brain. 2002;125(Pt 12):2691–8.

# Etiology

3

Melissa A. Walker

## Introduction

Aberrations in brain structure, metabolic substrate, or genetic composition can each lead to altered brain physiology and seizures. Furthermore, the lines are blurred across categories, as we now know that some single gene disorders have prominent structural or metabolic consequences, such as tuberous sclerosis complex and GLUT-1 encephalopathy. Thus, while etiologic classification schemes provide a helpful framework, they are routinely revised to reflect both new data and new questions revealed by novel and emerging technologies.

Most large epidemiological studies were performed prior to the introduction of advanced neuro-imaging and molecular genetics. One large retrospective epidemiologic study of the Rochester, Minnesota cohort published in 1996 categorized most cases of epilepsy as "idiopathic/cryptogenic," reflecting a likely preponderance of what we would currently describe as genetic or presumed genetic causes [1]. That finding is supported by recent retrospective analysis of 110 pediatric epilepsy patients at a tertiary care center, which found a genetic cause in 28% of patients [2]. The outline of this chapter reflects the 2011 ILAE Epilepsy Classification [3].

## Genetic

### Epilepsies Due to Mutations in Single Genes

With the advent of improved genetic technologies, the numbers of genetic causes of epilepsy and the phenotypic spectrum of known genetic disorders have both dramatically increased. Many of the genes associated with epilepsy encode proteins

M. A. Walker (✉)
Division of Pediatric Neurology, Massachusetts General Hospital, Boston, MA, USA
e-mail: walker.melissa@mgh.harvard.edu



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_3

that affect ion channels or neurotransmitter receptor subunits, thus altering neuronal membrane conductivity. Here, we highlight a representative subset of known single gene pure epilepsy disorders in detail. A summary listing of commonly identified genetic causes of epilepsy is provided in Table 3.1.

The voltage-gated potassium channels encoded by *KCNQ2* and *KCNQ3* were originally described in association with self-limited (benign) familial neonatal epilepsy, also called "fifth day fits" due to the timing of seizure onset. Affected patients experience focal or generalized seizures with onset on roughly the third day of life and resolution by 4 months of age, generally with normal development. More recently, *KCNQ2* mutations have also been reported in association with a neonatal epileptic encephalopathy and with myokymia. All these associated genetic mutations are inherited in an autosomal dominant pattern [4].

Similarly, perturbations of the voltage gated sodium channel subunit encoded by *SCN2A* can lead to self-limited familial neonatal-infantile seizures, a syndrome of secondarily generalized focal seizures resolving by 1 year of age without appreciable developmental impact. This gene has also been implicated in more malignant epileptic encephalopathy phenotypes, including Ohtahara and Dravet syndromes or Dravet syndrome [5].

Self-limited (benign) familial infantile seizures (SFIS) involves complex focal and generalized tonic-clonic seizures with spontaneous resolution within the first year of life. This epileptic syndrome is associated with mutations of the *PRRT2* (proline-rich transmembrane protein 2) gene inherited in an autosomal dominant fashion [6]. The phenotypic spectrum associated with mutations in this gene also includes familial infantile convulsion with paroxysmal choreoathetosis and paroxysmal kinesigenic dyskinesia [7].

Single gene changes may also predispose to syndromes of provoked as well as unprovoked seizures. Most notably, genetic epilepsy with febrile seizures plus (GEFS+) is a familial syndrome inherited in an autosomal dominant fashion, most often related to mutations of *SCN1A*, but also reported in association with *SCN1B, SCN2A,* and *GABRG2* (encoding a $GABA_A$ receptor subunit) with according phenotypic subtypes. A third of GEFS+ patient will have only febrile seizures, while the remainder have either focal or generalized unprovoked seizures. Development is typically not affected [8].

The same gene can also be associated with more than one type of epilepsy syndrome. For example, Dravet syndrome is characterized by initial normal development and then the development of seizures during infancy and associated developmental arrest or regression. Incidence is 0.5–1/40,000, occurring typically within the first 1–3 years of life [9]. Greater than 80% of cases are caused by truncation mutations in SCN1A [10, 11]. As mentioned above, this gene is also implicated in GEFS +. To complicate matters further, there are other genes associated with Dravet syndrome, including CN1B, GABRG2, PCDH19, and SCN2A. Patients with Dravet syndrome have recurrent provoked and unprovoked generalized seizures of multiple semiologies (tonic-clonic, tonic, myoclonic, absence, atonic) as well as partial seizures. Developmental regression and refractory epilepsy are typical.

**Table 3.1** Single genes associated with "pure" epilepsy syndromes

| Gene | Protein | Epilepsy type | Mode of inheritance |
|---|---|---|---|
| KCNQ2 | Potassium voltage-gated channel subfamily KQT member 2 | Self-limited (benign) familial neonatal seizures; Neonatal epileptic encephalopathy | AD |
| KCNQ3 | Potassium voltage-gated channel subfamily KQT member 3 | Self-limited (benign) familial neonatal seizures | AD |
| SCN2A | Sodium channel type 2, subunit alpha | Self-limited (benign) familial infantile seizures | AD |
| CDLK5 | Cyclin-dependent kinase-like 5 | Infantile spasms | XL |
| ARX | Aristaless-related homeobox | Infantile spasms | XL |
| SNC1A | Sodium channel type 1, subunit alpha | Dravet syndrome;GEFS+ | AD |
| PCDH19 | Protocadherin-19 | Infantile/childhood onset refractory epilepsy in females | XL |
| STXBP1 | Syntaxin binding protein 1 | Ohtahara syndrome | AD |
| SLC2A1 | Solute carrier family 2, facilitated glucose transporter member 1 | GLUT1 deficiency;early onset absence epilepsy | AD |
| ALDH7A1 | Alpha-aminoadipic semialdehyde dehydrogenase | Pyridoxine-dependent epilepsy | AR |
| GRIN2B | Glutamate receptor ionotropic NMDA 2B | Early onset epileptic encephalopathy | AD |
| CHRNA4 | Neuronal acetylcholine receptor alpha-4 | Autosomal dominant nocturnal frontal lobe epilepsy | AD |
| CHRNA2 | Neuronal acetylcholine receptor alpha-2 | Autosomal dominant nocturnal frontal lobe epilepsy | AD |
| KCNT1 | Potassium channel, sodium-activated subfamily T, member 1 | Malignant migrating partial seizures of infancy Autosomal dominant nocturnal frontal lobe epilepsy | AD |
| SCN1B | Sodium channel subunit beta-1 | GEFS+ | AD |
| SCN2A | Sodium channel type 2, subunit alpha | GEFS+ | AD |
| GABRG2 | Gamma-aminobutyric acid receptor subunit gamma-2 | GEFS+ | AD |
| PRRT2 | Proline-rich transmembrane protein 2 | Infantile convulsions; familial paroxysmal kinesigenic dyskinesia | AD |
| SCARB2 | Lysosome membrane protein 2 | Progressive myoclonic epilepsy type 4 | AR |
| KCNC1 | Potassium voltage-gated channel subfamily C member 1 | Myoclonic epilepsy with ataxia | AD |
| CHRNA7 | Neuronal acetylcholine receptor subunit alpha-7 | Idiopathic generalized epilepsy | AD |
| GRIN2A | Glutamate receptor ionotropic, NMDA2A | Atypical childhood epilepsy with centrotemporal spikes; epilepsy-aphasia | AD |

Epilepsy of infancy with migrating focal seizures (EIMFS) and autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) also constitute an interesting demonstration of the complex epileptic phenotypic spectra resulting from single gene changes. ADNFLE, a disorder of adulthood with normal intelligence, was originally reported in association with mutations of nicotinic acetylcholine receptor genes CHRNA4, CHRNB2, and CHRNA2 [12]. Subsequently, mutations in *KCNT1* were reported in patients with ADNFLE and EIMFS. Patients with EIMFS—a rare disorder with only dozens of cases reported to date—experience recurrent, refractory, focal seizures with onset before age 6 months. Classically, seizure foci migrate with consequent shifts in semiology, with progressive increase in frequency coinciding with profound developmental delay and microcephaly [13]. Notably, adult patients with *KCNT1* mutations and ADNFLE also have comorbidities of intellectual disability and psychiatric disturbances [14].

## Presumed Genetic Etiology

Idiopathic generalized electroclinical syndromes were defined by clinical and electroencephalographic (EEG) features by the ILAE in 2005 [15]. They include childhood absence epilepsy, epilepsy with myoclonic absences, epilepsy with myoclonic-atonic seizures, epilepsy with generalized tonic clonic seizures alone, juvenile absence epilepsy, and juvenile myoclonic epilepsy. Though single causative genes have not been identified, family and twin studies support a genetic etiology in this group. Onset may be in childhood, adolescence, or adulthood. The above electroclinical syndromes are delineated more completely in Chap. 4.

Self-limited childhood focal epilepsies are likewise defined by strict clinical and electrographic features. Three such syndromes are recognized by the ILAE including childhood epilepsy with centrotemporal spikes (CECTS, a.k.a. benign Rolandic epilepsy), early onset childhood occipital epilepsy (Panayiotopoulos syndrome), and late onset childhood occipital epilepsy (Gastaut syndrome) [16]. Together, these syndromes account for 22% of cases of primary epilepsy in children. Broadly, affected children have rare, generally nocturnal seizures, frequently with autonomic features. It is currently thought that these syndromes may represent part of a biologic continuum of age-limited seizure susceptibility [17]. Despite the relative frequency of these syndromes and the apparently autosomal dominant inheritance pattern, causative genes remain elusive. GRIN2A mutations among family members with variable childhood focal epilepsy presentations have been noted, but there is a broad phenotypic spectrum of epilepsy in patients with mutations in this gene [18].

## Multisystem Single-Gene Disorders

There are numerous multisystem monogenic syndromes in which epilepsy is a significant clinical feature. Rett syndrome, for example, is most often linked to *MECP2*

**Table 3.2** Single gene syndromes with epilepsy as a prominent feature

| Gene | Protein | Syndrome | Inheritance |
|---|---|---|---|
| MECP2 | Methyl CpG binding protein 2 | Rett | XL |
| CDKL5 | Cyclin-dependent kinase-like 5 | Atypical Rett | XL |
| UBE3A | Ubiquitin protein ligase E3A | Angelman | AD |
| TSC1 | Hamartin | Tuberous sclerosis | AD |
| TSC2 | Tuberin | Tuberous sclerosis | AD |
| ZEB2 | Zinc Finger E-box-binding homeobox 2 | Mowat Wilson | AD |
| EPM2A | Laforin | Lafora Disease | AR |
| NHLRC1 | NHL repeat-containing protein (malin) | Lafora Disease | AR |
| CSTB | Cystatin-B | Unverricht-Lundborg disease | AR |
| SLC6A8 | Solute carrier family 6, member 8 | Creatine deficiency | XL |
| PPT1 | Palmitoyl-protein thioesterase 1 | Neuronal ceroid lipofuscinosis type 1 | AR |
| TPP1 | Tripeptidyl-peptidase 1 | Neuronal ceroid lipofuscinosis type 2 | AR |
| CLN3 | Battenin | Neuronal ceroid lipofuscinosis type 3 | AR |
| DNAJC5 | DNA homolog subfamily C member 5 | Kufs disease (NCL type 4B) | AD |
| CLN8 | Ceroid-lipofuscinosis neuronal protein 8 | Finnish Northern epilepsy (NCL 8) | AR |
| ALDH5A1 | Aldehyde dehydrogenase 5 family member 1 | Succinic semialdehyde dehydrogenase deficiency | AR |
| ADSL | Adenylosuccinate lyase | Adenylosuccinate lyase deficiency | AR |
| FOLR1 | Folate receptor alpha | Cerebral folate deficiency | AR |
| GLDC | Glycine decarboxylase | Nonketotic hyperglycinemia | AR |
| NGLY1 | N-glycanase 1 | Congenital disorder of glycosylation | AR |
| FLNA | Filamin A | Periventricular, nodular, heterotopia | XL |
| KDM6A | Lysine demethylase 6A | Kabuki syndrome | XL |
| ATP1A2 | Sodium/potassium transporting ATPase subunit alpha-2 | Epilepsy and hemiplegic migraine | AD |
| ATP1A3 | Sodium/potassium transporting ATPase subunit alpha-3 | Epilepsy and alternating hemiplegic of childhood | AD |

(encoding a chromatin-binding protein) mutations [19] Epilepsy is a primary feature of Menkes disease, a disorder of copper transport caused by mutations in the *ATP7A* gene [20] (Table 3.2).

## Chromosomal Abnormalities

A population analysis of chromosomal abnormalities and epilepsy in Australia found 400 distinct chromosomal imbalances in patients with seizures or EEG abnormalities. Eight of these had a high association with epilepsy, including Wolf-Hirschhorn (4p-) syndrome, Miller-Dieker syndrome (del 17p13.3), Angelman

**Table 3.3** Chromosomal abnormalities associated with epilepsy

| Chromosomal abnormality | Genetic syndrome | Epilepsy | Other features |
|---|---|---|---|
| Trisomy 21 | Down syndrome | 8%<br>Infantile spasms, focal, GTC | ID, characteristic facial features, cardiac defects |
| 4p deletion | Wolf-Hirschhorn syndrome | 80–90% Hemi convulsions, IS | ID, craniofacial abnormalities (Greek warrior helmet), cleft lip/palate |
| 15q11-13 deletion (maternal) | Angelman syndrome | 80–90%<br>Atypical absence, myoclonic, non-convulsive SE | ID, ASD, microcephaly, ataxia, spasticity |
| 17p13.3 | Miller-Dieker syndrome | 90%<br>Focal, tonic, myoclonic, IS | Lissencephaly, ID, spasticity, craniofacial abnormalities |
| Ring 20 | Ring chromosome 20 syndrome | 90%<br>Focal seizures with ictal terror, oro-alimentary automatisms | ID, microcephaly, craniofacial, microgenitalia, spasticity |
| 18q deletion | 18 q- syndrome | Autonomic seizures with bradycardia | Craniofacial abnormalities, ID, ataxia, hypotonia, cardiac abnormalities, cerebellar hypoplasia, hydrocephalus |
| 1p36 monosomy | | 50–58%<br>Multiple seizure types (IS, GTC, myoclonic, absence, focal) | ID, microcephaly, large fontanel, craniofacial dysmorphisms |

*IS* infantile spasms, *GTC* generalized tonic-clonic, *ID* intellectual disability, *ASD* autism spectrum disorder

syndrome (del 15q11-q13), the inversion duplication 15 syndrome, terminal deletions of chromosome 1q and 1p, and ring chromosomes 14 and 20 [21]. Epilepsy, particularly epileptic spasms, is also commonly associated with Down syndrome (trisomy 21) (Table 3.3).

Seizures, often drug-resistant, have long been described as a significant feature of Angelman syndrome, a disease involving loss of function of a maternally inherited portion of chromosome 15. Interestingly, due to differences in imprinting, loss of function of the identical but paternally inherited region of chromosome 15 results in Prader Willi syndrome, which does not include epilepsy.

## Structural, Predominantly Genetic

### Malformations of Cortical Development

The prevalence of malformations of cortical development remains unknown. However, this heterogeneous group of disorders is frequently associated with

epilepsy and constitutes the most common reason for referral to surgical pediatric epilepsy centers (Table 3.4). The epileptogenic mechanism is presumed to relate to abnormal neuronal connectivity and/or imbalance in excitatory and inhibitory neurotransmission. Focal malformations of cortical development may arise from abnormal neuronal and/or glial proliferation or differentiation, as in tuberous sclerosis complex, focal cortical dysplasia, and hemi-megalencephaly. Abnormal neuronal migration can also produce diffuse malformations of cortical development, including lissencephaly, subcortical band heterotopia, and periventricular nodular heterotopia.

Lissencephaly (also termed agyria or pachygyria) describes absent or deficient gyration with varying degrees of severity and associated clinical presentations. (Fig. 3.1) Multiple monogenetic associations have been described with cortical malformations, including *LIS1, DCX, ARX, RELN, YWHAE, TUBA1A*, *TUBB2B,* and *DYNC1H1* [22].

In subcortical band heterotopia (also known as double cortex, subcortical laminar heterotopia), there is absence of normal lamination and organization of gray matter, yielding bilateral bands of heterotopic gray matter within the white matter between the lateral ventricles and cortex. Most patients present with varying degrees of intellectual impairment and seizures. Associated mutations have been identified in *DCX* and *LIS1* [23].

As the name describes, periventricular nodular heterotopia (PVNH) consists of nodules of gray matter in the periventricular areas due to failure of normal neuronal migration. PVNH can occur in isolation or as part of a larger syndrome. The most

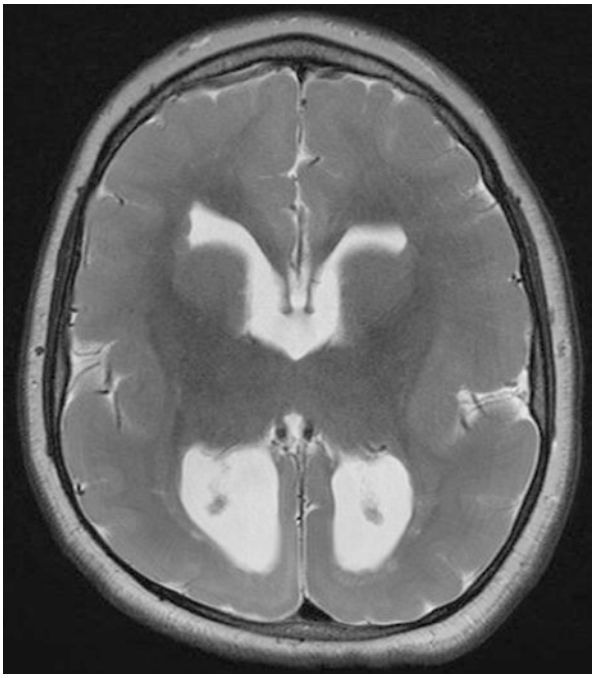


**Fig. 3.1** Lissencephaly**.** Note the paucity of sulci and relatively smooth cortex, most prominent posteriorly

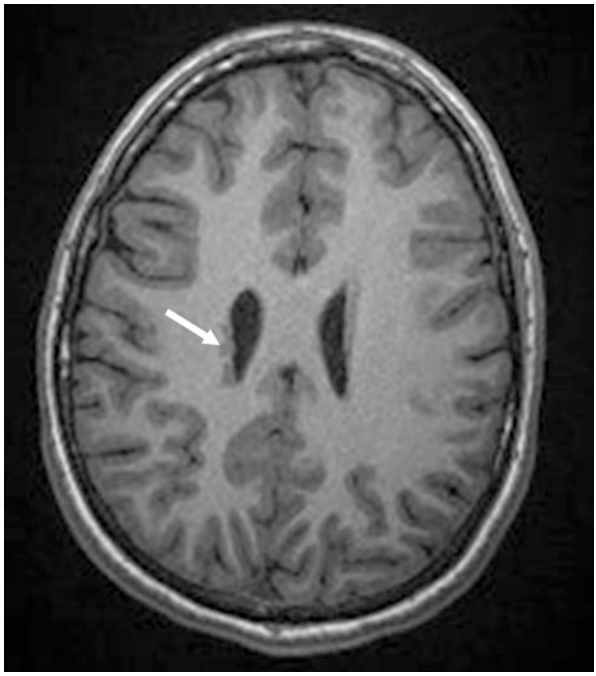


**Fig. 3.2** Periventricular nodular heterotopia. Note small nodules of heterotopic grey matter along the upper border of the right lateral ventricle (white arrow)

common clinical association is epilepsy (80–90%). Associated mutations include *FLNA* (which is X-linked) and *ARFGEF2* [23] (Fig. 3.2).

Polymicrogyria (PMG) is among the most common malformation of cortical development, referring to cortex with an excess of small, abnormal gyri. Clinical presentation varies with the location and extent of affected cortex, and epilepsy occurs in 60–85%. PMG can occur in genetic syndromes including Zellweger and 22q11.2 deletion syndromes. Putative monogenetic associations have been identified, including *AKT3, PIK3CA*, and *GPR56* [23] (Fig. 3.3).

Schizencephaly refers to clefts in the brain. More than half of affected patients have epilepsy. The etiology of schizencephaly—whether genetic or acquired—remains controversial [24, 25] (Fig. 3.4).

## Neurocutaneous Syndromes

Epilepsy is a common complication of many neurocutaneous syndromes, presumably reflecting underlying abnormalities of connectivity related to ectodermal dysplasia (Table 3.5). Skin and brain have the same origin (ectoderm) in embryonic development. Epilepsy occurs in 91% of patients with tuberous sclerosis complex (a multisystem disease of benign tumors related to *TSC1* or *TSC2* mutations). Seizure is a common presenting symptom in infancy, although seizures are not used as a diagnostic criterion [26]. Clinical features include hypopigmented skin lesions,

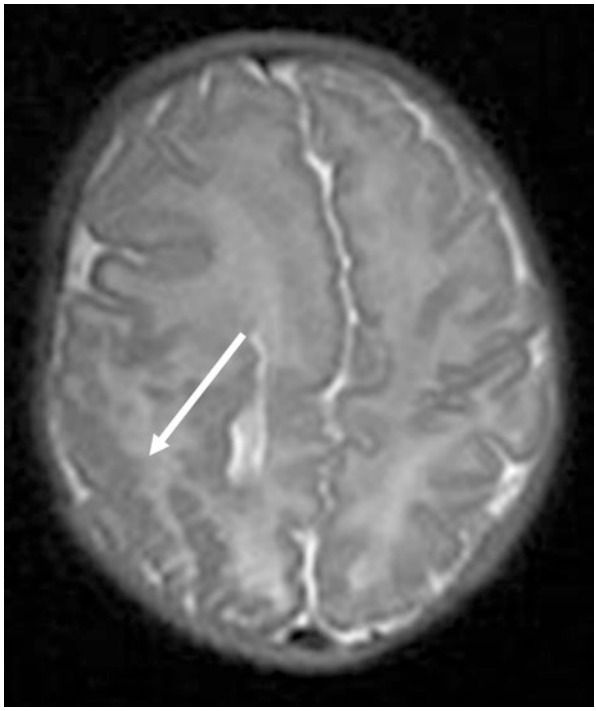


**Fig. 3.3** Polymicrogyria. Note thickened, irregular cortex in the right hemisphere (white arrow) [25]

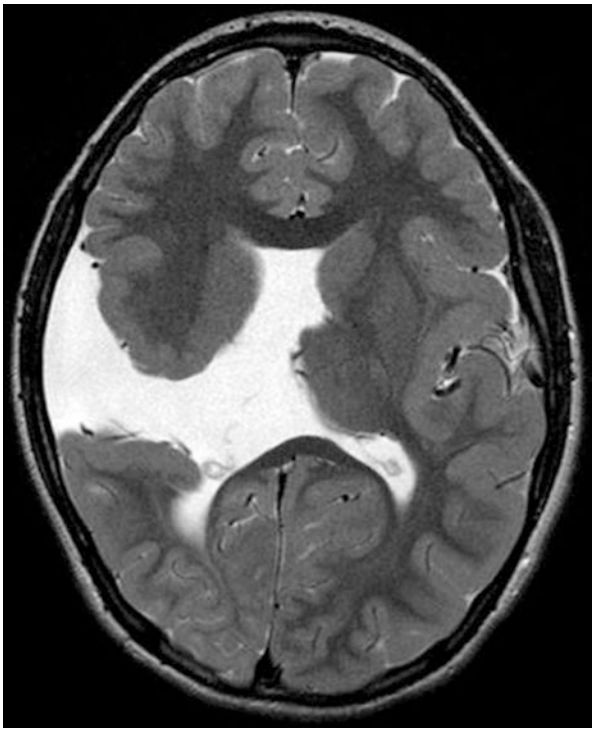


**Fig. 3.4** Schizencephaly. Note the cleft in the right hemisphere, with direct connection between the ventricle and extra-axial space [25]

**Table 3.4** Cerebral malformations associated with epilepsy [25]

| Malformation |
|---|
| Focal cortical dysplasia |
| Periventricular nodular heterotopia |
| Lissencephaly/pachygyria |
| Hemi-megalencephaly |
| Cortical tubers |
| Subcortical band heterotopia |
| Polymicrogyria |
| Schizencephaly |

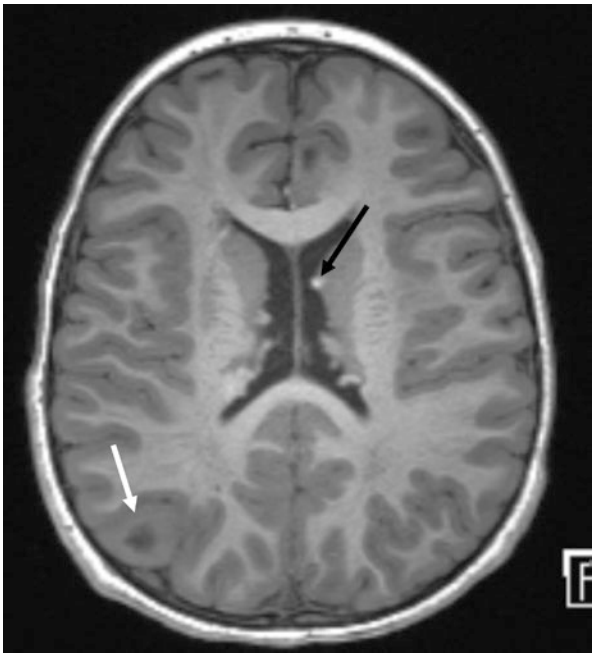


**Fig. 3.5** Tuberous sclerosis. Note the cortical tubers (white arrow) and subependymal nodules (black arrow) [26]

angiofibromas, connective tissue plaques, cardiac, and renal benign tumors. Neuropathology includes cortical tubers (focal dysplasias), subependymal nodules, and subependymal giant cells astrocytomas. TS is a significant cause of infantile spasms (see previous section) (Fig. 3.5).

Rates of epilepsy in Sturge-Weber syndrome, a disease of leptomeningeal angiomatosis most frequently caused by mosaic mutations of the *GNAQ* gene, are as high as 80%. Children with bilateral port wine stains may have a higher risk of seizures. Onset can occur at any age, though typically in childhood, and often heralds hemiparesis [27].

Patients with neurofibromatosis type 1 (caused by mutations in the *neurofibromin*) have a two-fold increased risk of seizure compared to the general population, frequently focal and related to intracranial neoplasm [28]. Seizures are not a typical

**Table 3.5** Neurocutaneous disorders associated with epilepsy [26–30]

| Syndrome | CNS structural abnormalities | Gene/etiology | Epilepsy | Cutaneous findings | Other system findings |
|---|---|---|---|---|---|
| Tuberous sclerosis complex | Cortical tubers<br>Subependymal nodules<br>Subependymal giant cell astrocytoma | TSC1, TSC2 | 90% with Epilepsy<br>Infantile spasms<br>Focal epilepsy | Hypopigmented macules<br>Shagreen patch<br>Periungual fibromas | Rhabdomyoma<br>Renal angiomyolipoma |
| Sturge-Webber Syndrome | Leptomeningeal angiomatosis | GNAQ | 80%<br>Focal onset | Facial port-wine macules | |
| Hypomelanosis of Ito | White matter abnormalities<br>FCD<br>Gray matter heterotopia | Unknown | 10–50%<br>Focal onset | Hypopigmentation along lines of Blaschko | Ocular dysplasia<br>Skeletal dysplasia |
| Neurofibromatosis type 1 | Gliomatosis<br>Optic pathway glioma | neurofibromin | 5%<br>Focal | Café au lait macules<br>Neurofibromas<br>Skin fold freckling | Dysplastic scoliosis<br>Renal artery stenosis<br>Lisch nodules |

feature of NF1, but do occur in this population. Seizures in neurofibromatosis type 2 are rare [29].

Hypomelanosis of Ito is a rare cutaneous disorder that commonly also manifests CNS pathology. The cutaneous findings consist of regions of decreased pigmentation forming striations, whorls, and patches on the trunk, typically following lines of Blaschko. Extracutaneous symptoms are common, including abnormalities in the CNS, eyes, and bones. Epilepsy occurs frequently, with estimates ranging from 11% to 50% of cases. Seizures may be refractory to treatment. Some cases have identifiable white matter abnormalities or cortical malformations, which can include hemi-megalencephaly, focal cortical dysplasia, gray matter heterotopias, or pachygyria. The cause of this disorder is not known, although mosaicism of chromosomal rearrangements has been identified in some cases [30].

## Structural, Predominantly Acquired

### Cerebral Trauma

Roughly one-third of traumatic brain injuries in the United States affect children under the age of 14 years [31]. Victims of cerebral trauma are vulnerable to both early (occurring within 1 week of injury) post-traumatic seizures and long-term post-traumatic epilepsy. As many as 19% of pediatric patients with TBI will experience associated seizures [32]. Younger age is associated with higher rates of early post-traumatic seizure (31% of children <7 years old, 20% of children 8–16 years old, 8.4% of children >16 years) [33]. The occurrence of early posttraumatic

seizures and depressed skull fracture are each associated with an increased risk of long-term posttraumatic epilepsy. Other risk factors for long-term posttraumatic epilepsy include severity of brain injury (as measured by Glasgow Coma Score), prolonged duration of unconsciousness, and posttraumatic amnesia [33, 34].

## Cerebral Tumors

A longitudinal, retrospective analysis of nearly 300 patients with pediatric primary brain tumors revealed that seizures are observed at presentation in 24% and were ongoing in 14%. Features associated with increased risk of seizure included tumor pathology (specifically low/high grade glioma, glioneuronal tumor), cortical location, and subtotal resection [35]. Tumors are not a common cause of seizures in childhood, accounting for 1–3% of patients with a new seizure. Seizures as the presenting symptom of a brain tumor in pediatrics are also rare, particularly given many of them are infratentorial. Slowly growing astrocytomas and dysembryoplastic neuroectodermal tumors are the pediatric tumors primarily associated with seizures, occurring in up to 75% of cases. Interestingly, late seizures, occurring years after treatment, have been described in up to 25% of long-term survivors of childhood brain tumors [36].

## Hippocampal Sclerosis

Hippocampal sclerosis, also termed mesial temporal sclerosis, is characterized by atrophy of the hippocampus with associated scarring and gliosis. It is an important cause of epilepsy in adults and, to a lesser extent, children. Clinically, identifying a patient with hippocampal sclerosis is significant, as it presents the opportunity for surgical treatment (and possibly cure) of his or her epilepsy. Rates of hippocampal sclerosis of 10–30% have been reported in pediatric patients receiving epilepsy surgery [37, 38]. The etiology is not clear. Injury to the hippocampus by hypoxia or prolonged seizure activity may be causal, but not in most cases. There appears to be an association with prolonged febrile seizures in early childhood and the development of hippocampal sclerosis later in life [39].

## Cerebral Infection

Nearly a third of patients with central nervous system (CNS) infections will develop early provoked seizures at or around time of a CNS infection. Among bacterial meningoencephalitides, beta-hemolytic streptococcus infections have the highest risk of seizure (78%), followed by H. influenza (44%), D. pneumonia (25%), and N. meningitidis (10%). Abscess or empyema can also present with seizure. As many as 20% of patients with CNS tuberculosis will develop symptomatic seizures. It is estimated that 30–50% of all epilepsy in endemic regions such as Latin America and

Africa are due to neurocysticercosis. Acute cerebral malaria and later resultant vascular lesions are an important cause of seizures and epilepsy in the developing world. Complications of human immunodeficiency virus infection and acquired immune deficiency syndrome include epilepsy. Following acute infection, an estimated 6.8–8.3% of patients surviving central nervous system infection will go on to develop epilepsy [40].

Numerous viral encephalitides may also cause seizures. Herpes simplex virus is the most common pathogen. Arboviruses such as West Nile virus and eastern equine encephalitis virus may cause seizures as part of their clinical course. The risk of developing epilepsy after viral encephalitis is 20 times the baseline population risk [40].

## Cerebrovascular Disorders

Anoxic injury and resultant cortical irritability related to either ischemia or hemorrhage can precipitate seizures acutely in ischemic or hemorrhagic stroke. The resultant cortical injury and gliosis may lead to epilepsy in survivors. The large majority of infants with neonatal arterial ischemic stroke (72%) will present with seizure while only 22% of children aged 2 months to 18 years have seizure as a manifestation of acute arterial ischemic stroke [41, 42]. In a large Canadian series of neonates and children with cerebral venous sinus thrombosis, 71% of affected neonates and 48% of affected children presented with seizure, most commonly generalized tonic-clonic. At follow up, 20% of neonates and 11% of children had persistent epilepsy [43]. In one small series, 9 of 37 patients experiencing stroke before age 16 years had persistent seizures at long-term follow-up [44].

Seizures can be an important acute manifestation or long-term sequelae of hemorrhage stroke secondary to arteriovenous malformations and cavernous hemangiomas [45]. Cavernous hemangiomas frequently present with seizure and are the most common CNS vascular lesion in children. They may be genetic/familial or associated with radiation therapy for intracranial neoplasm [46].

## Cerebral Immunologic Disorders

There is increasing interest in the roles of inflammation and autoimmunity in epilepsy and seizures. One population-based study of 2.5 million Americans revealed that 17.5% of all epilepsy patients had one of 12 autoimmune disorders. The risk of epilepsy was significantly higher in patients with autoimmune disease. The risk was even higher in children under 18 years old compared to the general population, with a five-fold risk increase of epilepsy in children with autoimmune disease [47].

While not proven, current thinking holds that Rasmussen encephalitis—a syndrome of unilateral cerebral atrophy and unilateral, refractory seizures and progressive hemiparesis with nonspecific inflammation noted on neuropathy—is likely immune-mediated [48]. This disorder often presents with epilepsia partialis

continua and is refractory to medical therapy. Surgical hemispheric disconnection is often required to control seizures.

Seizures can also complicate systemic inflammatory and autoimmune diseases. For example, seizures are well described in systemic lupus erythematosus, occurring at a rate of roughly 10%. They may be directly related to CNS vasculitis, or as a secondary result of hypertension, electrolyte disturbances, or disease treatment [49].

## Paraneoplastic Disorders

While the incidence is at present unclear, paraneoplastic syndromes presenting with seizures are an important epileptic etiology. Antibodies directed at both cell surface and intracellular antigens can result in epileptic encephalopathies. N-methyl-D-aspartate receptor (NMDAR) antibodies, first recognized in patients with ovarian teratomas, have now been identified in cases with and without associated tumors. NMDAR-antibody-mediated encephalitis has also been described in non-neoplastic conditions, particularly infections. The onset of this immune-mediated encephalopathy is often weeks after an infectious illness. Herpes simplex virus has been implicated in NMDAR encephalitis.

Other antibodies, including anti-metabotropic glutamate receptor 5 (cell surface), anti-Hu, anti-Ma2, anti-amphiphysin, and anti-collapsin response mediator protein-5 (all intracellular antigens) are associated with tumors more than 90% of the time. Of these, anti-Hu antibodies are most frequently associated with seizure and status epilepticus. All these antibodies are presumed to exert an epileptogenic effect by direct modulation of neurotransmitter receptors or precipitation of limbic encephalitis by other mechanisms [50].

## Metabolic

Epilepsy is an important feature of many inborn errors of metabolism. While individually rare, metabolic disorders constitute a significant proportion of pediatric neurological disease. Inborn errors of metabolism of amino acids, organic acids, fatty acids, neurotransmitters, urea cycle intermediates, vitamins, cofactors, and the primary mitochondrial disorders are the major categories associated with epilepsy. The mechanism by which the disorders of small-molecule metabolism lead to seizures remains unclear in many cases but may involve accumulation of toxic metabolites or secondary structural damage. Secondary effects of metabolic perturbations, including hypoglycemia or lactic acidemia, may in part underlie seizures in some cases (e.g., 3-Hydroxy-3-methylglutaric academia, hyperinsulinism-hyperammonemia, Glucose Transporter 1 Deficiency). Seizure semiology and EEG findings are diverse with this broad group, but the various disorders often present with characteristic seizure types and electrographic features [51].

Importantly, some of these disorders are treatable, including pyridoxine-dependent epilepsy, methylmalonic acidemia, cobalamin deficiency, maple syrup urine disease, homocystinuria, and to a lesser extent 3-Hydroxy-3-methylglutaric acidemia, glutaric acidemia, fatty oxidation disorders, primary cerebral folate deficiency, 3-phosphoglycerate dehydrogenase, urea cycle disorders, disorders of carnitine synthesis (GAMT, arginine-glycine amidinotransferase deficiency), and glycine encephalopathy [51].

## Metabolic Degenerative

Pediatric neurodegenerative disorders are frequently associated with seizure. Roughly two-thirds of lysosomal storage disorders, such as the neuronal ceroid lipofuscinoses, sphingolipidoses (including Gaucher disease), and gangliosidoses (including Tay-Sachs disease), produce progressive epileptic encephalopathy related to neurodegeneration. Conversely, epilepsy in peroxisomal disorders—which are also multisystem disorders—is posited to arise from cortical migration defects [51]. Alexander's disease, arising from disruption of the glial fibrillary acidic protein (GFAP) gene encoding astrocyte intermediate filaments, is somewhat unusual among the leukodystrophies in its frequent presentation with seizures [52]. The neuroacanthocytosis syndromes are another class of degenerative diseases characterized by red blood cell acanthocytosis and progressive neurodegeneration, sometimes with resultant epilepsy, as in chorea-acanthocytosis and MacLeod neuroacanthocytosis [53].

## Progressive Myoclonus Epilepsies

The progressive myoclonus epilepsies (PME) are a heterogenous group of disorders characterized by refractory epilepsy, multifocal myoclonus, and dementia, ultimately leading to developmental devastation and death. The myoclonus associated with PME is often induced by action or somatosensory stimulation. Lafora disease, myoclonic epilepsy with ragged red fibers (MERRF), neuronal ceroid lipofuscinosis (NCL), dentatorubral pallidoluysian atrophy, Unverricht-Lundborg disease (ULD), sialidosis, Gaucher disease, and subacute sclerosing panencephalitis (SSPE) are relatively common causes of PME, which is in general rare. Less frequent causes include action myoclonus-renal failure syndrome, juvenile Huntington disease, familial encephalopathy with neuroserpin inclusion bodies, noninfantile neuronopathic Gaucher disease, atypical inclusion body disease, neuroaxonal dystrophy, celiac disease, juvenile GM2 gangliosidosis, pantothenate kinase-associated neurodegeneration, early onset Alzheimer disease, and FARS2 mutations [54, 55].

## Mixed Etiologies

### West Syndrome

The term "West syndrome" refers to the triad of infantile spasms, psychomotor developmental arrest, and hypsarrhythmia on EEG. West syndrome is a phenomenon limited to the first year of life, and though to be related to specific stages of cortical development in infancy. The term infantile spasms (IS) is frequently used to refer to this disorder. While rare, roughly 70–90% of infants with West syndrome will experience profound developmental delay, which along with spasms is in many cases treatable, making the recognition of this syndrome critical [56].

Classification schemes proposed for infantile spasms reflect the diversity of associated etiologies. Historically, IS has been described as either symptomatic (identifiable etiology and developmental delay at onset) or cryptogenic (previously normal development, no identifiable etiology). A large, multicenter prospective study by the National Infantile Spasms Consortium identified a cause in 64.4% of 250 new IS cases. The etiologies identified were designated as follows: structural-acquired (22.4%), genetic (14.4%), structural-congenital, (10.8%), genetic-structural (10.0%), metabolic (4.8%), and infectious (2.0%). Representations of specific etiologies within each category were consistent with other studies and experience. Among acquired structural causes, periventricular leukomalacia, perinatal and postnatal hypoxic ischemic injury, stroke, and brain trauma were the most common causes. Down syndrome was the most common genetic cause, followed by *CDKL5* mutations. Tuberous sclerosis was the most common genetic structural cause, followed by neurofibromatosis. Primary mitochondrial disorders were important metabolic etiologies, and all infectious causes were related to TORCH infections, though postnatal infection can also cause IS [57].

### Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is defined by clinical criteria, not etiology. Numerous etiologies can produce or evolve into LGS. Defining criteria include the presence of multiple seizure types or semiologies (most patients experience nonconvulsive status at some time), slow (1–2 Hz) spike and wave pattern on EEG, and intellectual disability that may be progressive. As with West syndrome, genetic disorders, neurocutaneous syndromes, hypoxic ischemic injuries, and CNS infection are all important causes. Many patients with LGS have evolved from a phenotype of infantile spasms. Indeed, as many as 25% of patients with LGS carried an earlier diagnosis of IS [58]. About 40% of cases are cryptogenic in etiology, and as with IS, these cases may have a better prognosis [59, 60].

## Unknown

### NORSE, FIRES

Various terms have been used to describe a phenomenon in which children or young adults develop devastating refractory status epilepticus related to febrile illness. Terms used include new-onset refractory status epilepticus (NORSE), devastating epilepsy in school-age children (DESC), acute nonherpetic encephalitis with refractory repetitive partial seizures, acute encephalitis with refractory repetitive partial seizures (AERRPS), and fever induced refractory epileptic encephalopathy (FIRES). These entities are apparently linked by prior normal neurodevelopment and health with onset of devastating refractory epileptic encephalopathy (often fatal) with an antecedent history of febrile illness but no identifiable pathogen or other causal abnormality. Further work must be done to better delineate any unifying pathologies or etiologies [61].

## References

1. Hauser WA, Annegers JF, Kurland LT. Prevalence of epilepsy in Rochester, Minnesota: 1940–1980. Epilepsia. 1991;32(4):429.
2. Mercimek-Mahmutoglu S, et al. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. Epilepsia. 2015;56(5):707–16.
3. Shorvon SD. The etiologic classification of epilepsy. Epilepsia. 2011;52(6):1052–7.
4. Allen NM, et al. The variable phenotypes of KCNQ-related epilepsy. Epilepsia. 2014;55(9):e99–105.
5. Brunklaus A, et al. Genotype phenotype associations across the voltage-gated sodium channel family. J Med Genet. 2014;51(10):650–8.
6. Schubert J, Paravidino R, Becker F, et al. PRRT2 mutations are the major cause of benign familial infantile seizures. Hum Mutat. 2012;33(10):1439–43.
7. Ebrahimi-Fakhari D, et al. The evolving spectrum of PRRT2-associated paroxysmal diseases. Brain. 2015;138(Pt 12):3476–95.
8. Camfield P, Camfield C. Febrile seizures and genetic epilepsy with febrile seizures plus (GEFS+). Epileptic Disord. 2015;17(2):124–33.
9. Kural Z, Ozer A. Epileptic encephalopathies in adults and childhood. Epilepsy Res Treat. 2012;2012:205131.
10. Claes L, Ceulemans B, Audenaert D, et al. De novo SCN1A mutations are the most common cause of severe myoclonic epilepsy of infancy. Hum Mutat. 2003;21:615–21.
11. Harkin LA, McMahon JM, Iona X, et al. The spectrum of SCN1A-related infantile epileptic encephalopathies. Brain. 2007;130:843–52.
12. Marini C, Guerrini R. The role of the nicotinic acetylcholine receptors in sleep-related epilepsy. Biochem Pharmacol. 2007;74:1308–14.
13. Barcia G, Fleming MR, Deligniere A, et al. De novo gain-of-function KCNT1 channel mutations cause malignant migrating partial seizures of infancy. Nat Genet. 2012;44:1255–9.
14. Heron SE, Smith KR, Bahlo M, et al. Missense mutations in the sodium-gated potassium channel gene KCNT1 cause severe autosomal dominant nocturnal frontal lobe epilepsy. Nat Genet. 2012;44:1188–90.
15. Nordli DR Jr. Idiopathic generalized epilepsies recognized by the International League Against Epilepsy. Epilepsia. 2005;46 Suppl 9:48–56.
16. Engel J Jr. Report of the ILAE classification core group. Epilepsia. 2006;47:1558–68.

17. Panayiotopoulos CP, et al. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. Brain. 2008 Sep;131(Pt 9):2264–86.
18. Lesca G, Rudolf G, et al. GRIN2A mutations in acquired epileptic aphasia and related childhood focal epilepsies and encephalopathies with speech and language dysfunction. Nat Genet. 2013;45:1061–6.
19. Lyst MJ, Bird A. Rett syndrome: a complex disorder with simple roots. Nat Rev Genet. 2015;16:261–75.
20. Bahi-Buisson N, et al. Epilepsy in Menkes disease: analysis of clinical stages. Epilepsia. 2006;47:380–6.
21. Singh R, et al. Chromosomal abnormalities and epilepsy: a review of clinicians and gene hunters. Epilepsia. 2002;43:127–40.
22. Fry AE, Cushion TD, Pilz DT. The genetics of lissencephaly. Semin Med Genet. 2014;166C(2):198–210.
23. Parrini E, Conti V, Dobyns WB, Guerrini R. Genetic basis of brain malformations. Mol Syndromol. 2016;7(4):220–33.
24. Jamuar SS, et al. Somatic mutations in cerebral cortical malformations. N Engl J Med. 2014;371:733–43.
25. Leventer RJ, Guerrini R, Dobyns WB. Malformations of cortical development and epilepsy. Dialogues Clin Neurosci. 2008;10(1):47–62.
26. Yates JR, et al. The Tuberous Sclerosis 2000 study: presentation, initial assessments and implications for diagnosis and management. Arch Dis Child. 2011;96(11):1020–5.
27. Sujansky E, Conradi S. Sturge-Weber syndrome: age of onset of seizures and glaucoma and the prognosis for affected children. J Child Neurol. 1995;10(1):49.
28. Ostendorf AP, et al. Epilepsy in individuals with neurofibromatosis type 1. Epilepsia. 2013;54(10):1810–4.
29. Ruggieri M, et al. Earliest clinical manifestations and natural history of neurofibromatosis type 2 (NF2) in childhood: a study of 24 patients. Neuropediatrics. 2005;36(1):21–34.
30. Pavone P, Pratico AD, Ruggieri M. Hypomelanosis of Ito: a round on the frequency and type of epileptic complications. Neurol Sci. 2015;36(7):1173–80.
31. Faul MD, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States. Emergency department visits, hospitalizations, and deaths, 2002–2006. Atlanta: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
32. Arango JI, Deibert CP, Brown D, Bell M, Dvorchik I, Adelson PD. Posttraumatic seizures in children with severe traumatic brain injury. Childs Nerv Syst. 2012;28:1925–9.
33. O'Neill BR, Handler MH, Tong S, Chapman KE. Incidence of seizures on continuous EEG monitoring following traumatic brain injury in children. J Neurosurg Pediatr. 2015;16(2):167–76.
34. Asikainen I, Kaste M, Sarna S. Early and late posttraumatic seizures in traumatic brain injury rehabilitation patients: brain injury factors causing late seizures and influence of seizures on long-term outcome. Epilepsia. 1999;40(5):584.
35. Ullrich NJ, et al. Incidence, risk factors, and longitudinal outcome of seizures in long-term survivors of pediatric brain tumors. Epilepsia. 2015;56(10):1599–604.
36. Wells EM, Gaillard WD, Packer RJ. Pediatric brain tumors and epilepsy. Semin Pediatr Neurol. 2012;19(1):3–8.
37. Hauptman JS, et al. Pediatric epilepsy surgery: long-term 5-year seizure remission and medication use. Neurosurgery. 2012;71(5):985–93.
38. Duchowny M, et al. Temporal lobectomy in early childhood. Epilepsia. 1992;33(2):298.
39. Patterson KP, Baram TZ, Shinnar S. Origins of temporal lobe epilepsy: febrile seizures and febrile status epilepticus. Neurotherapeutics. 2014;11(2):242–50.
40. Vezzani A, Fujinami RS, White HS. Infections, inflammation and epilepsy. Acta Neuropathol. 2016;131:211–34.
41. Kirton A, Armstrong-Wells J, Chang T, Deveber G, Rivkin MJ, Hernandez M, Carpenter J, Yager JY, Lynch JK, Ferriero DM, International Pediatric Stroke Study Investigators. Symptomatic neonatal arterial ischemic stroke: the International Pediatric Stroke Study. Pediatrics. 2011;128(6):e1402–10.

42. Abend NS, Beslow LA, Smith SE, Kessler SK, Vossough A, Mason S, Agner S, Licht DJ, Ichord RN. Seizures as a presenting symptom of acute arterial ischemic stroke in childhood. J Pediatr. 2011;159(3):479–83.
43. deVeber G, Andrew M, Adams C, Bjornson B, Booth F, Buckley DJ, Camfield CS, David M, Humphreys P, Langevin P, MacDonald EA, Gillett J, Meaney B, Shevell M, Sinclair DB, Yager J, Canadian Pediatric Ischemic Stroke Study Group. N cerebral sinovenous thrombosis in children. Engl J Med. 2001;345:417–23.
44. De Schryver EL, Kappelle LJ, Jennekens-Schinkel A, Boudewyn Peters AC. Prognosis of ischemic stroke in childhood: a long-term follow-up study. Dev Med Child Neurol. 2000;42(5):313–8.
45. Liu S, Chen HX, Mao Q, You C, Xu JG. Factors associated with seizure occurrence and long-term seizure control in pediatric brain arteriovenous malformation: a retrospective analysis of 89 patients. BMC Neurol. 2015;15:155.
46. Acciarri N, et al. Cavernous malformations of the central nervous system in the pediatric age group. Pediatr Neurosurg. 2009;45(2):81–104.
47. Ong MS, et al. Population-level evidence for an autoimmune etiology of epilepsy. JAMA Neurol. 2014;71:569–74.
48. Mastrangelo M, et al. Eponym: Rasmussen syndrome. Eur J Pediatr. 2010;169(8):919.
49. Appenzeller S, et al. Epileptic seizures in systemic lupus erythematosus. Neurology. 2004;63:1808–12.
50. Davis R, Dalmau J. Autoimmunity, seizures, and status epilepticus. Epilepsia. 2013;54(06):46–9.
51. Yu J, Pearl PL. Metabolic causes of epileptic encephalopathy. Epilepsy Res Treat. 2013;2013:1–20.
52. Prust M, Wang J, Morizono H. GFAP mutations, age at onset and clinical subtypes of Alexander disease. Neurology. 2011;77(13):1287–94.
53. Jung HH, Danek A, Walker RH. Neurocanthocytosis syndromes. Orphanet J Rare Dis. 2011;6:68.
54. Shahwan A, Farrell M, Delanty N. Progressive myoclonic epilepsies: a review of genetic and therapeutic aspects. Lancet Neurol. 2005;4(4):239.
55. Walker MA, Mohler KP, Hopkins KW, Oakley DH, Sweetser DA, Ibba M, Frosch MP, Thibert RL. Novel compound heterozygous mutations expand the recognized phenotypes of FARS2-linked disease. J Child Neurol. 2016;31(9):1127–37.
56. Pellock JM, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51(10):2175.
57. Wirrell EC, et al. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. 2015;56(4):617–25.
58. Autry AR, Trevathan E, Van Naarden BK, Yeargin-Allsopp M. Increased risk of death among children with Lennox-Gastaut syndrome and infantile spasms. J Child Neurol. 2010;25(4):441.
59. Epi4K Consortium, Epilepsy Phenome/Genome Project, et al. De novo mutations in epileptic encephalopathies. Nature. 2013;501(7466):217–21.
60. Widdess-Walsh P, Dlugos D, Fahlstrom R, Joshi S, Shellhaas R, Boro A, Sullivan J, Geller E, EPGP Investigators. Lennox-Gastaut syndrome of unknown cause: phenotypic characteristics of patients in the Epilepsy Phenome/Genome Project. Epilepsia. 2013;54(11):1898.
61. Ismail FY, Kossoff EH. AERRPS, DESC, NORSE, FIRES: multi-labeling or distinct epileptic entities? Epilepsia. 2011;52(11):e185–9.

# Childhood Epilepsy Syndromes

4

Grace Yoonheekim Gombolay

## Introduction

One of the most interesting and poorly understood aspects of childhood epilepsy is the age-specific presentation of distinct electroclinical syndromes. Advances in genetic testing have opened new opportunities to further aid in the classification of syndromes. The International League Against Epilepsy (ILAE) periodically updates the classification of epileptic syndromes, most recently in 2010 [1]. In this chapter, we review the ILAE-recognized childhood epilepsy syndromes organized by age of onset. In addition to a few others that do not fit into a particular age range.

Many childhood epilepsy syndromes are considered "benign" because they remit later in life and are associated with good long-term outcomes. With the 2017 ILAE Classification update, the terms "self-limited" and "pharmacoresponsive" have supplanted the use of benign. This change came about with the recognition that many "benign" syndromes can be associated with comorbid developmental, learning, and behavioral disorders [2]. Similarly, syndromes previously called "catastrophic" or "malignant" have been reclassified as developmental or epileptic encephalopathies [2].

The term "epileptic encephalopathy" encompasses a diverse group of disorders, with etiologies ranging from single-gene mutations, brain malformations, and brain injury. The unifying features of epileptic encephalopathies include drug-resistance, multiple seizure types, and cognitive or developmental dysfunction. While many epileptic encephalopathies are associated with developmental delays prior to onset of seizures, in some cases there is a regression coincident with the onset of seizures and electroencephalographic (EEG) changes. Epileptic encephalopathies with onset in infancy can manifest as developmental delay or stagnation [3]. EEGs in epileptic

G. Y. Gombolay (✉)
Pediatric Neuroimmunology and Multiple Sclerosis Clinic, Children's Healthcare of Atlanta, Division of Neurology, Emory University, Atlanta, GA, USA
e-mail: grace.yoonheekim.gombolay@emory.edu



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_4

encephalopathies typically show severe abnormalities, including burst-suppression, hypsarrhythmia, multifocal epileptiform changes, and diffuse slowing. There is some debate regarding whether seizures or abnormal EEG activity are responsible for intellectual decline, or if the underlying pathology is primary. The disease course in epileptic encephalopathies typically includes progressive cognitive deterioration [2].

## Neonatal Onset

### Self-Limited (Benign) Familial Neonatal Epilepsy

Self-limited (benign) familial neonatal epilepsy (SFNE), colloquially called "fifth day fits," usually presents within the first few days of life. Seizures can be focal, multifocal, or generalized. The seizures are usually brief but can occur up to 20–30 times per day. Neonates with SFNE usually have a normal exam and interictal EEG. Ictal EEG often demonstrates focal epileptiform discharges. SFNE is an autosomal dominant disorder and a family history is often positive. Mutations in KCNQ2 and KCNQ3, which encode subunits of voltage-gated potassium channels expressed in the brain, have been found in many families with this syndrome [4]. Particular mutations in these genes can also be seen in more severe neonatal epilepsy syndromes, discussed below. Mutations in the SCN2A gene, which encodes a voltage-gated sodium channel, have also been implicated in some cases of SFNE [5]. The prognosis for SFNE is generally excellent. Development is normal and the seizures typically remit within weeks, although may persist until 12 months of age. A small subset of these children (8–13%) develop epilepsy later in life. In the neonatal period, antiepileptics are usually initiated to treat the initial cluster of seizures or if the diagnosis is uncertain. Most infants with this disorder require seizure treatment, but medications are successfully weaned within 3–6 months. SFNE is differentiated from self-limited (benign) familial infantile seizures (discussed later in this chapter) by its earlier onset [6].

### Early Myoclonic Encephalopathy

Early myoclonic encephalopathy (EME) begins during the neonatal period, sometimes as early as the first few hours of life. Clinically, the neonate presents with focal myoclonus, usually of the face or extremities [7]. The myoclonic jerks shift from one area to another erratically. Tonic posturing or tonic spasms can also occur in EME. Importantly, myoclonic seizures occur during wakefulness, distinguishing this disorder from benign neonatal sleep myoclonus.

Several inherited metabolic disorders have been associated with EME. Nonketotic hyperglycinemia is the most common, but other diseases such as D-glyceric aciduria, propionic acidemia, molybdenum cofactor deficiency, methylmalonic acidemia, pyridoxine deficiency, sulfite oxidase deficiency, Menkes disease, and

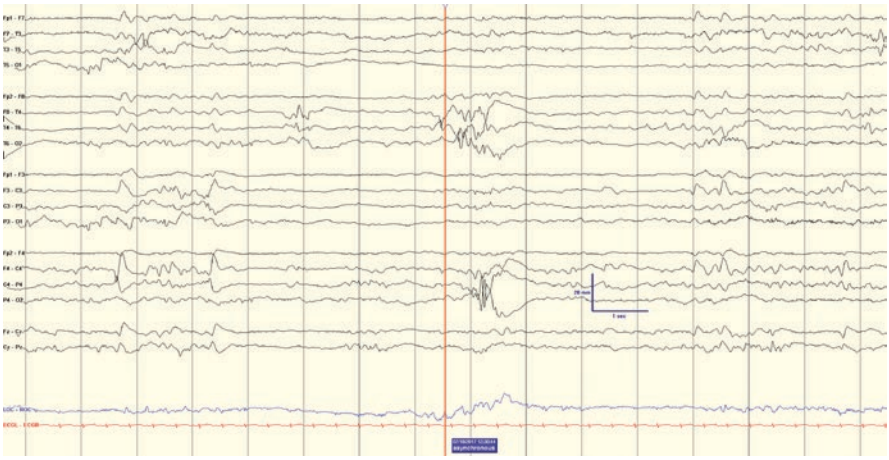


**Fig. 4.1** Burst suppression pattern in a neonate

Zellweger syndrome have also been described in conjunction with EME [7]. Several single genes have also been implicated in EME, including mutations in the ErbB4 gene [8].

The EEG in EME demonstrates a burst-suppression pattern that is more apparent during sleep, although initial EEGs may show a continuous pattern (Fig. 4.1). Treatment is challenging and drug-resistance is typical. Successful treatment with carbamazepine and lidocaine has been reported [9]. Vigabatrin has been reported to cause worsening of seizures in EME associated with nonketotic hyperglycinemia [10]. Prognosis is poor, as about 50% of patients will die before the age of 2 and the other patients will be severely neurodevelopmentally impaired [11].

## Ohtahara Syndrome

Also known as early infantile epileptic encephalopathy, Ohtahara syndrome presents in the first 3 months of age, usually within the first 2 weeks. The presenting seizures are tonic, occurring singly or in clusters, that can last up to 10 seconds. The tonic seizures can be lateralized or generalized and occur up to hundreds of times a day. About one-third of patients will go on to develop other seizure types including focal motor, hemi-clonic, or generalized tonic-clonic. The EEG demonstrates a burst-suppression pattern similar to that of EME [12].

Ohtahara syndrome can result from structural, metabolic, and/or genetic abnormalities. Structural abnormalities associated with this syndrome include hemimegalencephaly, porencephaly, cortical dysplasia, and hypoxic brain injury. Nonketotic hyperglycinemia, cytochrome C oxidase deficiency, pyridoxine dependency, and biotinidase deficiency have also been associated with Ohtahara syndrome [13]. Mutations in several single genes, including STXBP1, ARX and SLC25A22, have been implicated in Ohtahara Syndrome [14]. Prognosis is poor as

many patients will die prior to the age of 2. Survivors typically have severe neurodevelopmental disability. Neonates with Ohtahara syndrome can progress to West syndrome with hypsarrhythmia during infancy and then later evolve into Lennox-Gastaut syndrome with diffuse slow spike and waves during childhood [12].

Treatment is difficult and studies of AEDs including topiramate, ACTH, and pyridoxine have shown poor efficacy [15]. Successful treatment with ketogenic diet, folinic acid, vigabatrin, and chloral hydrate have been described [16–19]. The prognosis is generally poor, with continued seizures and significant developmental disability.

### KCNQ2 Encephalopathy

As mentioned above, mutations in KCNQ2 and KCNQ3 genes encoding potassium channels in the nervous system have been implicated in self-limited (benign) familial neonatal epilepsy. However, in some infants, the course of disease is not benign. These infants typically have an onset of tonic seizures on days 2–8 of life. The seizures can be associated with motor automatisms and apnea, and can be quite frequent, up to 30 times per day. These features are similar to those described in the benign disorder. However, in neonates with encephalopathy, seizures are refractory to medical therapy. The EEG in these cases demonstrates a burst-suppression pattern, and these infants have clear evidence of encephalopathy [20]. Phenobarbital, midazolam, levetiracetam, and valproic acid have been used with only modest success.

Many infants with KCNQ2 encephalopathy have eventual seizure remission, typically by age 3. However, most of them have significant developmental disability [20]. MRIs early in the course demonstrate T2 hyperintensity in the thalamus and basal ganglia which eventually resolve, but cortical atrophy frequently develops. The EEG can evolve from burst suppression to multifocal epileptiform discharges to diffuse slowing [20].

While the genotype-phenotype correlation is not always clear, KCNQ2 mutations that lead to SFNE tend to result in haploinsufficiency, are expressed in the intracellular domain of the channel, and are inherited. Mutations associated with KCNQ2 encephalopathy are often de novo missense mutations in the extracellular portion of the protein and directly affect channel gating [21] (Table 4.1).

## Infantile Onset

### Epilepsy of Infancy with Migrating Focal Seizures

Epilepsy of infancy with migrating focal seizures (EIMFS) is an epileptic encephalopathy that presents in infants within the first year of life, on average at about 3 months. As the name implies, seizures are focal, occurring in any region of the brain and typically migrate. Seizures can arise independently in both hemispheres

**Table 4.1** Neonatal epilepsy syndromes

| Name | Seizure types | EEG | Etiology | Treatment | Prognosis |
|---|---|---|---|---|---|
| Self-limited (benign) familial neonatal epilepsy | Focal, multifocal | Ictal-focal discharges<br>Interictal-normal | Genetic; KCNQ2, and KCNQ3 | Pharmacoresponsive<br>Phenobarbital<br>Phenytoin<br>Levetiracetam | Normal development<br>8–13% with later epilepsy |
| Early myoclonic encephalopathy | Myoclonic (multifocal or generalized)<br>Tonic | Burst suppression | Metabolic (NKH)<br>Genetic<br>(ErbB4) | Drug-resistant;carbamazepine, lidocaine, phenobarbital | Severe NDD,persistent seizures |
| Ohtahara syndrome | Tonic | Burst suppression | Structural (hemimegaloencephaly, cortical dysplasia)<br>Acquired<br>(HIE)<br>Metabolic (NKH, mitochondrial)<br>Genetic (STXBP1, ARX, SLC25A22) | Drug-resistant<br>Topiramate, ACTH, chloral hydrate, ketogenic diet | Severe NDD<br>Progress to West syndrome and/or Lennox Gastaut syndrome |
| KCNQ2 encephalopathy | Tonic, focal clonic | Burst suppression | Genetic: KCNQ2 | Drug-resistant; phenobarbital, midazolam, levetiracetam, valproic acid | Moderate long-term neurodevelopmental disability |

*NKH*=non-ketotic hyperglycinemia; *NDD*=neurodevelopmental disability; *HIE*=hypoxic-ischemic encephalopathy; *ACTH*=adrenocorticotropic hormone

and increase in frequency as time passes. The seizures are refractory to treatment and status epilepticus is common [22]. The EEG initially shows a normal background early which may evolve into diffuse slowing. Focal slowing can occur which may migrate from one area of the brain to another. Multifocal discharges on interictal EEG can occur later in the disease. Ictal EEG demonstrates rhythmic focal alpha or theta discharges and can involve multiple regions independently [22].

In this syndrome, development is typically normal until the onset of seizures, after which there is developmental stagnation or regression with concurrent progressive microcephaly. Family history is usually negative. Imaging is usually normal at onset, but may later show cortical atrophy or mesial temporal sclerosis. Mutations in the following genes have been associated with this disease: KCNT1, SCN1A, SCN2A, SCL25A22, PLCB1, TBC1D24, and CHD2. The prognosis is poor as seizures are usually refractory to treatment. Infants typically have permanent, severe developmental disability [23].

## West Syndrome

West syndrome is an epileptic encephalopathy comprised of the triad of infantile spasms, hypsarrhythmia, and developmental delay. The onset of spasms usually occurs between 3 months and 12 months of age, with a peak onset of 5–7 months [24]. The spasms typically occur in frequent clusters and are often present upon arousal from sleep. The clinical episodes typically involve truncal flexion or extension, with extremity flexion or extension (Appendix A, Video 2.5). Each spasm lasts seconds, but they frequently occur in clusters lasting minutes. Developmental arrest or regression usually presents near the time of spasm onset. Hypsarrhythmia is the characteristic EEG pattern seen in this syndrome and is defined by a disorganized, high voltage slow background with multifocal spikes and polyspikes (Fig. 4.2). The ictal EEG during a clinical spasm shows a high-voltage generalized sharp or slow wave with subsequent voltage attenuation (Fig. 4.3). Hypsarrhythmia may be better observed during sleep.

There are myriad etiologies of infantile spasms, including genetic, acquired structural abnormalities and malformations. Acquired structural causes include hypoxic-ischemic encephalopathy, cerebrovascular accidents, and intracranial infections. Spasms can occur in Aicardi syndrome and lissencephaly and are very common in tuberous sclerosis. Chromosomal disorders such as Down and Miller-Dieker Syndromes have been associated with infantile spasms. Several single gene disorders have also been implicated, including mutations in ARX, CDKL5, SPTAN1, and STXBP1. Inborn errors of metabolism, including nonketotic hyperglycinemia, phenylketonuria, methylmalonic aciduria, maple syrup urine disease, propionic acidemia, pyridoxine dependent epilepsy, and Menkes disease have been associated with West syndrome [25].

ACTH and high-dose oral steroids are first-line therapy in infantile spasms independent of baseline developmental status. Vigabatrin has been shown to be an efficacious initial therapy in infantile spasms associated with tuberous sclerosis but is used as second line to treat infantile spasms in general [26, 27]. The ketogenic diet

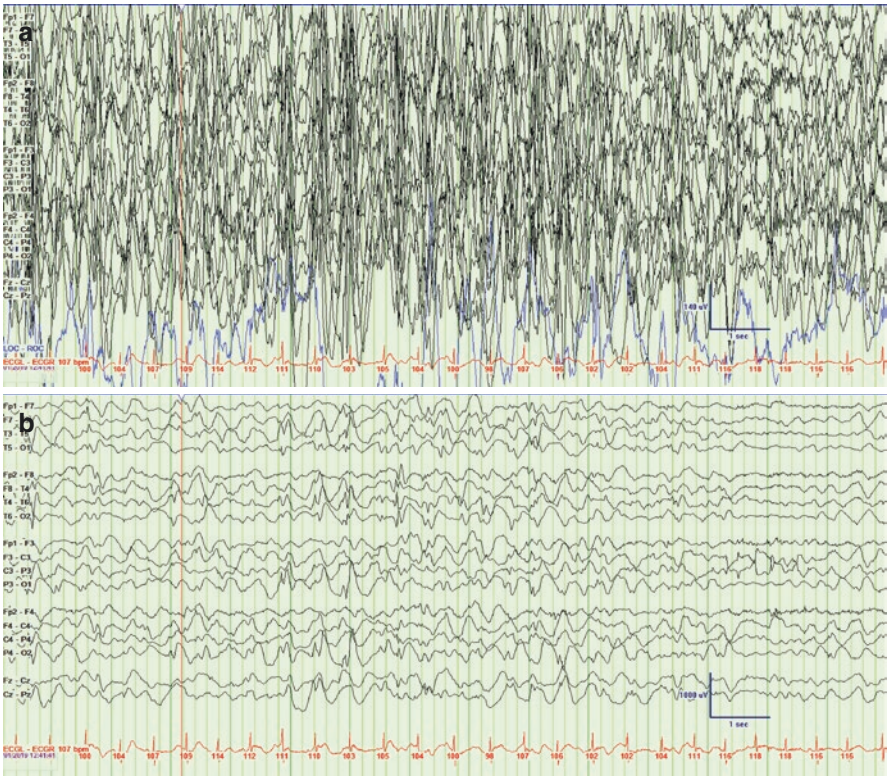



**Fig. 4.2** Hypsarrhythmia. (**a**) Standard recording sensitivity appears chaotic. (**b**) With the sensitivity adjusted we can see diffuse slowing, lack of a clear posterior dominant rhythm and multifocal epileptiform discharges

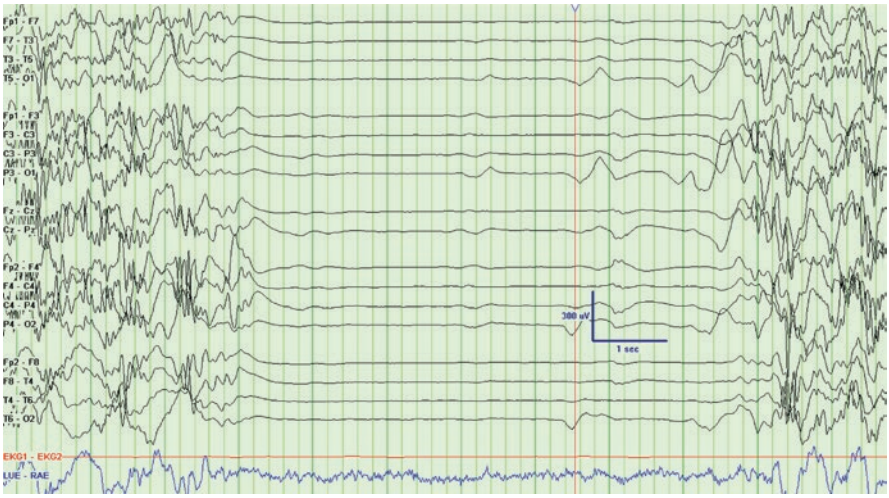


**Fig. 4.3** Infantile spasm characterized by electrodecrement

has demonstrated efficacy in some studies [28]. Numerous anti-epileptic drugs, including benzodiazepines, valproic acid and topiramate have been used with no clear evidence of efficacy. More recently, cannabidiol has been proposed as a potential therapy for refractory cases. Prognosis is influenced by the underlying etiology, early diagnosis, response to therapy, and presence or absence of improvement in the EEG background. In time, the spasms will cease regardless of seizure response to treatment but commonly evolve into other seizure types. Many patients will evolve into Lennox-Gastaut syndrome, which will be discussed later on in this chapter [27].

## Myoclonic Epilepsy in Infancy

Myoclonic epilepsy in infancy is a self-limited disorder with a generally good prognosis. The myoclonic seizures in this disorder can be triggered by photic, tactile, or auditory stimuli. The onset of myoclonic seizures occurs between the ages of 6 months and 2 years and remits between 6 months and 5 years after onset. About 10–20% of patients will then develop other forms of epilepsy later in life, including juvenile myoclonic epilepsy or focal epilepsy [29]. Development is generally normal, as is the interictal EEG. Other seizure types are not common in this syndrome. Ictal EEG reveals generalized polyspike- or spike-wave discharges. Cognitive and behavioral problems have been described if seizures are not well controlled.

## Self-Limited (Benign) Familial Infantile Epilepsy

Similar to SFNE described earlier in this chapter, self-limited (benign) familial infantile epilepsy (SFIE) is an epilepsy syndrome that is inherited in an autosomal dominant pattern. The seizures occur in normal infants with onset later than that of SFNE, usually between 4 and 8 months of age. Spontaneous remission occurs prior to 3 years. Focal motor seizures with and without secondary generalization are the most common seizure types [30]. Multifocal or generalized seizures have also been described. Like SFNE, the seizures are usually brief but can occur anywhere from 20 to 30 times per day. Infants are usually normal in between seizures and interictal EEG is generally normal. Ictal EEG can demonstrate focal discharges. Genes that are implicated in SFIE include PRRT2, SCN2A, KCNQ2, and KCNQ3 [30].

## Dravet Syndrome

Dravet syndrome, previously identified as severe myoclonic epilepsy of infancy, is a clinical syndrome that can be separated into three stages. Stage 1 starts between 4 and 12 months of age, with a previously normal infant presenting with a prolonged seizure commonly in the setting of fever. The initial seizure is usually clonic (either generalized or hemi-clonic), with or without secondary generalization. Focal motor or myoclonic features can also be seen. The initial event is often considered to be a complex febrile seizure. However, within several weeks frequent seizures occur,

often with status epilepticus. Stage 2 presents at one to four years of age, and is considered the "worsening stage" because the child will typically develop a mixture of seizure types, including myoclonic, atypical absence, and focal motor seizures. Convulsive and nonconvulsive status epilepticus is common during this stage [31]. Developmental regression or stagnation can occur during stage 2 or 3. Developmental delay and behavioral problems are also observed at this stage. Ataxia and pyramidal signs frequently manifest as well. Stage 3, the "stabilization stage," begins after about 5 years, when the seizures may improve, typically with convulsions that occur only in sleep. Imaging is normal initially, but as the disease progresses, generalized atrophy or hippocampal sclerosis can be observed [31].

Initial EEGs in Dravet syndrome are normal but evolve over time with disease progression. Diffuse slowing of the EEG background progresses over time. Generalized spike-waves, polyspike-waves, focal and multifocal discharges can occur during wakefulness and in sleep. The ictal EEG depends on seizure semiology. Treatment options for Dravet syndrome include valproic acid, benzodiazepines, levetiracetam, topiramate, and the ketogenic diet. Stiripentol has demonstrated to be efficacious but is not currently available in the United States. Cannabidiol was approved in 2018 for the treatment of Dravet syndrome [32]. Fenfluramine was approved for use in this disorder in 2020 [33]. Truncating mutations in SCN1A are the most common primary genetic etiology for Dravet syndrome. Medications that act on sodium channels, such as carbamazepine, phenytoin, oxcarbazepine, and lamotrigine can exacerbate seizures and should be avoided [34]. Prognosis is poor as many patients will have permanent cognitive impairment. Life expectancy is reduced due to complications of uncontrolled seizures and sudden unexplained death in epilepsy (SUDEP) [31].

## Myoclonic Encephalopathy in Nonprogressive Disorders

Myoclonic encephalopathy in nonprogressive disorders is characterized by multiple episodes of myoclonic status epilepticus that can last hours to days. The onset can occur anytime from the first day of life to 5 years old. Most patients will have a known etiology, which can include chromosomal disorders, structural brain abnormalities, or inborn errors of metabolism. Half of cases are secondary to genetic syndromes such as Angelman, Wolf-Hirschhorn, and Rett [35]. Structural malformations associated with myoclonic epilepsy include polymicrogyria, focal cortical dysplasia, or agenesis of the corpus callosum. Hypoxic ischemic encephalopathy along with cerebellar atrophy has also been associated with myoclonic epilepsy. The distinction between this category and progressive myoclonic epilepsies (see below) is that there is a static, rather than progressive, encephalopathy related to the underlying disorder. The EEG in myoclonic epilepsy with in non-progressive disorders demonstrates a slow background with multifocal spikes, sharp waves, or continuous slow waves. Eye closure can trigger rhythmic delta waves with superimposed spikes. Ictal EEG can demonstrate diffuse rhythmic slow spike-waves. ACTH, ethosuximide, and valproic acid have been used effectively to treat this syndrome [35] (Table 4.2).

**Table 4.2** Epilepsy syndromes with onset in infancy

| Name | Seizure types | EEG | Etiology | Treatment | Prognosis |
|---|---|---|---|---|---|
| Epilepsy of infancy with migrating focal seizures | Focal | Interictal: normal early, diffuse slowing late, multifocal epileptiform discharges<br>Ictal: Focal rhythmic activity | Genetic (KCNT1, SCN1A, SCN2A, SCL25A22, PLCB1, TBC1D24, and CHD2) | Drug-resistant | Regression at the onset of seizures, severe NDD |
| West syndrome | Epileptic spasms | Interictal: Hypsarrhythmia<br>Ictal: Electro decrement | Structural (HIE, malformations)<br>Genetic syndromes (Down syndrome, TSC)<br>Metabolic (NKH, PKU, MMA, Pyridoxine-dependent epilepsy)<br>Single gene (ARX, CDKL5, SPTAN1, STXBP1) | ACTH<br>Vigabatrin<br>Oral corticosteroids<br>Ketogenic diet<br>Cannabidiol | Regression at the onset of seizures<br>90% with significant NDD<br>Prognosis largely dependent on etiology and response to treatment |
| Myoclonic epilepsy of infancy | Myoclonic | Interictal: Normal<br>Ictal: GSW | Presumed genetic | | Favorable unless seizures not controlled<br>10–20% develop epilepsy later |
| Self-limited (benign) familial infantile epilepsy | Focal<br>Secondarily generalized | Interictal: Normal<br>Ictal: focal epileptiform discharges | Genetic (PRRT2, SCN2A, KCNQ2 and KCNQ3) | Pharmacoresponsive | Favorable<br>Normal in most cases |
| Dravet syndrome | Focal<br>GTC<br>Myoclonic<br>Tonic | Interictal: Normal early, then slowing, generalized or focal discharges<br>Ictal: Generalized or focal discharges | Genetic (SCN1A) | Drug-resistant<br>Valproic acid<br>Levetiracetam<br>Topiramate<br>Stiripentol<br>Fenfluramine<br>Benzodiazepines<br>Cannabidiol<br>Ketogenic diet | Poor<br>Significant developmental regression and long-term NDD |
| Myoclonic epilepsy in non-progressive disorders | Myoclonic | Interictal: Slow, multifocal spikes<br>Ictal: GSW | Genetic (Wolf-Hirschhorn, Angelman, Rett)<br>Structural (polymicrogyria, FCD, HIE) | Valproic acid<br>Levetiracetam<br>Benzodiazepines<br>Ethosuximide<br>ACTH | Depends on underlying etiology |

*NDD* neurodevelopmental disability; *HIE* hypoxic ischemic encephalopathy; *TSC* tuberous sclerosis complex; *NKH* nonketotic hyperglycinemia; *PKU* phenylketonuria; *MMA* methylmalonic aciduria; *GSW* generalized spike-wave; *GTC* generalized tonic-clonic; *FCD* focal cortical dysplasia; *ACTH* adrenocorticotropic hormone

## Childhood

### Childhood Absence Epilepsy

Comprising anywhere from 10–17% of childhood onset epilepsies, childhood absence epilepsy (CAE) is the most common seizure disorder in this age group. CAE is characterized by multiple absence seizures per day. Absence seizures present as abrupt behavioral arrest with impaired awareness lasting from 5 to 20 seconds (Appendix A, Video 2.4). Seizures often occur frequently, between 5 and 100 per day. The seizures may have associated subtle movements, such as facial twitching, repetitive blinking, or finger movements. There is no post-ictal period, and children will resume their previous activity. Onset is typically between ages 4 and 10 [36]. Ictal EEG demonstrates 3 Hz generalized spike-and-wave discharges (Fig. 4.4). Like other idiopathic generalized epilepsies, there may be an autosomal dominant inheritance pattern, but specific genes have not been consistently identified. Some familial cases have been associated with mutations in GABRG2 and CACNA1A. GLUT1 deficiency, which is caused by a mutation in the gene SLC2A1, is found in about 10% of patients under the age of 4 with absence seizures. In typical CAE, seizures remit by puberty and are typically easily controlled with AEDs. About 5% will require lifelong antiepileptics [37]. Between 5 and 10% will have at least one GTC seizure in their lifetime. Treatments include ethosuximide, valproic acid, and lamotrigine [38].

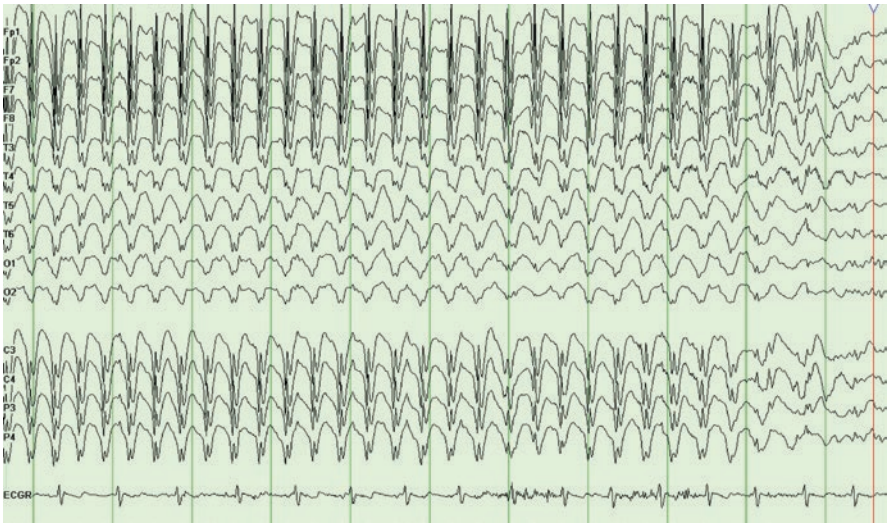



**Fig. 4.4** Typical absence seizure demonstrating 3 Hz generalized spike-wave discharges

## Early Onset Childhood Occipital Epilepsy (Panayiotopoulos Syndrome)

Early onset childhood occipital epilepsy is characterized by ictal autonomic phenomena. The onset is usually between 3 and 6 years of age, although it can occur in patients as young as 1 year. Emesis is the most common autonomic symptom, but others can include pallor, urinary and fecal incontinence, hypersalivation, cyanosis, mydriasis, miosis, coughing, and disturbances in intestinal motility. Oropharyngeal symptoms such as numbness or tingling on one side of the mouth or phonic phenomena such as grunting or guttural sounds can occur [39]. While pure autonomic seizures occur in about 10% of patients with early onset childhood occipital epilepsy, many patients have ictal features more typical of focal seizures, such as confusion, eye deviation, speech arrest, facial convulsions, and visual hallucinations. Hemi-convulsions and secondarily generalized seizures can also be seen in early onset childhood occipital epilepsy. Behavioral changes, such as restlessness or agitation, may occur at the onset of seizure. Seizures can be prolonged and can result in autonomic status epilepticus [40].

The interictal EEG frequently demonstrates occipital spikes, but multifocal epileptiform discharges that shift from one brain region to another are also seen. Prognosis is favorable as most patients will have remission in 1–2 years. On occasion, early onset childhood occipital epilepsy can evolve into childhood epilepsy with centrotemporal spikes [39].

## Childhood Epilepsy with Centrotemporal Spikes

Previously known as benign Rolandic epilepsy or benign epilepsy of childhood with centrotemporal spikes, childhood epilepsy with centrotemporal spikes (CECTS) is a common seizure disorder with onset typically between 4 and 10 years of age. Typical seizures in this syndrome are simple focal seizures that arouse children from sleep. Patients experience oropharyngeal motor or sensory symptoms, repetitive hand movements, speech arrest, and hypersalivation. Secondarily generalized seizures occur occasionally [41]. As described by its name, EEG findings include spikes located predominantly in the central and temporal regions. The discharges have a very characteristic diphasic morphology with an anterior to posterior horizontal dipole (Fig. 4.5). The discharges are usually bilaterally independent and are activated by sleep or drowsiness. Historically, development was thought to be normal, but cognitive, attention, learning, and behavioral problems are increasingly recognized in patients with this “benign” disorder. The role of antiepileptics is debated [42]. Many physicians will only treat if seizures are frequent, occur during the day, or evolve into generalized tonic-clonic events.

Studies in siblings of patients with CECTS have demonstrated centrotemporal spikes are present in up to 10–20% of siblings who have never had a seizure. The inheritance pattern and genetics of this disorder have not been clearly elucidated. Candidate genes include GRIN2A, BRWD3, KCNC3, and PRRT2 [39, 43]. The prognosis is excellent with all children outgrowing the syndrome by age 11–16 years.

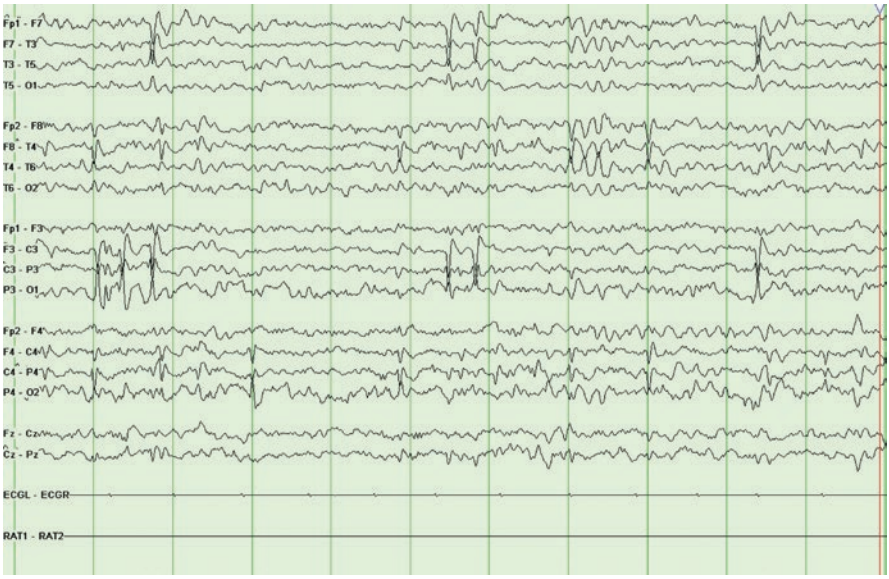



**Fig. 4.5** Typical EEG of childhood epilepsy with centrotemporal spikes. Note left-sided sharp waves in the central and temporal leads

However, 5–8% of children may progress to a more aggressive form of epilepsy during the course of their disease (epileptic encephalopathy with continuous spike and wave of sleep).

## Epilepsy with Myoclonic Atonic Seizures

Epilepsy with myoclonic atonic seizures, also known as Doose syndrome, is an epileptic encephalopathy defined by myoclonic and atonic seizures. Febrile seizures and generalized convulsions can also occur. Patients with myoclonic-atonic epilepsy frequently have episodes of status epilepticus. Other generalized seizures in this syndrome can include absence, atypical absence, tonic, and non-convulsive status epilepticus. Seizures start between the ages of 6 months and 6 years [44].

On EEG, the background can be normal but bi-parietal theta activity is also observed. Generalized spike- and polyspike-waves can occur on interictal EEG. Ictal EEG demonstrates generalized spikes followed by a high-voltage slow wave. Sleep architecture is generally preserved, which helps to distinguish this disorder from Lennox Gastaut syndrome. Seizures are commonly refractory to treatment. Treatments include ethosuximide, valproic acid, lamotrigine, and the ketogenic diet. Conversely, carbamazepine, phenytoin, and vigabatrin can worsen seizures. Levetiracetam has demonstrated mixed results [45]. Genetic etiologies are identified in a minority of cases. The majority of patients with this form of epilepsy have cognitive and behavioral challenges, particularly those who do not respond well to therapy [45].

## Genetic Epilepsy with Febrile Seizures Plus

Genetic epilepsy with febrile seizures plus (GEFS+) is a clinical syndrome that can include both generalized and focal seizures. The initial presenting feature is febrile seizures between the ages of 6 months to 6 years. Factors that distinguish this syndrome from typical simple febrile seizures are the persistence of febrile seizures beyond 6 years of age and evolution to include seizures without fever. The afebrile seizures may be GTCs, atonic, myoclonic, myoclonic-atonic, absence, or focal.

The EEG will have normal background and ictal abnormalities will be dependent on the clinical seizure type. Generalized polyspike-wave or generalized spike and slow wave activity is most common. Mutations in SCN1A, SCN1B, and SCN2A genes are associated with GEFS+ [46]. These genetic changes are typically inherited in an autosomal dominant manner, and the family history is commonly positive. Development and prognosis are generally favorable [47]. As in Dravet syndrome above, anti-epileptic medications that act on sodium channels should be avoided.

## Autosomal Dominant Nocturnal Frontal Lobe Epilepsy

This is a familial epilepsy syndrome that may start at any age. The average age of onset is 9 years old, but it can present as early as infancy or as late as the sixth decade of life. Nocturnal frontal seizures are commonly hyper-motor with dystonic or tonic features. There are often prominent affective symptoms, including extreme fear and screaming. Other described ictal movements include pedaling, thrashing, or pelvic thrusting. Seizures are of brief duration, usually less than one minute, but can occur multiple times per night [48] (Appendix A, Video 2.6). This feature helps distinguish frontal lobe seizures from parasomnias such as confusional arousals or night terrors. About two-thirds of patients will have preserved awareness and no post-ictal state. If seizures occur in the awake state, another seizure disorder should be considered.

EEG demonstrates a normal background, with rare frontal or frontotemporal sharp waves/spikes which may occur only during sleep. Ictal EEG patterns, when present, include sharp waves or repetitive 8–11 Hz spikes, rhythmic theta activity which can be unilateral frontal or bifrontal, or diffuse attenuation. Surface EEG may be normal or mildly abnormal, as many of these seizures have onset in the deep orbitofrontal cortex. Imaging is normal. Genes that have been implicated include nicotinic acetylcholine receptors (CHRNA2, CHRNA4, CHRNB2) and DEPDC5 [49]. As the name implies, genetic mutations in ADNFLE are inherited in an autosomal dominant pattern. Penetrance is variable and sporadic mutations can also occur. Most patients respond to medications used to treat focal epilepsy, but one-third of cases are resistant to treatment. There have been case reports of successful treatment with nicotine patches in adults, which directly modulate the nicotinic acetylcholine receptors [50].

## Late Onset Childhood Occipital Epilepsy

Late onset childhood occipital epilepsy is also known as benign occipital epilepsy of childhood, Gastaut-type. Onset occurs between 3 and 15 years but peak incidence is between 8 and 11 years. Visual hallucinations are the primary seizure type. Patients have described colored circles or other geometric patterns. Ictal blindness may occur. Seizures may include eye fluttering and eye deviation with ipsilateral head turning. The seizures are usually brief and mainly occur while awake [51]. Occipital spikes are seen on the EEG, and are often sleep-activated. Autonomic features are rare as compared to early onset occipital epilepsy. No genetic abnormalities have been identified as causative in this syndrome. Carbamazepine, oxcarbazepine, and other medications effective in treating focal seizures are typically effective. Seizures usually go into remission 2–4 years after onset [39] (Fig. 4.6).

## Epilepsy with Myoclonic Absences

Epilepsy with myoclonic absences (EMA) is an uncommon epilepsy typified by the seizure types within its name. Myoclonic absence seizures can last anywhere from 10 to 60 seconds and occur multiple times a day. The onset and cessation of seizures are abrupt. Generalized tonic-clonic or atonic seizures are also seen in this syndrome. Onset occurs anywhere between 1 and 12 years of age. EEG will show 3 Hz spike-waves like those of childhood absence epilepsy also accompanied by 3 Hz myoclonic bursts on electromyogram [44]. While no specific gene has been associated with EMA, other causes have been described such as brain malformations or chromosomal abnormalities including trisomy 12p, Angelman syndrome and chromosome 15 duplications. Treatment includes valproic acid monotherapy or in combination with topiramate. Lamotrigine, levetiracetam, clonazepam, or clobazam can also be considered. Avoidance of carbamazepine and phenobarbital is advised, as

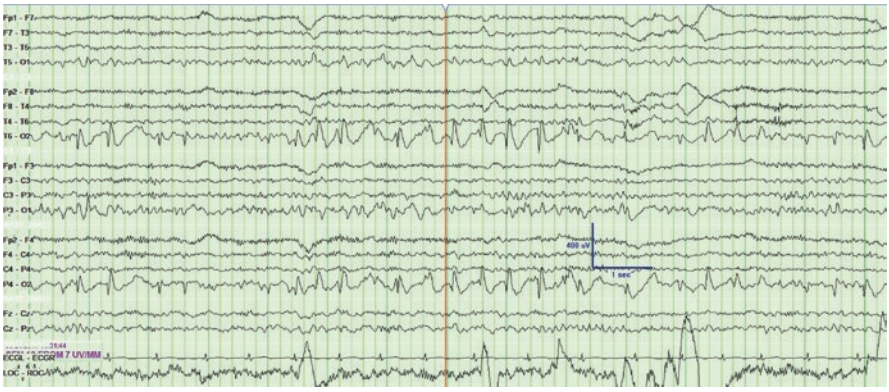


**Fig. 4.6** Late onset childhood occipital epilepsy. Note repetitive occipital spikes in the right hemisphere

these treatments can worsen myoclonic absence seizures. Prognosis is variable as about one-third of patients will have no further seizures while the other two-thirds will develop another type of epilepsy. Behavioral and cognitive impairment commonly occur [52].

## Eyelid Myoclonia with Absences (Jeavons Syndrome)

Eyelid myoclonia with absences is a photosensitive generalized epilepsy syndrome with childhood onset. The age of onset ranges from 2 to 14 years with the peak between 6 and 8 years. Jerking of the eyelids commonly occurs upon eye closure and is associated with generalized 3 Hz polyspike-wave discharges [53] (Fig. 4.7) (Appendix A, Video 2.7). Eyelid myoclonia can be followed by brief absence seizures. Interestingly, the eyelid myoclonia do not occur with eye closure in the dark. EEG demonstrates a photoparoxysmal response in most cases. A female predominance of as much as 80% has consistently been described [54]. Approximately 70% of patients will have at least one generalized tonic-clonic seizure during the course of disease. Other generalized seizures may also occur, including myoclonic and tonic [54]. Eyelid myoclonia with absences is often misdiagnosed as tics, and therefore a substantial delay in diagnosis of several years is common [55]. Frequently used medications include levetiracetam, valproic acid, clobazam, and other benzodiazepines. Approximately 80% will have drug-resistant epilepsy [54, 55]. There are case reports of successful therapy with ketogenic diet and vagus nerve stimulator [55].

## Sunflower Syndrome

Sunflower syndrome is a rare photosensitive epilepsy that presents with episodes of hand waving in the presence of light. Patients look toward a light source (usually the

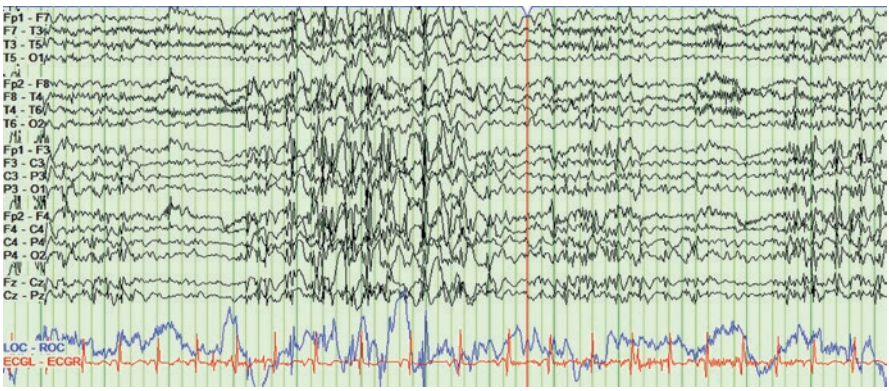



**Fig. 4.7** Generalized poly-spike discharges during eyelid closure with myoclonia

sun) and wave their hands in front of their face, inducing a paroxysmal response on EEG and clinical features that may include impaired awareness, eyelid fluttering, or myoclonic jerks [58]. Most patients report an attraction to light in general. Onset is typically between ages 2–8 and there is a female preponderance [56].

Historically the hand-waving episodes have been considered self-induction of seizures, implying a volitional component. However, recent data with EEG correlation suggests that the hand-waving itself may be part of the seizure [57]. EEGs usually have a normal background, with epileptiform discharges characterized by 1–4 Hz generalized spike- and polyspike-wave discharges [58]. About two-thirds of patients will have other seizure types, including absence, tonic-clonic, and myoclonic. Seizures can be very frequent and are commonly drug resistant. Medications used have included levetiracetam, valproic acid, ethosuximide, topiramate, clobazam, and cannabidiol. Non-pharmacological measures, such as avoiding bright light, consciously restricting the hand movements, and wearing sunglasses or hats have reduced seizure frequency in some cases. Despite the refractory nature of seizures, cognitive function is normal in most patients [58].

## Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome (LGS) is an epileptic encephalopathy composed of multiple seizure types, intellectual disability, and an abnormal EEG. Seizure types include tonic seizures during sleep, myoclonic, atonic, focal, atypical absence, and generalized tonic-clonic seizures. Development is delayed and moderate-to-severe intellectual disability is common [59]. Numerous etiologies have been associated with LGS, including structural, metabolic, and genetic disorders. Onset ranges from 2 to 10 years old. LGS evolves from West or Ohtahara syndromes in approximately 30% of cases. The EEG demonstrates an abnormal background with diffuse slowing and an interictal EEG pattern characterized by generalized slow (1.5–2.5 Hz) spike-wave discharges (Fig. 4.8). Independent, multifocal spikes or sharp waves may also be present. Seizures are usually refractory to pharmacological therapy. Potential effective therapies include rufinamide, lamotrigine, topiramate, clobazam, and felbamate. Rufinamide and clobazam may be especially useful for atonic seizures [60, 61]. Cannabidiol was approved for use in Lennox Gastaut Syndrome in 2018 [62]. The ketogenic diet has been shown to be helpful in some patients [60, 63]. Prognosis is poor with 5% of children dying in early childhood. Survivors will have refractory epilepsy and significant neurodevelopmental disability [59, 64].

## Epileptic Encephalopathy with Continuous Spike and Wave During Sleep

Epileptic encephalopathy with continuous spike and waves during sleep (CSWS) is a rare syndrome presenting with significant regression in language,

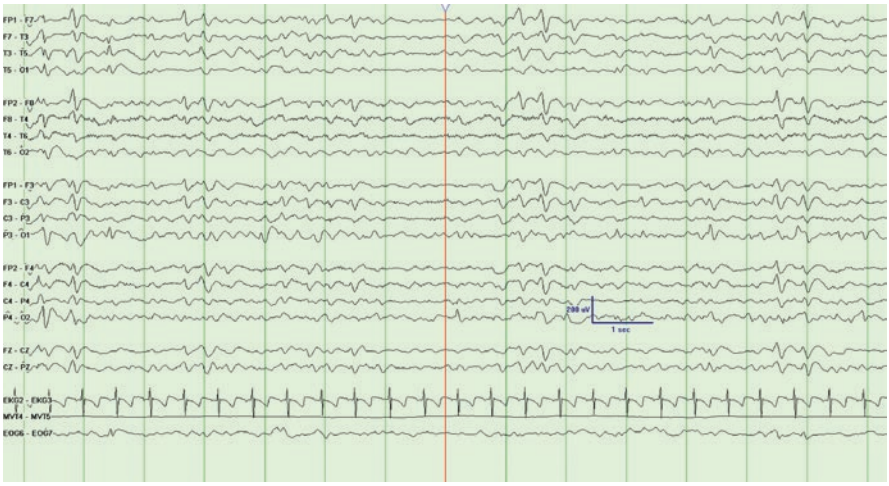


**Fig. 4.8** Lennox-Gastaut syndrome. Note the diffuse slowing and 1–2 Hz epileptiform discharges

cognition, and behavior. Seizures are often not a major feature of the initial presentation and can be focal or generalized. Characteristically, the EEG demonstrates spike-wave discharges dominating at least 80% of the non-REM sleep portions of the recording [65] (Fig. 4.9). The spike-wave discharges are usually generalized, but can be focal, especially centrotemporal. It is thought that CSWS is the most severe extreme on a spectrum of sleep-activated epilepsies, which also includes Landau-Kleffner syndrome and CECTS. Atypical CECTS evolving into CSWS has been described. Mutations in GRIN2A have been associated with some cases of CSWS [43]. Structural abnormalities have also been observed in this patient population. Treatments include high-dose benzodiazepines, valproic acid, levetiracetam, and corticosteroids. Carbamazepine, phenobarbital, and phenytoin can exacerbate symptoms [66]. Some patients who respond well to treatment will recover some of their lost skills, but many have persistent deficits.

## Landau-Kleffner Syndrome

Like CSWS, Landau-Kleffner syndrome (LKS) is also considered to be an epileptic encephalopathy. Despite the overlap between CSWS and LKS, the ILAE classifies them as separate entities. In LKS, children initially have normal language development. They then develop acquired verbal agnosia and then subsequently a severe expressive aphasia [67]. Some patients may not have seizures. If seizures are present, they include focal, atypical absence, and atonic seizures. EEG will demonstrate slow spike-and-waves, nearly continuously in sleep, commonly in the temporal lobes. Treatments are similar to CSWS [68] (Table 4.3).

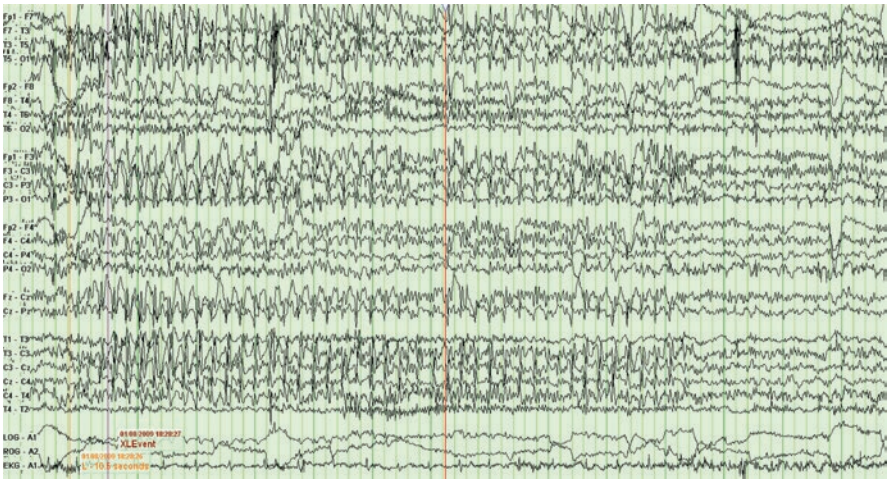


**Fig. 4.9** Epilepsy with continuous spike-waves during sleep

## Adolescent/Adult

### Juvenile Absence Epilepsy

As alluded to by its name, the onset of seizures in juvenile absence epilepsy (JAE) occurs during the second decade. The other distinguishing feature from childhood absence epilepsy is the frequency of seizures; seizures occur in JAE only a few times per day compared to numerous times per day in CAE. Otherwise, EEG findings and treatment are comparable [69]. The EEG in JAE can demonstrate a slightly faster 3–6 Hz frequency of spike- and polyspike-wave discharges. Many patients with JAE will also have generalized convulsions in addition to absence seizures. Treatment options in JAE include lamotrigine, ethosuximide, levetiracetam, zonisamide, and valproic acid [70]. Because there are many options, treatment choice can focus on minimizing side effects. A larger proportion of patients with JAE will have lifelong epilepsy as compared to CAE [37].

### Juvenile Myoclonic Epilepsy

Juvenile myoclonic epilepsy (JME) is the most common generalized epilepsy syndrome, comprising about 10% of epilepsy across all age groups [71]. JME is characterized by two main seizure types: myoclonic jerks and generalized tonic-clonic seizures. About 30% of patients will also experience absence seizures. Onset occurs between 10 and 25 years of age, with median age of onset of 15 years. Early in the course, myoclonic jerks occurring in early morning are not reported by the patient. These patients frequently present after their first generalized convulsive seizure, but a careful history will reveal episodes of myoclonus.

**Table 4.3** Childhood-onset epilepsy syndromes

| Syndrome | Seizure types | EEG | Etiology | Treatment | Prognosis |
|---|---|---|---|---|---|
| Childhood absence | Absence | Generalized 3 Hz spike-wave | Presumed genetic | Pharmacoresponsive Ethosuximide, valproic acid, lamotrigine | 95% with remission by puberty |
| Early onset childhood occipital epilepsy (Panayiotopoulos) | Autonomic (pallor, vomiting, syncope) | Occipital or multifocal discharges | Presumed genetic | Pharmacoresponsive Levetiracetam, oxcarbazepine, lamotrigine | Remission typical within 5 years of onset |
| Self-limited (benign) epilepsy of childhood with centrotemporal spikes (Rolandic) | Nocturnal simple focal seizures with oromotor phenomena | Bilateral, independent centrotemporal spikes | Presumed genetic | Pharmacoresponsive. Treatment is not always necessary. Levetiracetam, oxcarbazepine, lamotrigine | Remission by puberty Comorbid learning and behavior issues common |
| Late onset childhood occipital epilepsy (Gastaut) | Visual hallucinations, ictal blindness, focal with impaired awareness | Occipital spikes, sleep-activated | Presumed genetic | Pharmacoresponsive Levetiracetam, oxcarbazepine, lamotrigine | Remission 2–4 years after onset |
| Epilepsy with myoclonic atonic seizures (Doose) | Myoclonic, atonic | Generalized spike- and polyspike-wave | Presumed genetic | Drug-resistant Ethosuximide, valproic acid, levetiracetam, ketogenic diet | Cognitive and behavioral disability |
| Genetic epilepsy with febrile seizures + (GEFS+) | Febrile seizures initially, focal or generalized later in the course | Normal interictal, epileptiform discharges depend on seizure type | Genetic, SCN1A, SCN1B and SCN2A | Pharmacoresponsive Drug choice depends on seizure type, broad spectrum agents | Normal cognitive function, remission is variable |
| Autosomal dominant nocturnal frontal lobe epilepsy | Nocturnal dystonic and affective | Frontal epileptiform activity can be normal | Genetic CHRNA2, CHRNA4, CHRNB2 | 33% drug resistant Medications for focal seizures; possible role for nicotine | Remission variable; most have normal neurological function |

| | | | | | |
|---|---|---|---|---|---|
| Epilepsy with myoclonic absences | Absence seizures with myoclonic jerks | Generalized spike-wave | Associated with genetic disorders (Angelman, trisomy 12p, dup 15) | 33% respond well to treatment<br>Valproic acid, topiramate, levetiracetam, benzodiazepines | Most have neurodevelopmental disability |
| Eyelid myoclonia with absence (Jeavons) | Eyelid myoclonia on eye closure<br>Absence | Generalize polyspike-wave, photo paroxysmal response | Presumed genetic | 80% drug-resistant<br>Ethosuximide, valproic acid, levetiracetam, ketogenic diet | Most have normal cognitive function despite incomplete seizure control |
| Sunflower syndrome | Hand-waving episodes in light, absence or myoclonus can be seen | Generalized spike- and polyspike-wave, photo paroxysmal response | Unknown | Commonly drug-resistant<br>Levetiracetam, valproic acid, ethosuximide, topiramate, clobazam, and cannabidiol | Most have normal cognition |
| Lennox-Gastaut syndrome | Multiple seizure types, including tonic seizures during sleep, GTC, atypical absence, atonic, focal myoclonic | Slow spike-wave background<br>Diffuse slowing<br>Multifocal epileptiform discharges | Structural (malformations)<br>Acquired (HIE)<br>Genetic<br>Metabolic | Drug-resistant<br>Lamotrigine, valproic acid, clobazam, topiramate, cannabidiol, rufinamide, felbamate | Lifelong seizures, moderate–to-severe neurodevelopmental disability |
| Epileptic encephalopathy with continuous spike and wave during sleep | Focal or generalized | Generalized or focal spike-wave discharges for >80% of non-REM sleep | Genetic (GRIN2A)<br>Acquired/structural | High-dose diazepam<br>Corticosteroids<br>ACTH<br>Valproic acid<br>Levetiracetam | Cognitive regression at the onset of epilepsy; most have permanent deficits |
| Landau-Kleffner syndrome | Focal | Sleep-activated focal discharges (temporal) | Unknown | High-dose diazepam<br>Corticosteroids<br>ACTH<br>Valproic acid<br>Levetiracetam | Language regression, acquired aphasia at onset, most with permanent deficits |

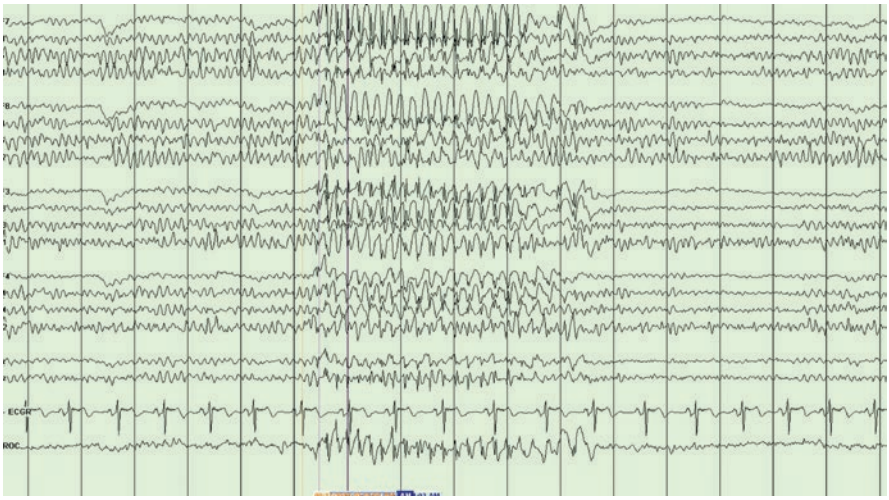


**Fig. 4.10** Fast 4–6 Hz spike-wave discharges in JME

EEG demonstrates 3–6 Hz bifrontally predominant generalized spike- and/or polyspike-wave discharges [72] (Fig. 4.10). Seizure control on medications is achieved in greater than 90% of patients, but the majority will require lifelong therapy with antiepileptic drugs. Levetiracetam, topiramate, zonisamide, and valproic acid are effective treatment options. Lamotrigine can also be used but may exacerbate myoclonic seizures. Carbamazepine, oxcarbazepine, and phenytoin can exacerbate absence and generalized tonic-clonic seizures and should be avoided [73].

## Epilepsy with Generalized Tonic-Clonic Seizures Alone

Previously referred to as "epilepsy with grand mal seizures on awakening," epilepsy with generalized tonic-clonic seizures alone (EGTC) is a generalized epilepsy with generalized convulsions, usually occurring upon awakening. Onset can occur between age 5 and 40 although 80% of patients will have the first convulsion between age 11 and 20. The EEG background is normal. A photoparoxysmal response can be seen. Interictal EEG reveals bursts of generalized spike- or polyspike-wave and half the time are only observed in sleep. On ictal EEG, generalized fast rhythmic spikes are correlated with tonic movements whereas burst of spikes followed by slow waves are correlated with clonic activity, with subsequent postictal irregularly slow activity. Lifelong treatment is generally required [69].

## Progressive Myoclonus Epilepsies

The progressive myoclonus epilepsies are a group of epileptic encephalopathies that involve myoclonic seizures in association with cognitive and motor impairments.

The myoclonic seizures are commonly refractory to anti-epileptic medications and the EEG becomes more abnormal, with increased background slowing, as the disease progresses [74]. This category includes metabolic, genetic, structural, or immune-mediated diseases of which myoclonic seizures are a prominent feature. Most have onset during late childhood and adolescence, and patients usually have a relentlessly progressive course that leads to death. The most common syndromes will be discussed here.

Unverricht-Lundborg (aka progressive myoclonic epilepsy type 1 or Baltic myoclonus) is the most common cause of progressive myoclonus. Seizures start between 6 and 18 years of age with worsening of myoclonic seizures and cognitive dysfunction. Cerebellar symptoms also occur with ataxia, tremor, and dysarthria. Mutations in the CSTB gene are causative [75].

Lafora body disease (progressive myoclonic epilepsy type 2) presents in mid-adolescence, although cases as young as 5 years have been reported. This disease is caused by recessively inherited mutations in the EPM2A or EPM2B gene. Seizures include myoclonic, generalized tonic-clonic, and visual hallucinations. Lafora bodies are polyglucosan aggregates found on skin biopsy [76].

Myoclonic epilepsy with ragged-red fibers (MERRF) is a mitochondrial disorder characterized by myoclonic seizures, cognitive decline, ataxia, short stature, optic atrophy, cardiomyopathy, and weakness. Muscle biopsy reveals ragged red fibers. The most common mutation are missense mutations in the mitochondrial tRNA genes [77].

Neuronal ceroid lipofuscinoses (NCL) are a collection of lysosomal storage disorders that result in cognitive and motor decline, vision loss, myoclonic seizures, generalized convulsions, and eventual death. The onset can occur at any age, with autosomal dominant and autosomal recessive forms. There are at least 13 forms, with different ages of onset and mutations in different genes [78].

## Autosomal Dominant Epilepsy with Auditory Features

Autosomal dominant epilepsy with auditory features is characterized by focal seizures associated with auditory cortex. Patients commonly describe humming, buzzing, ringing, volume changes, or hallucinations as their ictal phenomena. At times the seizures are so mild that they go undiagnosed. Secondarily generalized convulsions can occur, although are rare. Receptive aphasia can also occur in this syndrome. Onset is usually in adolescence or in younger adults, but can occur anywhere from 4 to 40 years of age. EEG demonstrates a normal background, although 30% of patients will have focal temporal interictal activity. Ictal EEG demonstrates repetitive discharges in the temporal lobe. This syndrome is autosomal dominantly inherited with high penetrance. 50% of families have a mutation in the LGI1 gene. Prognosis is favorable as seizures are generally well controlled [79] (Table 4.4).

**Table 4.4** Adolescent-onset epilepsy syndromes

| Syndrome | Seizure types | EEG | Etiology | Treatment | Prognosis |
|---|---|---|---|---|---|
| Juvenile absence | Absence | 3–4 Hz generalized spike-wave | Presumed genetic | Pharmacoresponsive Ethosuximide, valproic acid, lamotrigine, zonisamide, levetiracetam | Seizures controlled in most patients, but spontaneous remission is rare |
| Juvenile myoclonic epilepsy | GTC; Myoclonic Absence | 3–6 Hz generalized spike- and poly-spike wave Photo paroxysmal response | Presumed genetic | Pharmacoresponsive Levetiracteam, valproic acid, lamotrigine, topiramate, zonisamide | Seizures controlled in most patients, but spontaneous remission is rare |
| Epilepsy with generalized tonic-clonic seizures alone | GTC Myoclonic Absence | 3–6 Hz generalized spike- and polyspike-wave Photo paroxysmal response | Presumed genetic | Pharmacoresponsive Levetiracteam, valproic acid, lamotrigine, topiramate, zonisamide | Seizures controlled in most patients, but spontaneous remission is rare |
| Autosomal dominant epilepsy with auditory features | Auditory phenomena | Focal temporal lobe epileptiform discharges | Genetic, LGI1 | Pharmacoresponsive | Spontaneous remission is uncommon, normal cognitive function |
| Progressive myoclonic epilepsy type 1 (Unverricht-Lundborg) | Myoclonic | Generalized spike-wave, slow background | Genetic, CSTB | Drug-resistant | Progressive decline in motor and cognitive function resulting in death |
| Progressive myoclonic epilepsy type 2 (Lafora body) | Myoclonic | Generalized spike-wave, slow background | Genetic, EPM2A, EPM2B | Drug-resistant | Progressive decline in motor and cognitive function |
| Myoclonic epilepsy with ragged red fibers | Myoclonic | Generalized spike-wave, slow background | Genetic, mitochondrial tRNA point mutations | Drug-resistant | Progressive decline in motor and cognitive function |

**Table 4.4** (continued)

| Syndrome | Seizure types | EEG | Etiology | Treatment | Prognosis |
|---|---|---|---|---|---|
| Neuronal ceroid lipofuscinoses | Myoclonic | Generalized spike-wave, slow background | Genetic, 13 different genes | Drug-resistant | Progressive decline in motor, visual, and cognitive function resulting in death |

## Less Specific Age Relationship

### Familial Focal Epilepsy with Variable Foci

Familial focal epilepsy with variable foci, also known as familial partial epilepsy with variable foci (FPEVF), is an autosomal dominantly inherited disorder with incomplete penetrance. The age of onset varies, anywhere from infancy to adulthood. Focal seizures are present in this syndrome and can localize to any region, even varying within a single family. However, seizure semiology will be constant in each individual, as will be the localization of the EEG. The only gene that has been identified thus far is DEPDC5, which encodes for a protein that functions as a negative regulator of the mTOR complex 1, involved in cell proliferation and survival [80].

### Reflex Epilepsies

Reflex seizures are characterized by episodes that are triggered by a specific stimulus. The stimulus may be sensory phenomenon or movement initiated by the patient. Reflex seizures have been reported due to flashing light, tactile input, startle, tooth brushing, playing chess, or reading. Reflex startle epilepsy is commonly associated with structural abnormalities, either genetic or acquired. Ictal EEG may show midline vertex discharges with subsequent diffuse attenuation or low voltage fast activity [81]. Avoiding the provoking stimulus, if possible, can prevent reflex seizures in many cases.

### Gelastic Seizures with Hypothalamic Hamartoma

Gelastic seizures are characterized by ictal laughing. The laughing associated with seizure is typically described as unusual or "mirthless" [82]. The onset of

seizures is often in infancy or early childhood. Once seizures begin, they can be very difficult to control. The vast majority of cases of gelastic seizures are secondary to hypothalamic hamartomas. These are congenital, non-progressive tumors that are comprised of neuronal and glial cells. Hypothalamic hamartomas are rare, occurring in 1 in 100,000 children. The lesions themselves are thought to be epileptogenic, although the precise pathological mechanism is unknown.

Children with gelastic seizures related to hamartomas can also have behavioral disturbances, cognitive and developmental delay. Many have co-morbid pituitary dysfunction, most commonly manifesting as precocious puberty. Gelastic seizures are often not detectable on surface EEG, although they can be picked up on depth electrodes. Many children with hypothalamic hamartomas also develop other seizure types, including focal with impaired awareness or generalized tonic-clonic.

The seizures in this disorder are typically refractory to anti-epileptic medications. Surgical treatment results in the best long-term outcomes in terms of seizure control, cognitive, and behavioral function. Traditionally open surgical resection has been the standard of care. In recent years, gamma knife radiosurgery and stereotactic laser thermoablation have been promoted as less-invasive modes of therapy. Seizure freedom or reduction ranges from 40% to 90% depending on surgical modality used [83].

## Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis

Mesial temporal lobe epilepsy (MTLE) with hippocampal sclerosis typically has onset in adulthood, but bears inclusion here because as many as 30% of cases have a preceding history of complex febrile seizures and febrile status epilepticus. Onset in childhood and adolescence is described, but not common. Most patients experience the onset of epilepsy in their 20s and 30s. MTLE is responsible for approximately 60% of symptomatic focal epilepsies in adults.

Seizures can be focal with maintained or impaired awareness. Focal seizures with maintained awareness have historically been described as seizure "auras," which are commonly progress to seizures with altered awareness. Common auras include an epigastric rising sensation, olfactory hallucinations, affective symptoms (fear, anger, irritability), déjà vu, depersonalization, and a "dreamy state." Ictal activity causing auras often spreads to adjacent areas of the mesial temporal structures, and seizures evolve to include unresponsiveness and staring as well as motor automatisms such as oral movements (lip smacking, chewing), semi-purposeful or fumbling movements of the hands and complex motor activity such as walking. Secondarily generalized seizures are frequent [84].

Many patients with temporal lobe epilepsy experience drug resistance. Brain imaging typically demonstrates atrophy and gliosis in the hippocampus and adjacent structures. Patients with discrete lesions in the mesial temporal structures are considered good surgical candidates, and successful resective surgery can lead to

seizure remission. 90% of patients who undergo resective surgery have significant improvement in seizure frequency, and 60–70% will achieve seizure freedom [85] (Appendix B, EEG 9).

## Seizure Disorders Not Defined as Epilepsy

### Febrile Seizures

Febrile seizures (FS) are the most common type of childhood seizures, affecting about 2–5% of all children. The seizures occur in the setting of fever in children between 6 months and 6 years of age. Because these seizures are provoked, they are not considered to be a form of epilepsy, even if recurrent. The exact pathophysiology is debated, but there is some evidence in animal models that hyperthermia itself can be sufficient to trigger seizures in developing brains [86]. Cytokines released due to fever, including interleukin 1β, have been demonstrated to increase neuronal excitatory activity in animal models. Interleukin 1β is an NMDA receptor agonist [87]. Genetic susceptibility may also play a role, as febrile seizures may be inherited in an autosomal dominant pattern with incomplete penetrance. Genes associated with febrile seizure susceptibility, including mutations in sodium channels (SCN1A) and GABA receptors, have been identified in some families [87].

Simple febrile seizures are defined as seizures in an otherwise normal child that last less than 15 minutes, are generalized, and occur singly and within 24 hours of the onset of the febrile illness. Complex febrile seizures are seizures that do not fulfill the aforementioned criteria. 1–2% of children with simple febrile seizures will develop epilepsy, compared to 0.5–1% of the general population. However, up to 10–30% of patients with complex febrile seizures will develop subsequent epilepsy, depending on the number of complex features. Prophylactic treatment is not indicated. Several studies assessing the use of anti-epileptic drugs prophylactically have demonstrated lack of efficacy and problematic side effects [88, 89].

Rectal diazepam and other benzodiazepines can successfully be used to abort a prolonged febrile seizure. Short-term prophylaxis with diazepam during a febrile illness has been demonstrated to be effective in some studies, but with side effects of sedation and ataxia [90]. Although febrile seizures occur uniquely in the setting of fever, antipyretic prophylaxis has not been shown to effectively prevent febrile seizures [91].

Approximately 30–40% of children with febrile seizures will have recurrence. Risk factors for recurrence include a family history of febrile seizures, young age (<18 months), peak temperature ≤101 °F, and fever duration <1 hour before seizure onset. Febrile status epilepticus accounts for about 5% of cases. While debated, there is growing evidence that patients with febrile status epilepticus are at risk of developing hippocampal sclerosis and temporal lobe epilepsy later in life. Most patients with febrile seizures have remission by age 6 and a low risk of future unprovoked seizures [87].

## References


1. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. Epilepsia. 2010;51:676–85.
2. Scheffer IE, Berkovic S, Copovilla G. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58(4):512–21.
3. Scheffer IE, Liao J. Deciphering the concepts behing "epileptic encephalopathy" and "developmental and epileptic encephalopathy". Eur J Pediatr Neurol. 2020;24:11–4.
4. Allen NM, Mannion M, Conroy J, et al. The variable phenotypes of KCNQ-related epilepsy. Epilepsia. 2014;55(9):e99–105.
5. Berkovic SF, Heron SE, Giordano L, et al. Benign familial neonatal-infantile seizures: characterization of a new sodium channelopathy. Ann Neurol. 2004;55:550–7.
6. Grinton BE, Heron SE, Pelekanos JT, et al. Familial neonatal seizures in 36 families: clinical and genetic features correlate with outcome. Epilepsia. 2015;56:1071–80.
7. Shbarou R, Mikati MA. Expanding clinical spectrum of genetic pediatric epileptic encephalopathies. Semin Pediatr Neurol. 2016;23(2):134–42.
8. Backx L, Ceulemans B, Vermeesch JR, Devriendt K, Van Esch H. Early myoclonic encephalopathy caused by a disruption of the neuregulin-1 receptor ErbB4. Eur J Hum Genet. 2009;17:378–82.
9. Nakano K, Kobayashi K, Maniwa S, Kodani N, Ohtsuka Y. Successful treatment of early myoclonic encephalopathy using lidocaine and carbamazepine. Epileptic Disord. 2013;15:352–7.
10. Tekgul H, Serdaroglu G, Karapinar B, et al. Vigabatrin caused rapidly progressive deterioration in two cases with early myoclonic encephalopathy associated with nonketotic hyperglycinemia. J Child Neurol. 2006;21:82–4.
11. Beal JC, Cherian K, Moshe SL. Early-onset epileptic encephalopathies: Ohtahara syndrome and early myoclonic encephalopathy. Pediatr Neurol. 2012;47:317–23.
12. Yamatogi Y, Ohtahara S. Early-infantile epileptic encephalopathy with suppression-bursts, Ohtahara syndrome; its overview referring to our 16 cases. Brain Dev. 2002;24:13.
13. Pavone P, Spalice A, Polizzi A, Parisi P, Ruggieri M. Ohtahara syndrome with emphasis on recent genetic discovery. Brain Dev. 2012;34(6):459–68.
14. Deprez L, Weckhuysen S, Holmgren P, et al. Clinical spectrum of early-onset epileptic encephalopathies associated with STXBP1 mutations. Neurology. 2010;75:1159–65.
15. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. 2015;56:1185–97.
16. Sivaraju A, Nussbaum I, Cardoza CS, Mattson RH. Substantial and sustained seizure reduction with ketogenic diet in a patient with Ohtahara syndrome. Epilepsy Behav Case Rep. 2015;3:43–5.
17. Krsek P, Sebronova V, Prochazka T, Maulisova A, Komarek V. Successful treatment of Ohtahara syndrome with chloral hydrate. Pediatr Neurol. 2002;27:388–91.
18. Tso WW, Kwong AK, Fung CW, Wong VC. Folinic acid responsive epilepsy in Ohtahara syndrome caused by STXBP1 mutation. Pediatr Neurol. 2014;50:177–80.
19. Korff CM, Vulliemoz S, Picard F, Fluss J. Ohtahara syndrome or early-onset West syndrome? A case with overlapping features and favorable response to vigabatrin. Eur J Paediatr Neurol. 2012;16:753–7.
20. Weckhuysen S, et al. KCNQ2 encephalopathy: emerging phenotype of a neonatal epileptic encephalopathy. Ann Neurol. 2012;71(1):15–25.
21. Goto A, Ishii A, Shibata M, Ihara Y, Cooper EC, Hirose S. Characteristics of KCNQ2 variants causing either benign neonatal epilepsy or developmental and epileptic encephalopathy. Epilepsia. 2019;60(9):1870–80.
22. Burgess R, Wang S, McTague A, Boysen KE, et al. The genetic landscape of epilepsy of infancy with migrating focal seizures. Ann Neurol. 2019;86(6):821–31.

23. Coppola G. Malignant migrating partial seizures in infancy. Handb Clin Neurol. 2013;111:605–9.
24. Pavone P, Striano P, Falsaperla R, Pavone L, Ruggieri M. Infantile spasms syndrome, West syndrome and related phenotypes: what we know in 2013. Brain Dev. 2014;36:739–51.
25. Pavone P, Polizzi A, Marino SD, Corsello G, Falsaperla R, Marino S, Ruggieri M. West syndrome: a comprehensive review. Neurol Sci. 2020;41(12):3547–62.
26. Djuric M, Kravljanac R, Tadic B, Mrljes-Popovic N, Appleton RE. Long-term outcome in children with infantile spasms treated with vigabatrin: a cohort of 180 patients. Epilepsia. 2014;55:1918–25.
27. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev. 2013;6:CD001770.
28. Kossoff EH, Pyzik PL, McGrogan JR, Vining EP, Freeman JM. Efficacy of the ketogenic diet for infantile spasms. Pediatrics. 2002;109:780–3.
29. Auvin S, Pandit F, De Bellecize J, et al. Benign myoclonic epilepsy in infants: electroclinical features and long-term follow-up of 34 patients. Epilepsia. 2006;47:387–93.
30. Nardello R, Mangano GD, Miceli F, Fontana A, Piro E, Salpietro V. Benign familial infantile epilepsy associated with KCNQ3 mutation: a rare occurrence or an underestimated event? Epileptic Disord. 2020;22(6):807–10.
31. Dravet C, Oguni H. Dravet syndrome (severe myoclonic epilepsy in infancy). Handb Clin Neurol. 2013;111:627–33.
32. Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, Scheffer IE, Thiele EA, Wright S, Cannabidiol in Dravet Syndrome Study Group. Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. N Engl J Med. 2017;376(21):2011–20.
33. Lagae L, Sullivan J, Knupp K, Laux L, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019;394(10216):2243–54.
34. Brigo F, Storti M. Antiepileptic drugs for the treatment of severe myoclonic epilepsy in infancy. Cochrane Database Syst Rev. 2013;11:CD010483.
35. Elia M. Myoclonic status in nonprogressive encephalopathies: an update. Epilepsia. 2009;50 Suppl 5:41–4.
36. Matricardi S, Verrotti A, Chiarelli F, Cerminara C, Curatolo P. Current advances in childhood absence epilepsy. Pediatr Neurol. 2014;50:205–12.
37. Trinka E, Baumgartner S, Unterberger I, et al. Long-term prognosis for childhood and juvenile absence epilepsy. J Neurol. 2004;251:1235–41.
38. Glauser TA, Canaan A, Shinnar S, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med. 2010;362:790–9.
39. Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutroumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. Brain. 2008;131:2264–86.
40. Parisi P, Villa MP, Pelliccia A, Rollo VC, Chiarelli F, Verrotti A. Panayiotopoulos syndrome: diagnosis and management. Neurol Sci. 2007;28(2):72–9.
41. Wirrell EC. Benign epilepsy of childhood with centrotemporal spikes. Epilepsia. 1998;39(Suppl 4):S32–41.
42. Hughes JR. Benign epilepsy of childhood with centrotemporal spikes (BECTS): to treat or not to treat, that is the question. Epilepsy Behav. 2010;19(3):197–203.
43. Dimassi S, Labalme A, Lesca G, et al. A subset of genomic alterations detected in rolandic epilepsies contains candidate or known epilepsy genes including GRIN2A and PRRT2. Epilepsia. 2014;55:370–8.
44. Cherian A, Jabeen SA, Kandadai RM, et al. Epilepsy with myoclonic absences in siblings. Brain Dev. 2014;36:892–8.
45. Kelley SA, Kossoff EH. Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. Dev Med Child Neurol. 2010;52:988–93.
46. Scheffer IE, Nabbout R. SCN1A-related phenotypes: epilepsy and beyond. Epilepsia. 2019;60 Suppl 3:S17–24.

47. Camfield P, Camfield C. Febrile seizures and genetic epilepsy with febrile seizures plus (GEFS+). Epileptic Disord. 2015;17(2):124–33.
48. Kurahashi H, Hirose S. Autosomal dominant nocturnal frontal lobe epilepsy. 2002 May 16 [updated 2018 Mar 15]. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, LJH B, Mirzaa G, Amemiya A, editors. GeneReviews® [Internet]. Seattle: University of Washington, Seattle; 1993–2021.
49. Itier V, Bertrand D. Mutations of the neuronal nicotinic acetylcholine receptors and their association with ADNFLE. Neurophysiol Clin. 2002;32(2):99–107.
50. Fox J, Thodeson DM, Dolce AM. Nicotine: a targeted therapy for epilepsy due to nAChR gene variants. J Child Neurol. 2021;36(5):371–7.
51. Caraballo R, Koutroumanidis M, Panayiotopoulos CP, Fejerman N. Idiopathic childhood occipital epilepsy of Gastaut: a review and differentiation from migraine and other epilepsies. J Child Neurol. 2009;24(12):1536–42.
52. Bureau M, Tassinari CA. Epilepsy with myoclonic absences. Brain Dev. 2005;27:178–84.
53. Striano S, Capovilla G, Sofia V, et al. Eyelid myoclonia with absences (Jeavons syndrome): a well defined idiopathic generalized epilepsy syndrome or a spectrum of photosensitive conditions. Epilepsia. 2009;50(S5):15–9.
54. Smith KM, Youssef PE, Wirrel EC, et al. Jeavons syndrome: clinical features and resposne to treatment. Pediatr Neurol. 2018;86:46–51.
55. Reyhani A, Ozkara C. Pitfalls in the diagnosis of Jeavons syndrome: a study of 32 cases and review of the literature. Epileptic Disord. 2020;22(3):281–90.
56. Baumer FM, Porter BE. Clinical and electrographic features of sunflower syndrome. Epilepsy Res. 2018;142:58–63.
57. Geenen KR, Patel S, Thiele EA. Sunflower syndrome: a poorly understood photosensitive epilepsy. Dev Med Child Neurol. 2021;63:259–62.
58. Barnett JR, Fleming BM, Thiele EA, et al. Characterizing sunflower syndrome; a clinical series. Epileptic Disord. 2020;22(3):273–80.
59. Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. Epilepsia. 2014;55 Suppl 4:4–9.
60. Montouris GD, Wheless JW, Glauser TA. The efficacy and tolerability of pharmacologic treatment options for Lennox-Gastaut syndrome. Epilepsia. 2014;55 Suppl 4:10–20.
61. Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2013;2:CD003277.
62. Lattanzi S, Trinka E, Russo E, Striano P, Citraro R, Silvestrini M, Brigo F. Cannabidiol as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome. Drugs Today. 2019;55(3):177–96.
63. Lemmon ME, Terao NN, Ng YT, Reisig W, Rubenstein JE, Kossoff EH. Efficacy of the ketogenic diet in Lennox-Gastaut syndrome: a retrospective review of one institution's experience and summary of the literature. Dev Med Child Neurol. 2012;54:464–8.
64. Kaminska A, Oguni H. Lennox-Gastaut syndrome and epilepsy with myoclonic-astatic seizures. Handb Clin Neurol. 2013;111:641–52.
65. Samanta D, Al Khalili Y. Electrical status epilepticus in sleep. 2020 Jul 6. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021.
66. Van Bogaert P. Epileptic encephalopathy with continuous spike-waves during slow-wave sleep including Landau-Kleffner syndrome. Handb Clin Neurol. 2013;111:635–40.
67. Muzio MR, Cascella M, Al Khalili Y. Landau Kleffner Syndrome. 2021 Jan 16. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2021.
68. Caraballo RH, Cejas N, Chamorro N, Kaltenmeier MC, Fortini S, Soprano AM. Landau-Kleffner syndrome: a study of 29 patients. Seizure. 2014;23:98–104.
69. Caraballo RH, Dalla Bernardina B. Idiopathic generalized epilepsies. Handb Clin Neurol. 2013;111:579–89.
70. Velizarova R, Crespel A, Genton P, Serafini A, Gelisse P. Zonisamide for refractory juvenile absence epilepsy. Epilepsy Res. 2014;108:1263–6.

71. Camfield CS, Striano P, Camfield PR. Epidemiology of juvenile myoclonic epilepsy. Epilepsy Behav. 2013;28 Suppl 1:S15–7.
72. Genton P, Thomas P, Kasteleijn-Nolst Trenite DG, Medina MT, Salas-Puig J. Clinical aspects of juvenile myoclonic epilepsy. Epilepsy Behav. 2013;28 Suppl 1:S8–14.
73. Crespel A, Gelisse P, Reed RC, et al. Management of juvenile myoclonic epilepsy. Epilepsy Behav. 2013;28 Suppl 1:S81–6.
74. Malek N, Stewart W, Greene J. The progressive myoclonic epilepsies. Pract Neurol. 2015;15:164–71.
75. Crespel A, Ferlazzo E, Franceschetti S, Genton P, et al. Unverricht-Lundborg disease. Epileptic Disord. 2016;18(S2):28–37.
76. Cenacchi G, Papa V, Costa R, Pegoraro V, Marozzo R, Fanin M, Angelini C. Update on polyglucosan storage diseases. Virchows Arch. 2019;475(6):671–86.
77. Finsterer J, Zarrouk-Mahjoub S. Management of epilepsy in MERRF syndrome. Seizure. 2017;50:166–70.
78. Nita DA, Mole SE, Minassian BA. Neuronal ceroid lipofuscinoses. Epileptic Disord. 2016;18(S2):73–88.
79. Sadleir LG, Agher D, Chabrol E, et al. Seizure semiology in autosomal dominant epilepsy with auditory features, due to novel LGI1 mutations. Epilepsy Res. 2013;107:311–7.
80. Baulac S. Genetics advances in autosomal dominant focal epilepsies: focus on DEPDC5. Prog Brain Res. 2014;213:123–39.
81. Wolf P, Koepp M. Reflex epilepsies. Handb Clin Neurol. 2012;107:257–76.
82. Nguyen D, Singh S, Zaatreh M, Novotny E, Levy S, Testa F, Spencer SS. Hypothalamic hamartomas: seven cases and review of the literature. Epilepsy Behav. 2003;4(3):246–58.
83. Ferrand-Sorbets S, Fohlen M, Delalande O, Zuber K, Bulteau C, Levy M, Chamard P, Taussig D, Dorison N, Bekaert O, Tisdall M, Chipaux M, Dorfmüller G. Seizure outcome and prognostic factors for surgical management of hypothalamic hamartomas in children. Seizure. 2020;75:28–33.
84. Tatum WO. Mesial temporal lobe epilepsy. J Clin Neurophysiol. 2012;29(5):356–65.
85. Asadi-Pooya AA, Rostami C. History of surgery for temporal lobe epilepsy. Epilepsy Behav. 2017;70(Pt A):57–60.
86. Dube CM, Brewster AL, Baram TZ. Febrile seizures mechanisms and relationship to epilepsy. Brain Dev. 2009;31:366–71.
87. Shinnar S. Evaluation and management of simple and complex febrile seizures, a CME monograph. University of Kentucky, CE Central.
88. Wallace SJ, Smith JA. Successful prophylaxis against febrile convulsions with valproic acid or phenobarbitone. Br Med J. 1980;280(6211):353–4.
89. Antony JH, Hawke SH. Phenobarbital compared with carbamazepine in prevention of recurrent febrile convulsions: a double-blind study. Am J Dis Child. 1983;137(9):892–5.
90. Verotti A, Latini G, di Corcia G, et al. Intermittent oral diazepam prophylaxis in febrile convulsions: its effectiveness for febrile seizure recurrence. Eur J Pediatr Neurol. 2004;8(3):131–4.
91. Pavlidou E, Hagel C, Panteliadis C. Febrile seizures: recent developments and unanswered questions. Childs Nerv Syst. 2013;29:2011–7.

# Neonatal Seizures

5

David C. Dredge

## Introduction

Seizures in the neonatal period have several characteristics that distinguish them from seizures in other age groups, warranting a chapter devoted to this population. Seizure semiology, EEG findings, etiology, treatment, and prognosis are unique in neonates and will be presented in the following sections.

Estimates of seizure incidence in the neonatal population range from 2 to 3 per 1000 live births. Seizures in neonates are important potential contributors to mortality and long-term morbidity. In fact, mortality in patients with neonatal seizures ranges from 15 to 40%, increasing the risk of death beyond that attributed to the neuropathology alone [1, 2]. By age 7, 15–30% of children with a history of neonatal seizures will have at least one of the following: epilepsy, intellectual disability, or motor impairment [3–5]. Current treatment approaches have not demonstrated efficacy in this population.

There is much debate as to whether seizures in the newborn period directly contribute to brain injury, or if the etiology is a more important determinant of long-term outcome. Our current understanding is that rapid recognition and treatment of neonates is critical. Though the mechanism of neurological injury conferred by neonatal seizures is not well understood, animal studies suggest that neonatal seizures may impact future learning, memory, and behavior [6]. In neonatal patients there seems to be a correlation between seizure burden, mortality, and morbidity

**Supplementary Information** The online version of this chapter (https://doi.org/10.1007/978-3-319-08290-5_5) contains supplementary material, which is available to authorized users.

D. C. Dredge (✉)
Division of Pediatric Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
e-mail: ddredge@partners.org


D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_5

independent of seizure etiology. It has also been shown that rapid treatment can decrease seizure burden [7]. Treatment of subclinical neonatal seizures may decrease the rate of post-natal epilepsy [8].

## Diagnosis

There are several features of neonatal seizures that render making the correct diagnosis challenging. First, the semiology of seizures in neonates can be quite unique. Due to the stage of development of the neonatal brain, myelination and neural networks are incomplete. For these reasons, generalized tonic-clonic seizures are rarely observed in this population. Between 13 and 50% of neonatal seizures are classified as "subtle seizures." [9, 2] These ictal behaviors can include oral movements (lip smacking, pursing), bicycling movements of the lower extremities, "boxing" movements of the hands, or isolated eye deviation ± nystagmus. Another 25–61% are focal clonic (Video 5.1). 19–25% have generalized tonic seizures and another 7–10% have myoclonic seizures [9, 2].

The differential diagnosis of paroxysmal events in neonates also needs to be considered, as there are several benign and pathological movements in neonates that mimic seizures but are distinct entities. Benign neonatal sleep myoclonus is one of the most common seizure mimics. The movements in this condition are commonly migratory, multi-focal, brief myoclonic jerks. Occasionally they can be rhythmic and quite impressive (Video 5.2). These movements are present only in sleep and dissipate upon awakening.

Jitteriness is another common phenomenon in neonates. Typically, this movement is described as paroxysmal tremulousness involving the upper extremities, but the chin and lower extremities can be involved. These movements are often stimulus sensitive and can be triggered by noise and handling. Jitteriness can occur in normal neonates but is more common in infants with in-utero medication or drug exposure, hypoglycemia, and mild neonatal encephalopathy. Jittery movements typically can be suppressed by gentle restraint or swaddling.

Finally, a rare condition called hyperekplexia presents with an exaggerated startle response, tonic spasms with or without apnea, and myoclonus. Tapping on the chin or forehead can commonly trigger a tonic spasm. This rare disorder is associated with mutations in genes encoding glycine receptors and should at least be considered in the differential diagnosis [10].

To complicate matters further, about 50% of neonatal seizures captured on electroencephalogram (EEG) have no clear clinical correlate. The phenomenon was initially described by Mizrahi in 1987 and has been investigated since [11]. In one elegant study, Murray et al. studied 12 neonates with episodes concerning for seizures with video EEG and compared it with clinical seizures reported by experienced neonatal ICU staff. Electroencephalography, video analysis, and clinical identification data were collected separately. Of 526 seizures captured on EEG, only 34% had matching clinical events on video consistent with seizure. 33% of seizures were documented as such by the bedside. Only 9% of seizures were correctly

identified by the bedside staff. The authors arrived at the following conclusion: "in the recognition and management of neonatal seizures, clinical diagnosis alone is not enough." [12]

Recognizing the frequency of so-called electrical-clinical dissociation, the American Clinical Neurophysiology Society put forth recommendations regarding the use of electroencephalogram in at-risk neonates [13]. The current guidelines recommend a minimum of 24 hours of continuous video EEG monitoring in neonates that either have had clinical episodes concerning for seizure or are at high risk of developing seizures. Examples of the latter include infants diagnosed with neonatal encephalopathy (due to hypoxic/ischemic brain injury or other causes), infants with CNS infections, genetic syndromes, or known structural lesions. Infants treated with extracorporeal membrane oxygenation, treated for congenital heart disease and infants requiring neuromuscular blockade are also considered high-risk. If electrographic seizures are detected, the ACNS recommends continuing video EEG monitoring for at least 24 hours after the last documented seizure [13].

## Etiology

Except for a few benign genetic disorders and transient metabolic derangements, seizures in the neonatal population are usually an expression of significant underlying central nervous system pathology. The etiology of seizures will be discussed below in order of frequency. (Tables 5.1 and 5.2).

### Neonatal Hypoxic/Ischemic Encephalopathy (HIE)

HIE is the single most common cause of neonatal seizures accounting for 40–70% of seizures in this age group. Seizures due to this condition typically have onset within the first 24 hours. Seizures can be focal, multifocal, myoclonic, or subtle. The seizure burden in this group tends to be quite high, particularly in those with moderate encephalopathy. Seizures typically dissipate spontaneously after 72 hours, even without treatment. However, there is growing evidence that untreated seizures due to HIE can compound brain injury [1, 2, 9].

**Table 5.1** Etiology of neonatal seizures [2, 9]

| Etiology | % of cases |
|---|---|
| Hypoxic/ischemic encephalopathy | 38–70 |
| Vascular | 10–30 |
| Infectious | 4–15 |
| Cerebral dysgenesis | 4–10 |
| Transient metabolic disorders | 4–8 |
| Inborn errors of metabolism | 3–5 |
| Chromosomal and single-gene disorders | 3–10 |

**Table 5.2** Etiology vs. time at onset [1, 2, 9]

| Etiology | Typical age of onset |
|---|---|
| HIE | 12–24 hours |
| Arterial ischemic stroke | 3–5 days |
| BFNC | 5 days |
| Hypoglycemia | < 2 days |
| Hypocalcemia | 2–3 days |
| CNS infection | < 3 days |
| Systemic infection | > 3 days |
| Intracranial hemorrhage | 1–3 days |

## Vascular

Vascular insults are the second most common cause of neonatal seizures, ranging from 10 to 25% of neonates with seizures. This category includes arterial ischemic stroke (AIS), venous sinus thrombosis, and intracranial hemorrhage. Seizures due to AIS commonly present as focal clonic seizures on day 3–5 of life. Intraventricular hemorrhage is an important cause of seizures in pre-term infants [1, 2, 9].

## Infection

The next most common category of causes of seizures is infection, accounting for approximately 15% of cases of neonatal seizures. Viral encephalitides are the most common culprits. Herpes simplex virus (HSV) is the most common congenital viral encephalitis that causes seizures. Seizures associated with HSV tend to be focal and difficult to control. Other viruses associate with seizures in newborns are enteroviruses, parechovirus, lymphocytic choriomeningitis virus, Rubella, and cytomegalovirus. Bacterial meningitis or sepsis can also lead to seizures. The most common organisms are group B streptococcus and escherichia coli [1, 2, 9].

## Cerebral Malformations or Dysgenesis

Approximately 10% of neonatal seizures are due to *cerebral malformations or dysgenesis*. Seizure-causing malformations include schizencephaly, lissencephaly, focal cortical dysplasia, tubers associated with tuberous sclerosis complex (TSC), polymicrogyria, and hemimegalencephaly. (See Chap. 3) While individually these lesions are rare, taken together they comprise a substantial number of cases of neonatal seizures [1, 2, 9].

## Metabolic

Metabolic disturbances are responsible for approximately 8% of neonatal seizures. This category includes transient metabolic derangements, such as hypoglycemia, hyponatremia, and hypocalcemia. Inborn errors of metabolism are also included in

this category. Important disorders to consider are pyridoxine-dependent epilepsy, cerebral folate deficiency, and GLUT-1 transporter deficiency. These three entities all respond to specific treatments but not to conventional anticonvulsants. Amino acidopathies associated with seizure include non-ketotic hyperglycinemia, phenylketonuria, and maple syrup urine disease. Propionic, methylmalonic, and isovaleric acidemias can cause neonatal seizures. Urea cycle defects present with encephalopathy and seizures related to elevations of ammonia levels. Peroxisomal disorders such as Zellweger disease and neonatal adrenoleukodystrophy can cause seizures. Finally, biotinidase deficiency is an important, albeit rare, cause of seizures in neonates [1, 2, 9].

Pyridoxine-dependent epilepsy (PDE), mentioned above, is a unique seizure disorder that typically presents in the neonatal period with refractory seizures, although cases in older children are increasingly reported. Seizures can be focal clonic, myoclonic, or tonic. Progression to status epilepticus is common. This genetic disorder is caused by mutations in the ALDH7A1 gene, which encodes the enzyme α-aminoadipic semialdehyde dehydrogenase, which is one step in the breakdown of the amino acid lysine. The byproduct of this enzymatic block, α-amino adipic semialdehyde (AASA), interferes with the function of the active form of pyridoxine, pyridoxal phosphate [24]. Pyridoxal phosphate is an important cofactor for many enzymes involved in neurotransmitter metabolism. AASA can be detected in blood, urine, and CSF in patients with PDE. Treatment with IV pyridoxine can terminate seizures in this population and is recommended in any neonate (or older infant) with drug-resistant seizures.

### Genetic

Several single-gene disorders are also responsible for neonatal seizures. The advent of accessible genetic testing and development of next generation sequencing has allowed for easier identification of single gene diseases that can cause neonatal seizures. Mutations in KCNQ2 and KCNQ3 have been implicated in self-limited familial neonatal epilepsy [14]. Other genes associated with neonatal seizures include CDLK5 and STXBP1 [15]. (Table 5.3).

## Workup

Brain imaging is required in neonates with seizures unless a clear etiology can be identified, as seizures are typically an expression of significant underlying pathology. MRI is preferred due to superior imaging of brain parenchyma and the ability to detect acute ischemia. Most current neonatal MRI protocols include diffusion-weighted imaging for ischemia, high-resolution T1 sequences to assess anatomy, susceptibility-weighted imaging to detect blood products, and magnetic resonance spectroscopy to assess for inborn errors of metabolism. Ultrasound is limited to detecting hemorrhage or hydrocephalus. Computerized tomography (CT) scans can pick up blood, skull fractures, and major structural abnormalities. However, the low

**Table 5.3** Genes associated with neonatal seizures [15]

| Gene | Protein function | Associated seizure syndrome(s) |
|---|---|---|
| KCNQ2 | Voltage-gated potassium channel | SFNE, epileptic encephalopathy |
| KCNQ3 | Voltage-gated potassium channel | SFNE |
| SCN1A | Sodium channel | EIMFS |
| SCN2A | Sodium channel | Ohtahara, SFNE, EIMFS |
| KCNT1 | Sodium-activated potassium channel | EIMFS |
| GABARA1 | GABA receptor | EME, Ohtahara, non-specific epileptic encephalopathy |
| GABARB3 | GABA receptor | EME, Ohtahara, non-specific epileptic encephalopathy |
| GABARG2 | GABA receptor | EME, Ohtahara, non-specific epileptic encephalopathy |
| GABARB2 | GABA receptor | EME, Ohtahara, non-specific epileptic encephalopathy |
| CACNA1A | Calcium channel | Ohtahara |
| STXBP1 | Modulates synaptic binding vesicles | EME, Ohtahara |
| TBC1D24 | Regulates synaptic vesicle trafficking | Ohtahara |
| CDLK5 | Cell signaling and neuron morphogenesis | Neonatal seizures, often refractory |
| BRAT1 | Cell growth, proliferation, apoptosis | Rigidity and multifocal seizure syndrome (ref) |
| GNAO1 | G protein subunit expressed in brain | Ohtahara |
| ALDH7A1 | Lysine degradation pathway | Pyridoxine-dependent epilepsy |

*SFNE* self-limited familial neonatal epilepsy, *EME* early myoclonic epilepsy, *EIMFS* epilepsy of infancy with migrating focal seizures

resolution of CT scans limits its usefulness in assessing brain parenchyma. Additionally, CT scans use ionizing radiation for imaging, which may be associated with long-term risk of hematological malignancies and developmental abnormalities in exposed infants. CT scans have the advantages of being widely available and requiring short scan times (5 minutes, compared to 30–60 minutes for MRI) and as such are still used in some situations [16].

All infants should have basic laboratory investigations including complete blood cell counts, sodium, potassium, magnesium, and calcium levels. If infection is suspected, blood cultures, CRP, and lumbar puncture should be performed. The lumbar puncture should include culture, cell counts, chemistries, and PCRs for HSV and enterovirus. Antibiotic therapy is often initiated empirically before results return. Treatment of HSV should also be initiated pending results of lab testing [16]. (Table 5.4).

If brain imaging is unremarkable, or there is no history of perinatal stress or hypoxic encephalopathy, screening for inborn errors of metabolism should be initiated. Typically, this screening involves measurement of serum lactate, pyruvate, ammonia, acylcarnitine profile, and amino acids. Urine testing should include organic acids, reducing substances, and sulfites. Newborn screening programs in most states can detect many inborn errors of metabolism for which there is definitive treatment. Samples for newborn screening are usually collected at day 2 of life.

**Table 5.4** Laboratory investigations for neonatal seizures

| | Blood/serum | Urine | Cerebrospinal fluid |
|---|---|---|---|
| Basic investigations | CBC | Urinalysis | Cell counts |
| | Electrolytes (Na, K, Ca, Mg) | | Culture |
| | AST/ALT | | HSV PCR |
| | CRP | | |
| | Blood culture | | |
| Inborn errors of metabolism | Lactate | Organic acids | Amino acids |
| | Pyruvate | Sulfites | Glycine |
| | Ammonia | Reducing substances | Lactate |
| | Acylcarnitine profile | AASA | Neurotransmitter metabolites |
| | Newborn screen | Creatine | |
| | Pipecolic acid | Guanidinoacetate | |
| | Copper/ceruloplasmin | Oligosaccharides | |
| | Biotinidase | | |
| | AASA | | |
| Genetic testing | Chromosomal microarray analysis | | |
| | Epilepsy gene panel | | |
| | Whole exome | | |

*AASA* alpha-aminoadipic semialdehyde

Expedited newborn screening can be obtained in critically ill infants. Spinal fluid can also be analyzed for evidence of metabolic disorders. Pertinent tests include CSF lactate, glycine, and neurotransmitter metabolites. Simultaneous serum and cerebrospinal fluid glucose levels can identify seizures due to GLUT1 (cerebral glucose transporter type 1) mutations [17].

With the explosion of our knowledge of genetic causes of neonatal seizures in the last two decades, genetic testing is rapidly becoming essential in treating neonatal seizures and encephalopathy. Many commercial genetic testing companies have next-generation sequencing panels that specifically target neonatal/infant onset epilepsies. The ability to sequence hundreds of genes rapidly has revolutionized our understanding of early onset epilepsies. Some of the genetic disorders that cause seizures also have specific treatments, with obvious implications on the management of these patients [18].

## Treatment

Despite the frequency of neonatal seizures, the optimal treatment thereof has not been determined. There is limited evidence supporting the most commonly used treatment strategies, and some evidence that current treatments may be harmful to the developing brain. It is important to recognize the known (and unknown) risks of our current medications**.** In animal models and human studies, phenobarbital and phenytoin have been shown to have neurotoxic effects on the developing brain [19]. The long-term cognitive impact on children who have been treated with these

medications in infancy remains unknown. Historically, phenobarbital and phenytoin have been the primary agents used in the NICU, but increasingly levetiracetam has been employed. Additionally, current treatment trends are moving toward treating acute symptomatic seizures for shorter duration.

### First-Line Therapy

Initiation of an antiseizure medication is typically indicated for an infant experiencing a single seizure lasting longer than 30 seconds or a series of brief events [20]. Phenobarbital is typically used first-line for neonatal seizures with a starting dose of 20 mg/kg. For persistent seizures, two additional 10 mg/kg doses can be given for a total of 40 mg/kg in 24 hours or a serum level of 40–50 micrograms/mL. A typical maintenance dosing for phenobarbital is 3–6 mg/kg/day divided BID, and desired maintenance levels are usually in the 20–30 mcg/mL range.

### Second-Line Therapy

Approximately 64% of patients with neonatal seizures may be refractory to first-line treatment with no difference in response rates among patients with HIE, stroke, or ICH. Seizures among patients with inborn errors of metabolism and self-limited familial neonatal epilepsy often respond better to treatment [21]. Second-line agents typically include fosphenytoin or levetiracetam. In one seminal study, both phenobarbital and phenytoin were found to be "equally but incompletely effective." [22] Fosphenytoin dosing starts at 20 mg phenytoin equivalents (PE)/kg with subsequent maintenance dosing of 5–8 mg PE/kg/day divided TID or QID. Maintenance with oral phenytoin is challenging in newborns, who have inconsistent metabolism of this drug. Levetiracetam is dosed with an initial 40 mg/kg load with the option for subsequent loading doses up to a total of 100 mg/kg. Maintenance dosing for levetiracetam may range from 10–100 mg/kg/day divided BID-TID [23].

If seizures are not controlled (both electrographically and clinically), consideration should be given to a trial of IV pyridoxine. Treatment with 100 mg of IV pyridoxine in infants with pyridoxine dependent epilepsy can induce rapid cessation of seizure activity. Similarly, empiric treatment with folinic acid (3–5 mg/kg/day) for cerebral folate deficiency and/or pyridoxal phosphate for PMPO mutations should be considered [24].

Other agents that have been used in neonatal patients with refractory seizures include IV lidocaine, topiramate, oxcarbazepine, and rectal paraldehyde [25]. Data supporting these treatments is limited (Fig. 5.1).

## Neonatal Status Epilepticus

Infants who do not respond to the above therapies qualify for a diagnosis of status epilepticus. In these cases, a trial of a continuous infusion of an anti-epileptic drug may be warranted. The typical approach to treatment includes a loading dose of

midazolam 0.15 mg/kg load followed by a continuous infusion at 0.06 mg/kg/hr., titrated up to suppression of seizure activity (max 0.4 mg/kg/hr). Additional adjuvant agents may include topiramate or lidocaine [1].

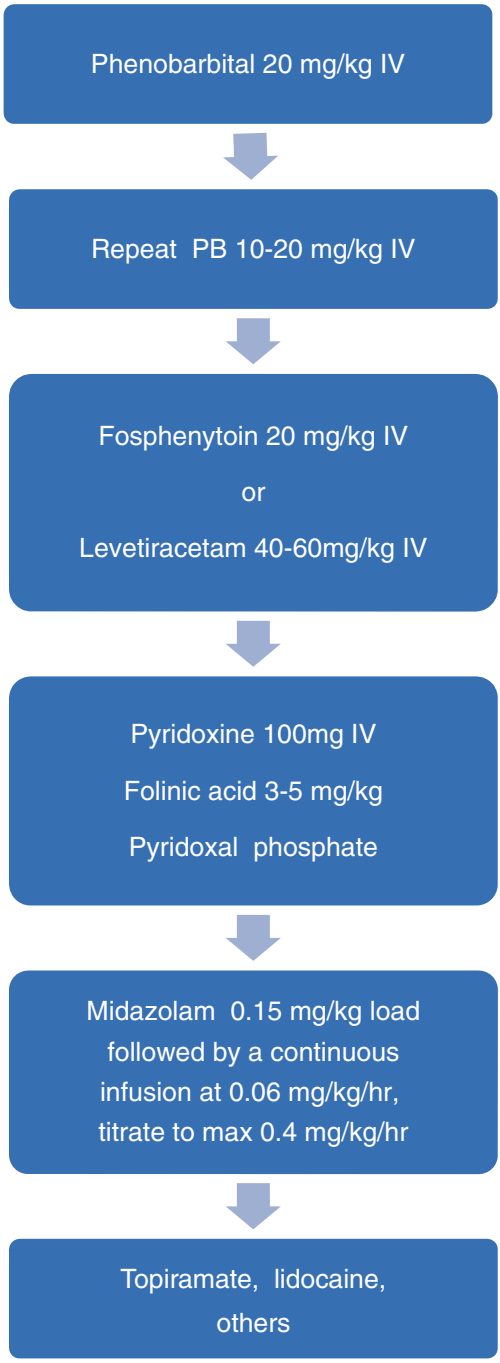



**Fig. 5.1** Neonatal seizure treatment algorithm

## Treatment-Related Controversy

As alluded to earlier, there is limited quality data to support the current standard of care. Painter et al., in one of the best quality studies, compared phenobarbital and phenytoin using EEG monitoring to measure response. 44% of patients in each group had 80% improvement in seizures on EEG. When both drugs were used simultaneously, after failure of the first agent, the responder rate was 57% [22]. In 2009 the Cochrane review stated that "at present there is little evidence from randomized controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period." [26]

There has also been much concern about the possibility of phenobarbital impairing normal brain development in neonates treated for seizure. In animal models, administration of phenobarbital has been demonstrated to cause apoptosis of neurons [19]. Phenobarbital has also been noted to decrease brain weight, reduce cell numbers in the cerebellum and hippocampus, and adversely affect learning and behavior [27–31]. In humans, fetuses exposed to phenobarbital had decreased head circumferences compared to those born to mothers not on medications [32]. Infants treated with phenobarbital to prevent febrile seizures had a significantly lower mean IQ compared to the placebo group, suggesting that the negative effects of phenobarbital on development persist into the first couple of years of life [33].

What is it about neonatal seizures that make them less responsive to our current anticonvulsant therapy? In the next section we will explore factors that make the neonatal brain more prone to seizures and less responsive to commonly used medications.

Human brain growth and development depends largely on excitatory activity to make and strengthen new connections; "neurons that fire together, wire together". Thus, the neonatal brain favors excitation, whereas the mature brain generally has achieved balance between excitation and inhibition. Some of the physiological factors that confer this tendency to excitation in neonates include differences in ion gradients, γ-aminobutyric acid (GABA) receptors, and glutamate receptors.

One area that has been explored in recent years is the physiology of GABA receptors and the maintenance of chloride gradients. Barbiturates (including phenobarbital) and benzodiazepines act by modulating the activity of GABA receptors, increasing their open time. The GABA receptor is a ligand-gated chloride (Cl-) channel with non-competitive binding sites for barbiturates and benzodiazepines. In mature neurons, GABA in inhibitory due to the higher extracellular concentration of Cl- ions. With GABA or ligand-induced channel opening, Cl- flows into the cell, hyperpolarizing the cell membrane and thus inhibiting action potential propagation. The extracellular chloride gradient is maintained by a potassium chloride cotransporter called KCC2.

In neonatal neurons, GABA receptors are actually *excitatory* [34]. Immature neurons have a much higher predominance of a different ion cotransporter called NKCC1. This cell membrane protein transports sodium, potassium, and chloride into the cell, causing a high intracellular chloride concentration. Consequently, upon channel opening, chloride flows out of the cell through the GABA receptor, causing depolarization [34]. (Fig. 5.2).

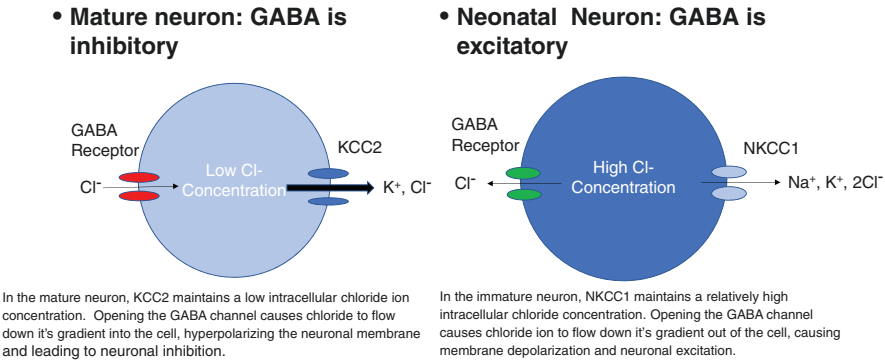



**Fig. 5.2** Mature vs. immature neurons and GABA receptors

The concentration of KCC2 begins to rise toward the end of the first month of life, whereas the percentage of NKCC1 peaks during the third trimester and first weeks of life and then declines. Additionally, the maturation of the chloride gradient occurs at different locations at different ages. The brainstem is the first portion of the neonatal nervous system to develop mature GABA-mediated inhibition, while the neocortex is last. This fact may explain the phenomenon of electrical-clinical dissociation mentioned above. If mature motor centers in the brainstem are inhibited by phenobarbital, there will be diminished motor signs of seizure. The excitatory nature of GABA receptors in neocortex promotes excessive electrical activity and seizures, as measured on EEG [35].

Understanding this reverse chloride gradient in maturing neurons has led to some investigations looking to exploit that information. Bumetanide, a loop diuretic that has been used in neonates for fluid balance, is a selective NKCC1 inhibitor. Theoretically, treatment with bumetanide should reduce NKCC1 activity resulting in an increased proportion of active KCC2 ion transporters, mimicking the chloride gradient of the mature neurons. Subsequent activation of the GABA receptor, therefore, should be inhibitory. This phenomenon was studied in rodent models with promising results [35]. Case reports in human neonates also reported a positive response [36].

With this idea in mind, two research studies were initiated investigating the safety and efficacy of adjunctive bumetanide added to phenobarbital compared to phenobarbital alone. The first study (NEMO) in Europe unfortunately was halted early due to increased incidence of hearing loss and clinically significant dehydration. Their limited data demonstrated meaningful reduction of seizures in only 33% [37]. A second trial is ongoing at the time of this writing.

Maturation-dependent differences in composition have also been described in glutamate receptors. There are three forms of glutamate receptors: kainite, N-Methyl-D-aspartic acid (NMDA), and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA). Most glutamate receptors are ion channels that cause influx or calcium, magnesium, and/or sodium into cells, causing cell depolarization. Glutamate receptors are expressed at higher levels in the neonatal brain compared to mature nervous systems. Ontologically this makes sense, given the need for excitatory activity to form synapses and networks.

**Table 5.5** Factors increasing susceptibility to seizures in the neonate [39]

| | |
|---|---|
| Excitatory action of γ-aminobutyric acid (GABA) | High synaptic density with over-expression of excitatory synapses |
| High glutamate receptor levels | Delayed development of the substantia nigra pars reticulata anticonvulsant network relative to the pro-convulsant network |
| Altered composition of NMDA and AMPA receptors favor excitation | Prolonged action potentials due to low levels of Na/K ATPase and slower kinetics of delayed rectifier K channels |

Glutamate receptors are cell membrane-bound proteins that consist of multiple subunits. In AMPA receptors, lower proportions of the GluR2 subunit in neonates render the AMPA receptor more permeable to calcium ions, increasing depolarization [38]. Other factors are mentioned below and also discussed in Chap. 1 (Table 5.5).

Topiramate selectively blocks AMPA receptors (among other mechanisms of action) and has been demonstrated in animal models to reduce seizures induced by hypoxia. Human data on topiramate in the neonatal population is limited, partially due to the absence of a parenteral formulation of this medication [40]. Animal models did not reveal neuronal apoptosis in neonatal rat pups exposed to topiramate [41]. Perampanel, another AMPA blocking agent, has also shown benefit in rodent models of neonatal seizures, but human data is lacking [42].

Levetiracetam has recently emerged as a potential treatment for neonatal seizures. This medication binds to synaptic vesicle binding protein 2A (SV2A). The exact function of SV2A is unknown. It likely modulates multiple neurotransmitter systems and may decrease glutamate release. There is an IV form available; it has no significant drug interactions, it has a high therapeutic/toxic ratio, and it does not cause neuronal apoptosis in animal models [43].

Small studies have demonstrated safety and efficacy of levetiracetam in neonates [44–50]. A recently published study comparing levetiracetam to phenobarbital in 83 neonates with seizure unfortunately was not supportive of the use of levetiracetam for neonatal seizures. Eighty percent of patients treated with phenobarbital remained seizure free for 24 hours, compared with 28% of patients assigned to levetiracetam. An additional dose of levetiracetam up to 60 mg/kg of levetiracetam improved the efficacy by 7.5%. Infants treated with phenobarbital had more adverse effects [23]. Given this data, we still do not know what the best treatment is for neonatal seizures.

## Duration of Treatment

The natural history of neonatal seizures shows peak onset within the first 24 hours of life and resolution within 3–7 days after onset of seizure. This pattern is particularly true in cases related to HIE [51]. Given this fact, early discontinuation of AEDs should be considered if a patient has been seizure-free for over 72 hours [52]. For patients on monotherapy, the AED can be stopped with a rapid taper. Ongoing treatment with phenobarbital as prophylaxis at hospital discharge has not been shown to

impact the rate of seizure recurrence [53]. For those on polytherapy, adjuvant therapies should be discontinued one at a time followed by discontinuation (vs. slow taper) of phenobarbital [34]. Patients undergoing AED discontinuation should be monitored closely clinically and by EEG for seizure recrudescence, and AEDs should be restarted if this occurs.

## Prognosis

As alluded to above, there is some controversy regarding whether seizures themselves effect long-term prognosis in neonates. Clearly there is a relationship between outcomes and etiology; infants with seizures due to hypoxic-ischemic encephalopathy and CNS infections tend to fare poorly compared to those with other etiologies. (Tables 5.6 and 5.7). Advances in neonatal care have improved mortality data, but significant morbidity is still common among neonates with seizures secondary to HIE. The real debate regards whether seizures compound brain injury in HIE or other etiologies, particularly in the light of the lack of effective treatments.

There is conflicting data in animal models of neonatal seizures with regard to the effect of seizures on brain injury. Wirrell et al. studied the mean percent of neurons damaged in ten-day-old rat pups exposed to 30 minutes of hypoxia with and without seizures. The pups with kainite-induced seizures after hypoxia had a significantly higher percentage of neuronal loss than those with hypoxia alone [54]. However, other authors have performed similar studies without demonstrating a significant difference in neuronal loss in rat pups with hypoxic brain injury with and without seizures [55].

**Table 5.6** Mortality and morbidity data related to etiology, 1980s [5,52]

| Etiology | Mortality (%) | Morbidity (%) |
|---|---|---|
| HIE | 30 | 85 |
| Infection | 40 | 80 |
| Metabolic | 20 | 70 |
| Dysgenesis | 5 | 80 |
| Vascular | 5 | 20 |
| SFNE | 0 | 10 |

**Table 5.7** Outcomes of neonatal seizures, 2006 [2]

| Etiology | Mild NDD (%) | Severe NDD (%) | Seizures after discharge (%) | Favorable overall outcome % |
|---|---|---|---|---|
| HIE | 42 | 36 | 31 | 50 |
| Focal ischemia | 37 | 0 | 0 | 100 |
| Hemorrhage | 27 | 13 | 20 | 87 |
| Dysgenesis | 0 | 100 | 75 | 0 |
| Transient metabolic | 33 | 0 | 33 | 67 |
| Infection | 0 | 33 | 0 | 67 |
| Unknown | 2 | 0 | 81 | 100 |

*NDD* neurodevelopmental disability

Whether seizures contribute to brain injury in human neonates is a difficult question to evaluate. Miller et al. used MR spectroscopy to investigate this subject in 90 term neonates with HIE. They found an increase in lactate peak frequency and a decrease in relative NAA peaks in neonates with seizures compared to those without [56].

Despite the lack of high-quality data in humans, there is a growing consensus that neonatal seizures should be regarded as an emergency and be treated aggressively. This fact underscores the importance of developing new, effective therapies for seizures in this population.

## References

1. Glass HC, Shellhaas RA, Wusthoff CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. J Pediatr. 2016;174:98–103.
2. Tekgul H, Gauvreau K, Soul J. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics. 2006;17(4):1270–80.
3. Garcias Da Silva LF, Nunes ML, da Costa JC. Risk factors for developing epilepsy after neonatal seizures. Pediatr Neurol. 2004;30:271–7.
4. Garfinkle J, Shevell MI. Cerebral palsy, developmental delay, and epilepsy after neonatal seizures. Pediatr Neurol. 2011;44:88–96.
5. Mellits ED, Holden KR, Freeman JM. Neonatal Seizures II. A multivariate analysis of factors associated with outcome. Pediatrics. 1982;70(2):177–85.
6. Holmes GL. Effects of seizures on brain development: lessons from the laboratory. Pediatr Neurol. 2005;33:1–11.
7. Van Rooij LGM, Toet MC, van Huffelen AC. Effect of treatment of subclinical neonatal Seizures detected with aEEG: randomized. Controlled Trial Pediatrics. 2010;125(2):e358–66.
8. Hellstrom-Westas L, Boylan G, Agren J. Systematic review of neonatal seizure management strategies provides guidance on anti-epileptic treatment. Acta Paediatr. 2015;104(2):123–9.
9. Volpe JJ. Neonatal seizures in neurology of the newborn. 5th ed. Philadelphia: Saunders Elsevier; 2008. p. 203–44.
10. Facini C, Spagnoli C, Pisani F. Epileptic and non-epileptic paroxysmal motor phenomena in newborns. J Matern Fetal Neonatal Med. 2016;29(22):3652.
11. Mizrahi EM, Kellaway P. Characterization and classification of neonatal seizures. Neurology. 1987;37:1837–44.
12. Murray DM, et al. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Ach Dis Child Fetal Neonatal. 2008;93:F187–91.
13. Shellhaas RA, Chang T, Tsuchida T. The American clinical neurophysiology society's guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011;28(6):611–7.
14. Allen NM, et al. The variable phenotypes of KCNQ-related epilepsy. Epilepsia. 2014;55(9):e99–105.
15. Axeen EJT, Olson HE. Neonatal epilepsy genetics. Seminars Fetal Neonatal Med. 2018;23(3):197–203.
16. Hallberg B, Blennow M. Investigations for neonatal seizures. Semin Fetal Neonatal Med. 2013;18(4):196–201.
17. Ficicioglu C, Bearden M. Isolated neonatal seizures: when to suspect inborn errors of metabolism. Pediatr Neurol. 2011;2011(45):283–91.
18. Pisani F, Percesepe A, Spagnoli C. Genetic diagnosis in neonatal-onset epilepsies: Back to the future. Eur J Paediatr Neurol. 2018;22(3):354–7.

19. Bittigau P, Sifringer M, Ikonomidou C. Antiepileptic drugs and apoptosis in the developing brain. Ann New York Acad Sci. 2003;993:103–14.
20. Donovan MD, Griffin BT, Kharoshankaya L, Cryan JF, Boylan GB. Pharmacotherapy for neonatal seizures: current knowledge and future perspectives. Drugs. 2016;76(6):647–61.
21. Boylan GB, et al. Second-line anticonvulsant treatment of neonatal seizures. Neurology. 2004;63:486–8.
22. Painter MJ, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med. 1999;341:485–9.
23. Sharpe C, Reiner GE, Davis SL. Levetiracetam versus phenobarbital for neonatal Seizures: a randomized controlled trial. Pediatrics. 2020;145(6):e20193182.
24. Gospe SM. Neonatal vitamin-responsive epileptic encephalopathies. Chang Gung Med J. 2010;33:1–12.
25. Puneet J, Sharma S, Dua T. Efficacy and safety of anti-epileptic drugs in patients with active convulsive seizures when no IV access is available: systematic review and meta-analysis. Epilepsy Res. 2016;122:47–55.
26. Booth D, Evan DJ. Anticonvulsants for neonates with seizures. Cochrane Database Syst Rev. 2004;3:CD004218.
27. Bergman A, et al. Neuronal losses in mice following both prenatal and neonatal exposure to phenobarbital. Acta Anat. 1982;114:185–92.
28. Fishman RHB, et al. Ultrastructural evidence of long-lasting cerebellar degeneration after early exposure to phenobarbital in mice. Exp Neurol. 1983;79:212–20.
29. Pick CG, Yanai J. Long-term reduction in eight arm maze performance after early exposure to phenobarbital. Int J Dev Neurosci. 1985;3:223–7.
30. Schain RJ, Watanabe K. Effect of chronic phenobarbital administration upon brain growth of the infant rat. Exp Neurol. 1975;47:509–17.
31. Yanai J, et al. Neural and behavioral alterations after early exposure to phenobarbital. Neurotoxicology. 1989;10:543–54.
32. Dessens AB, et al. Association of prenatal phenobarbital and phenytoin exposure with small head size at birth and with learning problems. Acta Pediatrics. 2000;89(5):533–41.
33. Farwell JR, et al. Phenobarbital for febrile seizures—effects on intelligence and on seizure recurrence. NEJM. 1990;322:364–9.
34. Dzhala VI, et al. NKCC1 transporter facilitates seizures in the developing brain. Nat Med. 2005;11(11):1205–13.
35. Dzhala VI, et al. Bumetanide enhances phenobarbital efficacy in neonatal seizure model. Ann Neurol. 2008;63:222–35.
36. Kahle KT. Decreased seizures activity in a human neonate treated with bumetanide. J Child Neuro. 2009;24:572–6.
37. Pressler RM, Boylan GB, Marlow N. Bumetanide for the treatment of seizures in newborn babies with hypoxic ischaemic encephalopathy (NEMO): an open-label, dose finding, and feasibility phase 1/2 trial. Lancet Neurol. 2015;14:469–77.
38. Law AJ, Weickert CS, Webster MJ. Expression of NMDA receptor NR1, NR2A,and NR2B subunit mRNAs during development of the human hippocampal formation. Eur J Neurosci. 2003;18:1197–205.
39. Jansen FE. Developmental factors regulating susceptibility to perinatal brain injury and seizures. Current Op Pediatrics. 2006;18:628–33.
40. Glass HC, et al. Topiramate for the treatment of neonatal seizures. Pediatr Neurol. 2011;44:439–42.
41. Glier C, et al. Therapeutic doses of topiramate are not toxic to the developing rat brain. Exp Neurol. 2004;187:403–9.
42. Jensen FE, Blume H, Alvarado S, Firkusny I, Geary C. NBQX blocks acute and late epileptogenic effects of perinatal hypoxia. Epilepsia. 1995;36(10):966–72.
43. Manthey D, et al. Sulthiame but not levetiracetam exerts neurotoxic effect in the developing rat brain. Exp Neurol. 2005;193:497–503.

44. Abend NS. Levetiracetam for the treatment of neonatal seizures. J Child Neurol online edition. 2011.
45. Fuhrwentsches A. Levetiracetam in the treatment of neonatal seizures: a pilot study. Seizure. 2010;19:185–9.
46. Khan O. Use of intravenous Levetiracetam for Management of Acute Seizures in neonates. Pediatr Neurol. 2011;44:265–9.
47. Khan O, et al. Role of intravenous levetiracetam for acute seizure management in preterm neonates. Pediatr Neurol. 2013;49(5):340–3.
48. Picker M, Thomas J, Koch C, Ramantani G, et al. Levetiracetam: safety and efficacy in neonatal seizures. Eur J Pediatr Neurol. 2011;15:1–7.
49. Rakshasbhuvankar A, et al. Intravenous levetiracetam for treatment of neonatal seizures. J Clin Neurosci. 2013;20(8):1165–7.
50. Shoemaker MT. Levetiracetam for the treatment of neonatal seizures. J Child Neurol. 2007;22(1):95–8.
51. Guillet R, Kwon JM. Prophylactic phenobarbital administration after resolution of neonatal Seizures: survey of current practice. Pediatrics. 2008;122(4):731–5.
52. World Health Organization. Guidelines on neonatal seizures. 2011.
53. Holden KR, Mellits ED, Freeman JM. Neonatal Seizures 1. Correlation of prenatal and perinatal events with outcomes. Pediatrics. 1982;70(2):165–76.
54. Wirrell EC, Armstrong EA, Osman LD. Prolonged Seizures exacerbate perinatal hypoxic-ischemic brain damage. Pediatr Res. 2001;50:445–54.
55. Vannucci RC, Towfighi J, Brucklacher RM, Vannucci SJ. Effect of extreme hypercapnia on hypoxic–ischemic brain damage in the immature rat. Pediatr Res. 2001;49:799–803.
56. Miller SP, Weiss BS, Barnwell A. et al. Seizure-associated brain injury in term newborns with perinatal asphyxia.

# Evaluation of the Pediatric Patient with Seizures

6

Albert Misko

## Introduction

Each year, an estimated 150,000–200,000 (around 50/100,000) Americans experience a first–time seizure [1]; 25,000–40,000 (around 80/100,000) are children below the age of 15 years [1, 2].

When approaching the pediatric patient presenting with their first seizure, the initial critical parameter to determine is whether the seizure is provoked or unprovoked through a thorough history and neurological examination. The provider should use EEG and imaging modalities (discussed below) judiciously, guided by clinical judgment. An understanding of the pre-test probability and utility of each auxiliary modality within a given clinical context is essential.

Provoked seizures may be caused by structural damage (traumatic brain injury, stroke, infection, or brain tumor) or metabolic disturbance (electrolyte imbalance, renal failure, or hepatic failure). In the case of a provoked seizure, the medical professional should address the underlying medical issues to prevent seizure recurrence. In the neurologically intact patient who has not sustained structural brain damage, recurrence of a provoked seizure is unlikely (3–8%) and lifetime antiseizure therapy is usually not warranted [3].

When a seizure is unprovoked, the risk of recurrence is estimated between 30% and 50%. After a second unprovoked seizure, the risk of recurrence increases to 70–80% within the next 2 years. A second unprovoked seizure is sufficient to assign a diagnosis of epilepsy and initiation of treatment is typically recommended [4–7]. In the case of the unprovoked seizure, the pediatric practitioner should also consider idiopathic epilepsy syndromes. Accurate diagnosis of an idiopathic epileptic syndrome can be reliably made with the initial diagnostic work up. An identification of

A. Misko (✉)
Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
e-mail: AMISKO@mgh.harvard.edu



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_6

a specific syndrome may guide treatment decisions and inform the discussion of prognosis [8]. Appropriate intervention is predicated on an accurate diagnosis. In the case of an ambiguous etiology, the practitioner must carefully weigh the risks and benefits of further testing and/or initiating an antiepileptic drug (AED).

## History

A careful history surrounding the event in question is critical for determining whether an epileptic etiology is likely. See Table 6.1. The history helps determine whether a seizure is provoked or unprovoked. A good history can also classify the specific type of seizure, which may influence workup. A complete history should include the following: (1) the condition of the patient prior to the event to elicit possible precipitating factors or preceding aura; (2) the location of the event; (3) whether the patient sustained an injury (head injury, tongue laceration, etc.); (4) a description of the position and movements of the eyes, face, trunk, and limbs during the event; (5) the duration of the event; (6) the presence or absence of color change (pallor, cyanosis); (7) the presence or absence of urinary or bowel incontinence; and (8) the period of time required for the patient to return to baseline.

Key descriptors supporting an epileptic etiology include: a preceding aura; unresponsiveness; maintenance of eye opening during the convulsion; fixed eye deviation; facial automatisms (smacking of lips, chewing, swallowing), biting the lateral edge of the tongue; rhythmic shaking of the extremities that cannot be suppressed or entrained to another frequency by an observer; paroxysmal autonomic dysfunction (tachy- or bradycardia, apnea, rise in blood pressure, sweating, emesis); and positive sensory phenomena. Features of the post-ictal period suggesting an

**Table 6.1** Important features of the patient history

| Seizure history quick reference | |
|---|---|
| *HPI* | Health prior to episode |
| | Precipitating factors |
| | Sleep deprivation |
| | New/change in medications |
| | Stress |
| | Trauma |
| | Infection |
| | Aura |
| | Seizure semiology |
| | Duration |
| | Post-ictal period |
| *Medications* | See Table 6.2 |
| *Birth Hx* | Signs of perinatal trauma |
| | Prematurity |
| *Development* | Any sign of delay or regression |
| *Family Hx* | Relatives with seizures or epilepsy |
| *Social Hx* | Travel |
| | Drug use |
| | Stressors |

epileptic event include confusion, anterograde amnesia, difficulty speaking, lethargy, hypertension, nausea, or headache.

Seizure mimics (discussed in detail in chap. 8) include syncope/presyncope (especially "convulsive syncope"), transient ischemic attacks, metabolic encephalopathy, sleepwalking, night terrors, complex migraines, cardiac arrhythmias, self-gratification behavior, or psychogenic non-epileptic seizures. In infants, gastroesophageal reflux (Sandifer syndrome), benign sleep myoclonus, and hyperekplexia can mimic seizures.

Key descriptors that suggest a non-epileptic etiology include: no alteration of mental status during or following a generalized convulsive event; eye closure; biting the anterior tip of tongue; change in posture immediately preceding the event (syncope); arrhythmic shaking of extremities that can be suppressed by an observer or entrained to a different frequency; negative sensory phenomena (transient ischemic attack or stroke); clustering around feeding times (Sandifer syndrome), or myoclonic movements that only occur during sleep (sleep myoclonus).

Whether a seizure is provoked can usually be determined from the history. Provoking factors include fever, infection, head injury, withdrawal from alcohol or drugs, intoxication, hypoglycemia, electrolyte disturbances, intracranial hemorrhage, stroke, and drugs that lower the seizure threshold (Table 6.2). Fever, altered mental status, or bulging fontanels in an infant less than 6 months in age should automatically trigger a complete workup for meningitis. Signs of meningismus are unreliable in children under the age of 2 years old, and the practitioner should exercise clinical discretion in determining whether a lumbar puncture and/or brain imaging are warranted. Recent changes in medications could also offer clues.

With an episode suggestive of an epileptic seizure, the practitioner should classify the semiology to assist with diagnosis. In 2017 the International League Against Epilepsy (ILAE) provided a new classification seizure types, largely based upon the existing classification first produced in 1981. (See chap. 2) To properly describe the semiology of a seizure, first decide whether the onset was focal, generalized, or unknown (i.e., unwitnessed). Next, in the case of a focal seizure, describe whether the patient had impaired awareness at any point during the episode. Seizures of focal onset are next classified by the first prominent sign or symptom. Descriptors of motor onset include automatisms, atonic, clonic, epileptic spasms, hyperkinetic, myoclonic, and tonic. Descriptors of nonmotor onset include autonomic, behavior arrest, cognitive, emotional, and sensory. Seizures of generalized onset are also characterized by a description of the first prominent signs or symptoms. Motor descriptors include tonic-clonic, clonic, tonic, myoclonic, atonic, and epileptic spasm. Non-motor descriptors (for absence seizures) include typical, atypical, myoclonic, and eyelid myoclonic. While the original guidelines from 1981 rely solely on clinical observation to describe seizure semiology, the new guidelines from 2017 allow incorporation of EEG or neuroimaging data and formulating the description of semiology. In this way, a seizure for which the onset was unwitnessed can still be described as focal if supported by a strong focality on EEG or focal structure anomaly on magnetic resonance imaging. See Chap. 2 for more details.

**Table 6.2** Medications that may lower the seizure threshold---Note: The table does not adequately separate the categories as presented here Enflurane, Isoflurane and propofol are anesthetics, aminophylline and theophylline are anti-asthmatics; the drugs from amphotericin to penicillins are antibiotics; tricyclics, SSRIs and Buproprion are antidepressants; cyproheptadine is the only antihistamine; drugs from promethazine to trifluoperazine are antipsychotics

| Medications that may lower the seizure threshold | |
|---|---|
| | Enflurane |
| Anesthetics | Isoflurane |
| | Propofol |
| Anti-asthmatics | Aminophylline |
| | Theophylline |
| | Amphotericin |
| | Cephalosporins |
| | Imipenem |
| Antibiotics | Isoniazid |
| | Metronidazole |
| | Penicillins |
| | Tricyclics |
| Antidepressants | SSRIs |
| | Bupropion |
| Antihistamines | Cyproheptadine |
| | Promethazine |
| | Chlorpromazine |
| | Clozapine |
| Antipsychotics | Haloperidol |
| | Olanzapine |
| | Risperidone |
| | Trifluoperazine |
| Hormones | Estrogen |
| Immunosuppressants | Cyclosporine A |
| | Chlorambucil |
| Narcotics | Opioids |
| | Meperidine |
| Stimulants | Amphetamines |
| | Cocaine |

## Medications

There are a number of medications that have the potential to lower the seizure threshold. Categories of medications include anesthetic agents, antibiotics, antipsychotics, and some antidepressants. See Table 6.2 for a list of relevant medications.

## Birth and Developmental History

Obtaining a careful birth history is most useful in the youngest patients. Premature birth should increase suspicion for prenatal injury secondary to intracerebral hemorrhage or periventricular leukomalacia. Complications at the time of birth may suggest a perinatal ischemic event. An abnormal developmental trajectory should raise

suspicion for genetic, structural, or developmental disorders associated with epilepsy. Neurological and cognitive regression or episodic decompensation strongly argues for a metabolic or genetic condition.

## Family History

Ask about other family members who may have had seizures or diagnosed with epilepsy. A thorough family history can assist with the diagnosis of idiopathic epilepsies and may help warrant genetic testing. Several common forms of childhood epilepsy appear to be inherited in an autosomal dominant pattern. Therefore, a careful family history of seizures at any age is essential.

## Social History

Identify recent travel and exposure to infectious or toxic agents. Recent physiological stressors such as sleep deprivation are also important precipitants. Psychosocial stressors may hint at a functional etiology. In adolescents, inquiring about drug and alcohol use without their parent present is essential.

## Examination

Every patient that presents for a workup of a first seizure should receive a complete general and neurological examination. The general examination should broadly assess for signs of systemic disease which may hint at a symptomatic cause of a seizure. In a young child, dysmorphic features and abnormal head circumference (macrocephaly or microcephaly) may hint at an underlying genetic condition. Assess for signs of neurocutaneous disease including café au lait macules, axillary or inguinal freckling, ash leaf spots, Lisch nodules in the iris, Shagreen patches, or periungual fibromas. The examination of the skin should also look for port wine stains, especially in the V1 distribution that may be an overt manifestation of the ipsilateral leptomeningeal angiomatosis characteristic of Sturge Weber syndrome. Signs of trauma including ecchymosis, abrasions, point tenderness, or retinal hemorrhage should be sought, and the possibility of non-accidental trauma considered in the appropriate context. Neurological exam should assess for focal or asymmetric deficits, which may result from an intracranial process or alternatively an ongoing Todd's paralysis. Asymmetry of tendon stretch reflexes or unilateral extensor plantar response (positive Babinski sign) suggests a focal onset of seizures and has lateralizing value.

## Laboratory Workup

Clinical context should guide the use of laboratory testing in all cases of first afebrile seizure in a pediatric patient. Specific examples include blood glucose testing

in a diabetic patient, CBC or lumbar puncture with CSF studies in a patient with signs of infection or meningitis and electrolytes in a patient with persistent vomiting or diarrhea. Any report of exposure to drugs or toxins should indicate routine urine and serum screens across the pediatric age spectrum.

A developmentally normal pediatric patient over the age of 6 months who presents with an isolated first-time afebrile seizure, and is back to baseline with a normal neurological exam, does not necessitate routine lab screening [2]. In 1 Class I study involving 30 children and 133 adults with seizures (15% first seizure), routine lab screening only revealed 1 patient with significant hypoglycemia which was already suspected on a clinical basis [9]. Two additional Class II studies involving 507 children also found that routine lab work did not contribute to diagnosis or treatment of patients [10, 11]. One exception to these data are children under the age of 6 months, in which hyponatremia was found in 70% of 47 patients who did not show clinical signs of electrolyte imbalance in one Class II study [12]. Multiple seizures, prolonged seizure, or failure to return to baseline post-ictally warrant further workup. If abnormalities are found on laboratory investigations, the care team should replete glucose, sodium, calcium, and magnesium.

The utility of prolactin levels in supporting an underlying epileptic etiology of a convulsion has not been established in the pediatric population, particularly in infants and young children. In adults and older children, a metanalysis suggests that drawing a serum prolactin level 10–20 minutes after an event has strong positive but poor negative predictive value in differentiating an epileptic from psychogenic event [13]. However, elevated prolactin levels have been observed following syncopal events, suggesting limited specificity.

## EEG

Following an unprovoked first seizure, an interictal EEG can provide useful information in (1) determining whether an event was epileptic in nature, (2) predicting risk of seizure recurrence, (3) localizing focal abnormalities, (4) estimating the pre-test probability of performing neuroimaging, and (5) identifying an idiopathic epilepsy syndrome. Alternatively, when a seizure is clearly provoked by an underlying medical condition or trauma, clinical discretion is needed to determine the necessity of an EEG.

The AAN currently recommends obtaining an EEG as part of the routine neurodiagnostic evaluation in all children presenting with first unprovoked seizure [2]. The American Clinical Neurophysiology Society further recommends that studies capture both sleep and awake states, including hyperventilation and photic stimulation to increase the yield of capturing an abnormality [14].

The optimal timing of obtaining an EEG, however, remains uncertain. While EEG is most sensitive in the first 24–48 hours following an event, revealing abnormalities in 51–70% of cases, transient abnormalities such as post-ictal slowing may confound interpretation [15]. In the emergency room setting, a study in adults with first seizure (Class II data) did not find an EEG useful in determining which cases

warranted admission [16]. Though similar data is not available in a pediatric population, similar lack of utility is probable.

While an abnormal neurological exam and remote symptomatic etiology are strong predictors of seizure recurrence, the EEG is the best predictor in the neurologically normal patient [4, 5, 7, 17]. Following a first-time seizure, 54–70% of children with epileptiform activity or focal slowing on EEG will experience seizure recurrence compared to 25% with a normal study [18]. On this basis, an abnormal EEG plays a significant role in the decision of whether to start an AED.

Focal abnormalities on EEG can be indicative of underlying cerebral pathology, including congenital anatomical malformations or acquired insults that merit further investigation with neuroimaging (see below). Alternatively, identifying an idiopathic epilepsy syndrome on EEG precludes the need for neuroimaging and provides valuable information in guiding treatment and prognosis.

## Neuroimaging

Up to one-third of patients presenting with first-time seizure will have abnormalities on neuroimaging, but the majority of findings do not influence management [15, 19–23]. Only 2% of identified lesions require intervention or change management in the acute setting. Determining the need for imaging should be based on a combination of seizure semiology, neurological examination, and EEG findings [2, 15].

In the most current community-based cohort study of MRI results in children with a new diagnosis of epilepsy, the most significant predictors of MRI findings were an abnormal neurological exam (positive 48.8%, negative 6%; relative risk 4.24, 95%CI 2.89–6.22) followed by pharmacoresistance to at least 2 AEDs (positive 48.8%, negative 21.1%; relative risk 1.42, 95%CI 0.99–2.02). The most significant predictor of a normal MRI was an identifiable idiopathic epilepsy syndrome (positive 6.1%, negative 36%; relative risk 0.26, 95%CI 0.10–0.65) [24].

Thus, imaging in a child with a first seizure should be initiated in the setting of focal seizure semiology, abnormal neurological examination, or EEG abnormalities not consistent with an idiopathic epilepsy syndrome.

The timing of neuroimaging can be divided into emergent or nonurgent. Emergent neuroimaging at the time of presentation should be initiated for a new persistent post-ictal deficit such as Todd's paralysis, persistent altered mental status beyond the expected time course for recovery, or history and exam findings suggesting acute pathology that might require rapid intervention (worsening cerebral edema, acute hydrocephalus, or hemorrhage). In this case, a CT may be reasonable over an MRI given time restrictions and availability. Otherwise neuroimaging can be obtained in a nonurgent manner as an outpatient. In young children requiring sedation, the possible long-term effects of anesthesia on neurodevelopment should be seriously weighed against the potential benefits [25]. When indicated, MRI is preferred over CT, both for its superior sensitivity in detecting subtle abnormalities (i.e., cortical dysplasia and vascular abnormalities) and its lack of radiation exposure. MRI, when possible, should be performed

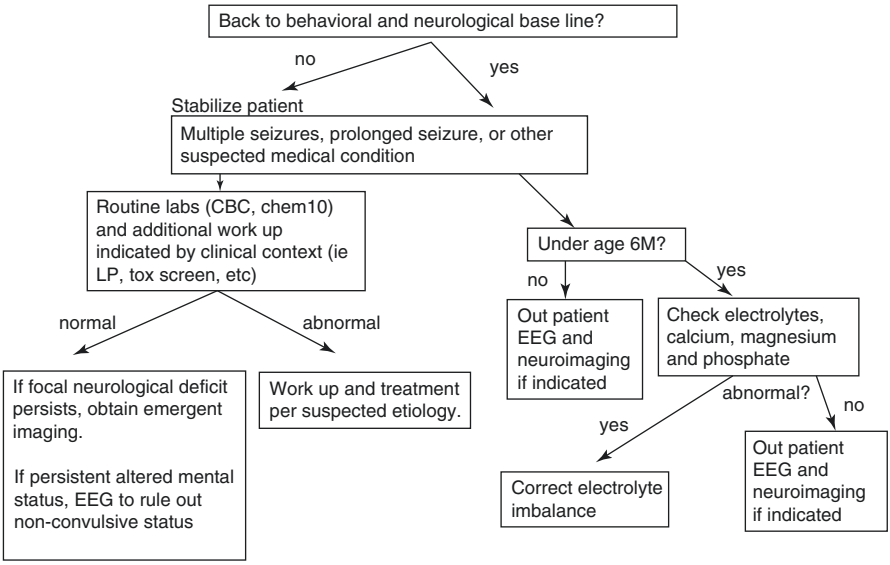



**Fig. 6.1** Algorithm for the evaluation of the first seizure

with a 3 Tesla magnet to aid in the identification subtle structural and abnormalities. Coronal T2-weighted images should be included in the MRI protocol for optimal visualization of the hippocampus and mesial temporal structures (Fig. 6.1).

## Further Evaluation of Epilepsy

The above section focuses on the evaluation of a patient after their first seizure, collecting data that may help guide diagnostic and treatment decisions. What about the patient newly diagnosed with *epilepsy*? In many cases the above workup is sufficient to establish a specific diagnosis. For example, the history and EEG are sufficient to make a diagnosis of childhood absence epilepsy or childhood epilepsy with centrotemporal spikes. In the appropriate clinical context, further investigation into the cause of epilepsy is often warranted. Finally, some patients with difficult to control seizures are evaluated for possible epilepsy surgery.

## Genetic Testing

The last two decades have seen a remarkable advance in our ability to assess and test for genetic causes of epilepsy. Single-gene causes of epilepsy are being discovered at a rapid rate. Many disorders previously categorized as “idiopathic” now have a determined underlying genetic etiology. The evolution of comparative genomic

microarrays and massive parallel/next generation sequencing has given the clinician tools to further understand their patient's disease.

Not every patient with epilepsy is an appropriate candidate for genetic testing. In the clinical setting, genetic testing is generally recommended in young patients with developmental and epileptic encephalopathies of undetermined etiology. Drug-resistant epilepsy of unclear etiology is another indication for genetic testing [26]. Structural abnormalities noted on brain imaging, such as lissencephaly, polymicrogyria, or cortical dysplasia may also provoke further genetic testing by the clinician. Finally, suspicion for a broader genetic syndrome of which epilepsy may be a feature (i.e., tuberous sclerosis complex, Angelman syndrome) can also lead to further investigation [27].

Genetic testing can take several forms. Karyotype has been available for decades and still has a role in diagnosing genetic disorders. Conditions that are often associated with epilepsy, such as Down syndrome or other trisomies, can be captured with this technology. Chromosomal microarray analysis has increased the resolution of the traditional karyotype and has been very effective in detecting copy number variations in patients with epilepsy [26]. This test is commonly considered the first tier of clinical genetic testing and, in appropriately selected candidates, can pick up clinically relevant changes in up to 5–10% of patients with pediatric epilepsy and developmental delay [28].

Whereas chromosomal microarrays can pick up copy number variants, many genetic epilepsy syndromes are caused by mutations in single genes that can only be detected by gene sequencing. Prior to the advent of next generation sequencing, Sanger sequencing was the available method. This line-by-line gene analysis is very accurate but expensive and labor intensive. Next-generation, or massive parallel, sequencing (NGS) technology has made it possible to sequence multiple genes, quickly, accurately, and, increasingly, affordably [26]. NGS has identified hundreds of single genes associated with epilepsy, with specific diagnoses being determined in 30–40% of patients with epileptic encephalopathies previously labeled "idiopathic." [28] While an exhaustive review of genetic causes of epilepsy is beyond the scope of this chapter, see select examples below (Table 6.3).

Many commercial labs now offer epilepsy gene panels that can sequence hundreds of relevant genes. In addition to specific gene panels, whole exome sequencing is being used increasingly in the clinical setting. Whole *genome* sequencing, which includes non-coding portions of DNA, is currently used in research settings, but use in the clinic is not far off.

Some genetic disorders may not be picked up by either chromosomal microarray or next-generation sequencing. This is particularly true for triplet expansion disorders (i.e., Fragile X syndrome), disorders with abnormal methylation patterns (Angelman syndrome), and large duplications or deletions. Understanding these nuances can help determine the order in which genetic investigations are undertaken [26]. (Table 6.4).

Genetic testing in epilepsy can provide many benefits such as achieving diagnostic clarity, informing long-term prognostic expectations, precluding expensive and possibly invasive testing, influencing reproductive decision making, and in some

**Table 6.3** Select examples of epilepsies caused by single-gene mutations

| Gene | Protein | Epilepsy type | Mode of inheritance |
|---|---|---|---|
| KCNQ2 | Potassium voltage-gated channel subfamily KQT member 2 | Self-limited familial neonatal seizures; neonatal epileptic encephalopathy | AD |
| KCNQ3 | Potassium voltage-gated channel subfamily KQT member 3 | Benign familial neonatal seizures | AD |
| SCN2A | Sodium channel type 2, subunit alpha | Benign familial infantile seizures | AD |
| CDLK5 | Cyclin-dependent kinase-like 5 | Infantile spasms | XL |
| ARX | Aristaless-related homeobox | Infantile spasms | XL |
| SNC1A | Sodium channel type 1, subunit alpha | Dravet syndrome; GEFS+ | AD |
| PCDH19 | Protocadherin-19 | Infantile/childhood onset refractory epilepsy in females | XL |
| STXBP1 | Syntaxin binding protein 1 | Ohtahara syndrome | AD |
| SLC2A1 | Solute carrier family 2, facilitated glucose transporter member 1 | GLUT1 deficiency; early-onset absence epilepsy | AD |
| ALDH7A1 | Alpha-aminoadipic semialdehyde dehydrogenase | Pyridoxine-dependent epilepsy | AR |
| GRIN2B | Glutamate receptor ionotropic NMDA 2B | Early-onset epileptic encephalopathy | AD |
| CHRNA4 | Neuronal acetylcholine receptor alpha-4 | Autosomal dominant nocturnal frontal lobe epilepsy | AD |
| CHRNA2 | Neuronal acetylcholine receptor alpha-2 | Autosomal dominant nocturnal frontal lobe epilepsy | AD |
| KCNT1 | Potassium channel, sodium-activated subfamily T, member 1 | Malignant migrating partial seizures of infancy; autosomal dominant nocturnal frontal lobe epilepsy | AD |
| SCN1B | Sodium channel subunit beta-1 | GEFS+ | AD |
| SCN2A | Sodium channel type 2, subunit alpha | GEFS+ | AD |
| GABRG2 | Gamma-aminobutyric acid receptor subunit gamma-2 | GEFS+ | AD |
| PRRT2 | Proline-rich transmembrane protein 2 | Infantile convulsions; familial paroxysmal kinesigenic dyskinesia | AD |
| SCARB2 | Lysosome membrane protein 2 | Progressive myoclonic epilepsy type 4 | AR |
| KCNC1 | Potassium voltage-gated channel subfamily C member 1 | Myoclonic epilepsy with ataxia | AD |
| CHRNA7 | Neuronal acetylcholine receptor subunit alpha-7 | Idiopathic generalized epilepsy | AD |
| GRIN2A | Glutamate receptor ionotropic, NMDA2A | Atypical epilepsy of childhood with centrotemporal spikes; epilepsy-aphasia | AD |

cases directly affecting treatment [27]. It is not without its downsides, however. Testing is still expensive and labor intensive, as there is an enormous amount of data to analyze. Normal genetic testing does not definitively rule out a genetic disorder, as our knowledge of genetics in epilepsy is incomplete. Variations of uncertain significance are common and often lead to further testing and confusion on the part of the patient and family. In the case of exome sequencing, clinically relevant genetic mutations, such as those predisposing to cancer risk, may be found incidentally and be a source of distress for the patient and family. Non-paternity and consanguinity have been incidentally discovered in some cases. Therefore, advanced genetic testing should be accompanied by genetic counseling and informed consent [27].

**Table 6.4** Summary of different methods of genetic testing for epilepsy

| Test | Data collected | Pros | Cons | Examples |
|---|---|---|---|---|
| Karyotype | High-resolution images of chromosomes<br>Detects aneuploidy, large deletions, duplications, and translocations | Inexpensive<br>Widely available | Low resolution | Trisomy 21<br>Ring chromosome 20 |
| Chromosomal microarray | Comparative genomic hybridization<br>Detects copy number variants | High yield (5–10%)<br>Relatively inexpensive | Cannot detect single gene disorders | Duplication 15 syndrome<br>Miller-Dieker syndrome (del 17p13.3) |
| Sanger sequencing | Single-gene sequencing | Highly accurate results for the gene in question | Expensive<br>Labor intensive | Numerous single gene disorders |
| Gene panel | Massive parallel sequencing<br>10s to 100 s of genes covered | High yield<br>Broad coverage of coding regions<br>Multiple relevant genes | Expensive<br>Labor intensive<br>Variations of unknow significance | Commercially available gene panels<br>Numerous single-gene disorders |
| Whole Exome | Massive parallel sequencing<br>100s to 1000s of genes covered | All coding regions covered | Expensive<br>Labor intensive<br>Long turn-around time<br>VUS<br>Unexpected findings | Commercial clinical exome testing is widely available<br>Numerous single-gene disorders |
| Methylation analysis | Detects repeat expansions and chromosome methylation abnormalities | Necessary for detecting some types of abnormalities | Need high index of suspicion for a specific disorder | Fragile X syndrome<br>Angelman syndrome |

## Pre-surgical Evaluation

Approximately 30% of patients with epilepsy are resistant to pharmacological treatment of their disease. In some cases, epilepsy surgery can be curative. Patients with an identified structural lesion that concords with EEG data and are not in eloquent cortex are the best surgical candidates. However, non-lesional cases can be amenable to resection if acquired data supports a specific focus. This section will briefly review specialized testing for patients being worked up for epilepsy surgery.

### MRI

Unless a clinical diagnosis of an epilepsy syndrome can be made by history and EEG, most patients with a new diagnosis of epilepsy will undergo imaging with MRI. For patients with refractory epilepsy, higher-resolution imaging is recommended to attempt to identify more subtle findings. Most centers recommend detailed structural imaging with a 3 Tesla magnet. Sequences should include high-resolution T1-weighted images with thin cuts (1–1.5 mm), T2 axial, and coronal images [29]. Post-image processing, including morphometric analysis, can detect subtle abnormalities not seen on source imaging [30].

### Invasive EEG Monitoring

In non-lesional drug-resistant epilepsy, attempts to pinpoint the location of seizure onset are essential in determining whether surgical resection is feasible. Surface EEG recordings are inadequate in detecting seizure onset from deeper regions of cortex such as the mesial temporal lobes and deep frontal cortex. In these cases, invasive EEG monitoring can be useful [29]. Invasive monitoring can include subdural grids and strips of electrodes which lay across cortical areas of interest. Stereotactic-guided depth electrode placement is also used, particularly in investigating the mesial temporal lobes. This type of investigation is not without risks and tends to be used more commonly in adult epilepsy. A study evaluating 242 patients across age groups found the complication rate at 23%, with only 9% requiring surgical revision. No cases of permanent morbidity and mortality were revealed. 99% of patients had successful mapping of the epileptic focus, and 50% had a good resective surgical outcome [31].

### MEG

Magnetoencephalography is a non-invasive technique used to measure brain magnetic fields. It is a valuable tool for localizing epileptiform activity and has very high temporal and spatial resolution [32]. The MEG data can identify the “irritative

zone" of cortex that is responsible for generating interictal discharges. In a study of 1000 patients who underwent MEG for presurgical evaluation, sensitivity of detecting interictal discharges was 72% across all subjects. 32% of the time MEG provided more localizing information than other modalities and was concordant with the other data in the presurgical evaluation in 51%. Complete resection of the irritable zone determined by MEG had the best long-term outcomes [33].

## PET

Positron emission tomography is an imaging technique that utilizes radio-isotope labeled compounds to assess functional status of brain regions. The most common tracer in clinical use is 2-deoxy-($^{18}$F)2-fluoro-D-glucose (FDG). Computed tomography detects the labeled glucose molecule after injection and can determine the metabolic activity of specific brain regions [30]. In the context of the epilepsy evaluation, PET scanning can detect areas of hypometabolism, suggesting a region of dysfunction that correlates with an epileptogenic region. In FDG pet, uptake occurs over about 30 minutes. Therefore, the images acquired do not demonstrate real-time activity, but average metabolic activity over the period of uptake [34]. In some cases, if the epileptogenic lesion is very active, PET hypermetabolism can be seen [34].

## SPECT

Single photon emission computed tomography (SPECT) measures regional cerebral blood flow in real time. Seizures may increase regional blood flow by as much as 300% [30]. Ictal SPECT recordings can accurately detect areas of increased blood flow corresponding to the locus of epileptic activity. For ictal SPECT to be informative, the radiotracer needs to be injected within seconds to minutes of seizure onset. To analyze the data more accurately, ictal images are co-registered to interictal images and superimposed on MRI images, a process called subtraction ictal SPECT co-registered to MRI (SISCOM) [30]. (Fig. 6.2) This technique has been found to have a sensitivity of 85% and specificity of 94% in detecting the seizure focus [35].

## fMRI

Functional magnetic resonance imaging is often used as part of the pre-surgical evaluation of potential epilepsy surgery patients to localize eloquent cortex and estimate the risk of post-surgical deficits. fMRI measures blood oxygen level–dependent (BOLD) signal changes, which correlates closely with cerebral activity. fMRI is performed with the patient awake and able to participate in specific cognitive and motor tasks. fMRI has largely supplanted the use of the Wada test, which involves catheter injection of amobarbital into the carotid artery to lateralize language, visuospatial, and other higher cognitive functions. Mapping of language centers and motor function is the commonest use of fMRI in the

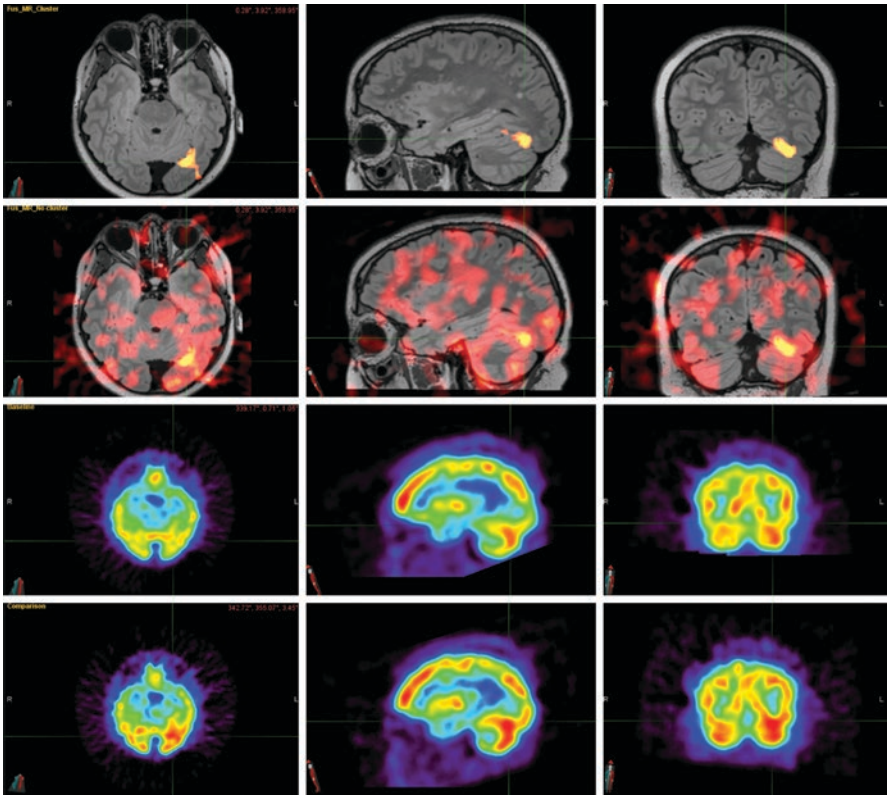


**Fig. 6.2** Subtraction ictal SPECT co-registered with MRI (SISCOM) demonstrating an epileptogenic zone in the right occipital cortex. The top panel is the final co-registered image; Panel 3 is the interictal SPECT; Panel 4 is the ictal SPECT

presurgical evaluation of epilepsy patients. One study compared fMRI and electrocortical stimulation mapping (ESM) while performing a sentence generation task in pediatric patients. The fMRI data demonstrated 100% sensitivity but 69% specificity in localizing language compared to ESM [36]. Mapping of motor cortex is best done with an active task, such as foot or finger tapping. However, Studies have also demonstrated that passive motor activity can be picked up on fMRI, so data can still be collected from sedated or uncooperative patients.

## References

1. Begley CE, Famulari M, Annegers JF, et al. The cost of epilepsy in the United States: an estimate from population-based clinical and survey data. Epilepsia. 2000;41(3):342–51.
2. Hirtz D, Ashwal S, Berg A, et al. Practice Parameter : Evaluating a First. Neurology. 2000;55:616–23.

3. Pohlmann-Eden B, Beghi E, Camfield C, Camfield P. The first seizure and its management in adults and children. BMJ. 2006;332(7537):339–42.
4. Shinnar S, Berg AT, Moshe SL, et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. Pediatrics. 1996;98(2 Pt 1):216–25.
5. Camfield PR, Camfield CS, Dooley JM, Tibbles JA, Fung T, Garner B. Epilepsy after a first unprovoked seizure in childhood. Neurology. 1985;35(11):1657–60.
6. Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE. Risk of recurrent seizures after two unprovoked seizures. N Engl J Med. 1998;338(7):429–34.
7. Shinnar S, Berg AT, O'Dell C, Newstein D, Moshe SL, Hauser WA. Predictors of multiple seizures in a cohort of children prospectively followed from the time of their first unprovoked seizure. Ann Neurol. 2000;48(2):140–7.
8. Berg AT, Shinnar S, Levy SR, Testa FM, Smith-Rapaport S, Beckerman B. How well can epilepsy syndromes be identified at diagnosis? A reassessment 2 years after initial diagnosis. Epilepsia. 2000;41(10):1269–75.
9. Eisner RF, Turnbull TL, Howes DS, Gold IW. Efficacy of a "standard" seizure workup in the emergency department. Ann Emerg Med. 1986;15(1):33–9. https://doi.org/10.1016/S0196-0644(86)80483-8.
10. Smith RA, Martland T, Lowry MF. Children with seizures presenting to accident and emergency. J Accid Emerg Med. 1996;13(1):54–8.
11. Nypaver MM, Reynolds SL, Tanz RR, Davis AT. Emergency department laboratory evaluation of children with seizures: dogma or dilemma? Pediatr Emerg Care. 1992;8(1):13–6.
12. Farrar HC, Chande VT, Fitzpatrick DF, Shema SJ. Hyponatremia as the cause of seizures in infants: a retrospective analysis of incidence, severity, and clinical predictors. Ann Emerg Med. 1995;26(1):42–8.
13. LaFrance WC. Use of serum prolactin in diagnosing epileptic seizures: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2006;66(8):1287–8. author reply 1287–1288
14. American Clinical Neurophysiology Society. Guideline 1: Minimum technical requirements for performing clinical electroencephalography. J Clin Neurophysiol. 2006;23(2):86–91.
15. King MA, Newton MR, Jackson GD, et al. Epileptology of the first-seizure presentation: a clinical, electroencephalographic, and magnetic resonance imaging study of 300 consecutive patients. Lancet (London, England). 1998;352(9133):1007–11.
16. Rosenthal RH, Heim ML, Waeckerle JF. First time major motor seizures in an emergency department. Ann Emerg Med. 1980;9(5):242–5.
17. Shinnar S, Berga T, Moshe SL, et al. The risk of seizure recurrence after a first unprovoked afebrile seizure in childhood: an extended follow-up. Pediatrics. 1996;98(2 Pt 1):216–25.
18. Shinnar S, Kang H, Berg AT, Goldensohn ES, Hauser WA, Moshé SL. EEG abnormalities in children with a first unprovoked seizure. Epilepsia. 1994;35(3):471–6.
19. Yang PJ, Berger PE, Cohen ME, Duffner PK. Computed tomography and childhood seizure disorders. Neurology. 1979;29(8):1084–8.
20. Garvey MA, Gaillard WD, Rusin JA, et al. Emergency brain computed tomography in children with seizures: who is most likely to benefit? J Pediatr. 1998;133(5):664–9.
21. Stroink H, Brouwer OF, Arts WF, Geerts AT, Peters AC, van Donselaar CA. The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. Dutch study of epilepsy in childhood. J Neurol Neurosurg Psychiatry. 1998;64(5):595–600.
22. Gibbs J, Appleton RE, Carty H, Beirne M, Acomb BA. Focal electroencephalographic abnormalities and computerised tomography findings in children with seizures. J Neurol Neurosurg Psychiatry. 1993;56(4):369–71.
23. Berg AT, Shinnar S, Levy SR, Testa FM. Status epilepticus in children with newly diagnosed epilepsy. Ann Neurol. 1999;45(5):618–23.
24. Berg AT, Mathern GW, Bronen RA, et al. Frequency, prognosis and surgical treatment of structural abnormalities seen with magnetic resonance imaging in childhood epilepsy. Brain. 2009;132(10):2785–97.

25. Rappaport BA, Suresh S, Hertz S, Evers AS, Orser BA. Anesthetic neurotoxicity--clinical implications of animal models. N Engl J Med. 2015;372(9):796–7.
26. Ream MA, Patel AD. Obtaining genetic testing in pediatric epilepsy. Epilepsia. 2015;56(10):1505–14.
27. Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies—report of the ILAE genetics commission. Epilepsia. 2010;51(4):655–70.
28. Hebbar M and Mefford HC. Recent advances in epilepsy genomics and genetic testing [version 1; peer review: 2 approved] F1000 Research 2020; 9: 185.
29. Jayakar P, Gaillard WD, Tripathi M, et al. Diagnostic test utilization in evaluation for resective epilepsy surgery in children. Epilepsia. 2014;55(4):507–18.
30. Juhasz C, Flora J. Utility of MRI, PET, and ictal SPECT in presurgical evaluation of nonlesional pediatric epilepsy. Seizure. 2020;77:15–28.
31. Wellmer J, von der Groeben F, Klarmann U, et al. Risks and benefits of invasive epilepsy surgery workup with implanted subdural and depth electrodes. Epilepsia. 2012;53(8):1322–32.
32. Papadelis C, Chen YH. Pediatric Magnetoencephalography in Clinical Practice and Research. Neuroimaging Clin N Am. 2020;30(2):239–48.
33. Rampp S, Stefan H, Wu X, et al. Magnetoencephalography for epileptic focus localization in a series of 1000 cases. Brain. 2019;142(10):3059–71.
34. Mountz JM, Patterson CM, Tamber MS. Pediatric Epilepsy: Neurology, functional imaging and neurosurgery. Semin Nucl Med. 2017;47:170–87.
35. Newey CR, Wong C, Wang ZI. Optimizing SPECT SISCOM analysis to localize seizure-onset zone by using varying z scores. Epilepsia. 2013;54(5):793–800.
36. de Ribaupierre S, Fohlen M. Bulteau et al. Presurgical language mapping in children with epilepsy: Clinical usefulness of functional magnetic resonance imaging for the planning of cortical stimulation. Epilepsia. 2012;53(1):67–78.

# Pediatric Epilepsy Treatment

7

Anna M. Larson, Ronald L. Thibert, and Elizabeth A. Thiele

## Introduction

In this chapter, we outline the primary pharmacologic, dietary, and surgical treatments for pediatric epilepsy. Over the past two decades, there has been a significant increase in available treatment options. The medications currently available are diverse in structure and proposed mechanisms of action (Table 7.1) [1–4]. Treatment decisions are often based on the consideration of seizure semiology, epilepsy syndrome, and side effects. Efficacy data is relatively limited in pediatric epilepsy treatment. We aim to highlight available data, as well as review treatment practices from the MassGeneral for Children Pediatric Epilepsy Program. This chapter is intended to be an overview of seizure treatment options. For individual patient care needs, please review the medication dosing recommendations at your institution and collaborate with the pharmacy team to guide specific therapeutic choices and titration schedules.

## Antiseizure Medication (ASM) Management

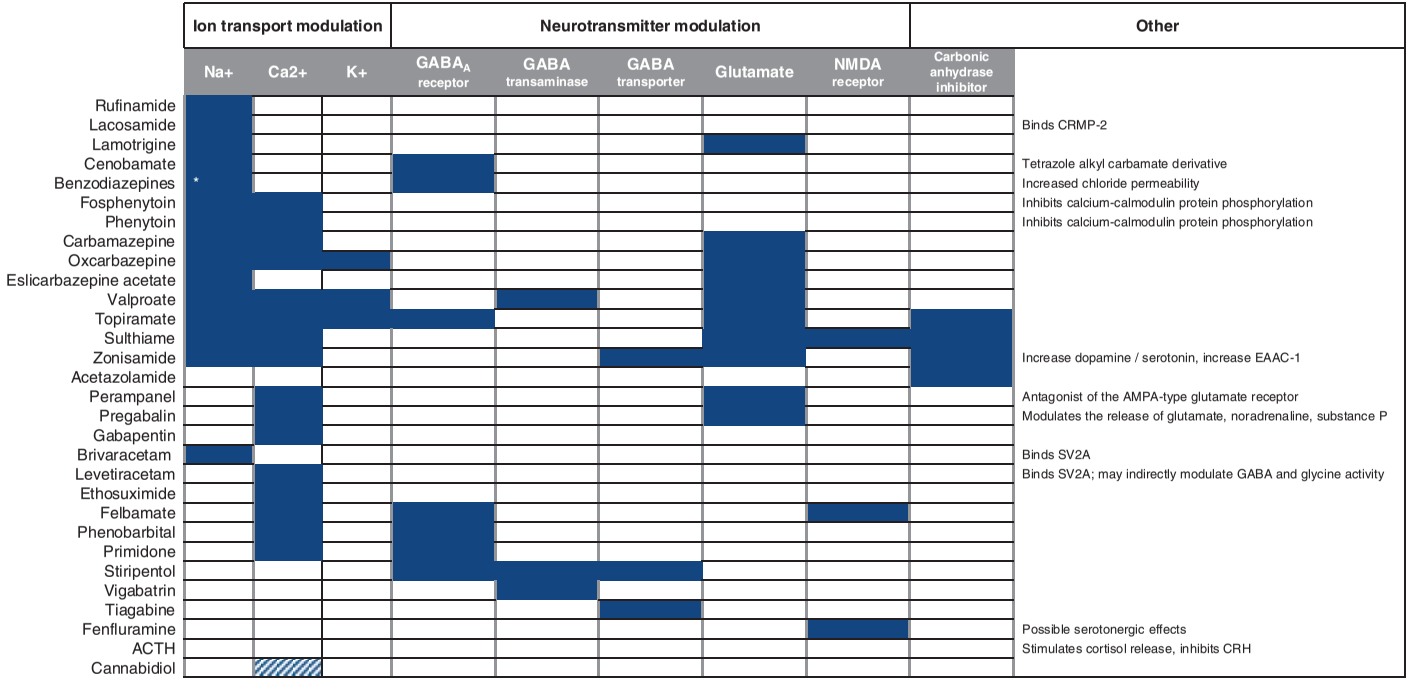
### Initiation of Treatment

Following a first-time seizure, treatment is typically deferred. After a single unprovoked event, Stroink et al. found that 46% of children did not have a second event within a two-year follow-up [5, 6]. However, after two unprovoked seizures, Hauser

A. M. Larson · R. L. Thibert · E. A. Thiele (✉)
Pediatric Epilepsy Program, MassGeneral for Children, Boston, MA, USA


D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_7

**Table 7.1** Proposed mechanisms of action for antiseizure medications



| | Ion transport modulation | | | Neurotransmitter modulation | | | | | Other | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Na+ | Ca2+ | K+ | $GABA_A$ receptor | GABA transaminase | GABA transporter | Glutamate | NMDA receptor | Carbonic anhydrase inhibitor | |
| Rufinamide | ■ | | | | | | | | | |
| Lacosamide | ■ | | | | | | | | | Binds CRMP-2 |
| Lamotrigine | ■ | | | | | | ■ | | | |
| Cenobamate | ■ | | | ■ | | | | | | Tetrazole alkyl carbamate derivative |
| Benzodiazepines | * | | | ■ | | | | | | Increased chloride permeability |
| Fosphenytoin | ■ | ■ | | | | | | | | Inhibits calcium-calmodulin protein phosphorylation |
| Phenytoin | ■ | ■ | | | | | | | | Inhibits calcium-calmodulin protein phosphorylation |
| Carbamazepine | ■ | ■ | | | | | ■ | | | |
| Oxcarbazepine | ■ | ■ | ■ | | | | ■ | | | |
| Eslicarbazepine acetate | ■ | | | | | | ■ | | | |
| Valproate | ■ | ■ | ■ | | ■ | | ■ | | | |
| Topiramate | ■ | ■ | ■ | ■ | | | ■ | | ■ | |
| Sulthiame | ■ | ■ | | | | | ■ | ■ | ■ | |
| Zonisamide | ■ | ■ | | | | ■ | ■ | | ■ | Increase dopamine / serotonin, increase EAAC-1 |
| Acetazolamide | | | | | | | | | ■ | |
| Perampanel | | ■ | | | | | ■ | | | Antagonist of the AMPA-type glutamate receptor |
| Pregabalin | | ■ | | | | | ■ | | | Modulates the release of glutamate, noradrenaline, substance P |
| Gabapentin | | ■ | | | | | | | | |
| Brivaracetam | ■ | | | | | | | | | Binds SV2A |
| Levetiracetam | | ■ | | | | | | | | Binds SV2A; may indirectly modulate GABA and glycine activity |
| Ethosuximide | | ■ | | | | | | | | |
| Felbamate | | ■ | | ■ | | | | ■ | | |
| Phenobarbital | | ■ | | ■ | | | | | | |
| Primidone | | ■ | | ■ | | | | | | |
| Stiripentol | | | | ■ | ■ | ■ | | | | |
| Vigabatrin | | | | | ■ | | | | | |
| Tiagabine | | | | | | ■ | | | | |
| Fenfluramine | | | | | | | | ■ | | Possible serotonergic effects |
| ACTH | | | | | | | | | | Stimulates cortisol release, inhibits CRH |
| Cannabidiol | | ▨ | | | | | | | | |

CRH: corticotropin-releasing hormone
CRMP-2: collapsin response mediator protein-2
EAAC-1: excitatory amino-acid carrier-1
* High concentrations

Reference (1–4)

et al. found that recurrence rates increased to about 75% in a population, across age groups [6, 7]. Treatment is therefore typically initiated after the second unprovoked seizure [6]. Patients with significant EEG abnormalities, or with a structural or metabolic etiology, are at higher risk for recurrence, and treatment may be initiated following a single event [8].

## First ASM

The following parameters should be considered when choosing the first antiseizure medication: seizure type(s), epilepsy syndrome/etiology, age, comorbidities, and medication interactions [6]. To date, there are relatively few randomized control trials to support recommendations for first-line treatment in pediatric epilepsy. The following is a brief review of the data in select seizure types.

In a multicenter study evaluating initial treatment for children less than 3 years of age presenting with new onset non-syndromic epilepsy, levetiracetam was most often used first-line (62%) regardless of semiology [9]. It is important to note that this treatment practice is not based on efficacy data but rather consensus. The International League Against Epilepsy Treatment Guidelines review efficacy data for specific treatments as initial monotherapy for patients with newly diagnosed or untreated epilepsy [10]. Criteria for levels of evidence are presented in Table 7.2 [10].

For focal seizures, there is evidence to support treatment with oxcarbazepine (level A) [10]. For carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin, evidence supports possible efficacy (level C) [10]. Finally, for clobazam, clonazepam, lamotrigine, and zonisamide, evidence supports potential efficacy (level D) for focal seizures [10].

For generalized tonic-clonic seizures, there is level C evidence to support treatment with carbamazepine, phenobarbital, phenytoin, topiramate, and valproate [10]. For absence seizures, there is level A evidence to support treatment with ethosuximide and valproate and level C evidence to support treatment with lamotrigine [10]. For juvenile myoclonic epilepsy, there is level D evidence for treatment with topiramate, levetiracetam, and valproate [10].

There is a growing body of literature to support treatment decisions based on epilepsy syndrome or genotype. A few examples will be briefly reviewed here. For patients with Dravet syndrome ~60% of whom have an *SCN1A* mutation, primary treatment recommendations include valproate, clobazam (and other benzodiazepines), stiripentol, and topiramate [11, 12]. For patients with myoclonic atonic epilepsy, primary pharmacologic treatment choices include valproate, ethosuximide, and topiramate [13–16]. For patients with Landau-Kleffner syndrome and epilepsy with continuous spike-wave during sleep (CSWS), high-dose oral diazepam, ACTH, or corticosteroids should be considered. Alternative treatments include lamotrigine, valproate, and topiramate [8]. See Chap. 4 for additional syndrome-specific treatment recommendations. General guidelines for treatment dosing are outlined in Table 7.3 [1–3, 17–26].

There are some medications that may increase seizure frequency in certain situations. This holds true primarily for treating generalized seizures with medications typically used for focal epilepsy. Glauser et al. review that carbamazepine,

**Table 7.2** Relationship between clinical trial ratings and level of evidence and conclusions by the International League Against Epilepsy

| Combinations of clinical trial ratings | Level of evidence | Conclusions for efficacy as monotherapy |
|---|---|---|
| ≥ 1 Class I study or meta-analysis meeting class I criteria sources<br>OR<br>≥ 2 Class II studies | A | **Established as effective** |
| 1 Class II study or meta-analysis meeting class II criteria | B | **Probably effective** |
| ≥ 2 Class III double-blind or open-label studies | C | **Possibly effective** |
| 1 Class III double-blind or open-label study<br>OR<br>≥ 1 Class IV clinical study<br>OR<br>Data from expert committee reports, opinions from experienced clinicians | D | **Potentially effective** |

Class I:
Prospective randomized control trial (RCT) or meta-analysis of RTCs that meets the following criteria:
1) Efficacy as a primary outcome
2) Treatment ≥ 48 weeks
3) Double blind
4) For superiority trials: superiority demonstrated
   For non-inferiority trials or failed superiority trials: rigorous criteria to demonstrate efficacy (methods described Ref. 10)
5) Study exit: not forced by a predetermined number of treatment emergent seizures
6) Appropriate statistics

Class II:
Prospective RCT or meta-analysis of RTCs that meets all the criteria of Class I except:
Treatment ≥ 24 weeks but <48 weeks
OR
For non-inferiority trials or failed superiority trials: rigorous criteria to demonstrate efficacy but wider parameter compared to Class I (methods described Ref. 10)

Class III:
Prospective RCT or meta-analysis not meeting criteria for Class I or Class II

Class IV:
Evidence from non-randomized, prospective, controlled or uncontrolled studies, case series or expert reports

Ref. [10]

**Table 7.3** Typical dosing for pediatric antiseizure medications

| | Starting dose (mg/kg/day) | Maintenance dose (mg/kg/day) | Number of daily doses | Target level (mcg/mL) |
|---|---|---|---|---|
| Acetazolamide | 3–6 | 10–20 | 1–2 | |
| ACTH [a] | 150 IU/m²/day | 85–250 IU/m²/day | 2 | |
| Brivaracetam [b] | 1–2.5 | 5 (max) | 2 | |
| Cannabidiol | 5 | 10–25 | 2 | |
| Carbamazepine | 2–10 | 10–30 | 2–4 | 4–12 |
| Cenobamate [c] | 12.5 mg/day | 200–400 mg/day | 1 | |
| Clobazam | 0.1–0.2 | 0.8–2 | 2 | |
| Clonazepam [d] | 0.01–0.02 | 0.1–0.2 | 2–3 | |
| Diazepam | IV 0.15–0.2 mg/kg/dose<br>Intranasal [e]<br>10–18 kg: 5 mg<br>19–37 kg: 10 mg<br>38–55 kg: 7.5 mg x2<br>≥ 56 kg: 10 mg x2<br>PR<br>2–5 y: 0.5 mg/kg<br>6–11 y: 0.3 mg/kg<br>≥ 12 y: 0.2 mg/kg | | | |
| Eslicarbazepine acetate [f] | 200 mg/day | 400–600 mg/day | 1 | |
| Ethosuximide | 5–10 | 20–40 | 1–3 | 40–100 |
| Felbamate | 15 | 15–45 | 3–4 | |
| Fenfluramine | 0.2 | 0.7 | 2 | |
| Fosphenytoin | 10–20 mg PE/kg Loading dose | 4–5 | 1–4 | 10–20 Phenytoin level |
| Gabapentin | 10–15 | 25–50 | 3 | |
| Lacosamide | 2 | 4–12 | 2 | |
| Lamotrigine – monotherapy | 0.4 | 2–8 | 2 | |
| Lamotrigine – with valproate | 0.15 | 1–5 | 2 | |
| Lamotrigine – with enzyme inducers | 0.6 | 5–15 | 2 | |
| Levetiracetam | 20 | 30–100 | 2 | |
| Lorazepam | IV 0.1 mg/kg | | | |
| Midazolam | IV 0.1 mg/kg<br>IM 0.2 mg/kg<br>Intranasal<br>0.2 mg/kg<br>≥ 12 y: 5mg, may repeat x1 after 10min | | | |
| Oxcarbazepine | 8–10 | 30–40 | 2–3 | |
| Perampanel [g] | 2 mg/day | 4–8 mg/day | 1 | |
| Phenobarbital | 1–4 | 5–6 [h] | 1–2 | 10–40 |
| Phenytoin | 5 | 5–10 | 1–2 | 10–20 |
| Pregabalin [i] | 3.5–5 | 14 (max) | 2–3 | |
| Primidone | 1–2 | 10–20 | 2-4 | 5–12 |
| Rufinamide | 10 | 45 | 2 | |
| Stiripentol | 10–50 | 50–75 | 2–3 | |
| Sulthiame | 5 | 5–10 | 2 | |
| Tiagabine [j] | 0.1 | 0.5–2.0 | 2–4 | |
| Topiramate | 0.5–3 | 3–9 | 2–3 | 5–20 |
| Valproate | 10–15 | 20–60 | 2–3 | 50–150 |
| Vigabatrin | 50 | 150 (max) | 2 | |
| Zonisamide | 1–2 | 5–12 | 1–2 | |

a. Treatment course is typically a minimum of 2 weeks followed by a 2-week taper
b. 11–19 kg; see appendix for other weight-specific dosing
c. Adolescents and adults
d. ≤ 12 years
e. Children 6–11 years, see appendix for dosing ≥ 12 years
f. 11–21kg; see appendix for dosing > 21kg
g. ≥ 4 years
h. Infants, see appendix for dosing across age groups
i. Infant to < 4 years
j. > 12 years; see appendix for dosing with enzyme-inducing ASMs

Refs. [1–3,17–26]

oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin are contraindicated in the treatment of absence seizures as they can exacerbate seizures in this context [10]. For juvenile myoclonic epilepsy, a similar set of treatments (with the addition of gabapentin and the exclusion of phenytoin) have been shown to exacerbate seizures [10]. In Dravet syndrome, sodium channel blockers, including carbamazepine, lamotrigine, and phenytoin, may worsen seizures and should be avoided [11, 27].

## Second- and Third-Line Therapy

Kwan et al. found that 53% of patients across age groups failed initial monotherapy [28]. By comparison, in a pediatric cohort, Camfield et al. found improved outcomes with only 17% of patients showing failure of first-line therapy [29]. Poor response to first-line treatment portends poor long-term prognosis. With ineffective treatment response to initial monotherapy, only 11% eventually became seizure free [28]. Fig. 7.1 depicts seizure response rates across age groups following sequential medication trials [28]. In their review, Raspall-Chaure et al. describe that for patients who do not show a therapeutic response at an average ASM dose, only an additional 13–15% of patients will respond to an increase to maximal dosing [8]. Despite this fact, a given medication should be trialed near or just under maximal dosing before determining it a treatment failure. When the treatment choice has been determined to be ineffective, the clinician should reduce the dose of the first agent to the average therapeutic range and then add a second agent [8]. Once the second agent is therapeutic, the first-line agent should be slowly tapered

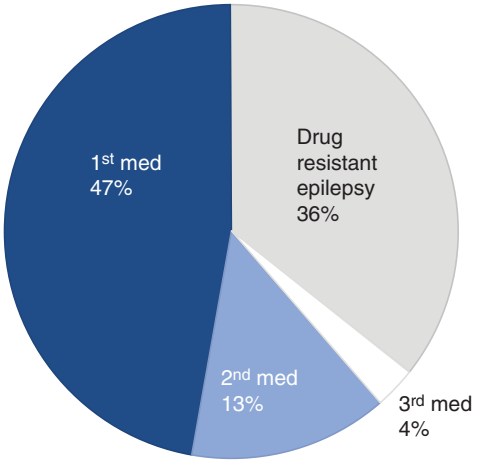



**Fig. 7.1** Response to medication in previously untreated epilepsy across age groups [28]

and stopped, if possible, as monotherapy is typically the goal at this stage [8]. In many circumstances, however, a second agent is simply added on when the initial agent has shown incomplete efficacy. Again, poor early treatment response seems to portend poor prognosis. With failure of second-line treatment, less than 10% of individuals typically achieve long-term seizure freedom [8]. After two or three medications have been trialed as monotherapy, polytherapy is considered [8].

## Drug-Resistant Epilepsy

In a prospective study of Dutch children, 12% of the cohort had a period of seizure intractability during the 15-year study interval [30]. Drug-resistant epilepsy is defined as failure to respond to two appropriately selected and trialed medications [6, 31]. At this point, dietary, surgical, and neuromodulating therapies should be considered. These non-pharmacologic treatments will be discussed later in the chapter.

There is no evidence to support increased efficacy with polytherapy compared to monotherapy [6]. Rational treatment theories recommend striving to choose two or more therapies that target different mechanisms of action. However, this hypothesis has limited data to support it as a superior treatment strategy. Human and animal data suggest three primary mechanistic combinations that may show improved clinical benefit: (1) combining a sodium channel blocker with a drug enhancing GABAergic inhibition; (2) combining two GABA mimetic agents; (3) combining an AMPA antagonist with an NMDA antagonist [32]. There are also a few specific ASM combinations that may have a synergistic effect in certain disease states. Examples of synergistic combinations include valproate with ethosuximide for absence seizures or myoclonic atonic epilepsy, valproate with lamotrigine for absence or myoclonic seizures, and stiripentol with clobazam for Dravet syndrome [11, 33–36].

With polytherapy, medication interactions are an important consideration. Many ASMs have interactions with each other as well as with many other classes of medications through hepatic enzyme-inducing or enzyme-inhibiting effects. A primary example is when valproate and lamotrigine are co-administered: valproate acts as a hepatic inhibitor of the metabolism of lamotrigine, and, as such, the lamotrigine dose typically needs to be significantly decreased to prevent toxicity (see appendix for detailed recommendations for valproate to lamotrigine cross titration) [1, 37, 38]. Table 7.4 highlights ASM interaction trends [1, 37]. Drug interactions should be evaluated by the treating provider whenever new medications are added and throughout the treatment course.

## Treatment Side Effects

Side-effect profile is one of the primary considerations when selecting an ASM. There are two primary types of ASM side effects: neurotoxic and idiosyncratic. Neurotoxic side effects are a risk with nearly all ASMs and include symptoms such as somnolence, cognitive impairment, behavioral changes, vision

changes, and ataxia [8]. These side effects are dose-dependent and are thought to be more common with older medications than the newer generations of ASMs [8]. Idiosyncratic reactions are unpredictable and may include rash, Stevens-Johnson syndrome (SJS), serum sickness, agranulocytosis, aplastic anemia, and hepatotoxicity [8, 39]. One of the most important idiosyncratic reactions is SJS, classically described with lamotrigine treatment but also seen with other ASMs. The risk of serious rash from lamotrigine can be significantly decreased with a slow titration schedule. Primary risk factors for developing a rash (serious or not) with lamotrigine treatment include: a history of another ASM-related rash, young age, and co-treatment with valproate [8, 40]. See Tables 7.5 [1–3, 11, 23, 41] and 7.6 [1–3, 11, 42] for further details regarding medication side effects.

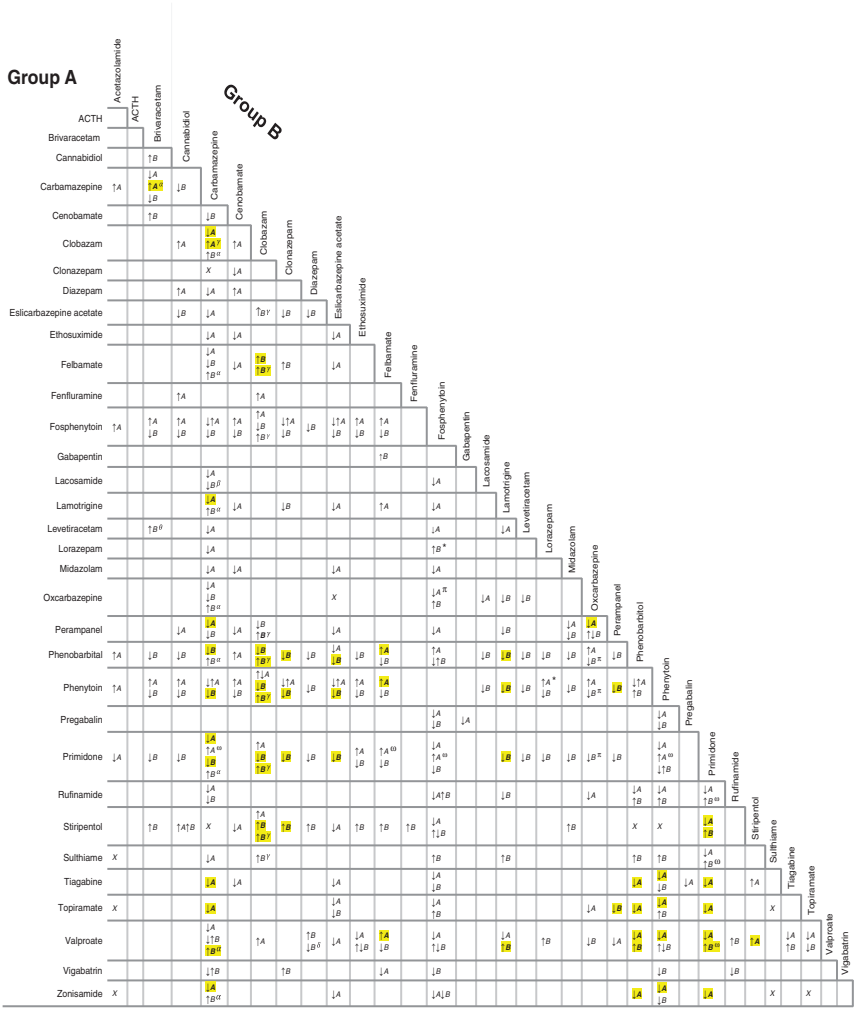
## Laboratory Monitoring

Epilepsy treatment may include monitoring goal serum levels (Table 7.3) and/or following routine laboratory screening data, depending on the medication and patient risk factors. For many medications, routine laboratory screening is not indicated, felbamate being the notable exception. Among adults taking felbamate, there have been reports of fatal hepatic failure and aplastic anemia. Given the severity of a possible reaction, routine monitoring for agranulocytosis and hepatotoxicity is recommended [8, 43]. For other medications, laboratory evaluation is recommended in specific clinical circumstances depending on the medication, such as prior to surgery in patients taking valproate. Laboratory studies in this case should be sent to evaluate for hemostatic dysfunction (labs may include platelet count, PT, aPTT, TT, fibrinogen, vWF, factor XIII) [8, 44]. The clinician should have a very low threshold for checking laboratory tests if a patient presents with symptoms that could be explained by ASM toxicity. For example, a patient on valproate who presents with vomiting should have pancreatic and liver enzymes checked [8]. Routine ASM serum levels are not typically monitored for all medications. Some medications require drug level monitoring, including phenytoin, given its nonlinear kinetics, and carbamazepine, given the narrow therapeutic window [11, 45] Camfield et al. suggest that for patients on monotherapy with incomplete seizure control and no evidence of neurotoxicity, dosing may be increased without obtaining a medication level [45]. Similarly, for patients on monotherapy experiencing neurotoxicity, dosing should be decreased, again without obtaining a level. Clinical circumstances in which ASM levels may be helpful typically surround polytherapy [45]. If a patient presents with possible toxicity and/or uncontrolled seizures and it is unclear which medication may be causing the problem, ASM levels may provide guidance [8, 45].

## Discontinuation of Treatment

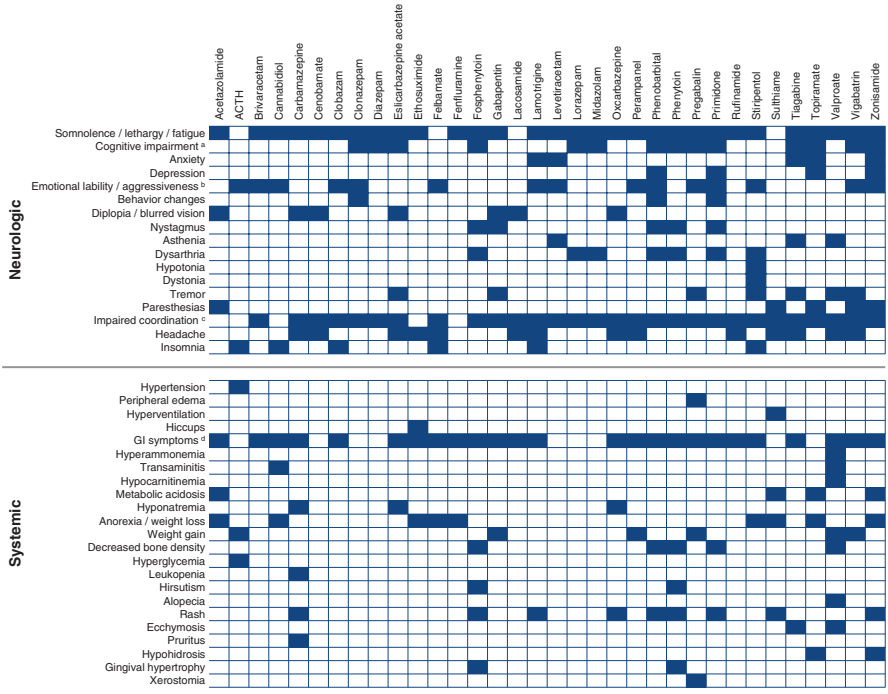
When patients have been seizure free for 2 years, treatment discontinuation is typically considered. This clinical practice is supported by results of a Cochrane Review, which showed a 34% increased risk of seizure recurrence in patients for whom

**Table 7.4** Potential impact on serum medication levels with concomitant dosing of antiseizure medications




ASM treatment was discontinued prior to the two-year mark [46]. This rate of recurrence was further increased for patients with an abnormal EEG and/or focal seizures, so for this cohort, a minimum of 2 years prior to medication discontinuation was recommended [46]. In this same review, however, the authors noted that there remains insufficient data to guide the timing of medication discontinuation for

**Table 7.5** Side-effects of antiseizure medications




a. Cognitive impairment: word finding difficulty, confusion, impaired attention
b. Emotional lability: hyperexcitable, agitation, irritability
c. Impaired coordination: ataxia / dizziness, gait disturbance
d. GI symptoms: abdominal discomfort, nausea / vomiting, diarrhea

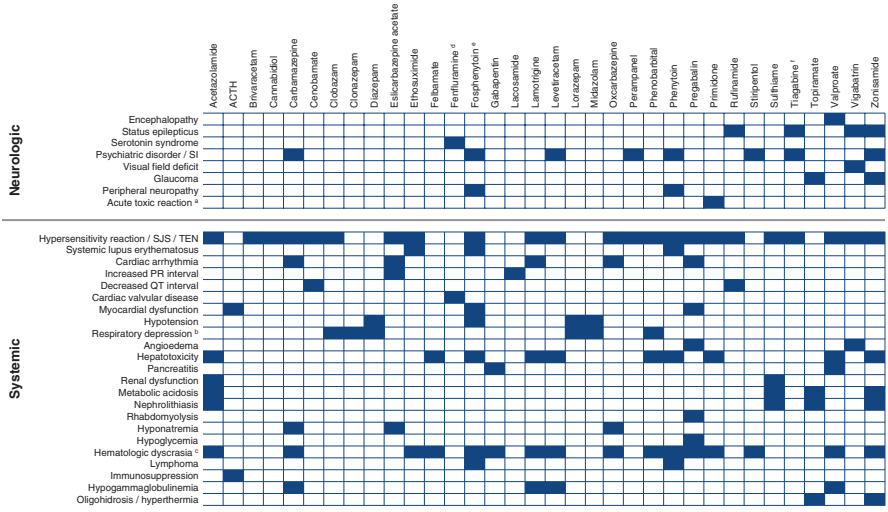
Refs. [1–3,11,23,41]

patients with generalized epilepsies [46]. In a prospective pediatric study, among patients who had been seizure free for 2 years, 68% remained seizure free over the subsequent 2 years following discontinuation of medication [6, 47]. In this study, children with remote symptomatic epilepsy (defined as static encephalopathy prior to seizure history and/or having sustained a prior neurological insult) had a higher risk of recurrence compared to patients with idiopathic epilepsy [47]. Among this higher risk cohort, over 52% remained seizure free following discontinuation of treatment [47]. ASMs are typically tapered slowly, over a period of 6 weeks or more, and in some cases over 3–12 months [8, 11]. Slower tapers are implemented for benzodiazepines or phenobarbital, as these pose a higher risk of precipitating withdrawal seizures [11].

## Deferring Treatment

Seizure treatment is not always indicated. Patients with childhood epilepsy with centrotemporal spikes and Panayiotopoulos syndrome often do not require treatment. The majority of patients with these epilepsy syndromes will have relatively few total lifetime events, most occur during sleep, and spontaneous remission is

**Table 7.6** Critical/potentially life-threatening side-effects of antiseizure medications




a. Acute toxic reaction: sedation, ataxia / dizziness, nausea / vomiting
b. Typically seen at high dose and/or in combination with additional CNS depressant
c. Hematologic dyscrasia: agranulocytosis, neutropenia / leukopenia, aplastic anemia, thrombocytopenia
d. Theoretical risk for cardiac valvular disease and pulmonary hypertension; not identified in recent studies
e. With long-term use, side-effect profile follows that of phenytoin; with acute IV infusion, there is risk for myocardial dysfunction and hypotension
f. Nonconvulsive or absence status epilepticus

SI: suicide ideation
SJS: Stevens-Johnson syndrome
TEN: toxic epidermal necrolysis

Reference [1–3,11,42]

expected [48]. In these self-limited syndromes, indications for initiating therapy include: frequent seizures, young age (4 years or less), daytime seizures, generalized tonic-clonic seizures, a history of status epilepticus, or seizures causing significant distress/limiting quality of life for the patient or their family [48]. Treatment is also indicated if seizures are a likely component of an epileptic encephalopathy.

Febrile seizures are typically not treated with ASMs. Provoked seizures, such as those related to intoxication or trauma, are typically not treated [11]. Prophylactic treatment in the setting of concomitant intraparenchymal hemorrhage or subdural hemorrhage in high-risk populations remains controversial, given that the evidence to support this practice is mixed [49, 50].

## Dietary Treatment

Dietary therapy is one of the most effective treatments available in the field of pediatric epilepsy. Consensus guidelines recommend offering dietary therapy to patients who have failed to respond to two appropriately selected and dosed anticonvulsants [51]. Dietary therapy is widely used in the treatment of both focal and generalized epilepsies. Therapeutic diets can also be effective in treating epileptic encephalopathies, such as infantile spasms [51–55]. The ketogenic diet is highly effective for patients across age groups and a range of seizure types and etiologies

[56]. In a meta-analysis of three randomized controlled trials of the ketogenic diet, 52% of the participants in the intervention group showed a seizure frequency reduction of ≥50% [57].

The classic ketogenic diet is a high-fat, low-carbohydrate diet. With this treatment, patients are followed by a dietician who works with their neurologist. The ketogenic diet simulates a fasting state, and metabolism shifts from glycolysis toward fatty acid oxidation. All meals maintain a macronutrient ratio of 4:1 or 3:1 of fats to combined carbohydrates and protein. Meal preparation requires special attention to the above ratios, micronutrients, and fluid status. Maintaining the appropriate nutrient ratios often requires the use of a gram scale. Formula preparations are also commercially available.

Historically, the ketogenic diet has been difficult to tolerate for some patients. However, in recent years, the availability of compatible foods and recipe books created by patients and families has made this approach more palatable. Although data supporting the classic ketogenic diet is most robust, there are also other less restrictive diets that may be equally as effective. The low glycemic index treatment and the modified Atkins diet have been developed as liberalized versions of the classic ketogenic diet [58, 59]. These less restrictive diets allow more freedom in food choice, and less precision is required with meal preparation compared to the classic diet.

There are some seizure and metabolic disorders in which ketogenic diet is considered a primary therapy. Patients with pyruvate dehydrogenase deficiency may receive significant benefit in general neurologic outcomes and longevity with the ketogenic diet, as this therapy allows for a bypass of the metabolic defect and provides ketones as an alternative form of fuel to glucose [60]. Ketogenic diet is considered first-line therapy in patients with GLUT-1 glucose transporter deficiency, as it provides ketone bodies to the CNS, rather than glucose which cannot enter neurons [61]. The following populations may also be particularly responsive to the ketogenic diet: Angelman syndrome, complex 1 mitochondrial disorders, Dravet syndrome, myoclonic atonic epilepsy, febrile infection-related epilepsy syndrome, Ohtahara syndrome, and tuberous sclerosis complex [51].

Dietary therapy is contraindicated in patients with certain inborn errors of metabolism, including disorders of fatty acid mitochondrial transport, β-oxidation, and other mitochondrial cytopathies [56]. Gastrointestinal side effects are the most common in ketogenic diet therapy and typically occur during the initial first few weeks of treatment [51]. Additional side effects may include decreased linear growth, transient hypertriglyceridemia, metabolic acidosis, and nephrolithiasis [51]. Concomitant treatment with oral citrate salts may help prevent renal stones [62]. There have been rare cases of increased liver transaminases, hepatosteatosis, and cholelithiasis during the first year of treatment with the ketogenic diet [63]. Other rare but reported adverse effects with dietary therapy include cardiomyopathy, prolonged QTc interval, as well as pancreatitis [56].

The duration of epilepsy diet treatment is variable. Reasons to discontinue treatment include: lack of efficacy, poor compliance, and/or intolerable side effects [64].

If the patient has not demonstrated a positive treatment response, treatment is typically discontinued after 3–6 months. If a significant treatment response is seen (>50% decrease in seizure frequency), clinicians may consider discontinuing therapy after 2 years [51]. In one study, 80% of patients who became seizure free on the ketogenic diet remained so after treatment was discontinued [65]. Dietary therapy can be abruptly stopped in an emergency, but often the diet is weaned with gradual reintroduction of carbohydrates over a period of 1–3 months [51].

## Epilepsy Surgery

For patients with drug-resistant epilepsy, epilepsy surgery should be considered. In recent years, there have been increased efforts to prevent the delay of surgical evaluation for pediatric patients with drug-resistant epilepsy [66]. Primary pathologies in pediatric epilepsy for which surgical intervention may be targeted include the following: cortical dysplasia, developmental brain tumors such as dysembryoplastic neuroepithelial tumor, gangliolioma, perinatal injuries including stroke, hippocampal sclerosis, gliosis of any cause, tuberous sclerosis, hypothalamic hamartoma, Rasmussen's encephalitis, and vascular malformations [66].

For lesional surgery, patients undergo an extensive workup to evaluate their candidacy for surgical resection. With this evaluation, teams aim to lateralize and localize an epileptic focus as well as determine the cortical function of the region at and surrounding it [67]. Phase 1 of the presurgical evaluation is largely noninvasive and may include some combination of the following: ictal and interictal EEG monitoring, magnetoencephalography (MEG), MRI/MRS, functional MR imaging, interictal positron emission tomography (PET), ictal/interictal single-photon emission computed tomography (SPECT), neuropsychological assessment, or intracarotid sodium amobarbital testing (Wada test). Phase 2 may include invasive monitoring with intracranial (subdural) or intracerebral electrodes, stereoelectroencephalography, electrocorticography, or cortical stimulation [67].

Lesional surgery is typically categorized as temporal and extra-temporal. Anterior temporal, selective mesial resection (amygdalohippocampectomy), and neocortical (extended) lesionectomy are the primary temporal resection strategies [68]. The most common primary temporal lesions are tumors, cortical dysplasia, and hippocampal sclerosis. Rates of seizure freedom following temporal resection range from 58% to 85% [68]. Surgical resection of extra-temporal lesions is often more challenging, given that the epileptic focus can be more difficult to localize and there is higher risk of damaging areas of eloquent cortex adjacent to the lesion [69]. Surgical planning may therefore involve more extensive invasive monitoring in extratemporal locations [69]. Typically, surgical outcomes are more guarded in extratemporal resection, but can still be quite successful. In a meta-analysis of 37 studies of pediatric extra-temporal epilepsy surgery, 56% of patients were seizure free post-operatively [69, 70].

Functional hemispherectomy is a surgical technique that has evolved from early iterations that involved complete resection of a hemisphere to modern

disconnection approaches [71]. Surgical hemispheric disconnection is considered for patients with catastrophic hemispheric epilepsy most frequently in the setting of Rasmussen syndrome. It may also be employed for patients with hemiconvulsion-hemiplegia-epilepsy syndrome, Sturge-Weber syndrome, hemimegalencephaly, multilobar cortical dysplasia, perinatal infarction, or porencephalic cysts [71].

Corpus callosotomy is a surgical disconnection technique that aims to block the spread of epileptic discharges between the hemispheres [72]. This surgical procedure may be staged, with an initial disconnection of the anterior corpus callosum, preserving the connection at the splenium. If seizures persist, the patient may return to the operating room for complete disconnection. In some cases, it may be undertaken as a single-stage complete callosotomy [72]. This procedure is considered for patients with severe refractory epilepsy for whom lesion resection is not possible, due to bilateral foci or primary generalized seizures. Corpus callosotomy is most frequently used to target a reduction in atonic seizures, which can result in severe injury. Patients with atonic seizures related to Lennox-Gastaut syndrome are often considered for corpus callosotomy [72].

Patients with an epileptic focus in eloquent cortex may not be candidates for lesion resection but might be considered for surgical intervention with multiple subpial transection of the lesion. This surgical technique involves multiple vertical incisions made perpendicular to the surface of the cortex, resulting in the interruption of the short horizontal fiber intracortical connections [73]. The goal is to disrupt the synchronization and spread of epileptogenic discharges while preserving baseline cortical function [73]. Populations who may benefit from this technique include patients with Landau-Kleffner syndrome, cortical dysplasia, epilepsia partialis continua, and Rasmussen's encephalitis [73].

A number of surgical techniques that have recently emerged may be less invasive than open resection. One example is stereotactic MRI-guided laser thermal ablation of the epileptogenic lesion [74, 75]. There are currently two FDA-approved systems, Visualase (Medtronic, Minneapolis, MN, USA), and NeuroBlate (Monteris Medical, Plymouth, NM, USA) [75]. In this technique, a laser probe is introduced through a burr hole in the skull and advanced with imaging guidance to the epileptic focus. Thermal ablation of the lesion is monitored in real time with MR-thermography [76]. One of the benefits is the ability to target deep lesions. There are few reports of the use of this technique in the pediatric epilepsy population, but the adult literature has shown some encouraging results [76]. Possible surgical targets for laser interstitial thermal therapy include hypothalamic hamartomas, cortical dysplasias (including insular lesions), corpora callosa, and periventricular heterotopias [76].

Finally, radiosurgical treatment for pediatric epilepsy is emerging as a viable treatment option. With the Gamma Knife technique, multiple stereotactic ionizing beams of radiation are targeted to the epileptic focus while limiting radiation exposure to the surrounding tissue [77]. This technique may be used for patients with mesial temporal lobe epilepsy with high risk for memory loss or who have previously undergone open surgery and had incomplete seizure control with prior resective surgery [77]. Radiosurgical intervention is also employed to treat hypothalamic hamartomas and cavernous malformations, and to perform callosotomies [77].

## Neurostimulation

For patients with drug-resistant epilepsy who are not candidates for surgical resection, neuromodulation may be considered. The primary technology used in pediatric epilepsy is the vagus nerve stimulator (VNS). It is FDA-approved for patients 4 years and older for focal seizures, but it is commonly used for multiple seizure types and drug-resistant epilepsy syndromes [78, 79]. With VNS, a device is surgically placed subcutaneously in the left clavicular or lateral thoracic region similar to a cardiac pacemaker. An electrode is wrapped around the left vagus nerve and directs electrical impulses afferently into the brain. Efferent stimulation along the vagus nerve is blocked to prevent disruption of normal autonomic function. Stimulation is cycled at scheduled frequencies and can be programmed by clinicians using an external device. In the setting of aura or a seizure event, a magnet can be swiped over the device by the patient or caregiver to trigger a longer pulse stimulus to potentially abort or truncate the seizure [79]. Newer models (since July 2015) have an auto-detect feature that triggers a pulse of stimulation if there is an abrupt increase in heart rate, considered a proxy for seizure activity [78]. A meta-analysis of 74 clinical studies across age groups demonstrated 50% of patients had a greater than 50% reduction in seizures [79, 80]. Early side effects include hoarseness and cough, but these frequently improve with time [78]. There are low rates of surgical adverse events, but there is a risk of possible vocal cord paralysis related to the implantation procedure [78].

A second type of neuromodulation for refractory epilepsy is responsive neurostimulation. Though not currently approved for patients under 18 years, responsive neurostimulation is a technique that involves surgical implantation of a stimulator in the skull that is connected to up to two subdural or depth electrodes placed at the seizure focus [78]. The device collects continuous EEG data and provides cortical stimulation when abnormal electrical activity is detected prior to a seizure. NeuroPace, Inc. (Mountain View, CA, USA) was the first system to become FDA-approved [75, 79]. In a randomized control trial of adult patients, 59% of subjects responded to treatment at the 6-year mark, with a median reduction in seizures of 66% [79, 81]. Current use in pediatrics is off-label in specialized epilepsy centers [79].

Deep brain stimulation (DBS) is an additional neuromodulatory technique that shows some promising results but is not currently approved for use in pediatric patients [79]. Similar to the use of this technique in movement disorders, a generator is placed subcutaneously superficial to the pectoral muscles, and depth electrodes are placed in the brain. Options for electrode placement include the anterior or centromedian nucleus of the thalamus, hippocampus, globus pallidus, cerebellum, or the site of suspected seizure onset [78, 79, 82]. The exact mechanism by which DBS exerts its antiseizure effect is unknown. It has been proposed that DBS may disrupt the neural networks involved in seizure propagation [79, 83]. Pediatric efficacy data are limited, but one series of 13 pediatric subjects with electrodes in the centromedian nucleus of the thalamus demonstrated greater than 50% reduction in seizures in 92% of patients at 18 months [84]. In a systematic review of DBS

treatment in 40 patients with drug-resistant epilepsy, 13% became seizure free and 85% showed reduction in seizure frequency [23, 85].

## Status Epilepticus

Convulsive status epilepticus is the most common pediatric neurologic emergency [86]. Though the duration of seizure activity qualifying as status epilepticus has fluctuated over the years, the current consensus from the 2012 Neurocritical Care Society's Guideline on the Evaluation and Management of Status Epilepticus and the 2016 American Epilepsy Society's Guideline for Status Epilepticus Management defines status epilepticus as 5 minutes of continuous clinical or electrographic seizure activity [87–89]. Refractory status epilepticus is defined as persistent seizure activity following an initial abortive treatment (benzodiazepine) and an appropriate second antiseizure medication [88].

Treatment algorithms aim to stop both clinical and electrographic seizures within 60 minutes of presentation [88]. However, treatment should be initiated after 5 minutes of seizure activity, whether in the community or in the emergency department. Timing is critical. Chin et al. found for every minute that passed between the onset of status epilepticus and initiation of therapy, there was a 5% cumulative increase in the risk of developing refractory status epilepticus [86, 90]. Lewena et al. found that the first one or two medications administered were effective for 86% of cases when given within 20 minutes of seizure onset but were effective for only 15% of cases when seizure duration exceeded 30 minutes [86, 91]. The time from status onset to first, second, and third ASM dosing is positively correlated with the duration of refractory status epilepticus [92, 93]. One proposed mechanism for this phenomenon is that with prolonged status epilepticus, inhibitory GABA receptors on the neuronal cell membrane are internalized, making benzodiazepines less effective [86, 94, 95].

## Etiology of Pediatric Status Epilepticus

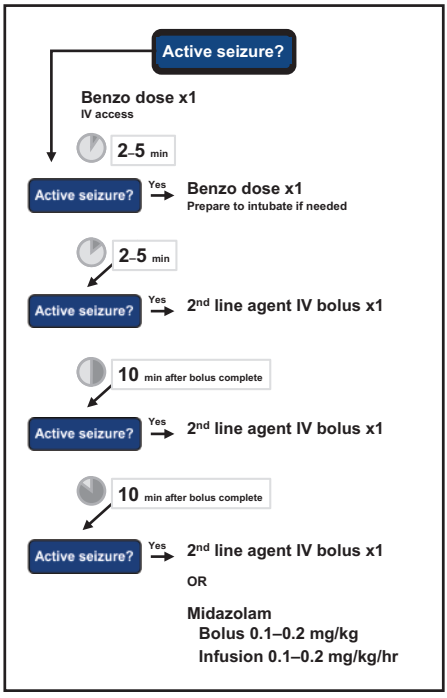
Etiology is critical when approaching the question of treatment. Status epilepticus is classified into 5 categories: prolonged febrile convulsion, acute symptomatic (CNS infection, head injury, acute vascular accident), remote symptomatic (previous neurological abnormality), idiopathic epilepsy-related (known idiopathic epilepsy, or when the presentation allows a diagnosis of idiopathic epilepsy to be made), progressive encephalopathy (epilepsy secondary to a neurodegenerative process), and unclassified [96]. In a multicenter study of infants in the United Kingdom presenting in refractory convulsive status epilepticus, acute symptomatic causes were the most common (28.5%); in patients 1–5 years of age, prolonged febrile convulsions were the most common (33.8%); in patients over 5 years of age, remote symptomatic status was the most common (36–40%) [96]. A multicenter study in Australia and New Zealand reported that 67% of patients presenting in status had a

history of prior seizure, and 35% carried a diagnosis of epilepsy. In this same study, 3% were found to have meningitis/encephalitis, and 1% had an electrolyte disturbance or hypoglycemia [97].

## Status Epilepticus Treatment Pathway

Stabilization of the airway, breathing, and circulation, emergent diagnostic, and emergent treatment for status epilepticus should occur in tandem [89]. Patients should be assessed for airway protection and adequacy of oxygenation, ventilation, and perfusion. Peripheral intravenous access should be established. Finger-stick glucose should be checked, and the following STAT labs should be sent: complete metabolic panel, complete blood count with differential, PT/PTT, blood gas, toxicology screen, and anticonvulsant levels [88, 89]. Fig. 7.2 outlines a status epilepticus treatment reference [86–89, 98–101].

The American Academy of Neurology reported the following clinical data for pediatric patients in status epilepticus: low antiseizure medication levels (32%), neuroimaging abnormalities (8%), electrolyte disturbances (6%), inborn errors of metabolism (4%), ingestion (4%), central nervous system infections (13%), and positive blood cultures (3%) [89, 98].




**Benzodiazepine options**

| | Lorazepam (mg/kg/dose) Max 4 mg/dose | Midazolam (mg/kg/dose) Max 10 mg/dose | Diazepam (mg/kg/dose) Max 10 mg/dose |
|---|---|---|---|
| IV | 0.1 | 0.1 | 0.2 |
| IM | 0.1 | 0.2 | 0.2 |
| Intranasal | | 0.2 | 6–11 years: 10–18 kg: 5 mg x1; 19–37 kg: 10 mg x1; 38–55 kg: 7.5 mg x2; 56–74 kg: 10 mg x2<br>≥12 years: 14–27 kg: 5 mg x1; 28–50 kg: 10 mg x1; 51–75 kg: 7.5 mg x2; ≥ 76 kg: 10 mg x2 |
| PR | | | 2–5y: 0.5 mg/kg; 6–11y: 0.3 mg/kg; ≥12y: 0.2 mg/kg; Max 20 mg/dose |

**2nd line agents**

| | 1st dose mg/kg/dose | 2nd dose mg/kg/dose | Infusion time | Max |
|---|---|---|---|---|
| Levetiracetam | 60 | 20 | 10 min | 4.5 g |
| Valproate | 40 | | 5 min | 3 g |
| Fosphenytoin (IV/IM) | 20 | 10 | 7 min | 1.5 g PE |
| Phenobarbital | 20 | | 20 min | 1 g |
| Lacosamide | 5 | | 15 min | 200 mg |

**STAT glucose / electrolytes**
**Urgent brain imaging if concern for trauma / increased ICP / hemorrhage**
**EEG placement**

Home ASM levels
Ammonia / LFTs / UA / serum and urine tox panel
If concern for infection: empiric antibiotics / blood culture / lumbar puncture (LP)

*LP may also be part of work-up for genetic / metabolic / inflammatory cause once patient is acutely stabilized*

**Fig. 7.2.** Status epilepticus treatment reference. Refs. [86–89,98–101]

## First-Line Treatment

Status epilepticus treatment is classified as (1) emergent, (2) urgent, and (3) refractory [86]. ***Emergent*** antiseizure treatment should start with a benzodiazepine.

If the patient has IV/IO access

Lorazepam IV 0.1 mg/kg/dose (max 4 mg) **or**
Diazepam IV 0.15–0.2 mg/kg/dose (max 10 mg)

If the patient does not have IV access

Midazolam IM 0.2 mg/kg/dose (MAX 10 mg) **or**
Midazolam intranasal 0.2 mg/kg/dose **or**
Midazolam buccal 0.5 mg/kg/dose
or
Diazepam PR
2–5 years: 0.5 mg/kg
6–11 years: 0.3 mg/kg
≥ 12 years: 0.2 mg/kg (max 20 mg)

If the seizure persists for 5 minutes following the first treatment, a second benzodiazepine dose should be administered [89]. Lorazepam, diazepam, and midazolam have equivalent efficacy and risk of respiratory depression [87, 89]. Metabolic derangements, including hypoglycemia, hypocalcemia, hyponatremia, and hypomagnesemia should be treated expeditiously [89].

## Second-Line Treatment

In a series of over 500 pediatric cases, 70% required additional treatment beyond benzodiazepines to control convulsive status epilepticus [89, 97]. If the seizure persists, ***urgent*** treatment with an intravenous loading dose of one of the following four agents is indicated: fosphenytoin, levetiracetam, phenobarbital, or valproate. Efficacy data are limited to guide rank order of these options. The Established Status Epilepticus Treatment Trial (ESETT), a randomized, blinded, adaptive trial, showed non-superiority between fosphenytoin, valproate, and levetiracetam for convulsive status epilepticus [102]. In this trial, these medications did not differ significantly with regard to safety [102]. Further analysis of the data showed no difference in the efficacy of the three options by age group, including a pediatric population (<18y) [103]. The American Epilepsy Society's guidelines, when comparing valproate and phenobarbital, describe that valproate has equivalent efficacy but better tolerability [87, 88]. A meta-analysis of the four medications found phenytoin had lower efficacy (50%) when compared to levetiracetam (69%), phenobarbital (74%), and valproate (76%) [89, 104]. Lacosamide is an alternative agent that may be used for acute status management, although data in children are limited. For patients with

epilepsy on standing ASM treatment, giving an IV loading dose of one of the patient's medications may be prudent. Beyond this, clinicians should consider the medication side-effect profiles in the context of the patient's current clinical circumstances and hemodynamics to help guide second-line agent selection. Valproate should be avoided in the setting of hepatic dysfunction, metabolic or mitochondrial disease, pancreatitis, or thrombocytopenia, or in patients less than 2 years of age with status epilepticus of unknown etiology [88, 89]. Given the risk for cardiac dysfunction, fosphenytoin should be avoided if a patient is in a low cardiac output state or at increased risk for arrhythmias. Similarly, particularly with rapid infusion, phenobarbital may precipitate hypotension, respiratory depression, or apnea and has the potential for prolonged sedative effect.

## Urgent Workup

For patients with a history of trauma or malignancy, or in cases when the etiology of status is unknown, neuroimaging should be performed urgently [89]. Glucose and electrolytes should be evaluated immediately. Further laboratory workup to evaluate the cause of status may include lumbar puncture, urine toxicology screen, and a screen for inborn errors of metabolism. If infectious source is on the differential, CSF should be sent for cell counts, gram stain, culture, protein, glucose, and herpes simplex virus PCR, followed by the initiation of empiric coverage with antibiotics and acyclovir [89].

## EEG Monitoring

EEG monitoring should be initiated within 15–60 minutes in cases where there is concern for ongoing seizure activity or the patient is not returning to baseline, raising concern for nonconvulsive status epilepticus [88, 89]. Long-term EEG monitoring may be indicated for 24–48 hours following presentation in status epilepticus depending on the clinical course.

## Refractory Status Epilepticus Treatment

Refractory status epilepticus occurs in 10–40% of children with status epilepticus [89]. In the ESETT trial, approximately half of patients showed seizure cessation following initial loading dose of a second-line agent [102]. For persistent seizure activity, the Neurocritical Care Guidelines indicate that clinicians may consider giving a repeat loading dose of the selected second-line treatment or may move on to load with an alternative agent (phenobarbital, fosphenytoin, valproic acid, levetiracetam) [88, 89].

For persistent seizure activity following repeat loading doses, treatment transitions to the initiation of continuous infusion of anesthetic agents. At this point, patients should have a secured airway and be in a critical care unit with EEG in

place. In a multicenter study of pediatric refractory status, midazolam (78%) was the first anesthetic agent used with an initial loading dose of 0.1–0.2 mg/kg and a continuous infusion rate of 0.1–0.2 mg/kg/hr [101]. EEG should be actively followed with possible repeat bolus doses of 0.1 mg/kg and titration of the midazolam infusion every 5–30 minutes by 0.05–0.1 mg/kg/hr, to a goal of seizure suppression. In the event that midazolam fails to achieve seizure control at a dose of 1 mg/kg/hour, a transition to pentobarbital should be considered. Pentobarbital treatment can be initiated with a loading dose of 2–5 mg/kg followed by a continuous infusion at a rate of 0.5–1 mg/kg/hour. The initial bolus may be repeated in the absence of seizure suppression. Titrate to seizure suppression on EEG, re-bolusing with 1–2 mg/kg and increasing the continuous infusion by 0.5 mg/kg/hr to a max rate of 5 mg/kg/hr. Alternative agents to consider include propofol and ketamine. Currently, there is no consensus standard of care for the rate of anesthetic titration and/or max dosing for pediatric refractory status epilepticus care. The above recommendations represent expert opinion.

The Neurocritical Care Society guidelines recommend 24–48 hours of electrographic seizure control prior to initiation of a wean of continuous infusion treatments for refractory status [88, 89]. Broader workup for refractory status epilepticus may include the following: antibodies or PCR for viral encephalitides, autoantibody testing, or testing for inborn errors of metabolism [89, 105]. EEG monitoring is indicated throughout anesthetic treatment and for at least 24 hours after treatment is weaned [89, 106]

## Conclusions

Pediatric epilepsy treatment requires evaluation and consideration of multiple variables and longitudinal care. Our collective goal for each child should be seizure freedom. Becoming comfortable with treatment options and effectively optimizing the regimen in an ever-changing research and clinical landscape is a true life's work. Unfortunately, head-to-head efficacy trials are limited, but there is a developing literature of syndrome-specific treatment and genotype-phenotype correlations to further guide treatment choice.

Dietary treatments have been shown to be as effective as any known pharmaceutical option and should be readily included among pediatric epilepsy treatment options. Our understanding of the therapeutic mechanisms and physiologic impact of dietary therapy continues to expand and will inform broader access and application. Evaluation for epilepsy surgery should be pursued in cases of refractory epilepsy without delay. Surgical techniques, specifically options for minimal and noninvasive intervention, continue to evolve offering the promise of improved seizure control and preserved function of surrounding eloquent cortex. The further development of treatment pathways for status epilepticus, focusing on the emergent nature of the disease and the necessity for rapid event capture, aims to improve outcomes and prevent lasting harm.

This work focusing on eliminating seizures for children, at the bench and at the bedside, holds immeasurable promise for the future for patients and families, in the

way of improved neurodevelopmental outcomes, systemic health and wellness, mitigating the risk of SUDEP, and improved quality of life.

## Appendix: Antiseizure Medications

### Acetazolamide

Section References: [1, 3, 107]

Acetazolamide is a broad-spectrum agent typically used for absence and focal seizures. It is also used in the treatment of GTCs, tonic/atonic, and myoclonic seizures. It may be used for catamenial epilepsy, Lennox-Gastaut syndrome (LGS), Landau-Kleffner/CSWS, and juvenile myoclonic epilepsy (JME).

**Mechanism of Action**
Inhibitor of brain carbonic anhydrase. This leads to increase in intracellular $CO_2$ and decrease in intracellular pH, which results in depression of neuronal activity.

**Dosing**

< 12 years:
Start treatment with 3–6 mg/kg/day given in 1–2 doses
Increase by 3–6 mg/kg/day every 3–7 days
Goal of 10–20 mg/kg/day

≥ 12 years:
Start 250 mg/day given in 1–2 doses
Increase by 250 mg/day every 3–7 days
Goal of 250–1000 mg/day

**Side Effects**
Neurologic: somnolence/lethargy, blurred vision, paresthesia
Systemic: GI symptoms, metabolic acidosis, anorexia

**Critical/Potentially Life-Threatening Side Effects**
Systemic: Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hepatotoxicity, renal failure, metabolic acidosis, nephrolithiasis, agranulocytosis, aplastic anemia

**Lab Monitoring**
May evaluate baseline and periodic sodium bicarbonate, but this is not routine practice.

## Adrenocorticotropic Hormone (ACTH)

Section References: [1, 3, 8, 108, 109]

ACTH is typically used to treat infantile spasms (IS). It may also be used for severe epileptic encephalopathies including Landau-Kleffner syndrome, CSWS, LGS, Doose syndrome, Dravet syndrome, and Ohtahara syndrome. This medication must be administered intramuscularly.

**Mechanism of Action**
Stimulates cortisol release and inhibits cortisol-releasing hormone which has been reported as a proconvulsive neuropeptide.

**Dosing**

< 2 years:
Start 150 units/$m^2$/day IM divided in 2 doses
Treatment course is typically a minimum of 2 weeks followed by a 2-week taper

**Side Effects**
Neurologic: irritability, insomnia
Systemic: hypertension, weight gain, hyperglycemia

**Critical/Potentially Life-Threatening Side Effects**
Systemic: myocardial dysfunction, immunosuppression, *Pneumocystis* pneumonia

**Clinical/Lab Monitoring**

Prior to treatment
Vital signs/blood pressure
UA, stool guaiac, CBC, Chem10 (electrolytes, BUN/Cr, Ca, Mg, phosphate)
Consider baseline echocardiogram

Throughout treatment
Blood pressure daily x1 week, then 3x weekly, urine glucose and stool guaiac 2x weekly

After 2–4 weeks: CBC with differential, Chem10
Consider follow-up echocardiogram

Avoid vaccines for 10 days prior to/during treatment. Treatment should include concomitant H2 antagonist for gut protection.

## Brivaracetam

Section References: [1–3, 24, 110]

Brivaracetam is a broad-spectrum agent. The majority of data has been gathered in the treatment of focal seizures, but it has also shown promising results in the treatment of generalized seizures in adults [110].

**Mechanism of Action**
The mechanism is incompletely understood. It binds synaptic vesicle protein SV2A, involved in synaptic vesicle exocytosis. It is also a partial antagonist of sodium channels.

**Dosing**

<11 kg:
Start 1.5–3 mg/kg/day divided in 2 doses
Max 6 mg/kg/day

11–19 kg:
Start 1–2.5 mg/kg/day divided in 2 doses
Max 5 mg/kg/day

20–49 kg:
Start 1–2 mg/kg/day divided in 2 doses
Max 4 mg/kg/day

≥ 50 kg or ≥ 16 years:
Start 50–100 mg/day divided in 2 doses
Max 200 mg/day

Adding to levetiracetam does not likely provide additional benefit and may cause decreased efficacy.

**Side Effects**
Neurologic: somnolence/fatigue, irritability, ataxia/dizziness
General: GI symptoms

**Critical/Potentially Life-Threatening Side Effects**
Systemic: Hypersensitivity reaction

**Lab Monitoring**
Not required

## Cannabidiol

Section References: [2–4, 20, 23, 111–113]

Cannabidiol is a broad-spectrum agent with suggested efficacy against both focal and generalized events. Treatment may be considered for LGS, Dravet syndrome, and tuberous sclerosis complex.

**Mechanism of Action**
The mechanism of action is incompletely understood. The antiseizure effect is likely not mediated by cannabinoid receptors [2, 111]. A potential mechanism has been proposed in which cannabidiol results in decreased intracellular calcium (via targets GPR55 and TRPV1), thereby reducing neuroexcitability. There may also be a therapeutic effect through modulation of adenosine-mediated signaling [4].

**Dosing**

Start 5 mg/kg/day divided in 2 doses
Increase by 5 mg/kg/day every 7 days
Goal 10–25 mg/kg/day

**Side Effects**
Neurologic: somnolence, irritability, insomnia
Systemic: GI symptoms, transaminitis, anorexia/weight loss

**Critical/Potentially Life-Threatening Side Effects**
Systemic: Hypersensitivity reaction

**Lab Monitoring**
Consider sending liver function tests (LFTs) at baseline, 1, 3, 6 months and then periodically; repeat labs within 1 month of dose change.

## Carbamazepine

Section References: [1–3, 8, 11, 20, 114]

Carbamazepine is used to treat both focal seizures and primary GTCs. In some cases, it may cause seizure worsening for patients with idiopathic generalized epilepsies and/or epileptic encephalopathies. Carbamazepine should not be used to treat myoclonic, atonic, or absence seizures, as it may cause seizure exacerbation.

**Mechanism of Action**
Inhibits voltage-gated sodium channels, L-type calcium channels, and glutamate release.

**Dosing**

< 6 years:
Start 2–10 mg/kg/day divided in 2–3 (tab) or 4 (suspension) doses
Increase by 5–10 mg/kg/day every 7 days
Goal of 10–30 mg/kg/day

6–12 years:
Start 100 mg/day divided in 2 doses (tab) or 4 doses (suspension)
Increase by 100 mg/day every 7 days
Goal 600–1000 mg/day

> 12 years:
Start 200 mg/day divided in 2 doses (tab) or 4 doses (suspension)
Increase by 200 mg/day every 7 days
Goal of 800–1200 mg/day

**Side Effects**
Neurologic: somnolence, diplopia/blurred vision, ataxia/dizziness, headache
Systemic: GI symptoms, hyponatremia, leukopenia, rash, pruritis

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: psychosis/mania
Systemic: SJS/TEN/hypersensitivity reaction, cardiac conduction disturbance, hyponatremia, bone marrow suppression, hypogammaglobulinemia

**Lab Monitoring**
Consider baseline CBC, Na, LFTs. Consider screening for HLA-B*1502 allele for patients with Asian ancestry due to potential increased risk for SJS/TEN. Repeat Na once treatment is therapeutic. Repeat Na and/or Chem10 periodically; LFTs and thyroid function tests as needed. Repeat CBC at 1–3 months after the start of treatment and every 6 months thereafter. Monitor for vitamin D deficiency with 25-hydroxyvitamin D levels.

## Cenobamate

Section References: [2, 115]

Cenobamate is typically used for the treatment of focal seizures.

**Mechanism of Action**
A tetrazole alkyl carbamate derivative, it acts as an inhibitor of voltage-gated sodium channels and potentially also enhances GABA inhibition.

**Dosing**

Adults:
Start 12.5 mg/daily
Week 3–4: 25 mg/daily
Week 5–6: 50 mg/daily
Week 7–8: 100 mg/daily
Week 9–10: 150 mg/daily
Week 11-ongoing: 200 mg/day

**Side Effects**
Neurologic: somnolence/fatigue, dizziness, headache, diplopia

**Critical/Potentially Life-Threatening Side Effects**
Systemic: decreased QT interval, hypersensitivity reaction

**Lab Monitoring**
Defer routine monitoring. Consider monitoring LFTs and potassium as clinically indicated.

## Clobazam

Section References: [1–3, 11, 20, 41, 116]

Clobazam is a broad-spectrum agent. It has a therapeutic role as monotherapy as well as adjuvant therapy. It is notably effective in the treatment of Dravet syndrome and LGS. For Dravet, clobazam can be paired with stiripentol for synergistic effect. Tolerance, dependence, and/or excessive sedation are not typically clinical limitations.

**Mechanism of Action**
Clobazam is a 1–5 benzodiazepine, with a nitrogen at the 1 and 5 positions on the diazepine ring. This differs from other benzodiazepines used in epilepsy treatment which host nitrogen at the 1 and 4 positions. Clobazam is a $GABA_A$ agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

**Dosing**

< 12 years:
Start 0.1–0.2 mg/kg/day daily at night

Increase by 0.1–0.25 mg/kg/day every 7 days
Goal of 0.8–2 mg/kg/day divided in 2 doses

≥12 years:
Start 5–10 mg/day at night
Increase by 5 mg/day every 7 days
Goal 40 mg/day given in 1–2 doses (max 80 mg/day)

**Side Effects**
Neurologic: somnolence, irritability/aggressiveness, ataxia, insomnia
Systemic: GI symptoms

**Critical/Potentially Life-Threatening Side Effects**
Systemic: SJS/TEN, respiratory depression

**Lab Monitoring**
Defer routine monitoring. May consider periodic monitoring of CBC and LFTs. Levels should be monitored when used with cannabidiol.

## Clonazepam

Section References: [1–3, 11, 20, 117]

Clonazepam is a broad-spectrum agent used to treat both focal and generalized seizures. Efficacy against myoclonic and atonic seizures is most notable. It has a wide range of uses, particularly for epileptic encephalopathies, and is often employed as adjunctive therapy. It may also be used as an acute abortive treatment for seizure clusters.

**Mechanism of Action**
Clobazam is a type of benzodiazepine, a $GABA_A$ agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

**Dosing**

≤ 12 years:
Start 0.01–0.02 mg/kg/day divided in 2–3 doses (max start 0.5 mg)
Increase by 0.05 mg/kg/day or ≤ 0.25 mg/day every 3–7 days
Goal of 0.1–0.2 mg/kg/day

> 12 years:
Start 0.25 mg at night
Increase by 0.25 mg/day every 7 days.
With titration, divide in 2–3 doses/day
Goal of 4–10 mg/day or 0.05–0.2 mg/kg/day

**Side Effects**
Neurologic: somnolence/fatigue, confusion, hyperexcitability, behavior changes, ataxia/impaired coordination

**Critical/Potentially Life-Threatening Side Effects**
Systemic: respiratory depression

**Lab Monitoring**
Defer routine monitoring. May consider periodic monitoring of CBC and LFTs.

## Diazepam

Section References: [1, 3, 20, 118]

Diazepam is typically used as an acute abortive therapy for status epilepticus or seizure clusters.

**Mechanism of Action**
Diazepam is a type of benzodiazepine. $GABA_A$ agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

**Dosing**

Abortive treatment options

PR dosing:
- 2–5 years: 0.5 mg/kg
- 6–11 years: 0.3 mg/kg
- ≥ 12 years: 0.2 mg/kg (max 20 mg)

Intranasal dosing:
- 6–11 years
  - 10–18 kg: 5 mg in 1 nostril
  - 19–37 kg: 10 mg in 1 nostril
  - 38–55 kg: 7.5 mg x2, 1 spray in each nostril
  - 56–74 kg: 10 mg x2, 1 spray in each nostril
- ≥ 12 years
  - 14–27 kg: 5 mg, 1 nostril
  - 28–50 kg: 10 mg, 1 nostril
  - 51–75 kg: 7.5 mg x2, 1 spray in each nostril
  - ≥ 76 kg: 10 mg x2, 1 spray in each nostril

IV dosing:
> 1 month
0.15–0.2 mg/kg/dose (max 10 mg/dose)

**Side Effects**
Neurologic: somnolence/fatigue, confusion, ataxia/dizziness

**Critical/Potentially Life-Threatening Side Effects**
Systemic: hypotension, respiratory depression

**Lab Monitoring**
Defer routine monitoring. May consider periodic monitoring of CBC and LFTs.

## Eslicarbazepine Acetate

Section References: [1–3, 20, 119–121]

Eslicarbazepine acetate is used to treat focal seizures with or without secondary generalization. Like carbamazepine, eslicarbazepine acetate is contraindicated for primary generalized seizures due to the potential for exacerbation.

Eslicarbazepine acetate shares a chemical structure with carbamazepine and oxcarbazepine, a dibenzapine nucleus with a 5-carboxamide substitute, but has an acetate group at the 10,11 position. Eslicarbazepine acetate and oxcarbazepine are pro-drugs, both metabolizing to the active licarbazepine. This metabolism results in both S and R chiral forms [120]. Both compounds are metabolically active, but the S form may cross the blood–brain barrier more effectively and potentially be less toxic. Oxcarbazepine metabolizes to chiral ratio S:R of 4:1, whereas eslicarbazepine acetate metabolizes to a ratio of 20:1 [120]. There is evidence for improved side-effect profile and stable seizure control when transitioning from oxcarbazepine to eslicarbazepine acetate [121].

**Mechanism of Action**
Inhibits voltage-gated sodium channels. May also impact glutamate release.

**Dosing**

11–21 kg:
Start 200 mg/day
Increase by 200 mg/day every 7 days
Goal 400–600 mg/day dosed daily

22–31 kg:
Start 300 mg/day
Increase by 300 mg/day every 7 days
Goal 500–800 mg/day

32–38 kg:
Start 300 mg/day
Increase by 300 mg/day every 7 days
Goal 600–900 mg/day

> 38 kg:
Start 400 mg/day
Increase by 400 mg/day every 7 days
Goal 800–1200 mg/day

≥ 12 years:
Start 400 mg daily
Increase by 400 mg/day every 2 weeks
Max dose 1200 mg/day

**Side Effects**
Neurologic: somnolence, impaired attention, diplopia/blurred vision, tremor, ataxia/dizziness, headache
Systemic: GI symptoms, abnormal liver function, hyponatremia

**Critical/Potentially Life-Threatening Side Effects**
Systemic: SJS/TEN, cardiac conduction disturbance (AV block, prolonged PR interval), hyponatremia

**Lab Monitoring**
Consider baseline CBC, sodium, LFTs. Consider screening for HLA-B*1502 allele for patients with Asian ancestry due to potential increased risk for SJS/TEN. Repeat sodium once treatment is therapeutic. Repeat Chem10 and LFTs to monitor for renal and hepatic function every 12 months. Consider monitoring 25-hydroxyvitamin D levels.

## Ethosuximide

Section References: [1–3, 122]

Ethosuximide is principally used to treat absence seizures. In rare cases, it may also be used to treat atonic or myoclonic seizures. Ethosuximide is ineffective and contraindicated in the treatment of focal seizures and generalized tonic-clonic-seizures.

**Mechanism of Action**
Reduces the number or the conductance of low-threshold (T-type) calcium channels in thalamic neurons.

**Dosing**

2–12 years:
Start 5–10 mg/kg/day
Increase by 5–10 mg/kg/day every 7 days
Goal 20–40 mg/kg/day in 1–3 doses (max 60 mg/kg/day or 2000 mg/day)

> 12 years:
Start 250 mg/day
Increase by 250 mg/day every 7 days
Goal 750–1500 mg/day divided in 2–3 doses

**Side Effects**
Neurologic: somnolence, headache
Systemic: hiccups, GI symptoms, anorexia/weight loss

**Critical/Potentially Life-Threatening Side Effects**
Systemic: SJS/TEN, systemic lupus erythematosus, agranulocytosis/aplastic anemia

**Lab Monitoring**
Baseline CBC with repeat at 2 months and then as needed thereafter.

## Felbamate

Section References: [1–3, 11, 20, 123]

Felbamate is a broad-spectrum agent used to treat both focal and generalized epilepsy. It is effective in the treatment of tonic/atonic, myoclonic, and absence seizures as well as infantile spasms. It is reserved for patients with LGS and/or severe refractory seizures. It is not currently first-line therapy for any indication. This is due to the side-effect profile which includes a black box warning for aplastic anemia and hepatotoxicity. Dosing can be challenging due to narrow therapeutic range and significant medication interactions. Given this, close laboratory monitoring follow-up with the prescribing team is essential for treatment.

**Mechanism of Action**
Inhibits N-methyl-D-aspartate (NMDA)-induced intracellular calcium currents and excitatory activity. It also potentiates GABA activity.

**Dosing**

2–14 years:
Start 15 mg/kg/day divided in 3–4 doses
Increase by 15 mg/kg/day at every 7 days
Goal 15–45 mg/kg/day

> 14 years:
Start 1200 mg/day divided in 3–4 doses
Increase by 600–1200 mg/day every 7 days
Goal 3600 mg/day

May consider 20% reduction in concomitant ASMs (phenytoin/valproate/phenobarbital/carbamazepine) with the start of felbamate to avoid toxicity. Provide slower medication titration if the patient is not taking an enzyme-inducing ASM prior to the start of felbamate.

**Side Effects**
Neurologic: irritability, ataxia/dizziness, headache, insomnia
Systemic: GI symptoms, anorexia/weight loss

**Critical/Potentially Life-Threatening Side Effects**
Systemic: hepatotoxicity, aplastic anemia

**Lab Monitoring**
Recommend baseline CBC and LFTs with repeat CBC every 2 weeks and repeat LFTs every 4 weeks.

## Fenfluramine

Section References: [23, 25, 41, 124]

Fenfluramine is an amphetamine derivative that has been shown to be effective for patients with LGS and Dravet syndrome. It was initially FDA approved for weight loss but was removed from the market in 1997 with safety concerns for the development of pulmonary hypertension and valvular heart disease. Over the past two decades there have been reports of potential efficacy against seizures with a novel serotonergic mechanism [23]. Fenfluramine was reapproved by the FDA in 2020 for treatment for patients with Dravet syndrome. In the 2019 trial, there were no reported cases of pulmonary hypertension or valvular disease in children or young adults [41, 124]. In the United States, there is a REMS program to facilitate prescriber education, routine cardiac monitoring, and reporting of these potential adverse events.

**Mechanism of Action**
The mechanism is unknown. Modulation of NMDA receptor-mediated excitation and/or serotonergic effects are two mechanisms that have been proposed.

**Dosing**

≥ 2 years:
Start 0.2 mg/kg/day divided in 2 doses
Increase by 0.2 mg/kg/day every 4–7 days
Goal of 0.7 mg/kg/day (max 13 mg)

**Side Effects**
Neurologic: somnolence/fatigue
Systemic: GI symptoms, anorexia/weight loss

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: serotonin syndrome
Systemic: cardiac valvular disease, pulmonary hypertension

**Clinical Monitoring**
Through the REMS program, cardiac echo is recommended at baseline prior to the start of treatment, every 6 months during treatment, and then once 3–6 months after the completion of treatment.

## Fosphenytoin

Section References: [1–3, 125]

Fosphenytoin is a water-soluble prodrug of phenytoin. It is an IV formulation primarily used as an abortive therapy for status epilepticus. It may also be used as a substitute for phenytoin when enteral access is limited; this is typically short term.

Both phenytoin and fosphenytoin are used for focal seizures with or without secondary generalization. They may also be effective against some generalized seizures including primary GTC or for patients with mixed semiology, including tonic seizures. Fosphenytoin has the potential to worsen a subset of generalized seizures, typically myoclonic and absence. Fosphenytoin should be avoided for patients with LGS and progressive myoclonic epilepsies.

**Mechanism of Action**
Blocks voltage-gated sodium channels and modulates sustained repetitive firing. It also inhibits calcium channels and calcium sequestration and inhibits calcium-calmodulin protein phosphorylation.

**Dosing**

Status epilepticus:
Loading dose: 20 mg PE/kg IV

Seizure prophylaxis:
Loading dose: 10–15 mg PE/kg IV
Maintenance dosing: 4–5 mg/kg/day divided in 1–4 doses

With acute IV infusion, there is risk for myocardial dysfunction and hypotension. With long-term use, the side-effect profile follows that of phenytoin (see below).

## Gabapentin

Section References: [1–3, 11, 20, 126]

Gabapentin is primarily used to treat focal seizures with or without secondary generalization. In some cases, it may worsen generalized seizures.

Gabapentin is a GABA analog and structurally similar to pregabalin. Its effect as an antiseizure treatment, however, does not seem to be mediated by modulation of GABA.

**Mechanism of Action**
Binds to voltage-gated presynaptic calcium channels which inhibit inward calcium currents and decrease neurotransmitter release.

**Dosing**

3–5 years:
Start 10–15 mg/kg/day divided in 3 doses
Increase by 8–10 mg/kg/day daily for 3 days
Goal 40–50 mg/kg/day

6–12 years:
Start 10–15 mg/kg/day divided in 3 doses
Increase by 10 mg/kg/day daily for 3 days
Goal 25–35 mg/kg/day

> 12 years:
Start 300 mg/day daily
Increase by 300 mg/day daily divided in 3 doses
Goal 900–1800 mg/day (max 3600 mg/day)

**Side Effects**
Neurologic: somnolence/fatigue, diplopia/blurred vision, nystagmus, tremor, ataxia/dizziness
Systemic: GI symptoms, increased appetite/weight gain

**Critical/Potentially Life-Threatening Side Effects**
Systemic: pancreatitis, leukopenia

**Lab Monitoring**
Consider baseline LFTs and Chem10 to evaluate liver and renal function. Baseline CBC with repeat after 3 and 6 months of treatment.

## Lacosamide

Section References: [1–3, 20, 127–129]

Lacosamide is primarily used to treat focal seizures. In some cases, it may be trialed for the treatment of refractory generalized seizures, but efficacy data are limited in

pediatrics [128, 129]. With parenteral administration, it may be used for status epilepticus or if enteral access is limited.

**Mechanism of Action**
Enhanced slow inactivation of sodium channels, leading to stabilization of hyperexcitable neuronal membranes and inhibition of repetitive firing. A second proposed mechanism suggests that lacosamide may bind collapsin response mediator protein-2 (CRMP-2), a possible contributor to epileptogenesis.

**Dosing**

11–29 kg:
Start 2 mg/kg/day divided in 2 doses
Increase by 2 mg/kg/day every 7 days
Goal 6–12 mg/kg/day

30–49 kg:
Start 2 mg/kg/day divided in 2 doses
Increase by 2 mg/kg/day every 7 days
Goal 4–8 mg/kg/day

≥ 16 years or ≥ 50 kg:
Start 100 mg/day divided in 2 doses
Increase by 100 mg/day every 7 days
Goal 200–400 mg/day

**Side Effects**
Neurologic: diplopia/blurred vision, ataxia/dizziness/impaired coordination, headache
Systemic: GI symptoms

**Critical/Potentially Life-Threatening Side Effects**
Systemic: prolonged PR interval

**Lab Monitoring**
May consider baseline LFTs and Chem10 to evaluate liver and renal function with repeat labs every 12 months. May alternatively defer routine lab monitoring. Recommend baseline ECG to evaluate PR interval and identify potential preexisting arrhythmias.

## Lamotrigine

Section References: [1–3, 20, 38, 130–132]

Lamotrigine is a broad-spectrum agent used to treat both focal and generalized seizures, including primary GTCs, tonic/atonic, and absence seizures. For generalized epilepsy syndromes with myoclonic seizures, specifically JME, lamotrigine can have mixed results with a subset showing worsening myoclonic seizures [3, 130, 132]. For patients with Dravet syndrome or progressive myoclonic epilepsy, lamotrigine is typically avoided [1].

**Mechanism of Action**

Inhibition of voltage-gated sodium channels limiting repetitive firing and stabilizing the neuronal membrane. The mechanism is incompletely understood, but there is a decrease in the release of excitatory neurotransmitters including glutamate and aspartate.

**Dosing**

2–12 years:
Week 1–2: 0.4 mg/kg/day
Week 3–4: 0.8 mg/kg/day
Increase by 0.4–0.8 mg/kg/day every 7–14 days thereafter
Goal 2–8 mg/kg/day divided in 2 doses

*Concomitant treatment with valproate*
Week 1–2: 0.15 mg/kg/day
Week 3–4: 0.3 mg/kg/day
Increase by 0.15–0.3 mg/kg/day every 7–14 days thereafter
Goal 1–5 mg/kg/day divided in 2 doses

*Concomitant treatment with enzyme inducing ASMs (carbamazepine, phenytoin, phenobarbital, primidone)*
Week 1–2: 0.6 mg/kg/day
Week 2–4: 1.2 mg/kg/day
Increase by 0.6–1.2 mg/kg/day every 7–14 days thereafter
Goal 5–15 mg/kg/day divided in 2 doses

> 12 years:
Week 1–2: 25 mg/day
Week 3–4: 50 mg/day
Increase by 50–100 mg/day every 7–14 days thereafter
Goal 100–400 mg/day divided in 2 doses

*Concomitant treatment with valproate*
Week 1–2: 25 mg every other day
Week 3–4: 25 mg/day
Increase by 25–50 mg/day every 7–14 days thereafter
Goal 100–200 mg/day divided in 2 doses

*Concomitant treatment with enzyme-inducing ASMs*
Week 1–2: 50 mg/day
Week 3–4: 100 mg/day
Increase by 50–100 mg/day every 7–14 days thereafter
Goal 200–500 mg/day divided in 2 doses

Steps for cross titration of valproate to lamotrigine [38]

1. Hold valproate dose constant and titrate lamotrigine up to 200 mg/day as above (*concomitant treatment with VPA*).
2. Maintain lamotrigine dose constant, and taper valproate by decrements of 500 mg/day every 7 days until a dose of 500 mg/day is reached.
3. Increase lamotrigine to 300 mg and simultaneously decrease valproate to 250 mg for one week.
4. Stop the valproate and increase lamotrigine by 100 mg/day each week until goal dose is reached.

**Side Effects**
Neurologic: somnolence, anxiety, irritability, ataxia/dizziness, headache, insomnia
Systemic: GI symptoms, rash

**Critical/Potentially Life-Threatening Side Effects**
Systemic: SJS/TEN, cardiac conduction abnormalities, hepatotoxicity, hematological abnormalities, hypogammaglobulinemia

**Lab Monitoring**
May consider baseline CBC with repeat at 3 and 6 months, and every 12 months thereafter; LFTs at baseline with repeat every 12 months.

## Levetiracetam

Section References: [1–3, 20, 133]

Levetiracetam is a broad-spectrum agent used to treat both focal and generalized seizure types. The IV formulation may also be used as abortive therapy in status epilepticus.

**Mechanism of Action**
The mechanism is incompletely understood. It binds synaptic vesicle protein SV2A, involved in synaptic vesicle exocytosis. It inhibits high-threshold (N-type) calcium channels and may indirectly modulate GABA and glycine activity.

**Dosing**
Status epilepticus
60 mg/kg IV loading dose

Seizure treatment

< 12 years:
Start 20 mg/kg/day divided in 2 doses
Increase by 10–20 mg/kg/day every 7–14 days
Goal 30–100 mg/kg/day

≥ 12 years:
Start 500–1000 mg/day divided in 2 doses
Increase by 500 mg/day every 7–14 days
Goal 2000–3000 mg/day

**Side Effects**
Neurologic: somnolence, anxiety, irritability/emotional lability, asthenia, dizziness/ataxia

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: suicide ideation/psychosis
Systemic: SJS/TEN, hepatotoxicity, pancytopenia, hypogammaglobulinemia

**Lab Monitoring**
Not required

## Lorazepam

Section References: [1–3, 134]

Lorazepam is a broad-spectrum agent typically used as an acute abortive therapy for status epilepticus or intermittent use for seizure clusters.

**Mechanism of Action**
Lorazepam is a type of benzodiazepine, a $GABA_A$ agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

**Dosing**

Status epilepticus
0.1 mg/kg IV

**Side Effects**
Neurologic: somnolence, cognitive dysfunction, dysarthria, ataxia/dizziness

**Critical/Potentially Life-Threatening Side Effects**
Systemic: respiratory depression, hypotension

## Midazolam

Section References: [1–3, 26]

Midazolam is a broad-spectrum agent typically used as an acute abortive therapy for status epilepticus or intermittent use of seizure clusters.

**Mechanism of Action**
Midazolam is a type of benzodiazepine. $GABA_A$ agonist resulting in increased chloride ion permeability and neuronal inhibition. At high concentrations, benzodiazepines also influence sodium channel function.

**Dosing**

Acute abortive treatment/status epilepticus

Intranasal dosing:
0.2 mg/kg once (max 10 mg/dose)

≥ 12 years:
5 mg to one nostril, after 10 min, may repeat dose to the other nostril if needed

IM dosing:
0.2 mg/kg/dose (max 10 mg/dose)

IV dosing:
0.1–0.2 mg/kg/dose

**Side Effects**
Neurologic: somnolence, cognitive dysfunction, dysarthria, ataxia/dizziness

**Critical/Potentially Life-Threatening Side Effects**
Systemic: hypotension, respiratory depression

## Oxcarbazepine

Section References: [1–3, 20, 135]

Oxcarbazepine is used to treat focal seizures with or without secondary generalization. Like carbamazepine, oxcarbazepine is contraindicated for primary generalized seizures due to the potential for exacerbation.

Oxcarbazepine shares a chemical structure with carbamazepine and eslicarbazepine acetate, a dibenzapine nucleus with a 5-carboxamide substitute, but differs with a keto group at the 10 position. Oxcarbazepine is a pro-drug, metabolizing to a 10-monohydroxy derivative.

**Mechanism of Action**
The 10-monohydroxy metabolite acts to block voltage-gated sodium channels. This stabilizes the membrane and prevents repetitive neuronal firing. It also increases potassium conductance, modulates high-threshold calcium channels, and reduces the release of glutamate.

**Dosing**

2–16 years:
Start 8–10 mg/kg/day divided in 2 (< 5y) or 3 (≥ 5y) doses
Increase by 5–10 mg/kg/day every 7 days
Goal 30–40 mg/kg/day (max 60 mg/kg/day)

or

< 20 kg: 600–900 mg/day
20–29 kg: 900–1200 mg/day
30–39 kg: 900–1500 mg/day
40–59 kg: 1500–1800 mg/day

> 16 years:
Start 300 mg/day divided in 2 doses
Increased by 150 mg/day every 2 days
Goal 1200–2400 mg/day

**Side Effects**
Neurologic: somnolence/lethargy, diplopia, ataxia/dizziness, headache
Systemic: GI symptoms, hyponatremia, rash

**Critical/Potentially Life-Threatening Side Effects**
Systemic: SJS/TEN/hypersensitivity reaction, cardiac arrhythmia, hyponatremia, agranulocytosis, aplastic anemia, pancytopenia, thrombocytopenia

**Lab Monitoring**
Consider baseline CBC, Na, LFTs. Consider screening for HLA-B*1502 allele for patients with Asian ancestry due to potential increased risk for SJS/TEN. Repeat Na at 1–2 months or once at treatment is therapeutic, and periodically thereafter. Repeat CBC at 3 and 6 months after the start of treatment. Consider monitoring 25–hydroxyvitamin D levels.

## Perampanel

Section References: [1, 2, 17]

Perampanel is a broad-spectrum agent used to treat both focal and generalized seizures.

**Mechanism of Action**
Antagonist of the AMPA-type glutamate receptor, reducing intracellular calcium, resulting in reduced neuronal excitability.

**Dosing**

≥ 4 years:
Start 2 mg daily; or 4 mg daily if taking enzyme-inducing ASMs*
Increase by 2 mg/day every 7–14 days
Goal 4–8 mg/day
** carbamazepine, phenytoin, phenobarbital, primidone*

**Side Effects**
Neurologic: somnolence/fatigue, irritability, ataxia/dizziness/gait disturbance, headache
Systemic: GI symptoms, weight gain

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: psychosis, suicide ideation
Systemic: hypersensitivity reaction/DRESS

**Lab Monitoring**
Defer routine monitoring.

## Phenobarbital

Section References: [1–3, 20, 42]

Phenobarbital is effective in the treatment of focal and primary generalized seizures. It is contraindicated for absence seizures. It is often used to treat neonatal seizures (see Chap. 5) and as an abortive therapy for status epilepticus across age groups.

**Mechanism of Action**
Binds the $GABA_A$ receptor leading to increased chloride ion permeability. This results in neuronal hyperpolarization and enhancing inhibition. May also result in a reduction in calcium-dependent action potentials.

**Dosing**

Status epilepticus:
15–20 mg/kg IV

Seizure treatment:

Infants:
5–6 mg/kg/day given in 1–2 doses

1–5 years:
3–8 mg/kg/day given in 1–2 doses

> 5 years to adolescents:
2–3 mg/kg/day given in 1–2 doses

> 12 years/adults:
1.5–4 mg/kg/day given in 1–2 doses
or
50–200 mg/day given in 1–2 doses

**Side Effects**
Neurologic: somnolence/lethargy, impaired attention/cognition, depression/mood changes, behavioral changes/hyperactivity, nystagmus, dysarthria, ataxia
Systemic: GI symptoms, decreased bone density, rash
Rare cases of connective tissue contractures/Dupuytren contracture

**Critical/Potentially Life-Threatening Side Effects**
Systemic: SJS/TEN/hypersensitivity reaction, respiratory depression/apnea (rapid IV infusion), hepatotoxicity, agranulocytosis/thrombocytopenia

**Lab Monitoring**
Drug levels, CBC, and LFTs should be monitored. Consider monitoring 25-hydroxyvitamin D levels.

## Phenytoin

Section References: [1–3, 20, 136]

Phenytoin is used for focal seizures with or without secondary generalization. They may also be effective against some generalized seizures including primary GTC or for patients with mixed semiology. Phenytoin has the potential to worsen a subset of generalized seizures, typically myoclonic and absence. Phenytoin should be avoided

for patients with LGS and progressive myoclonic epilepsies. For status epilepticus, fosphenytoin is preferred.

**Mechanism of Action**
Blocks voltage-gated sodium channels and modulates sustained repetitive firing. It also inhibits calcium channels and calcium sequestration and inhibits calcium-calmodulin protein phosphorylation.

**Dosing**

With the start of treatment, may consider enteral loading dose depending on the clinical circumstances.

Children:
Enteral loading dose:
15 mg/kg/day divided in 3 doses
24 hrs after loading dose: start 5 mg/kg/day given in 1–2 doses
or
Start 5 mg/kg/day given in 1–2 doses
Increase by 5 mg/kg/day every 3–4 weeks
Goal 5–10 mg/kg/day

Adults:
Enteral loading dose:
1 g divided in 3 doses
24 hrs after loading dose: start 300–400 mg/day given in 1–2 doses
or
Start 150–300 mg/day in 1–2 doses
Increase by 50 mg/day every 3–4 weeks
Goal 200–400 mg/day

**Side Effects**
Neurologic: somnolence, confusion, nystagmus, dysarthria, ataxia/dizziness
Systemic: GI symptoms, decreased bone density, hirsutism, rash, gingival hypertrophy

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: suicide ideation, peripheral neuropathy
Systemic: SJS/TEN, systemic lupus erythematosus, hepatotoxicity, agranulocytosis/aplastic anemia, lymphadenopathy/lymphoma

**Lab Monitoring**
Recommend baseline LFTs and Chem10 to evaluate liver and kidney function; repeat screening labs every 12 months. Alternatively, may defer routine monitoring. Consider monitoring folate and 25-hydroxyvitamin D levels.

## Pregabalin

Section References: [1–3, 18]

Pregabalin is used for focal seizures with or without secondary generalization. It has the potential to exacerbate primary generalized seizures, specifically myoclonus. Pregabalin is a broad-spectrum GABA analog and structurally similar to gabapentin. Its effect as an antiseizure treatment, however, does not seem to be mediated by modulation of GABA.

**Mechanism of Action**
Binds to voltage-gated presynaptic calcium channels, inhibiting inward calcium currents. This results in decreased release of neurotransmitters including glutamate, noradrenaline, and substance P.

**Dosing**

Infant to < 4 years:
Start 3.5–5 mg/kg/day divided in 2–3 doses
Increase by 3–5 mg/kg/day every 7 days
Max 14 mg/kg/day

4–16 years:
< 30 kg
Start 3.5 mg/kg/day divided in 2–3 doses
Increase by 3 mg/kg/day every 7 days
Max 14 mg/kg/day

≥ 30 kg
Start 2.5 mg/kg/day divided in 2–3 doses
Increase 3 mg/kg/day every 7 days
Max 10 mg/kg/day

≥ 17 years
Start 50–150 mg/day divided in 2–3 doses
Increase by 50–150 mg/day every 7 days
Goal 150–600 mg/day (max 600 mg/day)

**Side Effects**
Neurologic: somnolence, impaired attention, irritability/aggressiveness, tremor, ataxia/dizziness
Systemic: peripheral edema, GI symptoms, weight gain, xerostomia

**Critical/Potentially Life-Threatening Side Effects**
Systemic: hypersensitivity reaction, AV block, myocardial dysfunction, angioedema, rhabdomyolysis, hypoglycemia, neutropenia

**Lab Monitoring**
Consider baseline Chem10 to evaluate renal function in the setting of preexisting comorbidities and/or increased risk.

## Primidone

Section References: [1–3, 20, 137]

Primidone is effective in the treatment of focal and primary generalized seizures. It is contraindicated for absence seizures.

**Mechanism of Action**
Primidone has two active metabolites, phenobarbital and phenylethylmalonamide. Primidone has been shown to provide an antiseizure effect independent from phenobarbital, but the mechanism of this effect is not understood.

Phenobarbital is described above; it binds the $GABA_A$ receptor leading to increased chloride ion permeability. This results in neuronal hyperpolarization and enhancing inhibition. It may also result in a reduction in calcium-dependent action potentials.

**Dosing**

Infants–8 years:
Start 1–2 mg/kg/day given once
Increase every 3 days
Goal 10–25 mg/kg/day (infants); 10–20 mg/kg/day (children) divided in 2–4 doses
or
Day 1–3: 50 mg/day at bedtime
Day 4–6: 100 mg/day divided in 2 doses
Day 7–9: 200 mg/day divided in 2 doses
Day 10: 375–750 mg/day divided in 3 doses

> 8 years – adults:
Day 1–3: 125 mg/day given once
Day 4–6: 200–250 mg/day divided in 2 doses
Day 7–9: 300–375 mg/day divided by 3 doses
Day 10: 750 mg/day divided by 3 doses
Goal 750–1500 mg/day or 10–20 mg/kg/day divided in 3–4 doses

**Side Effects**
Neurologic: somnolence/lethargy, impaired attention/cognition, depression/mood changes, behavioral changes/hyperactivity, nystagmus, dysarthria, ataxia
Systemic: GI symptoms, decreased bone density, rash
Rare cases of connective tissue contractures

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: Acute toxic reaction (severe sedation, ataxia/dizziness, nausea/vomiting)
Systemic: SJS/TEN/hypersensitivity reaction, hepatotoxicity, agranulocytosis

**Lab Monitoring**
Defer routine monitoring. Consider monitoring 25-hydroxyvitamin D levels.

## Rufinamide

Section References: [1–3, 20, 138]

Rufinamide is a broad-spectrum agent used to treat both focal and primary generalized seizures with a role in treatment of LGS and epileptic spams. As a triazole derivative, the chemical structural is unique among current ASMs.

**Mechanism of Action**
Blocks voltage-gated sodium channels after inactivation, prolonging recovery and preventing return to an active state. This persistent depolarization reduces bursts of high-frequency action potentials.

**Dosing**

≥ 4 years and < 30 kg:
Start 10 mg/day or 200 mg/kg/day divided in 2 doses
Increase by 10 mg/day or 200 mg/kg/day every 2–7 days
Goal 45 mg/day or 1000 mg/kg/day
Goal 400–600 mg/day *
* *Concomitant treatment with valproate*

Children ≥ 30 kg and adults:
Start 400 mg/day divided in 2 doses
Increase by 400 mg/day every 2 days
Goal
30–50 kg: 1800 mg/day
51–70 kg: 2400 mg/day
> 70 kg: 3200 mg/day

**Side Effects**
Neurologic: somnolence/fatigue, dizziness/ataxia, headache
Systemic: GI symptoms

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: status epilepticus
Systemic: hypersensitivity reaction, decreased QTc interval

**Lab Monitoring**
Consider baseline LFTs and Chem10 for hepatic and renal function; repeat every 12 months. Alternatively, may defer routine monitoring. Recommend baseline ECG to evaluate QTc interval and identify potential preexisting arrhythmias.

## Stiripentol

Section References: [1–3, 19, 23]

Stiripentol is used as an adjuvant therapy for synergistic effect with clobazam or valproate, typically for patients with Dravet syndrome and refractory GTCs. Co-treatment with carbamazepine, phenytoin, or phenobarbital is typically avoided due to risk of toxicity.

**Mechanism of Action**
Activates $GABA_A$ receptor with barbiturate-like mechanisms of increasing chloride ion permeability, neuronal hyperpolarization, and enhanced inhibition. It may also increase GABA levels by inhibiting synaptic uptake and/or inhibiting GABA transaminase. Stiripentol has additional indirect effects; as a CYP inhibitor, it may act to increase serum levels of concomitant ASMs such as clobazam.

**Dosing**

A broad range of dosing has been reported:
Start 25–50 mg/kg/day divided in 2–3 doses
Increase by 10 mg/kg/day every 7–14 days
Goal 75 mg/kg/day

May consider lower dosing to start:
Start 10–20 mg/kg/day divided in 2–3 doses
Increase over 2–4 weeks
Goal 50 mg/kg/day

**Side Effects**
Neurologic: somnolence, agitation/irritability, dysarthria, hypotonia, dystonia, tremor, ataxia, insomnia
Systemic: GI symptoms, anorexia/weight-loss

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: suicide ideation
Systemic: aplastic anemia, leukopenia/neutropenia, thrombocytopenia

**Lab Monitoring**
Consider baseline LFTs and Chem10 for hepatic and renal function; repeat every 12 months.

## Sulthiame

Section References: [1–3]

Sulthiame is used for focal seizures with or without secondary generalization and self-limited epilepsy with centrotemporal spikes. It is also used for epileptic encephalopathies, with specific efficacy for patients with CSWS and myoclonic epilepsies. It is not currently approved for use in the United States but is widely used in Europe.

**Mechanism of Action**
Inhibits voltage-gated sodium channels and glutamate release. Inhibits carbonic anhydrase which results in decreased inward calcium flow of NMDA receptors, thereby reducing neuronal excitability.

**Dosing**

Children:
Start 5 mg/kg/day divided in 2 doses
Increase by 5 mg/kg/day after 7 days
Goal 5–10 mg/kg/day

Adults:
Start 100–250 mg/day divided in 2 doses
Increase by 100 mg/day every 7 days
Goal 200–600 mg/day

**Side Effects**
Neurologic: paresthesia, ataxia/dizziness, headache
Systemic: hyperventilation, metabolic acidosis, anorexia/weight loss, rash

**Critical/Potentially Life-Threatening Side Effects**
SJS/TEN, renal dysfunction, metabolic acidosis, nephrolithiasis

**Lab Monitoring**
Consider baseline CBC and Chem10 to evaluate renal function.

## Tiagabine

Section References: [1–3, 20, 139]

Tiagabine is used for focal seizures with or without secondary generalization. It may also be considered for epileptic spasms.

**Mechanism of Action**
Enhanced endogenous GABA effect by blocking GABA reuptake by inhibiting GABA transporter-1.

**Dosing**

Children > 12 years:
Start 0.1 mg/kg/day
Increase by 0.1 mg/kg/day every 7–14 days
Goal 0.5–2 mg/kg/day divided in 2–4 doses

*Concomitant treatment with enzyme-inducing ASMs*
> 12 years:
Start 0.25 mg/kg/day
Increase by 0.5–1 mg/kg/day every 7 days
Max 4–8 mg/kg/day divided in 3–4 doses

12–18 years:
Start 4 mg/day
Increase by 4 mg/day every 7 days
Max 32 mg/day divided in 2–4 doses

**Side Effects**
Neurologic: somnolence/fatigue, cognitive and attention impairment, anxiety, asthenia, tremor, dizziness, headache
Systemic: GI symptoms, ecchymosis

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: nonconvulsive status or absence status epilepticus, suicide ideation
Concern for possible risk of visual field deficits but data is limited
Systemic: SJS/TEN

**Lab Monitoring**
Consider baseline CBC as well as LFTs and Chem10 for hepatic and renal function; repeat every 6–12 months. Alternatively, may defer routine monitoring.

## Topiramate

Section References: [1–3, 20, 21]

Topiramate is a broad-spectrum agent used to treat both focal and primary generalized events, including primary GTCs, myoclonic and absence seizures. It is used for myoclonic syndromes including Dravet, progressive myoclonic epilepsies, myoclonic atonic epilepsy, and JME. It is also used for LGS and IS.

**Mechanism of Action**
Multiple described mechanisms of action including inhibition of voltage-gated sodium channels, L-type voltage-gated calcium channels, AMPA glutamate

receptors, and carbonic anhydrase. It binds $GABA_A$ receptors mediating neuronal inhibition. Finally, topiramate may increase potassium channel conduction.

**Dosing**

Infants and children <12 years:
Start 0.5–1 mg/kg/day divided in 2–3 doses
Increase by 0.5–1 mg/kg/day every 7–14 days
Goal 3–9 mg/kg/day

2–16 years:
Start 1–3 mg/kg/day divided in 2–3 doses
Increase by 1–3 mg/kg/day every 7–14 days
Goal 5–9 mg/kg/day

≥ 17 years:
Start 25–50 mg/day divided in 2 doses
Increase by 25–50 mg/day every 7–14 days
Goal 100–400 mg/day

**Side Effects**
Neurologic: somnolence/fatigue, cognitive and attention impairment, anxiety, depression/mood changes, paresthesia, ataxia/dizziness
Systemic: metabolic acidosis, anorexia/weight loss, hypohidrosis

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: acute myopia with secondary angle-closure glaucoma
Systemic: metabolic acidosis, nephrolithiasis, oligohydramnios/hyperthermia

**Lab Monitoring**
Consider CBC, LFTs, and Chem10 once maximum treatment dose is reached or at 3–6 months following the start of treatment. Alternatively, may defer routine monitoring.

## Valproate

Section References: [1–3, 20, 140]

Valproate is a broad-spectrum agent used to treat both focal and primary generalized events including GTCs, tonic/atonic, myoclonic seizures, and absence seizures. It is used for JME and LGS. It may also be used in status epilepticus.

**Mechanism of Action**
Multiple described mechanisms of action including inhibition of voltage-gated sodium channels and T-type calcium channels, as well as increased potassium

channel conduction. There is an increase in GABA concentrations by multiple proposed modalities including increased glutamic acid decarboxylase activity, inhibition of GABA transaminase or succinic semialdehyde dehydrogenase. Decreased expression of glutamate transporter-1 has also been described.

**Dosing**

Status epilepticus:
20–40 mg/kg IV

Seizure treatment:
≤ 12 years
Start 10–15 mg/kg/day divided in 2–3 doses
Increase by 5–15 mg/kg/day every 5–7 days
Goal 20–60 mg/kg/day

> 12 years
Start 200–500 mg/day divided in 2 doses
Increase by 200–500 mg/day every 3–7 days
Goal 1000–1500 mg/day

**Side Effects**
Neurologic: somnolence/lethargy, asthenia, tremor, ataxia/dizziness, headache
Systemic: GI symptoms, hyperammonemia, elevated liver enzymes, hypocarnitinemia, weight gain, decreased bone density, alopecia, ecchymosis

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: hyperammonemic encephalopathy
Systemic: SJS/TEN, hepatotoxicity, pancreatitis, agranulocytosis, aplastic anemia, thrombocytopenia, hypogammaglobulinemia

**Lab Monitoring**
Consider baseline CBC and LFTs; repeat at 2 months after the start of treatment and every 6 months thereafter. Consider monitoring 25-hydroxyvitamin D levels.

## Vigabatrin

Section References: [1–3, 11, 22, 141]

Vigabatrin is typically used to treat IS. For patients with tuberous sclerosis complex and IS, it is first line. It may also be used to treat refractory focal seizures with or without secondary generalization. It is contraindicated for primary generalized seizures including absence seizures.

**Mechanism of Action**
Increases synaptic GABA by irreversibly inhibiting GABA transaminase.

**Dosing**

Infants:
Start 50 mg/kg/day given in 2 doses
Increase by 25–50 mg/kg/day every 3 days
Max 150–200 mg/kg/day

2–16 years and ≤ 60 kg:
10–15 kg
Start 350 mg/day divided in 2 doses
Increase every 7 days
Goal 1050 mg/day

16–20 kg:
Start 450 mg/day divided in 2 doses
Increase every 7 days
Goal 1300 mg/day

21–25 kg:
Start 500 mg/day divided in 2 doses
Increase every 7 days
Goal 1500 mg/day

26–60 kg:
Start 500 mg/day divided in 2 doses
Increase every 7 days
Goal 2000 mg/day

≥ 17 years and/or > 60 kg:
Start 500–1000 mg/day given in 2 doses
Increase by 500 mg/day every 7 days
Goal 1000–3000 mg/day

**Side Effects**

Neurologic: Somnolence/fatigue, cognitive impairment, agitation/irritability, tremor, paresthesia, ataxia/dizziness, headache
MRI changes: restricted diffusion on T2 imaging of the basal ganglia, thalamus, brainstem, dentate
Systemic: GI symptoms, weight gain

A visual field deficit develops with vigabatrin treatment in about one third of cases [3, 141]. In the United States, there is a REMS program to support prescriber education and serial ophthalmologic monitoring.

**Critical/Potentially Life-Threatening Side Effects**

Neurologic: status epilepticus, psychosis
Systemic: hypersensitivity reaction, angioedema

**Lab Monitoring**
Consider baseline CBC as well as LFTs and Chem10 to evaluate hepatic and renal function; repeat labs every 6–12 months thereafter.

## Zonisamide

Section References: [1–3, 20, 108, 142]

Zonisamide is a broad-spectrum agent used to treat both focal and generalized events including primary GTCs, tonic/atonic, myoclonic, and absence seizures. It may be used for epileptic encephalopathies including IS, Ohtahara syndrome, progressive myoclonic epilepsies, and Dravet syndrome.

**Mechanism of Action**
Blocks voltage-gated sodium channels, T-type calcium channels, and carbonic anhydrase. Decreases GABA transporter-1 expression and glutamate release. Increases extracellular levels of dopamine and serotonin. Increased expression of excitatory amino-acid carrier-1 (EAAC-1).

**Dosing**

> 6 years:
Start 1–2 mg/kg/day given in 1–2 doses
Increase by 1–2 mg/kg/day every 7–14 days
Goal 5–12 mg/kg/day

Adults:
Start 100 mg/day given in 1–2 doses
Increase by 100 mg/day every 7–14 days
Goal 100–600 mg/day

**Side Effects**
Neurologic: somnolence/fatigue, cognitive and attention impairment, anxiety, depression, agitation/irritability, paresthesia, ataxia/dizziness
Systemic: GI symptoms, anorexia/weight loss, metabolic acidosis, rash, hypohidrosis

**Critical/Potentially Life-Threatening Side Effects**
Neurologic: status epilepticus, psychosis, acute myopia with secondary angle-closure glaucoma
Systemic: SJS/TEN, hepatotoxicity, metabolic acidosis, nephrolithiasis, agranulocytosis, aplastic anemia, anhidrosis, hyperthermia

**Lab Monitoring**
Consider baseline chemistry panel with repeat 3–6 months after the start of treatment. For patients with cognitive impairment, for whom it may be difficult to recognize early signs or symptoms of metabolic acidosis, plan for ongoing periodic lab monitoring of bicarbonate levels.

## References


1. Patsalos PN, St. Louis EK. The epilepsy prescriber's guide to antiepileptic drugs. 3rd ed. Cambridge, Cambridge University Press; 2018.
2. Schachter SC. Antiseizure drugs: Mechanism of action, pharmacology, and adverse effects [Internet]. Garcia P, Dashe J, editors. UpToDate. Waltham, MA: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: http://www.uptodate.com.
3. Panayiotopoulos C. Pharmacopedia. In: A clinical guide to epileptic syndromes and their treatment. 2nd ed. Springer; Berlin 2010. p. 565–620.
4. Gray RA, Whalley BJ. The proposed mechanism of action of CBD in epilepsy. Epileptic Disord. 2020;22(January):10–5.
5. Stroink H, Brouwer OF, Arts WF, Geerts AT, Peters ACB, Van Donselaar CA. The first unprovoked, untreated seizure in childhood: A hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. Dutch study of epilepsy in childhood. J Neurol Neurosurg Psychiatry. 1998;64(5):595–600.
6. Zuberi SM, Symonds JD. Update on diagnosis and management of childhood epilepsies. J Pediatr (Rio J). 2015;91(6):S67–77.
7. Hauser WA, Rich SS, Lee JR, Annegers JF, Anderson VE. Risk of recurrent seizures after two unprovoked seizures. N Engl J Med. 1998;338(7):429–34.
8. Raspall-Chaure M, Neville BG, Scott RC. The medical management of the epilepsies in children: conceptual and practical considerations. Lancet Neurol. 2008;7(1):57–69.
9. Shellhaas RA, Berg AT, Grinspan ZM, Wusthoff CJ, Millichap JJ, Loddenkemper T, et al. Initial treatment for nonsyndromic early-life epilepsy: an unexpected consensus. Pediatr Neurol. 2017;75:73–9.
10. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013;54(3):551–63.
11. Guerrini R. Epilepsy in children. Lancet. 2006;367(9509):499–524.
12. Nieto-Barrera M, Candau R, Nieto-Jimenez M, Correa A. Ruiz del Portal L. Topiramate in the treatment of severe myoclonic epilepsy in infancy. Seizure. 2000;9(8):590–4.
13. Wallace SJ. Myoclonus and epilepsy in childhood: A review of treatment with valproate, ethosuximide, lamotrigine and zonisamide. Epilepsy Res. 1998;29(2):147–54.
14. Covanis A, Gupta AK, Jeavons PM. Sodium valproate: monotherapy and polytherapy. Epilepsia. 1982;23(6):693–720.
15. Oguni H, Tanaka T, Hayashi K, Funatsuka M, Sakauchi M, Shirakawa S, et al. Treatment and long-term prognosis of myoclonic-astatic epilepsy of early childhood. Neuropediatrics. 2002;33(3):122–32.
16. Mikaeloff Y, De Saint-Martin A, Mancini J, Peudenier S, Pedespan JM, Vallée L, et al. Topiramate: Efficacy and tolerability in children according to epilepsy syndromes. Epilepsy Res. 2003;53(3):225–32.
17. Perampanel [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2020 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
18. Pregabalin [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
19. Stiripentol [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2020 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
20. Wilfong A. Seizures and epilepsy in children: Initial treatment and monitoring [Internet]. Nordli DR, Dashe JF, editors. UpToDate. Waltham, MA: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: http://www.uptodate.com.

21. Topiramate [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
22. Vigabatrin [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
23. Gonzalez-Giraldo E, Sullivan JE. Advances in the treatment of drug-resistant pediatric epilepsy. Semin Neurol. 2020;40(2):257–62.
24. Brivaracetam [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Oct 5]. Available from: https://online.lexi.com.
25. Fenfluramine [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
26. Midazolam [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
27. Guerrini R, Dravet C, Genton P, Belmonte A, Kaminska A, Dulac O. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia. 1998;39(5):508–12.
28. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. 2000;342(5):314–9.
29. Camfield PR, Camfield CS, Gordon K, Dooley JM. If a first antiepileptic drug fails to control a child's epilepsy, what are the chances of success with the next drug? J Pediatr. 1997;131(6):821–4.
30. Geerts A, Brouwer O, Stroink H, Van Donselaar C, Peters B, Peeters E, et al. Onset of intractability and its course over time: The Dutch study of epilepsy in childhood. Epilepsia. 2012;53(4):741–51.
31. Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia. 2010;51(6):1069–77.
32. Deckers CLP, Czuczwar SJ, Hekster YA, Kewser A, Kubova H, Meinardi H, et al. Selection of antiepileptic drug polytherapy based on mechanisms of action: The evidence reviewed. Epilepsia. 2000;41(11):1364–74.
33. Rowan AJ, Meijer JWA, Beer Pawlikowski N, Van Der Geest P, Meinardi H. Valproate-ethosuximide combination therapy for refractory absence seizures. Arch Neurol. 1983;40(13):797–802.
34. Perucca E. The management of refractory idiopathic epilepsies. Epilepsia. 2001;42(SUPPL. 3):31–5.
35. Ferrie CD, Panayiotopoulos CP. Therapeutic interaction of lamotrigine and sodium valproate in intractable myoclonic epilepsy. Seizure. 1994;3(2):157–9.
36. Chiron C, Marchand MC, Tran A, Rey E, D'Athis P, Vincent J, et al. Stiripentol in severe myoclonic epilepsy in infancy: A randomised placebo-controlled syndrome-dedicated trial. Lancet. 2000;356(9242):1638–42.
37. Interactions [Internet]. Lexicomp. Hudson, Ohio: UpToDate, Inc.; [cited 2021 Feb 8]. Available from: https://online.lexi.com.
38. Sale ME, Natarajan S, Biton V, Vuong A, Hammer AE, Messenheimer JA, et al. A dosing algorithm for converting from valproate monotherapy to lamotrigine monotherapy in patients with epilepsy. Epilepsy Behav. 2005;6(1):63–70.
39. Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia. 2007;48(7):1223–44.
40. Hirsch LJ, Weintraub DB, Buchsbaum R, Spencer HT, Straka T, Hager M, et al. Predictors of lamotrigine-associated rash. Epilepsia. 2006;47(2):318–22.
41. Andrade DM, Nascimento F. Dravet syndrome: management and prognosis [Internet]. Nordli DR, Dashe JF, editors. UpToDate. Waltham, MA: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: http://www.uptodate.com.
42. Phenobarbital [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.

43. French J, Smith M, Faught E, Brown L. Practice advisory: The use of felbamate in the treatment of patients with intractable epilepsy. Epilepsia. 1999;40(6):803–8.
44. Gerstner T, Teich M, Bell N, Longin E, Dempfle CE, Brand J, et al. Valproate-associated coagulopathies are frequent and variable in children. Epilepsia. 2006;47(7):1136–43.
45. Camfield P, Camfield C. Monitoring for adverse effects of antiepileptic drugs. Epilepsia. 2006;47(SUPPL. 1):31–4.
46. Strozzi I, Nolan SJ, Sperling MR, Wingerchuk DM, Sirven J. Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Cochrane Database Syst Rev. 2015;2015(2):CD001902.
47. Shinnar S, Berg AT, Moshé SL, Kang H, O'Dell C, Alemany M, et al. Discontinuing antiepileptic drugs in children with epilepsy: A prospective study. Ann Neurol. 1994;35(5):534–45.
48. Sánchez Fernández I, Loddenkemper T. Pediatric focal epilepsy syndromes. J Clin Neurophysiol. 2012;29(5):425–40.
49. Mahmoud SH, Buxton J. Seizures and choice of antiepileptic drugs following subarachnoid hemorrhage: A review. Can J Neurol Sci. 2017;44(6):643–53.
50. Cusack TJ, Carhuapoma JR, Ziai WC. Update on the treatment of spontaneous intraparenchymal hemorrhage: medical and interventional management. Curr Treat Options Neurol. 2018;20(1):1.
51. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3(2):175–92.
52. Kossoff EH, Pyzik PL, McGrogan JR, Vining EPG, Freeman JM. Efficacy of the ketogenic diet for infantile spasms. Pediatrics. 2002;109(5):780–3.
53. Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: Prospective single-center experience in 104 consecutive infants. Epilepsia. 2010;51(8):1403–7.
54. Eun SH, Kang HC, Kim DW, Kim HD. Ketogenic diet for treatment of infantile spasms. Brain Dev. 2006;28(9):566–71.
55. Prezioso G, Carlone G, Zaccara G, Verrotti A. Efficacy of ketogenic diet for infantile spasms: A systematic review. Acta Neurol Scand. 2018;137(1):4–11.
56. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group. Epilepsia. 2009;50(2):304–17.
57. Sourbron J, Klinkenberg S, van Kuijk SMJ, Lagae L, Lambrechts D, Braakman HMH, et al. Ketogenic diet for the treatment of pediatric epilepsy: review and meta-analysis. Childs Nerv Syst. 2020;36(6):1099–109.
58. Pfeifer HH, Thiele EA. Low-glycemic-Index treatment : A liberalized ketogenic diet for treatment of. Neurology. 2005;1–3.
59. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. Epilepsia. 2006;47(2):421–4.
60. Sofou K, Dahlin M, Hallböök T, Lindefeldt M, Viggedal G, Darin N. Ketogenic diet in pyruvate dehydrogenase complex deficiency: short- and long-term outcomes. J Inherit Metab Dis. 2017;40(2):237–45.
61. Sandu C, Burloiu CM, Barca DG, Magureanu SA, Craiu DC. Ketogenic diet in patients with GLUT1 deficiency syndrome. Maedica (Buchar). 2019;14(2):93–7.

62. McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff EH. Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. Pediatrics. 2009;124(2):e300–4.
63. Arslan N, Guzel O, Kose E, Yılmaz U, Kuyum P, Aksoy B, et al. Is ketogenic diet treatment hepatotoxic for children with intractable epilepsy? Seizure. 2016;43(June 2013):32–8.
64. Henderson CB, Filloux FM, Alder SC, Lyon JL, Caplin DA. Efficacy of the ketogenic diet as a treatment option for epilepsy: Meta-analysis. J Child Neurol. 2006;21(3):193–8.
65. Martinez CC, Pyzik PL, Kossoff EH. Discontinuing the ketogenic diet in seizure-free children: Recurrence and risk factors. Epilepsia. 2007;48(1):187–90.
66. Çataltepe O, Jallo G. Basic considerations of pediatric epilepsy surgery. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2020. p. 3–9.
67. Akman ÇI, Riviello JJ. Intractable epilepsy in children and selection of surgical candidates. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2019. p. 81–91.
68. Schramm J, Zentner J. Surgery for temporal lobe epilepsy. In: Arzimanoglou A, Helen Cross J, Gaillard WD, Holthausen H, Kyakar P, Kahane P, et al., editors. Pediatric epilepsy surgery. 2016. p. 347–59.
69. Russo G, Bhatia S, Ojemann JG. Extratemporal localization and eloquent areas. In: Arzimanoglou A, Helen Cross J, Gaillard WD, Holthausen H, Kyakar P, Kahane P, et al., editors. Pediatric epilepsy surgery. 2016. p. 361–79.
70. Englot DJ, Breshears JD, Sun PP, Chang EF, Auguste KI. Seizure outcomes after resective surgery for extra-temporal lobe epilepsy in pediatric patients: A systematic review. J Neurosurg Pediatr. 2013;12(2):126–33.
71. Çataltepe O. Hemipherectomy and hemipherotomy techniques in pediatric epilepsy surgery. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2019. p. 497–505.
72. Wong T-T, Kwan S-Y, Chang K-P, Tsai M-L, Hsieh KL-C. Corpus callosotomy. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2019. p. 581–8.
73. Tovar-Spinoza ZS, Rutka JT. Multiple subpial transections in children with refractory epilepsy. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2019. p. 603–7.
74. Curry D, Gadgil N. Steriotactic laser ablation for hypothalamic hamartomas. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2019. p. 640–4.
75. Karsy M, Guan J, Ducis K, Bollo RJ. Emerging surgical therapies in the treatment of pediatric epilepsy. Transl Pediatr. 2016;5(2):67–78.
76. Tovar-Spinoza ZS, Rutka JT. MRI-guided laser thermal therapy in pediatric epilepsy surgery. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2019. p. 645–52.
77. Régis J, Hamdi H, Chauvel P. Radiosurgical treatment for epilepsy. In: Çataltepe O, Jallo GI, editors. Pediatric epilepsy surgery: preoperative assessment and surgical treatment. 2nd ed. New York: Thieme; 2019. p. 625–39.
78. Nune G, DeGiorgio C, Heck C. Neuromodulation in the treatment of epilepsy. Curr Treat Options Neurol. 2015;17(10):5.
79. Starnes K, Miller K, Wong-Kisiel L, Lundstrom BN. A review of neurostimulation for epilepsy in pediatrics. Brain Sci. 2019;9(10):PMC6826633.
80. Englot DJ, Chang EF, Auguste KI. Vagus nerve stimulation for epilepsy: A meta-analysis of efficacy and predictors of response - A review. J Neurosurg. 2011;115(6):1248–55.

81. Bergey GK, Morrell MJ, Mizrahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory partial seizures. Neurology. 2015;84(8):810–7.
82. Li MCH, Cook MJ. Deep brain stimulation for drug-resistant epilepsy. Epilepsia. 2018;59(2):273–90.
83. Chiken S, Nambu A. Mechanism of deep brain stimulation: inhibition, excitation, or disruption? Neuroscientist. 2016;22(3):313–22.
84. Velasco AL, Velasco F, Jiménez F, Velasco M, Castro G, Carrillo-Ruiz JD, et al. Neuromodulation of the centromedian thalamic nuclei in the treatment of generalized seizures and the improvement of the quality of life in patients with Lennox-Gastaut syndrome. Epilepsia. 2006;47(7):1203–12.
85. Yan H, Toyota E, Anderson M, Abel TJ, Donner E, Kalia SK, et al. A systematic review of deep brain stimulation for the treatment of drug-resistant epilepsy in childhood. J Neurosurg Pediatr. 2019;23(3):274–84.
86. Abend NS, Loddenkemper T. Pediatric status epilepticus management. Curr Opin Pediatr. 2014;26(6):668–74.
87. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American epilepsy society. Epilepsy Curr. 2016;16(1):48–61.
88. Brophy GM, Bell R, Claassen J, Alldredge B, Bleck TP, Glauser T, et al. Guidelines for the evaluation and management of status epilepticus. Neurocrit Care. 2012;17(1):3–23.
89. Smith DM, McGinnis EL, Walleigh DJ, Abend NS. Management of status epilepticus in children. J Clin Med. 2016;5(4):PMC4850470.
90. Chin RF, Neville BG, Peckham C, Wade A, Bedford H, Scott RC. Treatment of community-onset, childhood convulsive status epilepticus: a prospective, population-based study. Lancet Neurol. 2008;7(8):696–703.
91. Lewena S, Young S. When benzodiazepines fail: How effective is second line therapy for status epilepticus in children? EMA - Emerg Med Australas. 2006;18(1):45–50.
92. Sánchez Fernández I, Abend NS, Agadi S, An S, Arya R, Brenton JN, et al. Time from convulsive status epilepticus onset to anticonvulsant administration in children. Neurology. 2015;84(23):2304–11.
93. Bennett KS. Treatment of refractory status epilepticus in children: current practice and opportunities to improve care. Pediatr Crit Care Med. 2016;17:1006–7.
94. Sánchez Fernández I, Goodkin HP, Scott RC. Pathophysiology of convulsive status epilepticus. Seizure. 2019;68(March 2018):16–21.
95. Goodkin HP, Joshi S, Mtchedlishvili Z, Brar J, Kapur J. Subunit-specific trafficking of GABAA receptors during status epilepticus. J Neurosci. 2008;28(10):2527–38.
96. Tully I, Draper ES, Lamming CR, Mattison D, Thomas C, Martland T, et al. Admissions to paediatric intensive care units (PICU) with refractory convulsive status epilepticus (RCSE): A two-year multi-centre study. Seizure. 2015;29:153–61.
97. Lewena S, Pennington V, Acworth J, Thornton S, Ngo P, McIntyre S, et al. Emergency management of pediatric convulsive status epilepticus: A multicenter study of 542 patients. Pediatr Emerg Care. 2009;25(2):83–7.
98. Riviello JJ, Ashwal S, Hirtz D, Glauser T, Ballaban-Gil K, Kelley K, et al. Practice parameter: Diagnostic assessment of the child with status epilepticus (an evidence-based review) - Report of the quality standards subcommittee of the American academy of neurology and the practice committee of the child neurology society. Neurology. 2006;67(9):1542–50.

99. Zhao ZY, Wang HY, Wen B, Yang ZB, Feng K, Fan JC. A comparison of midazolam, lorazepam, and diazepam for the treatment of status epilepticus in children: a network meta-analysis. J Child Neurol. 2016;31(9):1093–107.
100. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev. 2014;2014(9):CD003723.
101. Tasker RC, Goodkin HP, Sánchez Fernández I, Chapman KE, Abend NS, Arya R, et al. Refractory status epilepticus in children: intention to treat with continuous infusions of midazolam and pentobarbital∗. Pediatr Crit Care Med. 2016;17(10):968–75.
102. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;381(22):2103–13.
103. Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020;395(10231):1217–24.
104. Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: A meta-analysis of published studies. Seizure. 2014;23(3):167–74.
105. Watemberg N, Segal G. A suggested approach to the etiologic evaluation of status epilepticus in children: What to seek after the usual causes have been ruled out. J Child Neurol. 2010;25(2):203–11.
106. Herman ST, Abend NS, Bleck TP, Chapman KE, Drislane FW, Emerson RG, et al. Consensus statement on continuous EEG in critically Ill adults and children, part I: Indications. J Clin Neurophysiol. 2015;32(2):87–95.
107. Acetazolamide [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
108. Shbarou R. Current treatment options for early-onset pediatric epileptic encephalopathies. Curr Treat Options Neurol. 2016;18(10):1–9.
109. Corticotropin [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
110. Kwan P, Trinka E, Van Paesschen W, Rektor I, Johnson ME, Lu S. Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: Results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. Epilepsia. 2014;55(1):38–46.
111. Cannabidiol [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
112. Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on cannabidiol treatment for drug-resistant seizures in tuberous sclerosis complex: a placebo-controlled randomized clinical trial. JAMA Neurol. 2020;02114:1–9.
113. Head AA, Dpt PE, Arzimanoglou A, Brandl U, Cross JH, Gil-Nagel A, et al. Seminar in epileptology epilepsy and cannabidiol: a guide to treatment. Epileptic Disord. 2020;22(1):1–14.
114. Carbamazepine. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021.
115. Cenobamate [Internet]. Lexi-Drugs. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
116. Clobazam [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
117. Clonazepam [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.

118. Diazepam [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
119. Eslicarbazepine acetate [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
120. Galiana GL, Gauthier AC, Mattson RH. Eslicarbazepine acetate: a new improvement on a classic drug family for the treatment of partial-onset seizures. Drugs R D. 2017;17(3):329–39.
121. Mäkinen J, Rainesalo S, Peltola J. Transition from oxcarbazepine to eslicarbazepine acetate: A single center study. Brain Behav. 2017;7(3):1–6.
122. Ethosuximide [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
123. Felbamate [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
124. Lagae L, Sullivan J, Knupp K, Laux L, Polster T, Nikanorova M, et al. Fenfluramine hydrochloride for the treatment of seizures in Dravet syndrome: a randomised, double-blind, placebo-controlled trial. Lancet. 2019;394(10216):2243–54.
125. Fosphenytoin [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
126. Gabapentin [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
127. Lacosamide [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
128. Wechsler RT, Yates SL, Messenheimer J, Leroy R, Beller C, Doty P. Lacosamide for uncontrolled primary generalized tonic-clonic seizures: An open-label pilot study with 59-week extension. Epilepsy Res. 2017;130:13–20.
129. Hwang ST, Stevens SJ, Fu AX, Proteasa SV. Intractable generalized epilepsy: therapeutic approaches. Curr Neurol Neurosci Rep. 2019;19(4):16.
130. Morris GL, Hammer AE, Kustra RP, Messenheimer JA. Lamotrigine for patients with juvenile myoclonic epilepsy following prior treatment with valproate: Results of an open-label study. Epilepsy Behav. 2004;5(4):509–12.
131. Lamotrigine [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
132. Biraben A, Allain H, Scarabin JM, Schück S, Edan G. Exacerbation of juvenile myoclonic epilepsy with lamotrigine [5]. Neurology. 2001;56(10):1424–5.
133. Levetiracetam [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
134. Lorazepam [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
135. Oxcarbazepine [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
136. Phenytoin [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
137. Primidone [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
138. Rufinamide [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
139. Tiagabine [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.
140. Valproate [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021. Available from: https://online.lexi.com.

141. Maguire MJ, Hemming K, Wild JM, Hutton JL, Marson AG. Prevalence of visual field loss following exposure to vigabatrin therapy: A systematic review. Epilepsia. 2010;51(12):2423–31.
142. Zonisamide [Internet]. Lexi-Drugs, Pediatric and Neonatal. Hudson, Ohio: UpToDate, Inc.; 2021 [cited 2021 Feb 8]. Available from: https://online.lexi.com.

# Non-epileptic Paroxysmal Events

8

Amy Armstrong-Javors

## Neonates

Differentiating between normal and abnormal neonatal behaviors can be quite challenging, even for the experienced neurologist. The initial movements of newborns are typically described as "writhing" and subsequently evolve into "fidgety" movements by 6–9 weeks [1]. These motor patterns then resolve by 20 weeks as motor control improves. It is important to remember that 90% of abnormal movements in neonates are non-epileptic [2]. However, seizures in neonates can lead to poor outcome, especially if not identified early. See Table 8.1.

## Apnea

Apnea in the newborn is defined as 20 or more seconds of breathing cessation. It is particularly common in premature neonates who have immature central regulatory control of breathing. Non-epileptic apnea often coincides with bradycardia [3]. Apnea with tachycardia is more commonly associated with seizures. Ictal apnea is often accompanied by tonic extension of the limbs, abnormal eye, or mouth movements [4]. Apnea is not commonly the only symptom of seizure in a full-term newborn, but it does occur on occasion and there should be a low threshold for further work-up.

**Supplementary Information** The online version of this chapter (https://doi.org/10.1007/978-3-319-08290-5_8) contains supplementary material, which is available to authorized users.

A. Armstrong-Javors (✉)
Division of Pediatric Neurology, Massachusetts General Hospital, Boston, MA, USA
e-mail: AARMSTRONG-JAVORS@partners.org



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_8

**Table 8.1** Non-epileptic paroxysmal events in neonates

| Event | Age range (peak age of onset) |
|---|---|
| Apnea | All, mostly premature infants |
| Jitteriness | Birth–10.5 months (0–7 days) |
| Benign neonatal sleep myoclonus | 1 day–10 months (1–16 days) |
| Hyperekplexia | Birth–Infant (birth) |
| Hemifacial spasm | All ages (birth) |

## Jitteriness

Jitteriness is very common in healthy neonates but can be present in those with hypoxic ischemic encephalopathy, metabolic derangements (hypoglycemia or hypocalcemia) or intrauterine drug exposure. Jittery movements are typically described as low amplitude, oscillating tremors in the extremities. The chin can also be involved. Head and eye movements are not typically present. Jittery movements are most commonly observed in active or crying infants [5]. Episodes of jitteriness are often provoked by tactile or auditory stimuli and can be extinguished by removal of the trigger, restraint and/or swaddling. Appropriate treatment of metabolic derangements and drug withdrawal alleviates jitteriness in relevant cases. Of note, jitteriness can begin during or after the neonatal period and persist through infancy, with an average age of resolution of 7 months [6]. Development is typically normal when jitteriness is idiopathic.

## Benign Neonatal Sleep Myoclonus

Benign neonatal sleep myoclonus consists of repetitive jerking limb movements that occur during non-REM sleep in the first several weeks of life and disappear by 10 months of age [7] (Video 8.1). The myoclonic jerks can involve arms or legs and can be symmetric and rhythmic or multifocal and migratory. The myoclonus can occur in clusters. The movements are characteristically terminated by arousal from sleep. A normal neurological exam and development, as well as the absence of autonomic changes during myoclonic jerks, are supportive of this benign diagnosis. EEG is normal.

## Hyperekplexia

Hyperekplexia is a rare genetic disorder presenting at birth with generalized stiffness, myoclonus, and an exaggerated startle [8]. Since hypoxic brain injury can occur due to episodes of apnea related to severe uninterrupted tonic spasms, an accurate early diagnosis is critical. [9, 10] Episodes of tonic extension are often provoked by arousal, verbal, or tactile stimuli and can be relieved with neck or hip flexion, distinguishing them from epileptic seizures [11]. Tonic spasms can be provoked by tapping on the nose or forehead. Toddlers with hyperekplexia are often delayed in walking due to frequent falls from exaggerated startle [12]. In these

cases, a detailed history with the onset of symptoms at birth will suggest a diagnosis of hyperekplexia rather than atonic seizures.

### Hemifacial Spasm

Hemifacial spasm is a very rare, sometimes congenital, condition. It is more common in adults. This movement disorder is characterized by involuntary brief clonic or less commonly tonic spasms of the muscles near the eye, usually unilaterally. Facial nerve involvement increases over time, resulting in a larger area of unilateral facial spasm [13]. Eyelid blinking and, less frequently, hyperventilation, breathing irregularities, dystonia, or nystagmus can also be seen. Most pediatric cases present at birth, though onset in infancy and childhood has been reported [14]. The majority of cases are associated with an underlying intracranial mass, typically in the cerebellum or fourth ventricle [15].

## Infants

Seizure-mimics in infants tend to be benign, although they can be difficult to differentiate from epileptic events in many cases. See Table 8.2.

### Breath Holding Spells

Breath holding spells, which typically begin between 6 and 18 months of age, are typically provoked by crying in response to frustration, anger, or a minor injury. Crying precedes apnea, which usually occurs at the end of expiration, followed by color change. Spells can be either cyanotic or pallid. During cyanotic spells, color change appears rapidly and is followed by complete loss of tone and

**Table 8.2** Non-epileptic paroxysmal events in infants

| Event | Age range (peak age of onset) |
|---|---|
| Breath-holding spells | 6 months–6 years (6–18 months) |
| Sandifer syndrome | Pre-school age |
| Benign myoclonus of infancy | 3 months–3 years (4–7 months) |
| Benign paroxysmal torticollis in infancy | 1 week–3 years (5–7 months) |
| Shuddering attacks | Infant |
| Stereotypy/rhythmic movement disorder | All ages (9 months–4 years) |
| Infantile self-gratification | 2 months–3 years (4–13 months) |
| Alternating hemiplegia of childhood | 3 months–adult (< 18 months) |
| Paroxysmal extreme pain syndrome | Neonatal–adult (infancy) |
| Ocular phenomena | |
| Oculomotor apraxia | Neonatal–Infancy |
| Spasmus nutans | 2 months–5 years (4–12 months) |
| Opsoclonus-myoclonus | 6–36 months (6–18 months) |

unresponsiveness. Tonic posturing, clonic, or myoclonic movements are common during the loss of consciousness. Pallid spells are less common and may similarly accompanied by abnormal motor activity [16]. These spells are often initiated by a minor head trauma. Initial apnea, pallor, diaphoresis, and hypotonia quickly evolve into hypertonia, occasionally with urinary incontinence or clonic movements.

Breath-holding spells have an identifiable trigger, which distinguishes them from seizures. While children may be tired or frightened after the spells, true post-ictal confusion or mental status changes are not observed. An EKG during breath-holding episodes reveals sinus bradycardia and even periods of asystole [17].

A positive family history is present in over a quarter of patients. Treatment of iron deficiency, which is more common in these children, can reduce the frequency and severity of cyanotic episodes [18]. A ferritin level should be checked and treatment with iron supplementation should be initiated for a ferritin level < 50 ug/L. Despite the frightening nature of breathing holding spells, neurologic development is normal, and children outgrow these spells by 4–5 years of age.

## Stereotypies/Rhythmic Movement Disorder

Stereotypies are rhythmic and stereotyped movements that typically present prior to age 3. They are particularly common in children with autism or developmental delays but occur in typically developing children as well. A family history and association with ADHD and learning disability is present in up to 25% [19]. Children often perform these movements when anxious or excited, but they can also be seen in times of boredom, intense focus, or just prior to sleep. [20, 21]

The most common stereotypies are hand flapping, head banging, head rolling, tensing up of the extremities, and body rocking (Videos 8.2 and 8.3). The movements typically last seconds to minutes. In Rett syndrome, hand-wringing and flapping stereotypies are very common [22]. Unlike seizures, stereotypies are suppressible and terminate with distraction [ 23]. In developmentally typical children, stereotypies often resolve by age 4–6.

## Sandifer Syndrome

Sandifer syndrome is an uncommon response to gastroesophageal reflux involving paroxysmal episodes of stiffening, dystonia, and/or opisthotonic posturing. There can be associated bradycardia due to triggering of the vagal reflex [24]. Episodes often occur within 30 minutes after a meal and can involve staring, head/eye version, and subtle jerking. [25, 26] A temporal relationship to eating and lack of mental status changes suggest a non-epileptic etiology. The precise pathophysiology of these movements is not well understood.

## Benign Myoclonus of Infancy

Benign myoclonus of infancy is characterized by repetitive myoclonic jerks [27]. Initially the myoclonus appears very similar to that of infantile spasms, a potentially devastating epilepsy syndrome, and also cannot be suppressed by gentle pressure. [28, 29] Symmetric bilateral upper extremity jerks are most common, but the trunk and legs can be involved. Benign myoclonus is a diagnosis of exclusion; EEG is typically performed to rule out infantile spasms or myoclonic seizures [7]. The peak age onset is 3–9 months and symptoms typically resolve within 8 months, although cases with symptoms lasting 1–2 years have been reported [30].

## Benign Paroxysmal Torticollis

Benign paroxysmal torticollis of infancy involves sustained episodes of neck and head deviation to one side with the face deviated toward the other side. Episodes can last minutes to days and are associated with a family history of migraine [ 31]. The child is alert and responsive throughout the episodes, which are self-resolving and typically dissipate by 3 years of age [32]. The prolonged duration of episodes and the lack of mental status changes help differentiate these spells from seizures. Many children with benign paroxysmal torticollis develop typical migraine headaches later in life.

## Shuddering Attacks

Shuddering attacks are a benign movement disorder involving repetitive 5–15 second episodes of rapid tremor/shiver of the head and shoulders, often with stiffening and elevation of the arms, staring, and leaning to one side [33]. They most often occur during feeding, when excited or upset. They do not occur during sleep. Consciousness is preserved during episodes, distinguishing them from seizures. Onset is usually in infancy and symptoms can persist throughout early childhood but resolve by the second decade of life [34].

## Infantile Self-Gratification

Infantile self-gratification/masturbation can start in infants as young as 2–3 months but is most common in late infancy/early toddler stage. More common in females, this disorder is characterized by rocking against a car seat, rubbing their legs together, or making pelvic movements [35] (Video 8.4). Children may be flushed, grunting, or breathing irregularly, and are typically less aware of their surroundings. Unlike seizures, children can stop the behaviors on command [36]. This is a benign, self-limited condition and within the realm of normal development.

## Spasmus Nutans

Spasmus nutans is a rare, self-limited condition presenting between 4 and 18 months of age involving asymmetric pendular nystagmus, torticollis, and head nodding, which can fluctuate throughout the day. Not all cases have all three clinical features. While the movements can be reminiscent of seizures, the absence of mental status changes and nearly continuous nature of symptoms is distinct. [37, 38] In rare cases, similar symptoms can be due to an intracranial mass. A careful history and examination can determine whether brain imaging is necessary.

## Opsoclonus-Myoclonus Ataxia Syndrome

Opsoclonus-myoclonus ataxia syndrome is a rare condition in children which is most commonly associated with neuroblastoma. Symptoms of ataxia, myoclonus, abnormal eye movements ("dancing eyes"), irritability, and sleep disturbance are present and can be confused with seizure [39] (Video 8.5). The sub-acute progression of symptoms, characteristic eye movements, and sustained ataxia are not consistent with seizures. This syndrome is thought to be caused by an autoimmune reaction (either to a tumor or infection) that produces antibodies to cerebellar epitopes.

## Oculomotor Apraxia

In oculomotor apraxia, which is uncommonly confused with seizure, infants have impaired horizontal saccades and as a result make sudden rapid head movements, called head thrusts, to track objects [40]. Roughly one quarter of cases are idiopathic and associated only with developmental delay but no other neurologic anomalies [41]. The remainder of cases are associated with more widespread neurological disorders, including ataxia telangiectasia, lysosomal storage disorders, or Joubert syndrome. [42–44]

## Benign Paroxysmal Tonic Upgaze

This rare condition consists of episodes of sustained upgaze in infants and young children. Episodes of upgaze occur frequently and are of brief duration (10–30 seconds) (Video 8.6). There is often a compensating downward head tilt and downbeating nystagmus. Paroxysmal ataxia is present in up to 40%. Though the condition resolves completely in 50% of patients over several years, some children with the condition have a concomitant learning disability, persistent ataxia, or oculomotor symptoms [45]. Rarely this disorder can be secondary to structural abnormalities including periventricular leukomalacia, vein of Galen aneurysm, and pineal gland tumors [46]. The pathophysiology of this condition is not well understood.

### Alternating Hemiplegia of Childhood

This is a rare progressive disorder presenting before 18 months in which children have abrupt episodes of hemiplegia, often accompanied by abnormal eye movements, ataxia, or dystonia, which all resolve with sleep. In most patients, the eye movements start within the first 3 months of life [47]. Seizures occur in 50% of patients later in life, but early features of the condition can be confused with seizures as well. Most cases are caused by de novo mutations in the ATP1A3 gene [48].

### Paroxysmal Extreme Pain Disorder

This channelopathy is often first manifested in neonates and infants who have severe, burning rectal pain and present with spells of autonomic instability and tonic stiffening, sometimes with resultant bradycardia, syncope, and even asystolic cardiac arrest [49]. Older children are able to describe the pain, clarifying the diagnosis. This is a very rare condition.

## School-Aged Children

Benign paroxysmal non-epileptic events are very common in children. Children with epilepsy can also have non-epileptic events, clouding the picture. Distinguishing between the two can be very challenging and may require work-up including EEG and imaging in addition to a detailed history and clinical exam (Table 8.3).

### Tic Disorders

Tics are sudden, repetitive, stereotyped involuntary movements or vocalizations. They are very common, occurring in 6–12% of school-aged children.

**Table 8.3** Non-epileptic paroxysmal events in school-aged children

| Event | Age range (peak age of onset) |
|---|---|
| Non-epileptic staring spells | All (5 years) |
| Syncope (vasovagal, convulsive) | Childhood–adulthood (adolescence) |
| Parasomnias: | |
| Sleepwalking | 4 years–adulthood (8–12 years) |
| Night terrors | 1.5–12 years (5–7 years) |
| Confusional arousal | 3–13 years (2.5–5 years) |
| Tic disorders | 3 years–adulthood (6–10 years) |
| Tourette syndrome | 3 years–adulthood (6–10 years) |
| Benign paroxysmal vertigo | 2–10 years (2–4 years) |
| Migraine | 4 years–adulthood (7–11 years) |
| Acute confusional migraine | 7.5–17 years (11–12 years) |
| Stiff person syndrome | 1–14 years (5–11 years) |

Only a small percent develop a chronic tic disorder. Simple motor tics, such as blinking, grimacing, shrugging, or head jerking, can be confused for myoclonic jerks [50] (Video 8.7). Complex motor tics can involve unusual complex behaviors such as bending down and touching the floor. Common vocal tics include throat clearing, grunting, and sniffing. Words and sentences are less common; coprolalia is rare.

Unlike seizures, tics are suppressible and do not occur during sleep. Most children endorse an urge to perform the movement or sound and discomfort holding it in.

Patients who have vocal and motor tics that wax and wane for a period longer than 1 year are defined as having Tourette syndrome. ADHD, OCD, and other neuropsychiatric comorbidities are common in Tourette syndrome and are often more disruptive for patients than their tics [51].

## Behavioral Staring Episodes

Staring episodes are extremely common in children, particularly those with autism, developmental delay, ADHD, or behavioral problems [52]. Most commonly, staring spells are due to behavioral inattention or daydreaming. Apparent unresponsiveness can also be seen during periods of intense emotion, such as anger or fear [53]. Behavioral staring episodes can be interrupted by touch, usually occur during passive activities (i.e., sitting in class or watching television), and do not interrupt activities. The presence of specific motor automatisms, such as lip smacking, blinking, or swallowing, in addition to altered responsiveness, is highly suggestive of seizures [54].

## Parasomnias

The most common parasomnias seen in children are disorders of arousal. These conditions, which typically occur in infants and school-aged children, involve partial arousal from non-REM sleep, typically within the first 60–120 minutes after sleep onset.

### Confusional Arousals and Night Terrors

Confusional arousals are common in infants and toddlers. Children usually abruptly sit up in bed, appear distressed, whimper, or mumble softly [55]. Night terrors are very similar to confusional arousals but more intense; children wake up screaming and agitated. During these episodes, sweating, facial flushing, and stereotyped movements can be seen [56]. Some children even run from the room as if being chased. Attempts to console the child are futile and may even exacerbate their agitation.

### Sleepwalking

Sleepwalking is most common in 8 to 12-year-olds but can present in younger children and persist through adulthood [57]. Episodes can range from crawling around

one's bed to going outside, even during dangerous weather conditions. Children often have a blank stare and move slowly and deliberately. Flushing and sweating can also be seen [58].

In all three above-described parasomnias, unresponsiveness can last minutes to an hour, after which the child falls back to sleep. The child typically has no memory of the episode in the morning [59]. Waking the child up prior to the typical time of onset of spells can prevent the parasomnias from occurring.

Nocturnal frontal lobe seizures can look very similar to arousal disorders. Frontal lobe seizures are typically shorter in duration than parasomnias and occur multiple times per night. Nocturnal seizures generally are associated with stereotyped movements or dystonic posturing. As with seizures, there appears to be a genetic predisposition to parasomnias. Like seizures, episodes can also be triggered by sleep deprivation and fever.

## Confusional Migraine

Confusional migraines are a rare migraine variant characterized by agitation, disorientation, and aphasia, which may continue even after the headache has resolved [60]. This migraine variant is most common in younger, school-aged children. Minor head trauma has been described as a trigger in half of the cases reported [61, 62]. There is often a strong family history of migraines, and most children go on to develop more typical migraines later in life.

## Syncope

Syncope involves a sudden decrease in cerebral perfusion leading to loss of muscle tone and consciousness. Vasovagal syncope is common in people of all ages, including children and adolescents.

### Vasovagal Syncope

In vasovagal syncope, an increase heart rate leads to an increase in vagal tone, causing reflex bradycardia, vasodilation, and transient reduction in cerebral perfusion. Triggers include pain, dehydration, high temperatures, sleep deprivation, postural changes, prolonged standing or immobility, emotional upset, the sight of blood, and micturition [63]. A prodrome of lightheadedness, palpitations, dimming or tunnel vision, nausea, pallor, and changes in hearing is common. Once a child has fainted, myoclonic jerks of the extremities, at times rhythmic and synchronous, are commonly seen. Abnormal eye movements such as eye rolling and deviation are also common [63]. Convulsive syncope, as this is called, can be easily confused with tonic-clonic seizures. The most helpful factors in distinguishing between the two are the typical prodromal symptoms and the absence of a post-ictal state in syncope. Urinary incontinence can occur in both disorders; tongue biting is rare in syncope but is reported.

### Cardiac Syncope

Cardiac syncope involves reduced cerebral perfusion due to a cardiac dysfunction, most frequently from an arrhythmia or hypertrophic cardiomyopathy. Cardiac syncope should be suspected in children with a history of exercise-induced syncope or syncope when supine. A family history of cardiac dysrhythmias or sudden cardiac death should raise suspicion for a cardiac cause. In cardiac syncope, the typical presyncopal symptoms associated with vasovagal syncope are absent [64].

### Other Types of Syncope

Syncope can occur in the context of hyperventilation followed by Valsalva maneuvers, which occurs in some children with intellectual disability, particularly in girls with Rett syndrome [65]. Syncope due to neurologic conditions can be seen in patients with Chiari I malformations, hyperekplexia, and paroxysmal extreme pain disorder [66]. Cyanotic spells, which occur most commonly in Tetrology of Fallot, involve sudden panic, tachypnea, and cyanosis, in some cases leading to loss of tone and convulsive syncope [67]. Finally, postural orthostatic tachycardia syndrome (POTS) is a condition in adolescents in which profound orthostatic intolerance leads to recurrent syncope when changes in position occur [68].

## Benign Paroxysmal Vertigo

This is a migraine-related syndrome characterized by episodes of vertigo commonly associated with nystagmus, pallor, diaphoresis, nausea, and vomiting. A fearful expression often signals the start of an episode of benign paroxysmal vertigo, which can be confused with temporal lobe epilepsy. Episodes of vertigo often first present in children aged 1–3 years old and remit by age 5–8 years. Episodes are brief, lasting less than 1 minute but can occur in clusters. There is no change in mental status.

## Episodic Ataxias

Episodic ataxias are rare autosomal dominant channelopathies occurring in children. In episodic ataxia type 1, illness, strong emotions, or sudden movements can elicit brief episodes of cerebellar ataxia characterized by dysarthria, head tremor, and movements that resemble dystonia or chorea [69]. Episodic ataxia 1 is caused by mutations in KCNA1, a potassium channel gene.

In episodic ataxia type 2, episodes of ataxia, nystagmus, dysarthria, vertigo, and headache are triggered by physical or emotional stress [70]. Though seizures occur in 10%, the predominant movements associated with this condition can be distinguished from seizure when a careful history is obtained. Additionally, preserved awareness and recognition of triggers helps differentiate between ataxic episodes and seizures. Episode ataxia 2 is caused by mutations in CACNA1A, which encodes P/Q type calcium channels.

### Stiff Person Syndrome

Stiff person syndrome is a rare disorder involving severe muscle spasms and stiffness, beginning in the axial muscles and then spreading to proximal muscles. Rigidity is so pronounced that fixed cervical or lumbar spinal deformities can occur. Muscle spasms, which are triggered by noise, emotion, or sudden movement, can be strong enough to fracture bones [71]. These abrupt spasms have been confused with stimulus-induced seizures, but the spasms are painful and sustained [72]. Stiff person syndrome is thought to have an autoimmune etiology, with correlations with diabetes mellitus type 1, thyroid disease, and vitiligo in children. Glutamic acid decarboxylase antibodies are frequently positive [73].

## Adolescents (Tables 8.4)

### Migraine with Aura

The migraine aura, which can consist of visual phenomena and often bizarre sensory illusions or perceptions, can be confused with temporal or occipital lobe seizures [74]. Importantly, headaches rarely trigger or precede seizures but are common post-ictally.

### Basilar Migraine

Basilar migraine is a subtype of migraine with aura that may be easily mistaken for seizure or a post-ictal period. Common symptoms, which typically last 1 hour, include tinnitus, dysarthria, vertigo, visual disturbance, hyperacusis, and paresthesias. [75, 76] Confusion and altered consciousness also occur; complete loss of

**Table 8.4** Non-epileptic paroxysmal events in adolescents

| Event | Age range (peak age of onset) |
|---|---|
| Syncope | All (adolescence) |
| Migraines | 4 years–adulthood (adolescence) |
| Basilar migraine | 7–20 years (adolescence) |
| Familial hemiplegic migraine | 1 year–adulthood (12–17 years) |
| Tic disorders | 2 years–adulthood (3–9 years) |
| Periodic limb movements of sleep | 5 years–adulthood (adolescence) |
| Narcolepsy | 5 years–adulthood (14–16 years) |
| Paroxysmal dyskinesia | 4 months–adulthood (5–15 years) |
| Psychiatric conditions | |
| Psychogenic nonepileptic seizures | 5 years–adulthood (adolescents) |
| Panic attacks | 4 years–adulthood (15–19 years) |
| Hallucinations | 4 years–adult (adolescents) |
| Intermittent explosive disorder | 6 years–adulthood (13–21 years) |
| Sleep starts/hypnic jerks | All ages |

consciousness is described in one quarter of patients [77]. Headache occurs after aura in the majority of patients, and ultimately the symptoms resolve completely. As with confusional migraines in younger children, there is often a strong family history of migraine.

### Familial Hemiplegic Migraine

Another subtype of migraine with aura, familial hemiplegic migraine is a channelopathy characterized by unilateral weakness and often paresthesias, speech disturbance, and visual changes which precede headaches [78, 79]. There is often a family history of hemiplegic migraines, and the symptom progression can help distinguish these episodes from seizures. Familial hemiplegic migraine has been associated with mutations in several genes, the most common of which is CACNA1A, which encodes a calcium channel.

### Syncope

Syncope is very common in adolescent females. Female sex hormones are thought to play a role, with a possible reduction in vascular tone and a slower response to orthostatic changes. Like in younger children, there are numerous triggers for vasovagal syncope. Adolescents commonly faint in response to strong emotions or pain. [80, 81] For further details on syncope, please refer to prior section on syncope in children.

### Sleep Starts/Hypnic Jerks

Sleep starts, or hypnic jerks, are very common and can occur at any age. Sudden jerking of the extremities occurs upon falling asleep. Confusion between these episodes and myoclonic or even tonic-clonic seizures can occur when sleep starts are repetitive or violent [21]. However, they can be distinguished from seizures by occurrence only during sleep-wake transitions and absence of other clinical features of seizures. Hypnic jerks resolve with awakening.

### Periodic Leg Movements of Sleep

Periodic leg movements of sleep (PLMS) are frequent repetitive leg movements. They are a normal feature of sleep but in some patients can be excessive and associated with arousals and disturbed sleep. PLMS are often excessive in patients with restless leg syndrome [82]. An association has been made between PLMS and ADHD, anxiety, depression, and parasomnias. Unlike with seizures, these nocturnal

movements consist of regular 20–40 second intervals of toe extension and ankle, knee, and hip flexion and do not involve the arms or face [83].

## Psychiatric Conditions

### Psychogenic Nonepileptic Seizures

Psychogenic nonepileptic seizures (PNES) are a form of functional neurological disorder seen in children as young as 5 years but more commonly in adolescents. [84, 85] PNES involve reduced levels of consciousness, with complete unresponsiveness in one third, and seizure-like movements. The movements most commonly resemble tonic-clonic seizures, but without accompanying electrophysiologic changes. Episodes are often seen in patients with a history of difficulties in school or at home, fear of rejection, or physical or sexual abuse [86]. There is a strong association with mental health problems, typically anxiety, depression, and post-traumatic stress disorder. Children have a much better prognosis than adults, especially if the diagnosis is made early and the appropriate psychiatric interventions are initiated. [87, 88]

The challenge in diagnosing PNES is that episodes can sometimes very closely resemble seizures, and a large proportion of children with PNES also suffer from epilepsy [89]. To complicate matters further, PNES episodes in children with epilepsy resemble their own seizures nearly 50% of the time. Findings most suggestive of PNES are unusual clinical features (tremor, thrashing, pelvic thrusting, swooning), increased frequency with stress, forced eye closure, absence of lateral tongue biting, and refractoriness to anti-epileptic medications (Video 8.8). Over ¾ of episodes are witnessed by a family member or physician [90]. The correct diagnosis is often suspected based on the observation of an episode and confirmed by lack of electrographic seizure activity on video electroencephalography.

### Panic Disorder

In panic disorder, patients experience hyperventilation, severe anxiety, dyspnea, and palpitations. Tremor or carpo-pedal spasm can occur. A sense of fear or impending doom as well as the often sudden and unprovoked nature of episodes can be confused with temporal lobe epilepsy. [91, 92] Pseudoabsence, in which the adolescent stares blankly, can be confused with true absence epilepsy [93]. Unlike seizures, however, the patient is still responsive during episodes of panic, which are non-stereotyped, long-lasting, and are not associated with post-ictal confusion.

### Intermittent Explosive Disorder

School-aged children or adolescents with intermittent explosive disorder demonstrate abrupt onset of rage that can occur with or without obvious provocation. Episodes can be confused with temporal lobe epilepsy [94]. Unlike epilepsy, however, the anger and violence are often specific and directed [95]. A post-ictal state is not present, although the child is commonly tired once the episode ends. The duration is typically longer than typical for a seizure.

## Narcolepsy with Cataplexy

Cataplexy is characterized by abrupt loss of muscle tone triggered by laughing or other changes in emotional state. Cataplexy can appear similar to atonic seizures [96]. However, further history reveals excessive daytime sleepiness, rapid transitions to sleep, hypnagogic/hypnopompic hallucinations, and sleep paralysis in narcoleptic patients.

## Paroxysmal Dyskinesias

Paroxysmal dyskinesias are a rare group of abnormal movement disorders that may be characterized by ballism, dystonia, or choreoathetosis (Video 8.9). They can be sporadic, familial, or secondary to another medical condition [97]. Paroxysmal kinesigenic dyskinesia, the most common condition in this group of disorders, involves brief episodes of choreoathetosis and/or dystonia triggered by sudden movements. The patient is fully aware during the episodes [98]. Paroxysmal nonkinesigenic dyskinesia is characterized by longer episodes of severe dystonia triggered by alcohol, caffeine, fatigue, or stress. In paroxysmal exercise-induced dyskinesias, the muscle being exercised suddenly becomes dystonic within the first several minutes of exercise. The movement disorder abates gradually when exercise stops.

Prevalence of non-epileptic paroxysmal events

| **Most Common (>10% prevalence)** |
|---|
| *Neonates* |
| Apnea |
| Jitteriness |
| Benign neonatal sleep myoclonus |
| *Infants* |
| Breath-holding spells |
| Stereotypies |
| *Children* |
| Breath-holding spells |
| Tic disorders |
| Parasomnias (sleepwalking, night terrors, confusional arousals) |
| Non-epileptic staring spells |
| Hallucinations |
| *Adolescents* |
| Sleep starts |
| Tic disorders |
| Syncope (vasovagal, convulsive) |

(continued)

**Less Common (1–10% prevalence)**
- *Infants*
  - Sandifer syndrome
  - Benign myoclonus of infancy
  - Shuddering attacks
  - Infantile self-gratification
- *Children*
  - Syncope (vasovagal, convulsive)
  - Migraine with aura
- *Adolescents*
  - Psychogenic non-epileptic seizures
  - Migraine with aura
  - Hallucinations
  - Periodic limb movements of sleep
  - Panic attacks
  - Intermittent explosive disorder

**Uncommon/rare (<1% prevalence)**
- *Neonates*
  - Hemifacial spasm
  - Hyperekplexia
- *Infants*
  - Benign paroxysmal torticollis of infancy
  - Opsoclonus-myoclonus
  - Spasmus nutans
  - Oculomotor apraxia
  - Paroxysmal extreme pain syndrome
  - Alternating hemiplegia of childhood
- *Children*
  - Benign paroxysmal vertigo
  - Cardiogenic syncope
  - Stiff person syndrome
- *Adolescents*
  - Tourette syndrome
  - Familial hemiplegic migraine
  - Narcolepsy
  - Paroxysmal dyskinesia

Specific seizure mimics

| **Generalized seizures** |
|---|
| Myoclonic |
| Neonates: |
| Jitteriness |
| Benign neonatal sleep myoclonus |
| Hyperekplexia |
| Hemifacial spasm |
| Infants: |
| Benign myoclonus/sleep myoclonus of infancy |
| Hemifacial spasm |
| Opsoclonus myoclonus |
| Stereotypies/rhythmic movement disorders of sleep |
| Shuddering attacks |
| Children: |
| Stiff person syndrome |
| Tic disorders |
| Adolescents: |
| Tic disorders/Tourette syndrome |
| Narcolepsy/cataplexy |
| Sleep starts |
| Tonic-clonic convulsions |
| Neonates: |
| Hyperekplexia |
| Benign neonatal sleep myoclonus |
| Infants: |
| Benign sleep myoclonus |
| Breath-holding spells |
| Children: |
| Vasovagal, convulsive syncope |
| Adolescents: |
| Psychogenic non-epileptic seizures |
| Tonic |
| Neonates: |
| Hyperekplexia |
| Infants: |
| Sandifer syndrome |
| Breath-holding spells |
| Paroxysmal extreme pain syndrome |
| Children: |
| Syncope |
| Alternating hemiplegia of childhood |
| Stiff person syndrome |
| Dystonia |
| Benign paroxysmal torticollis |
| Atonic |
| Adolescents: |
| Narcolepsy/cataplexy |

(continued)

- Absence
  - Infants:
    - Infantile self-gratification
    - Shuddering attacks
  - Children:
    - Behavioral staring spells
  - Adolescents:
    - Narcolepsy/cataplexy
- **Focal seizures**
- Occipital lobe
  - Children/adolescents:
    - Migraine with visual aura
- Temporal lobe
  - Infants:
    - Stereotypies
    - Night terrors
    - Confusional arousals
  - Adolescents:
    - Basilar-type migraine
    - Panic disorder
    - Hallucinations
    - Narcolepsy
    - Intermittent explosive disorder
- Frontal lobe
  - Infants:
    - Confusional arousals
  - Children:
    - Paroxysmal kinesigenic dyskinesia
  - Adolescents:
    - Psychogenic non-epileptic seizures
- Not lobe specific:
  - Neonates:
    - Hemifacial spasm
  - Infants:
    - Shuddering attacks
    - Infantile self-gratification
    - Confusional arousals
  - Children:
    - Tic disorders/Tourette syndrome
    - Benign paroxysmal vertigo
    - Acute confusional migraine
    - Alternating hemiplegia of childhood
    - Paroxysmal non-kinesigenic dyskinesia
  - Adolescents:
    - Tic disorders/Tourette syndrome
    - Basilar-type migraine
    - Periodic limb movements of sleep
    - Psychogenic non-epileptic seizures
    - Narcolepsy/cataplexy

## References


1. Volpe JJ. Neurology of the newborn. 4th ed. Philadelphia: WB Saunders Co; 2001.
2. Scher MS, Painter MJ. Controversies concerning neonatal seizures. Pediatr Clin N Am. 1989;36(2):281.
3. Fenichel GM, Olson BJ, Fitzpatrick JE. Heart rate changes in convulsive and nonconvulsive neonatal apnea. Ann Neurol. 1980;7(6):577.
4. O'Regan ME, Brown JK. Abnormalities in cardiac and respiratory function observed during seizures in childhood. Dev Med Child Neurol. 2005;47(1):4.
5. Parker S, Zuckerman B, Bauchner H, Frank D, Vinci R, Cabral H. Jitteriness in full-term neonates: prevalence and correlates. Pediatrics. 1990;85(1):17.
6. Shuper A, Zalzberg J, Weitz R, Mimouni M. Jitteriness beyond the neonatal period: a benign pattern of movement in infancy. J Child Neurol. 1991;6(3):243.
7. Paro-Panjan D, Neubauer D. Benign neonatal sleep myoclonus: experience from the study of 38 infants. Eur J Paediatr Neurol. 2008;12(1):14.
8. Bakker MJ, van Dijk JG, van den Maagdenberg AM, Tijssen MA. Startle syndromes. Lancet Neurol. 2006;5(6):513.
9. Giacoia GP, Ryan SG. Hyperekplexia associated with apnea and sudden infant death syndrome. Arch Pediatr Adolesc Med. 1994;148(5):540.
10. Mineyko A, Whiting S, Graham GE. Hyperekplexia: treatment of a severe phenotype and review of the literature. Can J Neurol Sci. 2011;38(3):411–6.
11. Praveen V, Patole SK, Whitehall JS. Hyperekplexia in neonates. Postgrad Med J. 2001;77(911):570.
12. Zhou L, Chillag KL, Nigro MA. Hyperekplexia: a treatable neurogenetic disease. Brain and Development. 2002;24(7):669.
13. Chaundhry N, Srivastava A, Joshi L. Hemifacial spasm: the past, present and future. J Neurol Sci. 2015;356(1–2):27–31.
14. Singer C, Pappetropoulos S, Farronay O. Childhood-onset hemifacial spasm: successful treatment with botulinum toxin. Pediatr Neurol. 2005;33(2):220–2.
15. Tan NC, Chan LL, Tan EK. Hemifacial spasm and involuntary facial movements. QJM. 2002;95(8):493.
16. DiMario FJ Jr. Prospective study of children with cyanotic and pallid breath-holding spells. Pediatrics. 2001;107(2):265.
17. Breningstall GN. Breath-holding spells. Pediatr Neurol. 1996;14(2):91.
18. Orii KE, Kato Z, Osamu F, Funato M, Kubodera U, Inoue R, Shimozawa N, Kondo N. Changes of autonomic nervous system function in patients with breath-holding spells treated with iron. J Child Neurol. 2002;17(5):337.
19. Harris KM, Mahone M, Singer HS. Nonautistic motor stereotypies: clinical features and longitudinal follow-up. Pediatr Neurol. 2008;38(4):267–72.
20. Manni R, Terzaghi M. Rhythmic movements during sleep: a physiological and pathological profile. Neurol Sci. 2005;26(Suppl 3):s181.
21. Walters AS. Clinical identification of the simple sleep-related movement disorders. Chest. 2007;131(4):1260.
22. Ghosh D, Rajan PV, Erenberg G. A comparative study of primary and secondary stereotypies. J Child Neurol. 2013;28(12):1562–8.
23. Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. Mov Disord. 2010;25(11):1538.
24. Frankel EA, Shalaby TM, Orenstein SR. Sandifer syndrome posturing: relation to abdominal wall contractions, gastroesophageal reflux, and fundoplication. Dig Dis Sci. 2006;51(4):635.
25. Kabakuş N, Kurt A. Sandifer syndrome: a continuing problem of misdiagnosis. Pediatr Int. 2006;48(6):622.
26. Sheikh S, Stephen TC, Sisson B. Prevalence of gastroesophageal reflux in infants with recurrent brief apneic episodes. Can Respir J. 1999;6(5):401.

27. Fusco L, Specchio N. Non-epileptic paroxysmal manifestations during sleep in infancy and childhood. Neurol Sci. 2005;26:s205–9.
28. Maurer VO, Rizzi M, Bianchetti MG, Ramelli GP. Benign neonatal sleep myoclonus: a review of the literature. Pediatrics. 2010;125(4):e919–24.
29. Caraballo RH, Capovilla G, Vigevano F, Beccaria F, Specchio N, Fejerman N. The spectrum of benign myoclonus of early infancy: clinical and neurophysiologic features in 102 patients. Epilepsia. 2009;50(5):1176.
30. Lombroso C. Early myoclonic encephalopathy, early infantile epileptic encephalopathy, and benign and severe infantile myoclonic epilepsies: a critical review and personal contributions. J Clinic Neurophys. 1990;7:380–408.
31. Cohen HA, Nussinovitch M, Ashkenasi A, Straussberg R, Kauschanksy A, Frydman M. Benign paroxysmal torticollis in infancy. Pediatr Neurol. 1993;9(6):488.
32. Drigo P, Carli G, Laverda AM. Benign paroxysmal torticollis of infancy. Brain and Development. 2000;22(3):169.
33. Holmes GL, Russman BS. Shuddering attacks. Evaluation using electroencephalographic frequency modulation radiotelemetry and videotape monitoring. Am J Dis Child. 1986;140(1):72.
34. Kanazawa O. Shuddering attacks-report of four children. Pediatr Neurol. 2000;23(5):421.
35. Jan MM, Al Banji MH, Fallatah BA. Long-term outcome of infantile gratification phenomena. Can J Neurol Sci. 2013;40:416–9.
36. Yang ML, Fullwood E, Goldstein J, Mink JW. Masturbation in infancy and early childhood presenting as a movement disorder: 12 cases and a review of the literature. Pediatrics. 2005;116(6):1427–32.
37. Delorme C, Gras D, Roze E. Spasmus nutans: more than meets the eye. Pediatr Neurol. 2015;53(4):367–8.
38. Chillag KL, Chillag EM. A child with benign neonatal jitteriness and spasmus nutans. J Child Neurol. 2014;29(2):247–8.
39. Singhi P, Sahu JK, Sarkar J, Bansal D. Clinical profile and outcome of children with opsoclonus-myoclonus syndrome. J Child Neurol. 2014;29(1):58–61.
40. Orssaud C, Ingster-Moati I, Roche O, Quoc EB, Dufier JL. Familial congenital oculomotor apraxia: clinical and electro-oculographic features. Eur J Paediatr Neurol. 2009;13(4):370–2.
41. Harris CM, Shawkat F, Russell-Eggitt I, Wilson J, Taylor D. Intermittent horizontal saccade failure ('ocular motor apraxia') in children. Br J Ophthalmol. 1996;80(2):151–6.
42. Phillips PH, Brodsky MC, Henry PM. Congenital ocular motor apraxia with autosomal dominant inheritance. Am J Ophthalmol. 2000;129:820–2.
43. Lewis RF, Lederman HM, Crawford TO. Ocular motor abnormalities in ataxia telangiectasia. Ann Neurol. 1999;46(3):287.
44. Papanagnu E, Klaehn LD, Bang GM, Ghadban R, Mohney BG, Brodsky MC. Congenital ocular motor apraxia with wheel-rolling ocular torsion-a neurodiagnostic phenotype of Joubert syndrome. J AAPOS. 2014;18(4):404–7.
45. Ozbay OE. Idiopathic paroxysmal tonic upward gaze. Pediatr Neurol. 2012;47(4):306–8.
46. Ouvrier R, Bilson F. Paroxysmal tonic upgaze of childhood—a review. Brain Dev. 2005;27:185–9.
47. Vila-Pueyo M, Pons R, Raspall-Chaure M, et al. Clinical and genetic analysis in alternating hemiplegia of childhood: ten new patients from southern Europe. J Neurol Sci. 2014;344(1):37–42.
48. Heinzen E, Swoboda K. De novo mutations in ATP1A3 cause alternating hemiplegia of childhood. Nat Genet. 2012;44:1030–4.
49. Beck J, Cramp P, Noden J. Paroxysmal extreme pain disorder. Br J Anaesth. 2013;110(5):850–1.
50. Sethi NK, Labar D, Torgovnick J. Myoclonic epilepsy masquerading as a tic disorder. Clin Neurol Neurosurg. 2007;109(6):509.
51. Pollak Y, Benarroch F, Kanengisser L, et al. Tourette syndrome-associated psychopathology: roles of comorbid attention-deficit hyperactivity disorder and obsessive-compulsive disorder. J Dev Behav Pediatr. 2009;30(5):413–9.

52. Hindley D, Ali A, Robson C. Diagnoses made in a secondary care "fits, faints, and funny turns" clinic. Arch Dis Child. 2006;91(3):214.
53. Bye AME, Kok DJM, Ferenschild FTJ, Vles JSH. Paroxysmal non-epileptic events in children: a retrospective study over a period of 10 years. J Paediatr Child Health. 2000;36:244–8.
54. Fejerman N. Nonepileptic disorders imitating generalized idiopathic epilepsies. Epilepsia. 2005;46(suppl 9):80–3.
55. Sheldon SH. Parasomnias in childhood. Pediatr Clin N Am. 2004;51(1):69.
56. Mason TB 2nd, Pack AI. Sleep terrors in childhood. J Pediatr. 2005;147(3):388.
57. Klackenberg G. Somnambulism in childhood–prevalence, course and behavioral correlations. A prospective longitudinal study (6-16 years). Acta Paediatr Scand. 1982;71(3):495–9.
58. Plazzi G, Vetrugno R, Provini F, Montagna P. Sleepwalking and other ambulatory behaviours during sleep. Neurol Sci. 2005;26(Suppl 3):s193.
59. Sheldon S, Ferber R, Kryger M and Gozalp D, editors. Principles and practice of pediatric sleep medicine. Philadelphia: Saunders; 2014. p. 313–320.
60. MacNeill EC, Vashist S. Approach to syncope and altered mental status. Pediatr Clin N Am. 2013;60(5):1083–106.
61. Teixeira KCS, Montenegro MA, Guerreiro MM. Migraine equivalents in childhood. J Child Neurol. 2014;29(10):1366–9.
62. Sheth RD, Riggs JE, Bodensteiner JB. Acute confusional migraine: variant of transient global amnesia. Pediatr Neurol. 1995;12(2):129.
63. Sheldon R, Rose S, Ritchie D, Connolly SJ, et al. Historical criteria that distinguish syncope from seizures. J Am Coll Cardiol. 2002;40(1):142.
64. MacCormick JM, McAlister H, Crawford J, French JK, Crozier I, Shelling AN, Eddy CA, Rees MI, Skinner JR. Misdiagnosis of long QT syndrome as epilepsy at first presentation. Ann Emerg Med. 2009;54(1):26.
65. David JE, Yale SH, Vidaillet HJ. Hyperventilation-induced syncope: no need to panic. Clin Med Res. 2003;1(2):137.
66. Ireland PD, Mickelsen D, Rodenhouse TG, Bakos RS, Goldstein B. Evaluation of the autonomic cardiovascular response in Arnold-Chiari deformities and cough syncope syndrome. Arch Neurol. 1996;53(6):526–31.
67. van Roekens CN, Zuckerberg AL. Emergency management of hypercyanotic crises in tetralogy of Fallot. Ann Emerg Med. 1995;25(2):256–8.
68. Benarroch EE. Postural tachycardia syndrome: a heterogenous and multifactorial disorder. Mayo Clin Proc. 2012;87(12):1214–25.
69. Tomlinson SE, Rajakulendran S, Tan SV, et al. Clinical, genetic, neurophysiological and functional study of new mutations in episodic ataxia type 1. J Neurol Neurosurg Psychiatry. 2013;84(10):1107–12.
70. Nachbauer W, Nocker M, Karner E, et al. Episodic ataxia type 2: phenotype characteristics of a novel CACNA1A mutation and review of the literature. J Neurol. 2014;261(5):983–91.
71. Markandeyulu V, Joseph TP, Solomon T, Jacob J, Kumar S, Gnanamuthu C. Stiff-man syndrome in childhood. J R Soc Med. 2001;94(6):296–7.
72. Clardy SL, Lennon VA, Dalmau J, et al. Childhood onset of stiff-man syndrome. JAMA Neurol. 2013;70(12):1531–6.
73. Solimena M, Folli F, Denis-Donini S, et al. Autoantibodies to glutamic acid decarboxylase in a patient with stiff-man syndrome, epilepsy, and type I diabetes mellitus. N Engl J Med. 1988;318(16):1012–20.
74. Eidlitz-Markus T, Haimi-Cohen Y, Zeharia A. Association of age at onset of migraine with family history of migraine in children attending a pediatric headache clinic: a retrospective cohort study. Cephalalgia. 2015;35(8):722–7.
75. Evans RW, Linder SL. Management of basilar migraine. Headache. 2002;42(5):383–4.
76. Lapkin ML, Golden GS. Basilar artery migraine. A review of 30 cases. Am J Dis Child. 1978;132(3):278.
77. Kirchmann M, Thomsen LL, Olesen J. Basilar-type migraine: clinical, epidemiologic, and genetic features. Neurology. 2006;66(6):880.

78. Ducros A, Denier C, Joutel A, et al. The clinical spectrum of familial hemiplegic migraine associated with mutations in a neuronal calcium channel. N Engl J Med. 2001;345(1):17.
79. Thomsen LL, Eriksen MK, Roemer SF, Andersen I, Olesen J, Russell MB. A population-based study of familial hemiplegic migraine suggests revised diagnostic criteria. Brain. 2002;125(6):1379.
80. Kanjwal K, Calkins H. Syncope in children and adolescents. Cardiol Clin. 2015;33(3):397–409.
81. Park EG, Lee J, Lee BL, Lee M, Lee J. Paroxysmal nonepileptic events in pediatric patients. Epilepsy Behav. 2015;48:83–7.
82. Carter KA, Hathaway NE, Lettieri CF. Common sleep disorders in children. Am Fam Physician. 2014;89(5):368–77.
83. Derry CP, Duncan JS, Berkovic SF. Paroxysmal motor disorders of sleep: the clinical spectrum and differentiation from epilepsy. Epilepsia. 2006;47(11):1775.
84. Kutluay E, Selwa L, Minecan D, Edwards J, Beydoun A. Nonepileptic paroxysmal events in a pediatric population. Epilepsy Behav. 2010;17(2):272.
85. Kotagal P, Costa M, Wyllie E, Wolgamuth B. Paroxysmal nonepileptic events in children and adolescents. Pediatrics. 2002;110(4):e46.
86. Patel H, Scott E, Dunn D, Garg B. Nonepileptic seizures in children. Epilepsia. 2007;48(11):2086.
87. Wyllie E, Friedman D, Lüders H, Morris H, Rothner D, Turnbull J. Outcome of psychogenic seizures in children and adolescents compared with adults. Neurology. 1991;41(5):742.
88. Lortie A. Psychogenic nonepileptic seizures. Handb Clin Neurol. 2013;112:875–9.
89. Plioplys S, Doss J, Siddarth P, et al. A multisite controlled study of risk factors in pediatric psychogenic nonepileptic seizures. Epilepsia. 2014;55(11):1739–47.
90. Szabó L, Siegler Z, Zubek L, et al. A detailed semiologic analysis of childhood psychogenic nonepileptic seizures. Epilepsia. 2012;53(3):565–70.
91. Johanson M, Valli K, Revonsuo A, Wedlund JE. Content analysis of subjective experiences in partial epileptic seizures. Epilepsy Behav. 2008;12(1):170.
92. Elkins RM, Pincus DB, Comer JS. A psychometric evaluation of the panic disorder severity scale for children and adolescents. Psychol Assess. 2014;26(2):609–18.
93. North KN, Ouvrier RA, Nugent M. Pseudoseizures caused by hyperventilation resembling absence epilepsy. J Child Neurol. 1990;5(4):288.
94. Coccaro EF, Posternak MA, Zimmerman M. Prevalence and features of intermittent explosive disorder in a clinical setting. J Clin Psychiatry. 2005;66(10):1221.
95. McTague A, Appleton R. Episodic dyscontrol syndrome. Arch Dis Child. 2010;95(10):841–2.
96. Macleod S, Ferrie C, Zuberi SM. Symptoms of narcolepsy in children misinterpreted as epilepsy. Epileptic Disord. 2005;7(1):13.
97. Mink JW. Treatment of paroxysmal dyskinesias in children. Curr Treat Options Neurol. 2015;17(6):350.
98. Bruno MK, Hallett M, Gwinn-Hardy K, et al. Clinical evaluation of idiopathic paroxysmal kinesigenic dyskinesia: new diagnostic criteria. Neurology. 2004;63(12):2280–7.

# Neuropsychological Comorbidities in Pediatric Epilepsy

9

Britt C. Emerton and Amy K. Morgan

## Introduction

Neuropsychology is the study of the relationships between the brain, cognitive function, and behavior. A neuropsychological evaluation assesses the overall functional integrity of the brain (i.e., general intellectual functioning) in addition to cognitive and behavioral functions associated with specific cortical systems.

Neuropsychological evaluations are tailored to the specific referral question, disease characteristics, child's age, and/or estimated developmental level. Psychosocial considerations such as emotional and behavioral stability, cultural and linguistic background, and educational exposure also inform the approach to testing. In general, epilepsy neuropsychologists will provide a comprehensive evaluation of intellectual function, attention, executive functioning, language, visuospatial, memory, fine motor, emotional, social, behavioral, and adaptive abilities [1]. The evaluation often also assesses academic skills, as school is one of the most important functional domains for children and adolescents.

Neuropsychological assessment tools are standardized in administration and scoring procedures to permit comparison to normative samples that are typically stratified by age; some measures are also normed by sex and/or grade level (Fig. 9.1). The interpretation of the data is a multivariate process that involves both quantitative and qualitative information about the patient. The clinical context is also an integral feature of the assessment, as it includes factors that would impact the validity of the assessment procedures. Common factors include sensory or motor deficits, level of engagement or effort, educational, cultural, and linguistic backgrounds that diverge from the available normative samples.

B. C. Emerton · A. K. Morgan (✉)
Psychology Assessment Center, Massachusetts General Hospital, Boston, MA, USA
e-mail: bemerton@mgh.harvard.edu; AKMorgan@mgh.harvard.edu



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_9

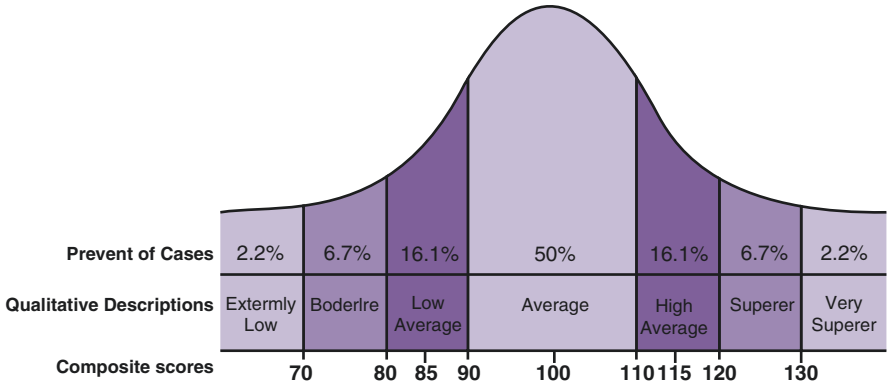



**Fig. 9.1** Wechsler cognitive scores are provided as standard and scaled scores. Standard / composite scores (mean = 100, standard deviation = 15); scaled scores (mean = 10; sd = 3). *A normal distribution of scores is in the shape of a "bell" or "normal curve"; the majority of scores are in the middle

Epilepsy-specific factors include seizure type, seizure frequency, post-ictal recovery, and subclinical epileptiform activity (e.g., transient cognitive impairment) and medication side effects.

In pediatric epilepsy, neuropsychological assessment:

- Provides data to assist with epilepsy-specific diagnostic and management questions (e.g., surgical decision making or evaluating effects of other treatments), using tests that are valid and reliable for children
- Provides a longitudinal and holistic perspective to support optimal development and quality of life
- Diagnoses developmental and psychiatric comorbidities, measures adaptive functioning, makes recommendations for non-medical interventions, and facilitates communication amongst medical, educational, community, and family systems

## General Neuropsychological Principles Relevant to Pediatric Epilepsy

### Generalized Epilepsies

Early onset of generalized symptomatic epilepsies is associated with diffuse disruption to the developing brain and often results in intellectual disability. Cryptogenic or idiopathic generalized disorders (e.g., "benign" epilepsies of childhood, absence syndromes) may be associated with disruption to developing language, attention, and/or executive functioning networks, although general intellectual functioning is often within the normal range [2].

## Focal Epilepsies

General intellectual functioning or intelligence quotient (IQ) is often normal in children with focal epilepsies. However, relative weaknesses and/or deficits in specific functions can be associated epilepsy and depend on which specific brain structures and networks are involved (Table 9.1). The left hemisphere is responsible for language functions in 90% of right-handed individuals and 50% of left-handers. The right hemisphere is typically associated with visual-spatial functions and nonverbal communication (social pragmatics). Frontal systems are associated with motor, expressive language, attention, and executive functions, including inhibition (self-control), monitoring, working memory (holding information in mind while working toward a goal), and cognitive flexibility (adapting to changed circumstances). Lateral temporal systems are associated with auditory processing (e.g., receptive language, semantic knowledge) and visual processing (e.g., object and face recognition). Mesial temporal systems are associated with verbal and visuospatial declarative memory. Parietal systems are associated with somatosensory processing and spatial cognition, including integration of motor and visual information. Dysfunction of the parietal lobe can also be associated with reading, writing, and math disorders, finger agnosia, difficulty with right-left discrimination, and neglect. Occipital systems are associated with visual processing. Disruptions associated with visual symptoms including elemental visual perception, visual field defects, and visual hallucinations. An important caveat related to these general principles is that the young brain is still in the process of developing. Localizing function with language and motor systems are the most "plastic." Therefore, cortical regions not affected by epileptic activity may take over the role of the involved cortex [3, 4].

**Table 9.1** Cognitive functions of cortical regions

| Cortical region | Common functions |
|---|---|
| Left hemisphere | Language in 90% of RH<br>50% of LH |
| Right hemisphere | Visuospatial function<br>Non-verbal communication |
| Frontal lobe | Motor (primary and supplementary)<br>Expressive language<br>Attention<br>Executive function<br>Inhibition<br>Working memory<br>Cognitive flexibility |
| Lateral temporal lobe | Auditory processing<br>Receptive language<br>Visual processing |
| Mesial temporal lobe | Verbal and visuospatial memory |
| Parietal lobe | Somatosensory processing<br>Spatial cognition<br>Integration of motor and visual information |
| Occipital lobe | Primary vision<br>Visual processing |

## Common Areas of Concern

### Attention

Children with epilepsy often have attention difficulties due to seizures [5], interictal activity, and disruption of attention networks, which involve structures in frontal, parietal, and temporal cortices as well as the basal ganglia. Some antiepileptic drugs adversely affect attention, particularly topiramate, valproate, and older medications such as phenobarbital [6]. Attention deficits are often associated with learning, peer/social interaction, and behavioral difficulties. Attention deficit hyperactivity disorder is a common comorbid condition in patients with epilepsy.

### Executive Function (EF)

Executive function comprises the voluntary control of thought and action and involves neural networks with connectivity to the prefrontal cortex (PFC). Children with epilepsy often have greater difficulty with executive functions, which contribute to problems with academic performance, learning ability, and social skills, directly affecting quality of life [7]. Because the PFC matures later in development than other regions of the brain, there is an extended period of plasticity during which disruption to these networks can occur. In infancy and early childhood, the foundations of EF are evident in children's ability to regulate their behavior or their responses to stress. Throughout development, executive functions are reflected in the child's ability to control emotions, make good decisions, form positive social relationships, and remain focused.

### Language

The left hemisphere is typically the language-dominant hemisphere, although atypical language dominance (mixed or right-hemispheric) is well documented and estimated to occur in 12–19% of individuals with epilepsy [8, 9]. Auditory processing and language comprehension localize to the dominant superior temporal gyrus (Wernicke's area) and temporal association cortex. Expressive language is mediated through the inferior frontal gyrus (Broca's area) and neighboring frontal association cortex. Frontal and temporal language areas are linked via the arcuate fasciculus. Disruption in any of these networks, particularly during critical stages of development, can in turn disrupt language development and the acquisition of higher-order verbally mediated cognitive skills.

### Memory

Memory complaints are frequently reported in individuals with epilepsy. Memory disorders in the pediatric population are commonly secondary and related to attention deficit, anxiety, executive function disorders, and other neurocognitive or

emotional disruptions [10]. Neuropsychological assessment can differentiate primary versus secondary memory disorders.

Mesial temporal (MT) systems are critical for the formation of new declarative memories. That is, encoding, consolidation, and storage of new episodic (events/personal experiences) and semantic (facts) knowledge, but not in nondeclarative memory (e.g., procedural learning). MT structures within the language-dominant hemisphere typically mediate verbal learning while those within the non-dominant hemisphere can be associated with spatial learning. Anterograde memory difficulties are commonly seen in temporal lobe epilepsy and a risk of memory decline is associated with anterior temporal lobectomy. However, the degree of association and post-operative risk is mediated in individuals by a number of seizure factors including age of onset, lateralization of language and memory functions and seizure freedom following surgery. Neuropsychological evaluation, functional MRI, and Wada testing (limited use) can be used in addition to functional imaging to evaluate and predict language lateralization and surgical risk.

Memory difficulties can also stem from deficits in other cognitive domains, including language or visuospatial processing and from deficits in attention and executive functioning which limit initial encoding and/or subsequent retrieval. Depression, anxiety, and reduced quality of life can also contribute to subjective concerns about memory in the absence of objective memory impairment.

## Motor

Motor skill difficulties, including cerebral palsy and dyspraxia, are also common in patients with epilepsy. While comprehensive evaluation of motor functioning is assessed in the neurological examination, assessment of fine motor skills, visual-motor integration, and the impact of motor skills on adaptive functioning falls within the domain of neuropsychology. Fine motor and visuomotor weaknesses have implications for handwriting difficulties and can negatively impact the development of written expression, particularly if these issues also occur in the setting of other deficits (language processing, EF, and/or visuospatial).

## Attention Deficit Hyperactivity Disorder (ADHD)

ADHD is a prevalent comorbidity, with attention and regulatory deficits occurring at 2.5–5.5 times the rate of healthy controls and in up to 30–40% of children with epilepsy [6, 11]. Risk factors include poor seizure control and other developmental disabilities. Behavioral problems are more prevalent in the context of polypharmacy [6].

## Autism Spectrum Disorders

Epilepsy and autism commonly co-occur in children. Prevalence rates of autism in epilepsy vary, with systematic reviews suggesting ranges of ~6–9% [12–14]. Conversely, the prevalence of epilepsy in patients with autism may be as high as 30%

[14]. Higher prevalence rates are associated with younger age groups, intellectual disability, and specific epilepsy syndromes, e.g., acquired epileptic aphasia (Landau–Kleffner syndrome), infantile spasms, Dravet syndrome, and tuberous sclerosis complex (TSC). Disorders with frequent epileptiform discharges, particularly during sleep, have a higher preponderance of patients with autism spectrum disorders [13, 15]. Children with epilepsy with continuous spike-waves during sleep, for example, commonly have autistic features. In some cases, the autistic features resolve with successful treatment and normalization of the electroencephalogram.

### Emotional, Behavioral, and Social Dysfunction

Children with epilepsy are at higher risk for anxiety, depression, social withdrawal, and disruptive behaviors [16]. Incidence rates of depression vary within the range of 12–33% but can be higher in those with more refractory disease [16]. Comorbid social dysfunction may be more common when there is a frontal or temporal lobe seizure focus [17]. Seizures also represent a loss of predictability and control, which are important factors in a child's development. Children with epilepsy can have difficulty establishing friendships, acquiring and maintaining the activities of daily living, and can experience a loss of confidence and self-esteem.

## Factors Influencing Neuropsychiatric Disorders

### Age of Onset

Epileptogenicity is most prominent during the rapid stages of development that occur early in life. Seizures and interictal epileptiform activity disrupt the normal maturation of neuronal processes. Disruption in connectivity and synaptogenesis may occur, leading to disruption in cognitive skill development [18, 19]. Onset prior to age 5 is associated with the greatest disruption to cognitive functioning as young brains are in the midst of the period of most rapid development [20].

Reorganization of language functions most often occurs when seizure onset is earlier in life. The result can be right-hemisphere or mixed-dominance for language [4]. Language can be preserved, although weaknesses often exist and other skills (often visual-spatial skills in the right hemisphere) may be affected as the neural space for those functions is "crowded" out. Thus, stronger verbal/language than nonverbal/visual spatial skills does not necessarily signify lateralization of functions.

Cognitive weaknesses may appear later in development as learning demands increase. Higher order language, math, planning and organization, reasoning, and problem-solving difficulties may not become apparent or occur until later elementary, middle, or high school and in some cases not until the college years.

### Seizure Frequency, Duration, and Severity

Increased seizure burden is directly associated with a greater risk of cognitive and/or behavioral comorbidities [21]. These factors have been associated with progressive cognitive decline or failure to make expected developmental gains over time. However, cognitive morbidity varies significantly across epilepsy syndromes.

### Network Effects

There is growing evidence that cognitive difficulties can be evident prior to seizure onset, suggesting that neural network disruptions are present prior to the onset of seizures and seizure treatment [11, 20, 22].

### Psychosocial Factors

Family/parent factors affect children's quality of life in pediatric epilepsy. Thus, psychosocial interventions to address family stress and parenting style can serve as important protective factors for improving a child's health-related quality of life [23].

## Neuropsychological Profiles in Select Epilepsy Syndromes

### West Syndrome/Infantile Spasms

Seizure onset typically occurs between 4 and 12 months of age. West syndrome is associated with global cognitive impairment and autism. Cognitive outcome is dependent in part on the underlying etiology and duration of the period of infantile spasms [24, 25].

### Dravet Syndrome

The mean age of onset is 5 months, with a range of 1–18 months. Dravet syndrome is associated with slowing of acquisition of cognitive skills often resulting in cognitive impairment. Attention deficit, behavioral difficulties, and autistic behaviors are often evident [26, 27].

### Epilepsy with Myoclonic Atonic Seizures (Doose Syndrome)

Seizure onset ranges from 7 months to 6 years. Patients with epilepsy with myoclonic atonic seizures have cognitive abilities ranging from normal to mild cognitive delay. Early and successful treatment is associated with the best outcomes. Later

onset of myoclonic seizures (>age 4) and sleep onset seizures associated with a poorer prognosis [28]. Patients who do not respond to therapy may have more severe cognitive disability.

### Lennox-Gastaut Syndrome

Seizure onset typically occurs between 1 and 6 years. LGS is associated with moderate-to-severe impairment and/or regression in cognitive abilities, severe attention deficits, and autistic symptoms [29].

### Landau-Kleffner Syndrome

Symptom onset occurs between 3 and 10 years. In this syndrome, seizures are a minor feature of the phenotype, as LKS presents with with auditory agnosia, followed by language, cognitive, and social deficits which emerge after a period of normal development. Deterioration of language typically occurs with seizure onset, but can precede it. Early treatment of seizures and EEG abnormalities is associated with the best outcomes, although the resolution of EEG abnormalities with age is not strongly associated with the resolution of language deficits [30].

### Childhood and Juvenile Absence Epilepsy

Onset of CAE is between 4 and 10 years and 10 and 17 years for JAE. Both forms of absence epilepsy can present more subtle cognitive deficits: vulnerabilities are in attention/EF; language processing weaknesses and constructional difficulties; psychiatric difficulties including attention deficit hyperactivity disorder and anxiety. Seizure frequency and duration of the disorder can be predictive of cognitive outcome [31].

### Childhood Epilepsy with Centrotemporal Spikes (CECTS)

Seizure onset between 3 and 13 years, peak 8 and 10 years. Although considered "benign," weaknesses in attention, executive functions, language, and visual-motor coordination are often evident. Even in the absence of clinical seizures, epileptic discharges may be associated with cognitive and behavioral difficulties [32, 33].

### Juvenile Myoclonic Epilepsy

Onset is in adolescence. This epileptic disorder is typically correlated with a normal IQ, although mild deficits in EF (processing speed, attention/working memory, and language retrieval) are commonly seen. Mood, social, and behavioral difficulties

may be present and out of proportion to the patient's peers, corresponding to frontal system dysfunction. Improvements are often associated with behavioral treatment (e.g., cognitive behavioral therapy) [34, 35].

## Impact of Interictal Epileptic Discharges (IEDs) on Neurocognitive Development

### Transient Cognitive Impairment (TCI)

This term describes neurocognitive disruption that arises from subclinical epileptiform activity, which can still disrupt or impair function and development [36]. This epileptiform activity can be most impactful during critical or sensitive periods in neurodevelopment (i.e., the acquisition of language and executive functioning skills).

### Electrical Status Epilepticus of Sleep (ESES)

ESES is the electroencephalographic phenomenon of continuous (>80%) spike-wave discharges during non-REM sleep. These EEG feature can be seen in epilepsy with continuous spikes and waves during sleep (CSWS), Landau-Kleffner syndrome, and atypical childhood epilepsy with centrotemporal spikes [37]. Onset is often between 3 and 5 years of age and is associated with cognitive and behavioral regression. Actual seizures are not a prominent feature of the phenotype. Localization of discharges correspond to the cognitive domains most impacted. ESES is generally a gradual progressive process that can disrupt neurodevelopmental trajectory and result in widespread cognitive and behavioral dysfunction that persists after seizures remit.

### Epileptic Encephalopathy

As discussed in previous chapters, the concept of epileptic encephalopathy refers to progressive neuropsychological dysfunction related to the epileptiform activity on EEG. This concept suggests that ongoing seizures or abnormal encephalographic features are negatively impacting cognitive function, leading to developmental plateau or regression [38]. This term has been used in reference to several epilepsy syndromes, including West syndrome, Lennox-Gastaut Syndrome, Epilepsy with CSWS, and others.

## Impact of Anti-Epileptic Drugs (AEDs)

Adverse cognitive and behavioral effects can result from AEDs. The severity varies across AEDs, but conventionally, cognitive and behavioral burden is typically greater at higher doses and blood levels and with polypharmacy [39, 40].

Attention-related difficulties and reduced psychomotor processing speed are the most common neurocognitive domains negatively impacted by AEDs. Learning, memory, and aspects of language can also be affected [40–42].

"Older" AEDs are associated with greater cognitive burden than most "newer" AEDs, with phenobarbital and benzodiazepines associated with greatest dysfunction and more modest dysfunction associated with carbamazepine, phenytoin and valproate [42]. Topiramate and zonisamide are newer AEDs that may adversely affect cognition [41, 43]. AEDs associated with less cognitive burden include levetiracetam and lamotrigine. In fact, improvements in alertness and attention can be seen, particularly for lamotrigine [44, 45]. However, these medications can be linked to mood and behavioral effects, with negative effects for levetiracetam (depression, irritability, mood lability, hyperactivity, and/or aggression) [46] and mood stabilizing effects for lamotrigine [43].

There is less information available about cognitive and behavioral effects of AEDs for children than adults. Data regarding cognitive effects of ethosuximide, clobazam, vigabatrin, felbamate, pregabalin, stiripentol, rufinamide, lacosamide, and retigabine are not yet conclusive [43].

During neurodevelopment, adverse cognitive and behavioral effects, even at modest levels, can be additive over time [40]. It can be difficult to disentangle the impact of AEDs from effects of epilepsy and the underlying neurodevelopmental substrate of an individual child [47]. Developmental trajectory should be closely monitored.

## Psychosocial and Educational Supports

Children and adolescents with epilepsy are at risk for functional difficulties and academic underachievement given the impact of seizures on development and quality of life. As such, many children with epilepsy are entitled to educational services through Free and Appropriate Public Education (FAPE) under the Rehabilitation Act of 1973 and the Individuals with Disabilities Education Act (IDEA). Formalized plans for supports and accommodations include:

### 504 Accommodation Plans

504 plans provide supports and accommodations to children that allow them to access the general education curriculum. Children with 504 plans do not necessarily require special education services. Examples of accommodations in 504 plans include: preferential seating, extended time on testing, modified assignments, access to assistive technology (computers, FM systems), note taking assistance and other study skills supports, excused absences, and breaks as needed.

## Individualized Education Plans (IEPs)

IEPs provide special education services for children who are unable to fully access the educational curriculum at the appropriate grade level. IEPs are formal contracts detailing specific learning and developmental goals and metrics for monitoring progress and achievement. These terms are agreed upon by the school district and a minor's legal guardians. In addition to examples of accommodations often provided through 504 Plans, IEPs will include additional services such as access to individual or small group specialized educational instruction methodology (e.g., evidence-based multisensory literacy and math instruction), speech and language therapy, occupational therapy, physical therapy, mobility supports, psychotherapy and/or counseling, behavioral interventions, social skills training, and vocational and adaptive skill training.

Public education services are provided on the basis of a "health disability" (epilepsy). At minimum, a 504 Plan for seizures, medical absences, and medication side effects (i.e., fatigue) should be in place for an otherwise typically developing child. However, as above, pediatric epilepsy often presents with significant neuropsychological comorbidities and additional services and supports as above are warranted.

Given that attentional control and higher order executive functions are more important for school readiness than IQ, it is important that a focus of intervention for any child with epilepsy be on strengthening both [48]. At home and school, the provision of structure and predictability, breaking tasks into manageable steps, and guidance to use the skills independently are deemed most important for a child's success.

## References

1. Wilson SJ, Baxendale S, Barr W, Hamed S, Langfitt J, Samson S, et al. Indications and expectations for neuropsychological assessment in routine epilepsy care: report of the ILAE neuropsychology task force, diagnostic methods commission, 2013–2017. Epilepsia. 2015;56(5):674–81.
2. Loughman A, Bowden SC, D'Souza W. Cognitive functioning in idiopathic generalised epilepsies: a systematic review and meta-analysis. Neurosci Biobehav Rev. 2014;43:20–34.
3. Chou N, Serafini S, Muh CR. Cortical language areas and plasticity in pediatric patients with epilepsy: a review. Pediatr Neurol. 2018;78:3–12.
4. Devinsky O, Perrine K, Llinas R, Luciano DJ, Dogali M. Anterior temporal language areas in patients with early onset of temporal lobe epilepsy. Ann Neurol. 1993;34(5):727–32.
5. Dunn DW, Kroninberger WG. Childhood epilepsy, attention problems, and ADHD: review and practical considerations. Semin Pediatr Neurol. 2005;12(4):222–8.
6. Auvin S, Wirrell E, Donald KA, Berl M, Hartmann H, Valente KD, et al. Systematic review of the screening, diagnosis, and management of ADHD in children with epilepsy. Consensus paper of the task force on comorbidities of the ILAE pediatric commission. Epilepsia. 2018;59(10):1867–80.
7. Love CE, Webbe F, Kim G, Lee KH, Westerveld M, Salinas CM. The role of executive functioning in quality of life in pediatric intractable epilepsy. Epilepsy Behav. 2016;64(Pt A):37–43.

8. Rosenbaum T, DeToledo J, Smith DB, Kramer RE, Stanulis RG, Kennedy RM. Preoperative assessment of language laterality is necessary in all epilepsy surgery candidates: a case report. Epilepsia. 1989;30:712.
9. Risse GL, Gates JR, Fangman MC. A reconsideration of bilateral language representation based on the intracarotid amobarbital procedure. Brain Cogn. 1997;33(1):118–32.
10. Lee SE, Kibby MY, Cohen MJ, Stanford L, Park Y, Strickland S. Differences in memory functioning between children with attention-deficit/hyperactivity disorder and/or focal epilepsy. Child Neuropsychol. 2016;22(8):979–1000.
11. Hermann B, Seidenberg M. Epilepsy and cognition. Epilepsy Curr. 2007;7(1):1–6.
12. Jokiranta E, Sourander A, Suominen A, Timonen-Soivio L, Brown AS, Sillanpää M. Epilepsy among children and adolescents with autism spectrum disorders: a population-based study. J Autism Dev Disord. 2014;44(10):2547–57.
13. Strasser L, Downes M, Kung J, Cross JH, De Haan M. Prevalence and risk factors for autism spectrum disorder in epilepsy: a systematic review and meta-analysis. Dev Med Child Neurol. 2018;60(1):19–29.
14. Lukmanji S, Manji SA, Kadhim S, Sauro KM, Wirrell EC, Kwon CS, et al. The co-occurrence of epilepsy and autism: a systematic review. Epilepsy Behav. 2019;98(Pt A):238–48.
15. Wiznitzer M. Autism and tuberous sclerosis. J Child Neurol. 2004;19(9):675–9.
16. Reilly C, Agnew R, Neville BG. Depression and anxiety in childhood epilepsy: a review. Seizure. 2011;20(8):589–97.
17. Thome-Souza S, Kuczynski E, Assumpção F Jr, Rzezak P, Fuentes D, Fiore L, et al. Which factors may play a pivotal role on determining the type of psychiatric disorder in children and adolescents with epilepsy? Epil Behav. Dec. 2004;5:988–94.
18. Holmes GL. Effect of seizures on the developing brain and cognition. Semin Pediatr Neurol. 2016;23(2):120–6.
19. Tran LH, Zupanc ML. Neurocognitive comorbidities in pediatric epilepsy: lessons in the laboratory and clinical profile. Semin Pediatr Neurol. 2017;24(4):276–81.
20. Berg AT. Epilepsy, cognition, and behavior: the clinical picture. Epilepsia. 2011;52:7–12.
21. Meador KJ. Cognitive outcomes and predictive factors in epilepsy. Neurology. 2002;58(8 Suppl 5):S21–6.
22. Jones JE, Watson R, Sheth R, Caplan R, Koehn M, Seidenberg M, Hermann B. Psychiatric comorbidity in children with new onset epilepsy. Dev Med Child Neurol. 2007;49(7):493–7.
23. Wu YP, Follansbee-Junger K, Rausch J, Modi A. Parent and family stress factors predict health-related quality in pediatric patients with new-onset epilepsy. Epilepsia. 2014;55(6):866–77.
24. Jambaque I, Lassonde M, Dulac O. Neuropsychology of childhood epilepsy. New York: Kluwer Academic/Plenum Publishers; 2001.
25. Guzzetta F. Cognitive and behavioral outcome in west syndrome. Epilepsia. 2006;47(Suppl 2):49–52.
26. Dravet C. The core Dravet syndrome phenotype. Epilepsia. 2011;52(Suppl 2):3–9.
27. Ouss L, Leunen D, Laschet J, Chemaly N, Barcia G, Losito EM, et al. Autism spectrum disorder and cognitive profile in children with Dravet syndrome: delineation of a specific phenotype. Epilepsia Open. 2018;4(1):40–53.
28. Kelley SA, Kossoff EH. Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. Dev Med Child Neurol. 2010;52(11):988–93.
29. Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2018;39:403–14.
30. Pearl PL, Carrazana EJ, Holmes GL. The Landau-Kleffner syndrome. Epilepsy Curr. 2001;1(2):39–45.
31. Caplan R, Siddarth P, Stahl L, Lanphier E, Vona P, Gurbani S, et al. Childhood absence epilepsy: behavioral, cognitive, and linguistic comorbidities. Epilepsia. 2008;49(11):1838–46.
32. Baglietto MG, Battaglia FM, Nobili L, Tortorelli S, De Negri E, Calevo MG, et al. Neuropsychological disorders related to interictal epileptic discharges during sleep in benign epilepsy of childhood with centrotemporal or Rolandic spikes. Dev Med Child Neurol. 2001;43(6):407–12.

33. Kramer MA, Stoyell SM, Chinappen D, Ostrowski LM, Spencer ER, Morgan AK, et al. Focal sleep spindle deficits reveal focal thalamocortical dysfunction and predict cognitive deficits in sleep activated developmental epilepsy. J Neurosci. 2021;41(8):1816–29.
34. Kim SY, Hwang YH, Lee HW, Suh CK, Kwon SH, Park SP. Cognitive impairment in juvenile myoclonic epilepsy. J Clin Neurol. 2007;3(2):86–92.
35. Sonmez F, Atakli D, Sari H, Atay T, Arpaci B. Cognitive function in juvenile myoclonic epilepsy. Epilepsy Behav. 2004;5(3):329–36.
36. Landi S, Petrucco L, Sicca F, Ratto GM. Transient cognitive impairment in epilepsy. Front Mol Neurosci. 2019;11:458.
37. Tassinari CA, Rubboli G. Cognition and paroxysmal EEG activities: from a single spike to electrical status epilepticus during sleep. Epilepsia. 2006;47(Suppl 2):40–3.
38. Camfield P, Camfield C. Regression in children with epilepsy. Neurosci Biobehav Rev. 2019;96:210–8.
39. Bromley RL, Leeman BA, Baker GA, Meador KJ. Cognitive and neurodevelopmental effects of antiepileptic drugs. Epilepsy Behav. 2011;22:9–16.
40. Kim EH, Ko TS. Cognitive impairment in childhood onset epilepsy: up-to-date information about its causes. Korean J Pediatri. 2016;59(4):155–64.
41. Eddy C, Rickards HE, Cavanna AE. The cognitive impact of antiepileptic drugs. Ther Adv Neurol Disord. 2011;4(6):385–407.
42. Loring DW, Meador KJ. Cognitive side effects of antiepileptic drugs in children. Neurology. 2004;64:872–7.
43. Aldenkamp A, Besag F, Gobbi G, Caplan R, Dunn DW, Sillanpää M. Psychiatric and behavioural disorders in children with epilepsy (ILAE task force report): adverse cognitive and behavioural effects of antiepileptic drugs in children. Epileptic Disord. 2016;18:S55–67.
44. Han SA, Yang EJ, Song MK, Kim SJ. Effects of lamotrigine on attention-deficit hyperactivity disorder in pediatric epilepsy patients. Korean J Pediatr. 2017;60(6):189–95.
45. Pavuluri MN, Passarotti AM, Mohammed T, Carbray JA, Sweeney JA. Enhanced working and verbal memory after lamotrigine treatment in pediatric bipolar disorder. Bipolar Disord. 2010;12(2):213–20.
46. Jung DE, Yu R, Yoon JR, Eun BL, Kwon SH, Lee YJ, et al. Neuropsychological effects of levetiracetam and carbamazepine in children with focal epilepsy. Neurology. 2015;84(23):2312–9.
47. Herman B, Meador KJ, Gaillard WD, Cramer JA. Cognition across the lifespan: antiepileptic drugs, epilepsy, or both? Epilepsy Behav. 2010;17:1–5.
48. Diamond A, Lee K. Interventions shown to aid executive function development in children 4 to 12 years old. Science. 2011;333(6045):959–64.

# Prognosis of Childhood Epilepsy

10

Yancheng Luo

## Remission

Many forms of childhood epilepsy have a good prognosis. Several cohort studies have suggested about half to two-thirds of patients with childhood epilepsy will eventually experience sustained seizure freedom. [1–7]

In 2014, the International League Against Epilepsy (ILAE) proposed that epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome they have outgrown or who have remained seizure-free for the last 10 years and off antiseizure medications for at least 5 years [8]. However, this revised operational definition was chosen conservatively by the Task Force and the ILAE recognizing that relapse rates for people (children and adults) with epilepsy will probably always remain above the risk of seizure in the general population. [9] In childhood epilepsy cohort studies, remission has been defined as 5 years without seizures, with some studies including the stipulation of the last 2 years being off of seizure medications [2].

Several cohort studies have been conducted to better delineate the course of childhood-onset epilepsy (Table 10.1). In a Minnesota retrospective cohort study, 179 children and young adults (age 0–19) were followed within the Mayo Clinic system between 1935 and 1974 for at least 10 years. At the time of data collection, 73% had been seizure-free for at least 5 years, and 47% had stopped medication [1]. Several prospective cohort studies from Finland, the Netherlands, and the United States revealed similar findings, with 5-year remission rates ranging from 70.9% to 81% and 5-year remission rate off medication ranging from 57% to 63.6% [2, 5–7]. All studies demonstrated that the longer the follow-up, the higher the proportion with remission. For example, in the Finnish cohort, 5-year remission was achieved in 56% of the subjects after 10 years of follow up, 58% after 20 years, 64% after 30 years, 67% after 40 years, and 79% after 45 years [2, 10–13].

Y. Luo (✉)
Division of Pediatric Neurology, Massachusetts General Hospital, Boston, MA, USA



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_10

**Table 10.1** Rates of seizure remission in several cohorts of pediatric epilepsy

| Cohort | Methods | Years of recruitment | Size | Mean years of follow-up | Remission on or off drugs |
|---|---|---|---|---|---|
| Minnesota [1] | Retrospective chart review identified patients with epilepsy between 1935 and 1974 | NA | 179 | >10 years | 73% in 5-year remission; 47% in 5-year remission off drugs |
| Finland [ 2] | Prospective | 1961–1964 | 148 | ~44 years | 79% in 5-year remission; 57% in 5-year remission off drugs |
| Sweden [ 3] | Prospective | 1960s–1970s | 194 | ~12 years | 64% in 3-year remission; 40% in 3-year remission off drugs |
| Nova Scotia [ 4] | Prospective | 1977–1985 | 421 | ~26 years | 62% seizure-free off drugs |
| Netherlands [ 5] | Prospective | 1988–1992 | 472 | ~15 years | 70.9% in 5-year remission; 60.3% in 5-year remission off drugs |
| Connecticut [ 6] | Prospective | 1993–1997 | 516 | 15.3 years | 81% in 5-year remission; 63.6% in 5-year remission off drugs |
| Minnesota [7] | Retrospective chart review identified children with non-idiopathic (cryptogenic vs. symptomatic) focal epilepsy diagnosed from 1980 to 2004 | NA | 206 | ~12 years | 81% with cryptogenic focal epilepsy in 1-year remission; 68% with cryptogenic focal epilepsy in 1-year remission off drugs |

Within those studies, multivariate and subgroup analyses have been undertaken to identify predictors of good and poor outcomes. Risk factors predicting poor outcomes include, but are not limited to, intellectual or neurological deficits, frequent early seizures, failure of the first AED, an MRI lesion, age of onset <1 year or > 12 years, and remote symptomatic etiology [14, 15]. Seizure etiology continues to be the most significant predictor for outcomes and mortality [16]. Generally speaking, most children with well-delineated idiopathic epilepsy syndromes, such as childhood epilepsy with centrotemporal spikes and childhood absence epilepsy outgrow their epilepsy. Children with cryptogenic epilepsy are difficult to predict, but often enter remission. Children with symptomatic epilepsy tend to have a more complex course and are less likely to achieve seizure remission [7]. None of the aforementioned factors are absolute indicators for remission or intractability. The early and accurate prediction of outcomes in children with newly diagnosed epilepsy continues to be challenging, with the exception of self-limited age-dependent epilepsy syndrome such as CECTS.

## Morbidity

Co-morbidities, such as neurocognitive deficits and behavioral disorders are common in children with epilepsy, especially in those who experience refractory seizures [ 17]. Although the majority (~ 74%) of children with epilepsy have normal global cognitive function, several reports have suggested that children with epilepsy are at a higher risk of academic underachievement and negative social outcomes [18–22], in particular those who have poor seizure control and early seizure onset.

In the Finnish cohort, 48 subjects (36 in remission and 12 with continuing seizures) with childhood-onset epilepsy were followed for more than 50 years [23]. The risk of cognitive dysfunction was highest in those who have continuing seizures, with an odds ratio of 11.7. In those with epilepsy in remission, the risk of intellectual impairment was elevated compared to the general population but did not achieve statistical significance. In another analysis of the Finnish cohort, 245 subjects were identified, of which 119 (49%) had normal childhood neurocognition and 126 (51%) had various degrees of neurocognitive impairment [ 24] The severity of neurocognitive impairment during childhood showed a parallel increase in the risk of death. In comparison with children with normal neurocognition, subjects with lower childhood neurocognition were less likely to enter seizure remission.

In the Connecticut Study of Epilepsy, 361 subjects were identified and followed for more than 15 years [25]. Several social outcome variables including employment, education, living conditions, driving, and legal issues were examined. The social outcomes for subjects with greater than 5 years of seizure remission were comparable to controls. However, the uncomplicated subjects with less than 5 years of remission were found to be less productive in school and employment and were less likely to have a driver's license. The complicated cases with continuing seizures were found to have worse outcomes across multiple domains. Similar findings of a high occurrence of unemployment, social isolation, and impulsivity were also observed in other population-based studies primarily following adults with childhood-onset epilepsy [20, 26, 27].

Children with epilepsy are also more vulnerable to accidents and injuries than the general population. In a large UK population-based cohort study, children and young adults with epilepsy had an 18% increase in the risk of fracture and a 49% increase in the risk of thermal injury. Unintentional overdose or Intoxication was more than twice the risk when compared with controls [28]. In a Finnish register-based study, the gender-adjusted hazard ratio of hospital-treated injuries was 1.30 for children with epilepsy when compared with the control group [29]. The epilepsy-related attributable risk was 23%. Children with epilepsy and comorbid intellectual disability had a higher incidence of injury compared with epilepsy alone, with an unadjusted hazard ratio of 1.41 for intellectual disability [29].

## Mortality

Children with epilepsy are at higher risk of premature death compared to the general population [30]. Several large cohort studies have demonstrated increased mortality rates in children with epilepsy [31–35]. (Table 10.2) Mortality in children with epilepsy is commonly measured using the standardized mortality ratio (SMR), which is the ratio between the number of observed and expected deaths. SMRs for children with epilepsy in all of those prospective cohorts range from approximately 6 to 9, which means that children with epilepsy are 6–9 times more likely to die when compared to their age- and sex-matched control group. The comparative risks of premature death are significantly higher in the younger population as SMRs reported in older adults (>45 years) range from 1.4 to 2.6 [30].

In a more recent retrospective population-based study that included over 13,000 children with epilepsy residing in South Carolina from 2000 through 2011, the annual risk of death among children with epilepsy was 0.84%, which was fourfold higher compared with age-matched children without epilepsy [33]. Developmental conditions, cardiovascular disorders, and injuries were the most common causes of death among those children with epilepsy [33]. In the subgroup analyses of the aforementioned cohort studies, children without neurologic deficits and without symptomatic causes of their epilepsy have a similar risk of death compared to the general population.

The majority of deaths observed were not directly related to seizures or SUDEP. The vast majority are the result of underlying etiology as well as co-morbidities such as aspiration pneumonia. Berg et al. combined the data from the four large cohorts with pediatric incidence cases (Nova Scotia, the Netherlands, Connecticut, and Minnesota) [37]. Of the 2229 subjects followed up for >30,000 person-years, 69 deaths occurred (14–26 per cohort), ten of which were attributed to SUDEP. Three were attributed to seizure. Other causes accounted for 53 deaths, mostly mostly due to infections. Mortality was found to be significantly higher in children with complicated epilepsy when compared to the general population. In uncomplicated epilepsy, sudden and

**Table 10.2** Standardized mortality ratio in patients with epilepsy

| Cohort | Methods | Years of recruitment | Size | Mean years of follow–up | Standardized Mortality Ratio (SMR) |
|---|---|---|---|---|---|
| Finland [ 31] | Prospective | 1961–1964 | 245 | 40 | 6.4 (95% CI 5.9–7.0) |
| Nova Scotia [ 32] | Prospective | 1977–1985 | 686 | >12 | 5.3 (95% CI 2.29–8.32) in the 1980s and 8.8 (4.16–13.43) in the 1990s |
| Netherlands [ 33] | Prospective | 1988–1992 | 472 | >5 | 7.0 (95% CI 2.4–11.5) |
| Connecticut [ 34] | Prospective | 1993–1997 | 613 | 7.9 | 7.5 (95% CI 4.4–13.0) |
| Minnesota [ 35] | Retrospective chart review 1980–2009 | NA | 468 | 7.9 | 9.05 (95% CI 5.35–14.37) |

seizure-related death rates were similar to or slightly higher than the rates for other common causes of death in young people.

## Sudden Unexplained Death in Epilepsy

Sudden unexpected death in epilepsy (SUDEP) is defined as "a sudden, unexpected death in a person with epilepsy, with or without evidence for a seizure preceding the death (excluding documented status epilepticus ≥30 minutes in duration), in which there is no evidence of other disease, injury, or drowning that caused the death." [38] SUDEP is thought to account for 5–18% of all deaths in all patients with epilepsy [39, 40]. This number may be higher in the pediatric patient population, with estimates over 30% [31, 41]. Based on 12 Class I studies, the American Academy of Neurology put forward a practice guideline on SUDEP in 2017. Based on these studies, the overall incidence was estimated at 0.22 per 1000 person-years (95% CI 0.16–0.31) in children and 1.2 per 1000 person-years (95% CI 0.64–2.32) in adults (Table 10.3) [41].

When counseling patients and their families on the risk of SUDEP, the AAN guideline recommends using numbers in addition to words and frequencies rather than percentages to convey the risk to avoid overestimation. For example, in 1 year, SUDEP typically affects 1 in 4500 children with epilepsy; in other words, annually, 4499 of 4500 children will not be affected by SUDEP [ 41].

The exact pathophysiology of SUDEP remains unclear. An association with cardiovascular and respiratory dysfunction following GTCS has been postulated. Cardiac arrhythmias and cardiovascular disease have been linked with SUDEP. Bradycardia, prolonged QTc interval, tachyarrhythmias, and myocardial infarction have all been observed as ictal phenomena, raising possibility of concurrent cardiac arrest in SUDEP. A recent systematic review suggested a potential overlap between the genetics of SUDEP and sudden cardiac death with the identification of arrhythmia-related genes in 161 unique individuals. The most frequent pathogenic or likely pathogenic variants identified by molecular autopsy were in sodium and potassium ion channel subunits, with an 11% discovery rate. However, the majority of variants were of unknown significance [42]. Respiratory dysfunction is also commonly associated with seizures. According to the multicenter MORTEMUS study, peri-ictal desaturation to less than 90% was observed in 33% of seizures [43]. This retrospective observational study also suggested that postictal rather than ictal respiratory effects of seizures seem most strongly related to

**Table 10.3** Incidence of SUDEP [41]

| Population | SUDEP/1000 patient-years (95% CI) | Confidence |
|---|---|---|
| Overall | 0.58 (0.31–1.08) | Low |
| Childhood | 0.22 (0.16–0.31) | Moderate |
| Adulthood | 1.2 (0.64–2.32) | Low |

SUDEP. The mechanism of postictal hypoxia may be seizure-related apnea or sympathetically mediated postictal pulmonary edema [43].

Several case-control and cohort studies have attempted to identify the risk factors for SUDEP [44–48]. Generalized tonic seizures (GTCs), seizure frequency, age, male sex, drug-resistant epilepsy and genetic predisposition factors such as an underlying channelopathy are all identified as potential risk factors. Seizure type, particularly GTCS, and frequency are among the most important risk factors. One case-control study suggested that a history of GTCS was associated with a tenfold increased risk of SUDEP (95% CI 3.44–26.82) [48]. In those experiencing GTCS during the preceding year, the risk was increased 27-fold (95% CI 14.86–48.38), whereas no excess risk was seen in those with exclusively non-GTCS seizures [48].

To date, no prospective studies have evaluated the efficacy of interventions to reduce the risk of SUDEP. Most recommendations are made based on case-control studies and expert opinions. As SUDEP risk is significantly higher in patients with a history of GTCs, especially a recent history of uncontrolled nocturnal GTCS, strategies including identifying high-risk patients, optimizing care for intractable epilepsy, and providing supervision at night have been proposed. A meta-analysis identified 112 double-blind, placebo-controlled randomized trials of add-on AEDs performed in adult patients with uncontrolled generalized tonic-clonic seizures. The result showed that definite or probable SUDEP and all causes of death were significantly less frequent in the patients with effective AED responses than in those who did not, with odds ratios of 0.17 (95% CI 0.05–0.57), and 0.37 (0.17–0.81), respectively. Rates of definite or probable SUDEP per 1000 person-years were 0.9 (95% CI 0.2–2.7) in patients who received efficacious AED doses and 6.9 (3.8–11.6) in those allocated to placebo [49].

For appropriate candidates with medically refractory epilepsy, several retrospective cohort studies have shown a reduced all-cause mortality and SUDEP rate after successful epilepsy surgery. A study followed patients with medically refractory epilepsy who underwent surgery ($n = 590$) compared to those who did not ($n = 122$). The standardized mortality ratio (SMR) for the surgery group was 1.6, and the SUDEP rate was 1.9 per 1000 patient-years. SMR for the comparison group was 3.6, and SUDEP rate was 4.6 per 1000 patient-years [50].

In patients with frequent nocturnal GTCs, sleeping alone is associated with dramatically increased SUDEP risk. One study suggested that 69% of SUDEP cases in patients who have GTCS and live alone could be prevented if the patients were not unattended at night or were free from GTCS [48]. Based on four observational studies, a Cochrane review in 2020 found limited evidence that supervision at night reduces the incidence of SUDEP [51]. Other interventions such as seizure detection devices have been considered. So far, the FDA has cleared several commercially available seizure monitoring devices such as smartwatches, mattress sensors, and camera systems. Most devices were tested against continuous EEG monitoring in the epilepsy monitoring units. The reported sensitivities of GTCs detection ranges from 50% to 100% with false-positive rates between 0.1 and 2.5 per 24 hours. Further research is required to identify the effectiveness of seizure detection devices in preventing SUDEP.

## Prognostic Outcomes in Select Epileptic Syndromes

### Neonatal Onset

#### Self-Limited Familial Neonatal Epilepsy

This disorder is commonly associated with autosomal dominantly inherited mutations in genes such as KCNQ2, KCNQ3, and SCN2A. The prognosis is generally favorable. Seizures tend to subside by the age of 6 months. In a study that followed 36 families with a history of family neonatal epilepsy, seizures ceased by 6 months in 94% of the cases [52]. However, seizures persisted after age 6 months in 31% of patients with pathogenic KCNQ2 variants. Additionally, higher neonatal seizure frequency appears to be one of the major risk factors for persistent epilepsy.

#### Early Myoclonic Encephalopathy (EME)

Early myoclonic encephalopathy is a severe form of neonatal epilepsy. The prognosis is poor. Seizures are frequently refractory to treatment. About 50% of patients with EME will die before the age of 2 and the surviving patients are often severely developmentally delayed [53].

#### Early Infantile Epileptic Encephalopathy (EIEE) or Ohtahara Syndrome

The prognosis is generally poor. Patients with EIEE frequently die during infancy, and survivors almost always have developmental delay regardless of the seizure control [54]. EIEE can later evolve into West syndrome and ultimately Lennox-Gastaut syndrome. Yamatogi and Ohtahara described in their patient series that about 75% of patients developed West syndrome between 2 and 6 months of age, and 12% subsequently developed Lennox-Gastaut syndrome [55].

### Infantile Onset

#### Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)

Seizure outcome and developmental prognosis are generally poor. In the largest cohort to date, 135 patients were studied. All patients experienced refractory epilepsy at the onset of their course, 7 patients became seizure-free at a median age of 24 months. Severe-to-profound intellectual disability were noted in 95% of patients. Mortality occurred in 33% of the patients at median age 2 years 7 months [55].

#### West Syndrome

West syndrome is a triad of infantile spasms, hypsarrhythmia, and developmental delay. Prognosis is largely predicted by the underlying etiology. Cryptogenic infantile spasms have a potentially more favorable outcome, but the prognosis is still poor for the majority. A meta-analysis showed good neurodevelopmental outcomes in 54% of infants with cryptogenic infantile spasms and 12.5% with symptomatic infantile spasms [56]. Spasms usually stop by age of 3 with the vast majority by age

of 5. However, 50–90% of patients develop other seizure types, with many evolving into Lennox-Gastaut syndrome or refractory epilepsy [57]. In two large studies that followed 150 and 214 patients respectively, mortality occurred in 17–31% of the patients during the observation period. The majority of deaths occurred before the age of 10 [57, 58].

### Myoclonic Epilepsy of Infancy

The prognosis is good and the course is generally self-limited. Most patients have seizure resolution within 2 years of onset and have a normal neurodevelopment trajectory. About 10–20% of patients will develop other seizure disorders such as juvenile myoclonic epilepsy or focal epilepsy. Developmental, cognitive, and behavioral problems have been described in patients with poor seizure control [59, 60].

### Self-Limited Familial Infantile Epilepsy

Similar to self-limited familial neonatal epilepsy, self-limited familial infantile epilepsy is commonly associated with an autosomal dominant mutation in genes such as PRRT2, SCN2A, KCNQ2, and KCNQ3. Prognosis is good with a self-limited course. Seizures typically resolve within one year of onset and almost all children continue to have normal development [61].

### Dravet Syndrome

Seizures tend to be medically refractory in most patients with Dravet syndrome, although more and more treatment options with better efficacy have been approved for Dravet syndrome in recent years. Increased mortality has been reported in patients with Dravet syndrome, with mortality rates before early adulthood ranging from 3.7% to 15% [62–64]. A review identified 30 publications and 177 fatal cases were included. Sudden unexpected death in epilepsy (SUDEP) was the likely cause in nearly half of the cases ($n$ = 87, 49%), followed by status epilepticus ($n$ = 56, 32%). Age at death was reported for 142 of the 177 cases (80%), with a mean age of 8.7; 73% died before the age of 10 years [ 65].

## Childhood Onset

### Genetic Epilepsy with Febrile Seizures Plus (GEFS+)

Although patients with GEFS+ present as a spectrum, the majority of them have a relatively good prognosis. About one-third of the patients only have febrile seizures, although the febrile seizures can happen well beyond 6 years of age. About one-third develop afebrile generalized tonic-clonic seizures but enter remission in adolescence. The rest of the patients may develop a variety of seizure types, including absence epilepsy and epilepsy with myoclonic-atonic seizures. For patients who develop other types of generalized epilepsies, the seizures can be difficult to control initially, but many will enter remission before adulthood. Development is generally normal in this population [66, 67].

### Early Onset Childhood Occipital Epilepsy (Panayiotopoulos Syndrome)

The prognosis of Panayiotopoulos syndrome is favorable, and the clinical course is often self-limited. Most patients have spontaneous seizure remission within 3 years from the onset of the disease. A study followed 93 patients with Panayiotopoulos syndrome and reported a cumulative probability of recurrence of 57.6%, 45.6%, 35.1%, and 11.7% at 6, 12, 24, and 36 months, respectively, after the first seizure [68]. About 15% of patients may later evolve into childhood epilepsy with centrotemporal spikes (CECTS), which is also considered to be a self-limited disease. Neurocognitive development is usually normal in this population [69].

### Late-Onset Childhood Occipital Epilepsy (Gastaut-Type Occipital Epilepsy)

Unlike early-onset childhood occipital epilepsy, seizures are more frequent in this group. Prognosis is unclear, but about half of the patients will have seizure remission in 2–4 years [69, 70].

### Epilepsy with Myoclonic-Atonic Seizures (Doose Dyndrome)

Prognosis is generally favorable. Seizures will eventually remit in most of the patients. In the original series reported by Doose, 54% of the children older than 7 years of age remained seizure-free for at least 2 years [71]. Oguni reported complete seizure remission in 68% of the patients from their series [72]. The neurocognitive outcome is variable and depends largely on the success of seizure control [73].

### Childhood Epilepsy with Centrotemporal Spikes (CECTS)

Natural history studies have suggested an excellent prognosis, with the vast majority of patients achieving seizure freedom by the age of 13 [74]. Although it is generally regarded as benign, neurodevelopmental comorbidities are now increasingly recognized. A meta-analysis included 1237 patients with CECTS and 1137 healthy control and found that patients with CECTS demonstrated significantly lower scores on neuropsychological tests across all cognitive realms, with the largest effects in long-term storage and retrieval and the smallest effects in visual processing [75].

### Lennox-Gastaut Syndrome

Prognosis is poor in this population. Daily seizures are common, especially in the majority of patients who have seizure onset before the age of 3 [76]. Premature mortality in early childhood has been reported in 5% of the patients and the rest will likely continue with refractory seizures, developmental delay, and inability to live independently [77, 78].

### Childhood Absence Epilepsy (CAE)

Although CAE is generally considered a benign condition, the prognosis is variable. Several natural history studies have reported seizure remission rates ranging from 21% to 82% [79–81]. It was thought that the remission rates are significantly affected by the selection criteria. A study has found that patients who were selected

by a stricter International League Against Epilepsy (ILAE) classification criteria had significantly higher rates of seizure control (95% vs. 77%) and higher rates of terminal remission (82% vs. 51%) [82]. Neurocognitive comorbidities, especially executive dysfunction, are common but the deficits are typically mild [83].

## Adult/Adolescent Onset

### Juvenile Myoclonic Epilepsy (JME)

JME is widely considered as a life-long condition, although eventual seizure remissions off medication have been reported in about 28% of the patients late in life [84, 85]. Similar to other idiopathic generalized epilepsies, cognition is typically in the normal range, although mild cognitive deficits especially in the domains of executive function are common [86, 87].

### Juvenile Absence Epilepsy (JAE)

In contrast to childhood absence epilepsy, JAE tends to be a life-long condition. Some patients will also develop GTCS or myoclonic seizures.

## References

1. Annegers J, Hauser W, Elveback L. Remission of seizures and relapse in patients with epilepsy. Epilepsia. 1979;20(6):729–37.
2. Sillanpää M, Schmidt D, Saarinen M, Shinnar S. Remission in epilepsy: how long is enough? Epilepsia. 2017;58(5):901–6.
3. Bronson L, Wranne L. Long-term prognosis in childhood epilepsy: survival and seizure prognosis. Epilepsia. 1987;28(4):324–30.
4. Camfield C, Camfield P, Smith B. Poor versus rich children with epilepsy have the same clinical course and remission rates but a less favorable social outcome: a population-based study with 25 years of follow-up. Epilepsia. 2016;57(11):1826–33.
5. Geerts A, Arts W, Stroink H, et al. Course and outcome of childhood epilepsy: a 15-year follow-up of the Dutch study of epilepsy in childhood. Epilepsia. 2010;51(7):1189–97.
6. Berg A, Rychlik K. The course of childhood-onset epilepsy over the first two decades: a prospective, longitudinal study. Epilepsia. 2014;56(1):40–8.
7. Wirrell E, Grossardt B, So E, Nickels K. A population-based study of long-term outcomes of cryptogenic focal epilepsy in childhood: cryptogenic epilepsy is probably not symptomatic epilepsy. Epilepsia. 2011;52(4):738–45.
8. Fisher R, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55(4):475–82.
9. Fisher R, Acevedo C, Arzimanoglou A, et al. How long for epilepsy remission in the ILAE definition? Epilepsia. 2017;58(8):1486–7.
10. Sillanpää M. Social functioning and seizure status of young adults with onset of epilepsy in childhood. Acta Neurol Scand. 1983;68:7–81.
11. Sillanpää M. Children with epilepsy as adults: outcome after 30 years of follow-up. Acta Pediatric Scand Suppl. 1990;79(Suppl. 368):1–78.
12. Sillanpää M, Jalava M, Kaleva O, Shinnar S. Long-term prognosis of seizures with onset in childhood. N Engl J Med. 1998;338(24):1715–22.

13. Sillanpää M, Schmidt D. Natural history of treated childhood-onset epilepsy: prospective, long-term population-based study. Brain. 2006;129(3):617–24.
14. Camfield C, Camfield P, Gordon K, Smith B, Dooley J. Outcome of childhood epilepsy: a population-based study with a simple predictive scoring system for those treated with medication. J Pediatr. 1993;122(6):861–8.
15. Sillanpää M. Predicting long-term outcome of childhood epilepsy in Nova Scotia, Canada, and Turku. Finland Arch Neurol. 1995;52(6):589.
16. Sillanpää M, Schmidt D. Predicting antiepileptic drug response in children with epilepsy. Expert Rev Neurother. 2011;11(6):877–86.
17. Lhatoo SD, Sander JWAS. The epidemiology of epilepsy and learning disability. Epilepsia. 2001;42:6–9.
18. Berg AT, Langfitt JT, Testa FM, et al. Global cognitive function in children with epilepsy: a community-based study. Epilepsia. 2008;49(4):608–14.
19. Geerts A, Brouwer O, Donselaar CV, et al. Health perception and socioeconomic status following childhood-onset epilepsy: the Dutch study of epilepsy in childhood. Epilepsia. 2011;52(12):2192–202.
20. Berg AT, Baca CB, Rychlik K, et al. Determinants of social outcomes in adults with childhood-onset epilepsy. Pediatrics. 2016;137(4):e20153944.
21. Sillanpää M, Haataja L, Shinnar S. Perceived impact of childhood-onset epilepsy on quality of life as an adult. Epilepsia. 2004;45(8):971–7.
22. Camfield C, Camfield P, Smith B, Gordon K, Dooley J. Biologic factors as predictors of social outcome of epilepsy in intellectually normal children: a population-based study. J Pediatr. 1993;122(6):869–73.
23. Karrasch M, Tiitta P, Hermann B, et al. Cognitive outcome in childhood-onset epilepsy: a five-decade prospective cohort study. J Int Neuropsychol Soc. 2017;23(4):332–40.
24. Sillanpää M, Saarinen MM, Karrasch M, Schmidt D, Hermann BP. Neurocognition in childhood epilepsy: impact on mortality and complete seizure remission 50 years later. Epilepsia. 2018;60(1):131–8.
25. Baca CB, Barry F, Vickrey BG, Caplan R, Berg AT. Social outcomes of young adults with childhood-onset epilepsy: a case-sibling-control study. Epilepsia. 2017;58(5):781–91.
26. Sillanpää M, Schmidt D. Long-term employment of adults with childhood-onset epilepsy: a prospective population-based study. Epilepsia. 2010;51(6):1053–60.
27. Shackleton DP, Trenite DGK-N, Craen AJD, Vandenbroucke JP, Westendorp RG. Living with epilepsy: long-term prognosis and psychosocial outcomes. Neurology. 2003;61(1):64–70.
28. Prasad V, Kendrick D, Sayal K, Thomas SL, West J. Injury among children and young adults with epilepsy. Pediatrics. 2014;133(5):827–35.
29. Määttänen L, Sillanpää M, Rautava P, Haataja L, Rautava L. Impact of epilepsy on the incidence of injury in Finnish children. A register-based study. Eur J Paediatr Neurol. 2017;21:E187.
30. Thurman DJ, Logroscino G, Beghi E, et al. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the mortality task force of the international league against epilepsy. Epilepsia. 2016;58(1):17–26.
31. Sillanpää M, Shinnar S. Long-term mortality in childhood-onset epilepsy. N Engl J Med. 2010;363(26):2522–9.
32. Camfield CS, Camfield PR, Veugelers PJ. Death in children with epilepsy: a population-based study. Lancet. 2002;359(9321):1891–5.
33. Callenbach PMC, Westendorp RGJ, Geerts AT, et al. Mortality risk in children with epilepsy: the Dutch study of epilepsy in childhood. Pediatrics. 2001;107(6):1259–63.
34. Berg AT, Shinnar S, Testa FM, Levy SR, Smith SN, Beckerman B. Mortality in childhood-onset epilepsy. Arch Pediatr Adolesc Med. 2004;158(12):1147.
35. Nickels KC, Grossardt BR, Wirrell EC. Epilepsy-related mortality is low in children: a 30-year population-based study in Olmsted County. MN Epilepsia. 2012;53(12):2164–71.
36. Selassie AW, Wilson DA, Malek AM, et al. Premature deaths among children with epilepsy – South Carolina, 2000–2011. MMWR Morb Mortal Wkly Rep. 2014;63(44):989–94.

37. Berg AT, Nickels K, Wirrell EC, et al. Mortality risks in new-onset childhood epilepsy. Pediatrics. 2013;132(1):124–31.
38. Nashef L, So EL, Ryvlin P, Tomson T. Unifying the definitions of sudden unexpected death in epilepsy. Epilepsia. 2012;53(2):227–33.
39. Walczak TS, Leppik IE, D'Amelio M, Rarick J, So E, Ahman P, Ruggles K, Cascino GD, Annegers JF, Hauser WA. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology. 2001;56(4):519.
40. Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: a nationwide population-based cohort study. Neurology. 2017;89(2):170. Epub 2017 Jun 7
41. Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, French JA, Gil-Nagel A, Hesdorffer DC, Smithson WH, Spitz MC, Walczak TS, Sander JW, Ryvlin P. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology and the American Epilepsy Society. Neurology. 2017;88(17):1674.
42. Anwar C, Chahal A, Salloum MN, Alahdab F, et al. Systematic review of the genetics of sudden unexpected death in epilepsy: potential overlap with sudden cardiac death and arrhythmia-related genes. J Am Heart Assoc. 2020;9(1):e012264.
43. Ryvlin P, Nashef L, Lhatoo SD, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurol. 2016;15(10):1075–88.
44. Walczak TS, Leppik IE, D'Amelio M, et al. Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study. Neurology. 2001;56:519–25.
45. Hitiris N, Suratman S, Kelly K, Stephen LJ, Sills GJ, Brodie MJ. Sudden unexpected death in epilepsy: a search for risk factors. Epilepsy Behav. 2007;10:138–41.
46. Nilsson L, Farahmand BY, Persson PG, Thiblin I, Tomson T. Risk factors for sudden unexpected death in epilepsy: a case-control study. Lancet. 1999;353:888–93.
47. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology. 2005;64:1131–3.
48. Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: a nationwide population-based case-control study. Neurology. 2020;94(4):e419.
49. Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomized trials. Lancet Neurol. 2011;10(11):961.
50. Casadei CH, Carson KW, Mendiratta A, et al. All-cause mortality and SUDEP in a surgical epilepsy population. Epilepsy Behav. 2020;108:107093.
51. Maguire MJ, Jackson CF, Marson AG, Nevitt SJ. Treatments for the prevention of sudden unexpected death in epilepsy (SUDEP). Cochrane Database Syst Rev. 2020;
52. Grinton BE, Heron SE, Pelekanos JT, et al. Familial neonatal seizures in 36 families: clinical and genetic features correlate with outcome. Epilepsia. 2015 Jul;56(7):1071–80.
53. Beal JC, Cherian K, Moshe SL. Early-onset epileptic encephalopathies: Ohtahara syndrome and early myoclonic encephalopathy. Pediatr Neurol. 2012;47:317–23.
54. Yamatogi Y, Ohtahara S. Early-infantile epileptic encephalopathy with suppression-bursts, Ohtahara syndrome: its overview referring to our 16 cases. Brain and Development. 2002;24:13–23.
55. Burgess R, et al. The genetic landscape of epilepsy of infancy with migrating focal seizures. Ann Neurol. 2019;86(6):821–31. https://doi.org/10.1002/ana.25619.
56. Widjaja E, Go C, McCoy B, et al. Neurodevelopmental outcome of infantile spasms: a systematic review and meta-analysis. Epilepsy Res. 2015;109:155–62.
57. Riikonen R. Long-term outcome of patients with West syndrome. Brain Dev. 2001;23:683–7.
58. Harini C, Nagarajan E, Bergin AM, et al. Mortality in infantile spasms: a hospital-based study. Epilepsia. 2020;61(4):702.
59. Auvin S, Pandit F, De Bellecize J, et al. Benign myoclonic epilepsy in infants: electroclinical features and long-term follow-up of 34 patients. Epilepsia. 2006;47:387–93.

60. Caraballo RH, Flesler S, Pasteris MC, Lopez Avaria MF, Fortini S, Vilte C. Myoclonic epilepsy in infancy: an electroclinical study and long-term follow-up of 38 patients. Epilepsia. 2013;54:1605–12.
61. Vigevano F. Benign familial infantile seizures. Brain and Development. 2005;27(3):172–7.
62. Cooper MS, Mcintosh A, Crompton DE, McMahon JM, Schneider A, Farrell K, Ganesan V, Gill D, Kivity S, Lerman-Sagie T, McLellan A, Pelekanos J, Ramesh V, Sadleir L, Wirrell E, Scheffer IE. Mortality in Dravet syndrome. Epilepsy Res. 2016;128:43.
63. Akiyama M, Kobayashi K, Yoshinaga H, et al. A long-term follow-up study of Dravet syndrome up to adulthood. Epilepsia. 2010;51:1043–52.
64. Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia. 2011;52:44–9.
65. Sharon Shmuely, Sanjay M. Sisodiya, . W Boudewijn Gunning, Josemir W. Sander and Roland D. Thijs Mortality in Dravet syndrome: a review. Epilepsy Behav, 2016, 64, 69–74.
66. Scheffer IE, Berkovic SF. Generalized epilepsy with febrile seizures plus. A genetic disorder with heterogeneous clinical phenotypes. Brain. 1997;120:479–90.
67. Singh R, Scheffer IE, Crossland K, et al. Generalized epilepsy with febrile seizures plus: a common childhood-onset genetic epilepsy syndrome. Ann Neurol. 1999;45:75–81.
68. Specchio N, Trivisano M, Di Ciommo V, Cappelletti S, Masciarelli G, Volkov J, Fusco L, Vigevano F. Panayiotopoulos syndrome: a clinical, EEG, and neuropsychological study of 93 consecutive patients. Epilepsia. 2010;51(10):2098.
69. Panayiotopoulos CP, Michael M, Sanders S, Valeta T, Koutroumanidis M. Benign childhood focal epilepsies: assessment of established and newly recognized syndromes. Brain. 2008;131:2264–86.
70. Gastaut H. Benign epilepsy of childhood with occipital paroxysms. In: Dravet R, Bureau C, et al., editors. Epileptic syndromes in infancy, childhood, and adolescence. London: John Libbey; 1985. p. 159–70.
71. Doose H. Myoclonic-astatic epilepsy. Epilepsy Res Suppl. 1992;6:163–8.
72. Oguni H, Tanaka T, Hayashi K, Funatsuka M, Sakauchi M, Shirakawa S, Osawa M. Treatment and long-term prognosis of myoclonic-astatic epilepsy of early childhood. Neuropediatrics. 2002;33:122–32.
73. Kelley SA, Kossoff EH. Doose syndrome (myoclonic-astatic epilepsy): 40 years of progress. Dev Med Child Neurol. 2010;52:988–93.
74. Bouma PA, Bovenkerk AC, Westendorp RG, et al. The course of benign partial epilepsy of childhood with centrotemporal spikes: a meta-analysis. Neurology. 1997;48:430–7.
75. Wickens S, Bowden SC, D'Souza W. Cognitive functioning in children with self-limited epilepsy with centrotemporal spikes: a systematic review and meta-analysis. Epilepsia. 2017;58(10):1673–85.
76. Blume WT, David RB, Gomez MR. Generalized sharp and slow wave complexes. Associated clinical features and long-term follow-up. Brain. 1973;96:289–306.
77. Bourgeois BF, Douglass LM, Sankar R. Lennox-Gastaut syndrome: a consensus approach to differential diagnosis. Epilepsia. 2014;55(Suppl 4):4–9.
78. Kaminska A, Oguni H. Lennox-Gastaut syndrome and epilepsy with myoclonic-astatic seizures. Handbook of Clinical Neurol. 2013;111:641–52.
79. Sillanpaa M, Jalava M, Kaleva O, et al. Long-term prognosis of seizures with onset in childhood. N Engl J Med. 1998;338:1715–22.
80. Berg AT, Shinnar S, Levy SR, et al. Two-year remission and subsequent relapse in children with newly diagnosed epilepsy. Epilepsia. 2001;42:1553–62.
81. Grosso S, Galimberti D, Vezzosi P, et al. Childhood absence epilepsy: evolution and prognostic factors. Epilepsia. 2005;46:1796–801.
82. Grosso S, Galimberti D, Vezzosi P, Farnetani M, Di Bartolo RM, Bazzotti S, Morgese G, Balestri P. Childhood absence epilepsy: evolution and prognostic factors. Epilepsia. 2005;46(11):1796.
83. Pavone P, Bianchini R, Trifiletti RR, Incorpora G, Pavone A, Parano E. Neuropsychological assessment in children with absence epilepsy. Neurology. 2001;56:1047–51.

84. Geithner J, Schneider F, Wang Z, Berneiser J, Herzer R, Kessler C, Runge U. Predictors for long-term seizure outcome in juvenile myoclonic epilepsy: 25-63 years of follow-up. Epilepsia. 2012;53(8):1379–86.
85. Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology. 2009;73:1041–5.
86. Almane DN, Jones JE, McMillan T, Stafstrom CE, Hsu DA, Seidenberg M, Hermann BP, Oyegbile TO. The timing, nature, and range of neurobehavioral comorbidities in juvenile myoclonic epilepsy. Pediatr Neurol. 2019;101:47.
87. Lin JJ, Dabbs K, Riley JD, Jones JE, Jackson DC, Hsu DA, Stafstrom CE, Seidenberg M, Hermann BP. Neurodevelopment in new-onset juvenile myoclonic epilepsy over the first 2 years. Ann Neurol. 2014;76(5):660–8. Epub 2014 Aug 18

# Case Reports

# 11

Amanda Tourjee and Ron Thibert

## Juvenile Myoclonic Epilepsy

NM is a 13-year-old female with an unremarkable past medical history. Her pediatrician referred her for an evaluation of involuntary shaking and body movements. During the clinic visit, the patient reported that jerking movements had started several months prior to her appointment and had gradually increased in frequency and intensity. She also reported that the episodes were experienced almost every morning upon waking and occasionally when she would take a daytime nap. The patient's episodes involved bilateral abrupt movements of her arms and legs. She never lost consciousness and was always completely aware of her surroundings during the episodes. During the episodes, she would often lose control of her hands and drop objects. On a few occasions the shaking would cause her to fall to the ground resulting in mild injury. These movements were very brief but commonly occurred in clusters that could last up to 10 minutes.

During her clinic visit, a thorough patient history and a review of systems were obtained, and a neurologic examination was completed, all of which were within normal limits.

The patient's history was concerning for epilepsy and she was scheduled to have an outpatient EEG to confirm diagnosis. The outpatient EEG was normal; thus, no antiepileptic mediations were initiated. The patient and her father were educated and instructed to observe her closely and to follow up should any issues arise.

NM did not follow up with neurology until 3 years later when she experienced a generalized tonic-clonic seizure and came to the emergency room. She reported that shortly after waking she experienced a prolonged episode of repetitive jerks of her upper extremities lasting longer than her usual 10–15-minute episodes. The patient

A. Tourjee (✉) · R. Thibert
Pediatric Epilepsy, Department of Neurology, Massachusetts General Hospital, Boston, MA, USA
e-mail: ATOURJEE@partners.org; rthibert@mgh.harvard.edu



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5_11

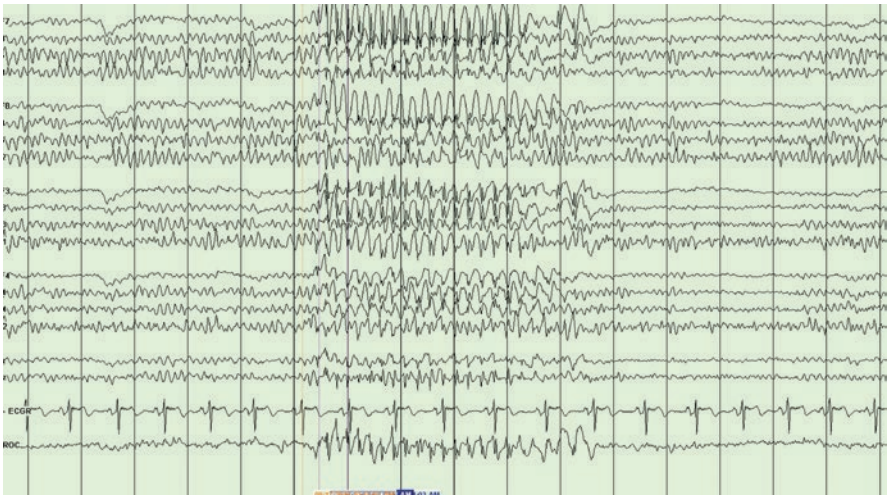


**Fig. 11.1** Fast (4–5 Hz) generalized spike-wave discharges in JME

reported that she had difficulty catching her breath and was gasping for air when she passed out. Her boyfriend then witnessed her fall to the ground and have shaking movements in all extremities. The episode lasted 1–2 minutes.

While in the ED, a review of systems and a neurological examination were performed, as well as routine laboratory tests, all of which were unremarkable. She was discharged with plans for a 24-hour EEG admission in order to capture her events and characterize the EEG findings associated with each event.

During the EEG admission, she experienced myoclonic jerks of her arms and legs at night and in the early morning. During these myoclonic episodes, the EEG showed bursts of 3–4 Hz generalized spike- and polyspike-waves with maximum amplitudes bi-frontally, consistent with myoclonic seizures (Fig. 11.1).

NM's clinical history and seizure semiology captured on video, combined with her ictal and interictal EEG findings, are diagnostic of juvenile myoclonic epilepsy (JME).

JME responds well to broad-spectrum antiepileptic medications, and she was initially started on levetiracetam with excellent seizure control.

## Epileptic Encephalopathy with Continuous Spike-Waves During Sleep (CSWS)

AW is a 13-year-old boy with a history of autism and well-controlled epilepsy with an abnormal EEG including increased frequency of spikes during sleep.

AW presented in clinic seeking a second opinion after being treated for epilepsy at a different facility. The patient's mother reported that he had normal cognitive and physical development and reached all of his milestones on time until he was

approximately 18–22 months of age. At that time, he began to regress in terms of his social and language skills and was no longer able to recall words that he had previously acquired.

At the time of his initial clinic visit, AW had regained a few of the words that he lost at 22 months of age but continued to have very limited expressive speech. He used pointing, gestures, and bringing object to others as ways of communicating. He had some receptive speech and was able to follow single-step commands. He also had an array of repetitive behaviors, such as hand flapping, hand wringing, vocalizations, singing, pacing around the room, jumping, and a fixation with water. AW's mother reported that his fine motor skills were fair until he stopped coloring at age four, at which point his parents noticed a significant decline in his gross and fine motor skills.

An initial EEG obtained at his previous treatment facility was normal, but a second EEG was later performed which showed multi-focal spikes during wakefulness with no significant epileptiform activity during sleep. Three years later, AW then had an overnight EEG, which showed with frequent left centroparietal spikes that were activated during sleep. He was then treated with a 3-month trial of oral steroids, during which time he experienced improved memory but generally did not acquire any new skills. Several months prior to his clinic visit, AW had an EEG performed which showed runs of continuous spike and wave activity during sleep.

AW very rarely experienced clinical seizures, which consisted of brief episodes of eye fluttering lasting a few seconds and occasional myoclonic jerks while falling asleep.

A family history was significant for a cousin with high-functioning autism, a brother with an autism spectrum disorder, and an uncle with schizophrenia.

A review of systems was performed during the clinic visit and was noncontributory. At the time of the visit, AW was taking valproic acid, 350 mg TID and lamotrigine, 50 mg BID.

AW was diagnosed with epileptic encephalopathy with continuous spike-waves of sleep (CSWS). His developmental regression was associated with increasing sleep-activated epileptiform discharges. At a young age, AW experienced a neurocognitive regression followed by the onset of seizures, with several EEGs that progressively worsened into CSWS. His EEG initially showed no epileptiform activity, then multi-focal spikes during wakefulness, then progressed to frequent left centroparietal spikes that were activated during sleep, eventually with near continuous spike and wave activity. As his EEG worsened, his autistic features and behaviors continued to decline.

At his initial clinic visit, a 24-hour EEG was scheduled, with a plan to trial high-dose diazepam his EEG were to show a significant amount of sleep-activated discharges. This EEG showed that 90% of sleep was comprised of 2 Hz generalized spike and wave activity with no sleep architecture. (Fig. 11.2) The following day he was treated with a high dose of valium at 1 mg/kg per our high-dose valium protocol. The EEG on his second inpatient night showed marked decrease in epileptiform activity, with discharges only occupying approximately 15% of his sleep record with some periods of normal sleep architecture. (Fig. 11.3) AW was then discharged

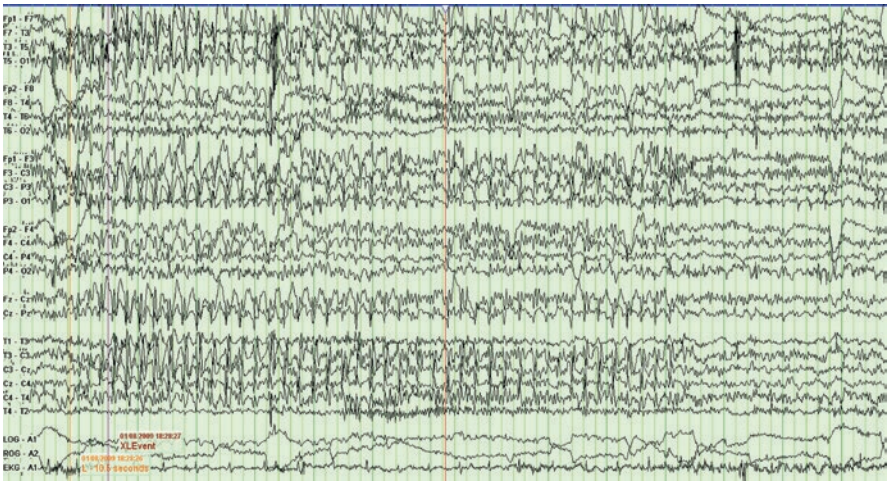


**Fig. 11.2** Sleep EEG prior to treatment with high dose diazepam, demonstrating continuous spike-wave discharges

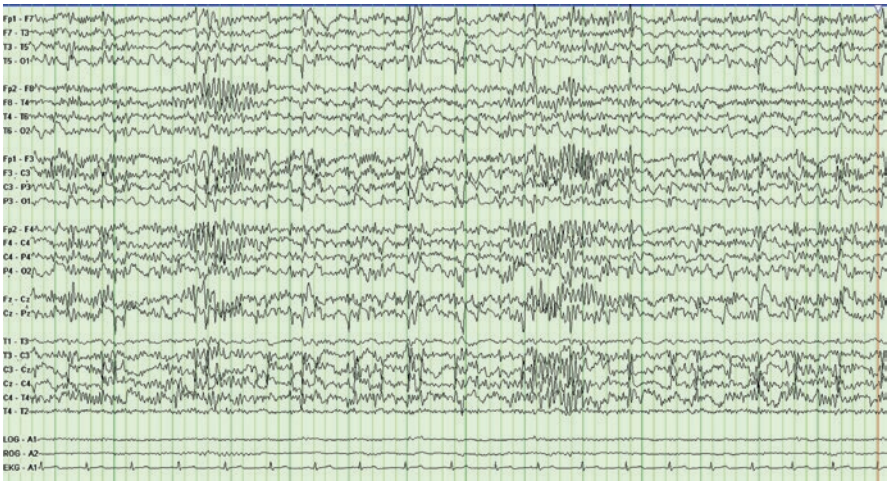


**Fig. 11.3** Sleep EEG after high-dose valium. Note reduction is spike frequency and the emergency of normal sleep features (sleep spindles)

home on Valium 0.5 mg/kg/day with intent to slowly taper over the course of 6 months.

At the follow-up, 1 month after the high-dose valium, protocol, the patient had experienced no seizures and had a remarkable improvement in overall functioning. His mother reported a significant decrease in self-stimulating behaviors, much improved eye contact, and improved sleep. His effective non-verbal communication

was markedly improved including signing "thank you" appropriately. His behavioral issues also improved.

A repeat 24-hour EEG 4 months later showed even fewer sleep-activated discharges, occupying approximately 10% of the sleep record.

## West Syndrome

RM is a 7-month-old boy with a previously unremarkable medical history. RM presented in clinic with episodes that his parents noticed over the course of 2 weeks. These episodes typically occurred when he was feeding. His mother reports that he would become withdrawn and then experience head drops with shoulder shrugging and eye deviation. The movements were brief but would occur in clusters lasting several minutes. RM's parents reported that the episodes had become a daily occurrence.

RM's parents also reported that he had become less socially responsive and his demeanor had become irritable. However, he did have some periods with typical alertness and social skills. Developmentally, RM had been achieving his milestones on time prior to the onset of the events, but he now displayed decreased eye contact and reduced babbling and had decreased muscle tone.

RM was brought to an outside emergency room at the onset of symptoms but was discharged home with instructions to follow up with his primary care physician. The primary care physician ordered an EEG that was performed prior to his clinic visit, which showed hypsarrhythmia, with one clinical episode captured on video.

RM's family history revealed one paternal cousin with developmental delay and one paternal cousin with Down's syndrome, but no history of seizures or epilepsy. The complete neurological examination was within normal limits and a review of systems was non-contributory.

His clinical presentation and EEG findings were concerning for infantile spasms, so he was directly admitted to the hospital, as prompt treatment may improve long-term outcomes for patients with this diagnosis. Based on his clinical features, including onset within the first year, the semiology of the episodes, developmental stagnation, and abnormal EEG, he was diagnosed with West syndrome.

The plan upon admission was for EEG monitoring, an MRI, genetic testing, a metabolic work-up and initiation of therapy with adrenocorticotropin hormone (ACTH). His genetic/metabolic workup and MRI were unremarkable with no clear lesion on MRI.

RM's inpatient EEG showed a diffusely poorly organized, high-amplitude delta background with abundant multi-focal high-amplitude epileptiform discharges, consistent with hypsarrhythmia. (Fig. 11.4) There were occasional electrodecrements, but only one with clear clinical correlate. (Fig. 11.5).

RM remained in the hospital for 5 days. He seizures decreased in frequency and intensity over the course of his stay and were nearly resolved upon discharge. He was discharged home to complete his course of ACTH.

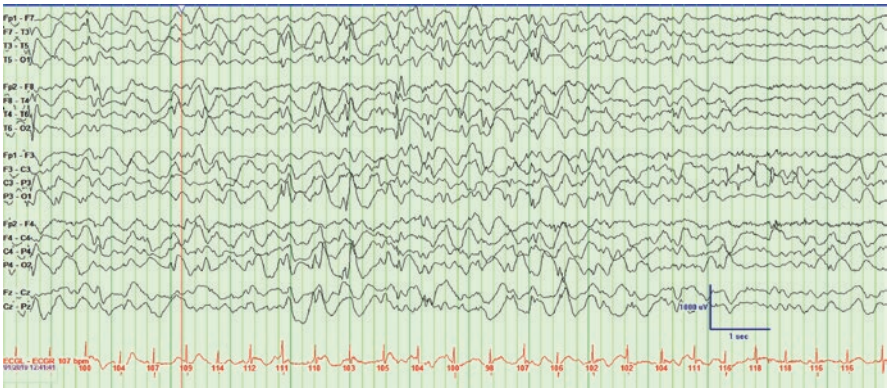


**Fig. 11.4** Hypsarrhythmia. Note the poorly organized background, high amplitude slowing, and multifocal epileptiform discharges. Note the amplitude sensitivity of the EEG in this figure is reduced to more clearly display abnormal features

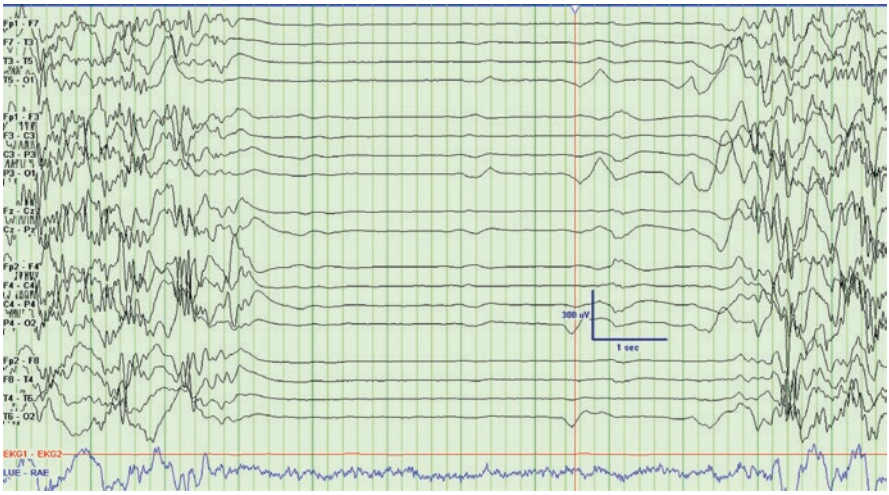


**Fig. 11.5** Period of electrodecrement consistent with an epileptic spasm

RM's spasms stopped the day after his discharge. At his follow-up appointment, 3 weeks post-admission, he had regained nearly all of the skills that were lost pre-treatment. His follow-up EEG showed a slow background, but was negative for epileptiform discharges, and had no longer qualified as hypsarrhythmia.

RM is now 12 months old and he has remained seizure-free since discharge from the hospital. His most recent EEG from his 12-month visit was normal for age and he has also made excellent developmental progress. His language and cognition are essentially normal, and his motor skills are progressing but he is mildly delayed.

## Childhood Epilepsy with Centrotemporal Spikes

RB is an 8-year-old girl with an unremarkable past medical history. She experienced a generalized tonic-clonic seizure that started while she was at home in bed and lasted approximately 2 minutes. Her parents noticed muscle stiffening combined with jerking movements, loss of consciousness, clenched jaw, and perioral cyanosis. There were no prodromal symptoms of fever, illness, or fatigue. EMS was called and she was brought to the emergency department.

While in the emergency department, blood work including a CBC, electrolytes, and liver function tests were within normal limits. The complete neurological exam was unremarkable, and a review of systems showed no significant findings. Because this seizure spontaneously resolved, the patient went home with orders for an outpatient EEG and a follow-up appointment with a neurologist.

The patient's father noted that several months prior to her emergency room visit, he found her asleep in bed with left facial twitching and drooling. Medical attention was not sought at that time because her parents did not witness any further incidents.

Her family history is negative for seizure. During the clinic visit, a complete review of systems was obtained and proved non-contributory. Her early development was normal, and her parents reported no social or academic difficulties.

During the sleep phase of the EEG, the patient had twitching of the left side of the face, followed by left facial clenching and then generalized tonic-clonic activity lasting 2.5 minutes.

The EEG showed right centrotemporal spikes with an anterior positive, posterior negative dipole during sleep. (Fig. 11.6) The seizure arose from the right centrotemporal region prior to generalizing.

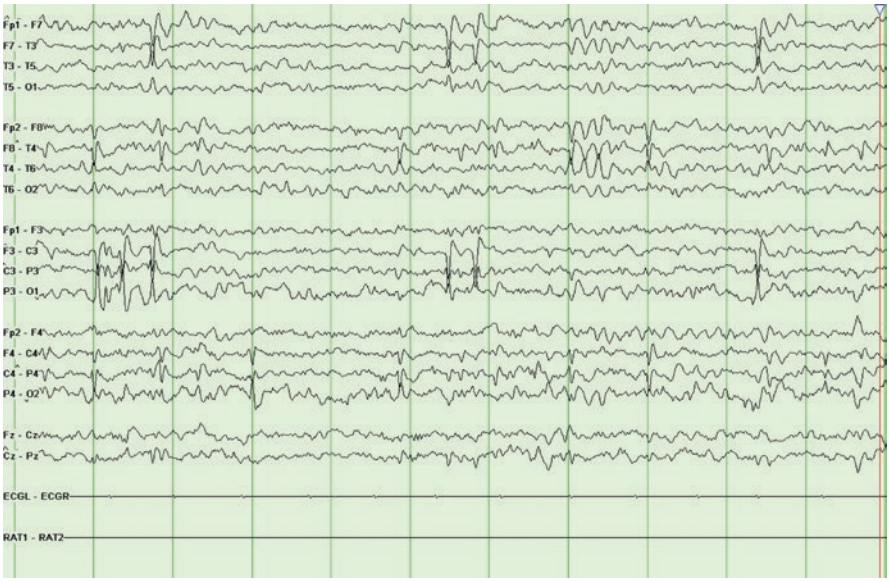



**Fig. 11.6** CECTS with typical bilateral centrotemporal spikes

The EEG and clinical history were consistent with childhood epilepsy with centrotemporal spikes (CECTS). Many children with CECTS have only rare nocturnal simple focal seizures and may not require antiepileptic medications. This self-limited epilepsy commonly remits around the onset of puberty. In patients with daytime seizures, frequent nocturnal events or secondarily generalized seizures, treatment with antiepileptic drugs should be considered. Due to her history of 2 secondarily generalized seizures, 1 of which occurred during the day she was started on levetiracetam. She had no further seizures over the next 3 years, her EEG normalized, and she was tapered off of her levetiracetam without incident.

## Childhood Absence Epilepsy

DS is an 8-year-old female with a history of seasonal allergies, controlled on diphenhydramine. DS was referred to clinic after experiencing a 5-minute generalized tonic-clonic seizure upon awakening. The patient's mother reported having heard a strange noise and finding DS lying in bed with her eyes rolled back and shaking of all four extremities. EMS was called and she was taken to her local hospital. While in the emergency room, routine blood tests were taken and a head CT was performed, all of which were within normal limits. She was discharged from the emergency room with rectal diazepam in case of a prolonged seizure and instructed to follow up in the neurology clinic.

DS's mother noted that during the year prior to her presentation, she had been experiencing at least one episode per week of staring straight ahead for 5–10 seconds. During these episodes she was unable to respond to her environment. The episodes commonly interrupted her activities.

During the clinic visit, the patient was asked to hyperventilate for 3 minutes. After 2 minutes of hyperventilation, she had an 8–10 second behavioral arrest, during which she was unresponsive. After the event she continued hyperventilating but was aware that something unusual had happened. Her EEG subsequently showed five runs of 3 Hz generalized spike and wave activity, two of which were accompanied by staring and eye blinking. (Fig. 11.7) The EEG confirmed the clinical diagnoses of childhood absence epilepsy.

DS was treated with lamotrigine, and she responded well to this medication with no further seizures over the next 2 years.

About 5% of children with childhood absence epilepsy will experience a generalized tonic-clonic seizure during the course of their disease. The usual drug of choice for absence epilepsy is ethosuximide. However, this medication is not effective for seizure types other than absence seizures, so lamotrigine was selected.

Childhood absence epilepsy is a common disorder. Seizures are brief and subtle, but occur frequently and can interfere with learning and development. Most patients respond well to therapy and outgrow the disorder by the time they reach puberty.

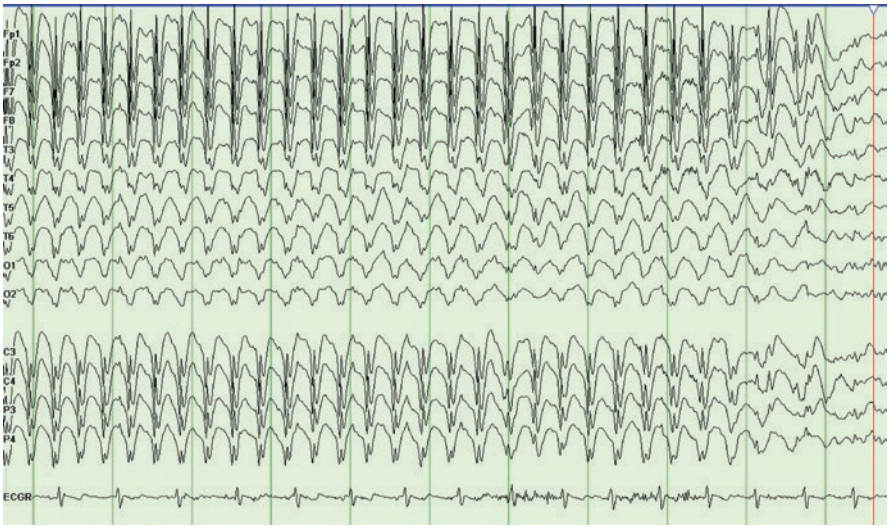



**Fig. 11.7** Childhood absence epilepsy. Note the diffuse, bifrontally predominant, generalized 3 Hz spike-wave discharges

# Appendix A: Videos

1. Generalized tonic-clonic seizure
2. Myoclonic seizure
3. Atonic seizure
4. Absence seizure
5. Eyelid myoclonia
6. Epileptic spasms
7. Nocturnal frontal lobe seizure
8. Temporal lobe seizure
9. Neonatal focal clonic seizure
10. Benign neonatal sleep myoclonus
11. Complex motor stereotypy
12. Complex motor stereotypy/shuddering
13. Infantile gratification/masturbation
14. Opsoclonus
15. Paroxysmal tonic upgaze
16. Motor tic
17. Psychogenic nonepileptic seizures
18. Paroxysmal dyskinesia



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5

# Appendix B: EEG Atlas

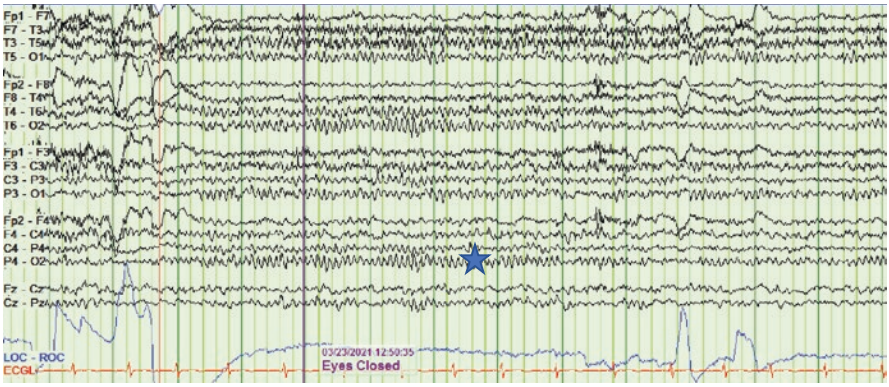



**Fig. A1** Normal awake EEG in a 10-year-old. This is a bipolar montage, meaning each channel compares the electrical potential difference between two points on the scalp. Letters denote location (FP-frontopolar, F-frontal, T-temporal, C-central, P-parietal and O-occipital) and numbers indicate laterality (left = odd, right = even, Z = midline). Note the well-organized background with low voltage fast activity anteriorly and increasing amplitude but decreasing frequency of wave forms as one moves posteriorly. In this case, the posterior dominant rhythm (in the occipital leads) is 9–11 Hz (blue star)



D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5

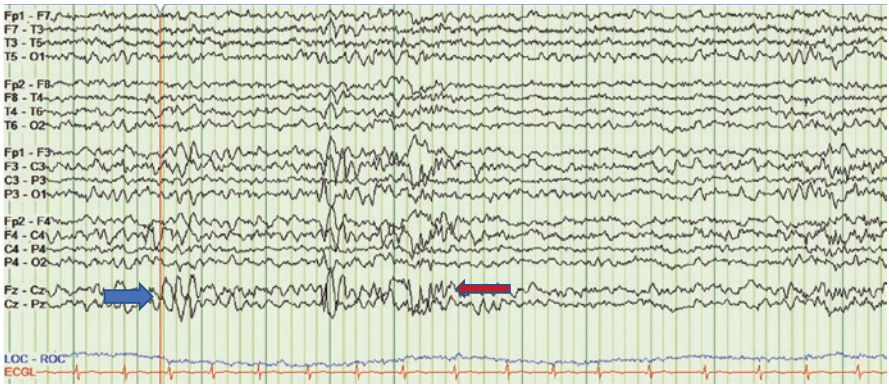



**Fig. A2** Normal stage 2 sleep EEG. Note vertex waves in the midline (blue arrow) and sleep spindles (red arrow)

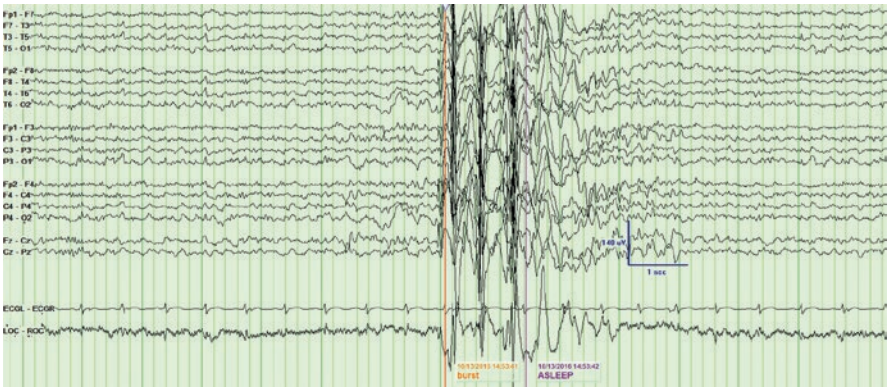



**Fig. A3** Myoclonic seizure with generalized spike-wave burst

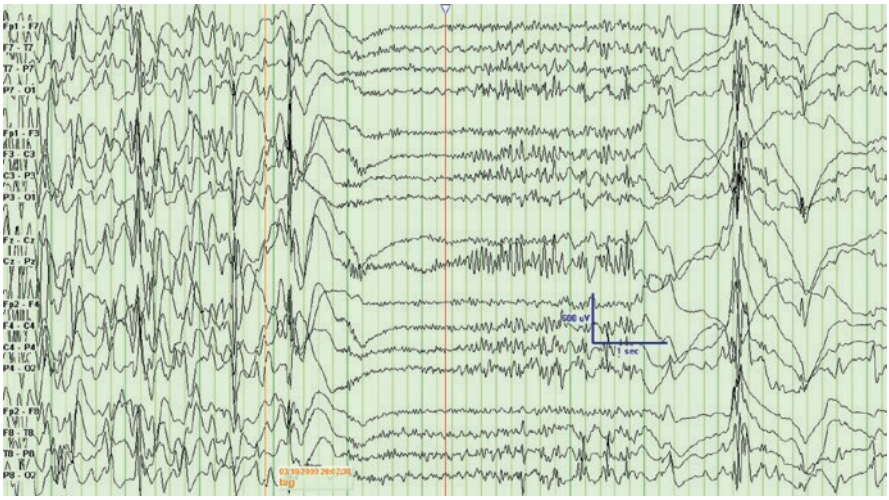


**Fig. A4** Tonic seizure. Note the high-voltage slow-wave followed by electrodecrement that evolves into low-voltage fast spikes

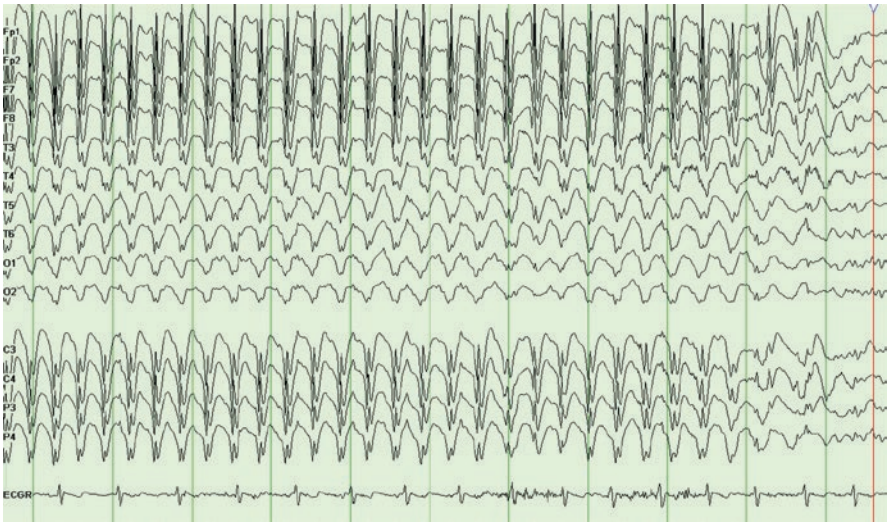



**Fig. A5** Childhood absence epilepsy. Note the typical bi-frontally predominant generalized 3 Hz spike-wave discharges

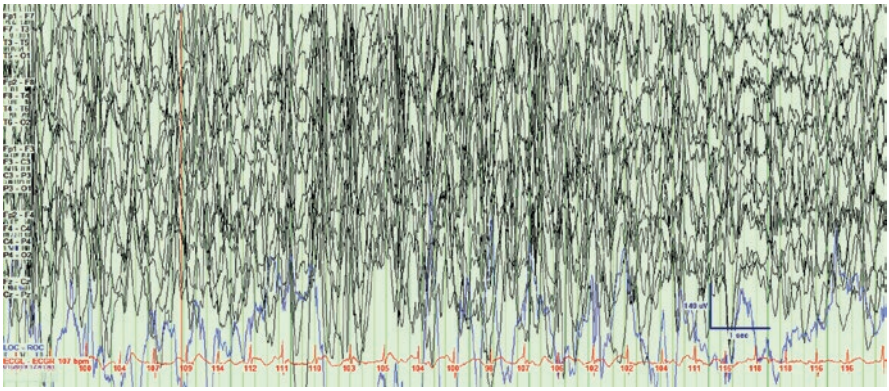


**Fig. A6** Hypsarrhythmia. This is the EEG at standard recording sensitivity, depicting a very chaotic tracing

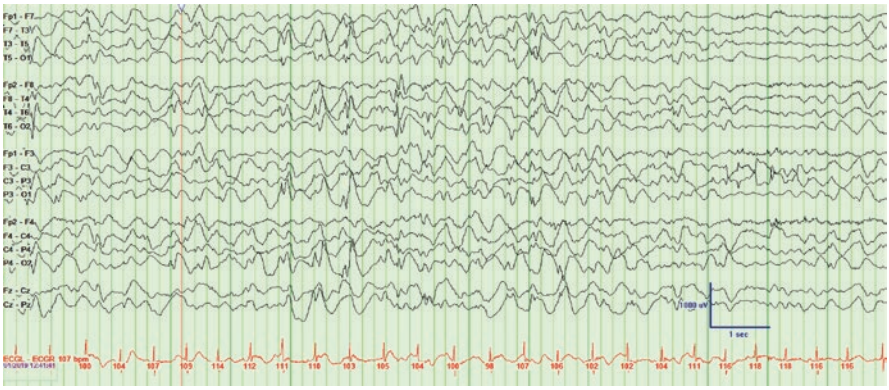


**Fig. A7** Hypsarrhythmia. This is the EEG from the same patient as Fig. A6, with the sensitivity reduced. Note diffuse, high-voltage slowing, poor organization of the background and multifocal epileptiform discharges

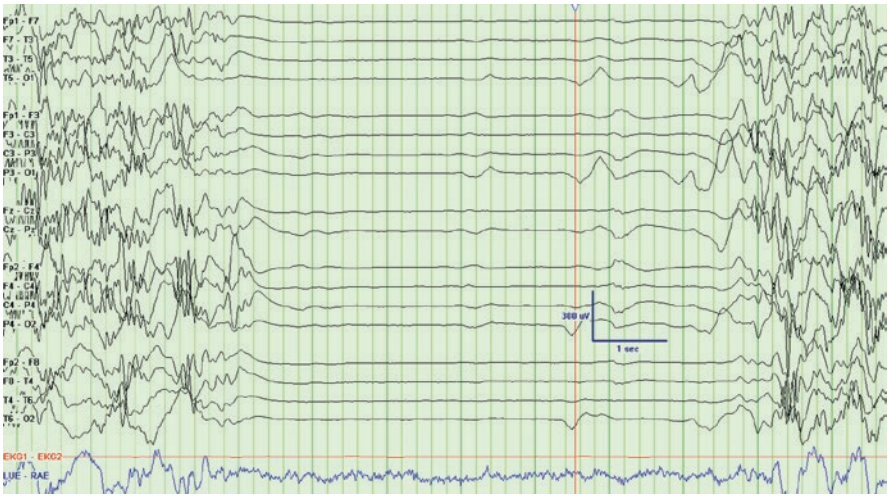



**Fig. A8** Epileptic spasm. During the spasm, there is diffuse suppression of the background, termed electrodecrement. The hypsarrhythmia pattern is evident before and after the seizure

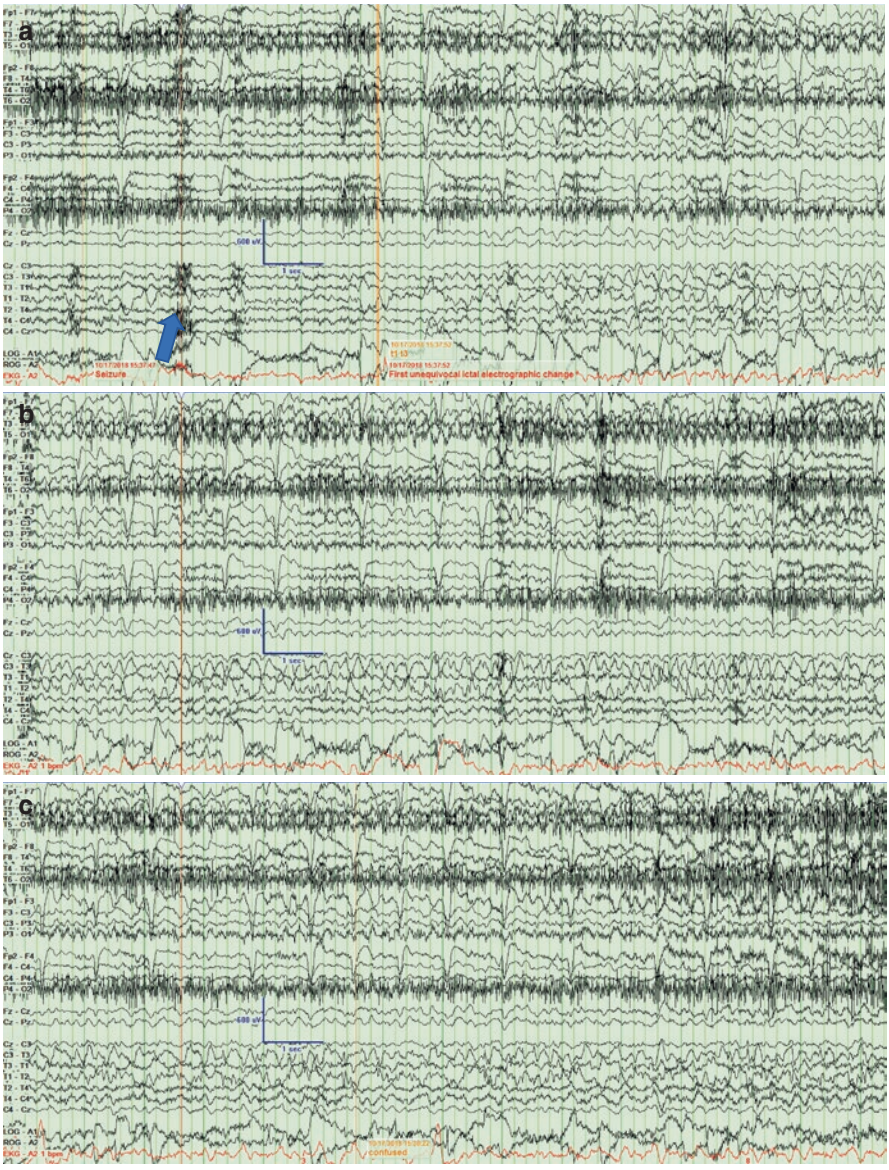



**Fig. A9** (**a**) Temporal lobe seizure. This montage includes a set of transverse leads. Note onset of rhythmic activity in the left temporal lobe (blue arrow). (**b**) Temporal lobe seizure. The rhythmic temporal activity becomes more defined and a bit faster (blue arrow). (**c**) Rhythmic activity spreads more diffusely. Muscle artifact is prominent. (**d**) Rhythmic activity spreads more diffusely. (**e**) Rhythmic activity spreads more diffusely. (**f**) Rhythmic activity spreads more diffusely. (**g**) Temporal lobe seizure. Post-ictal slowing

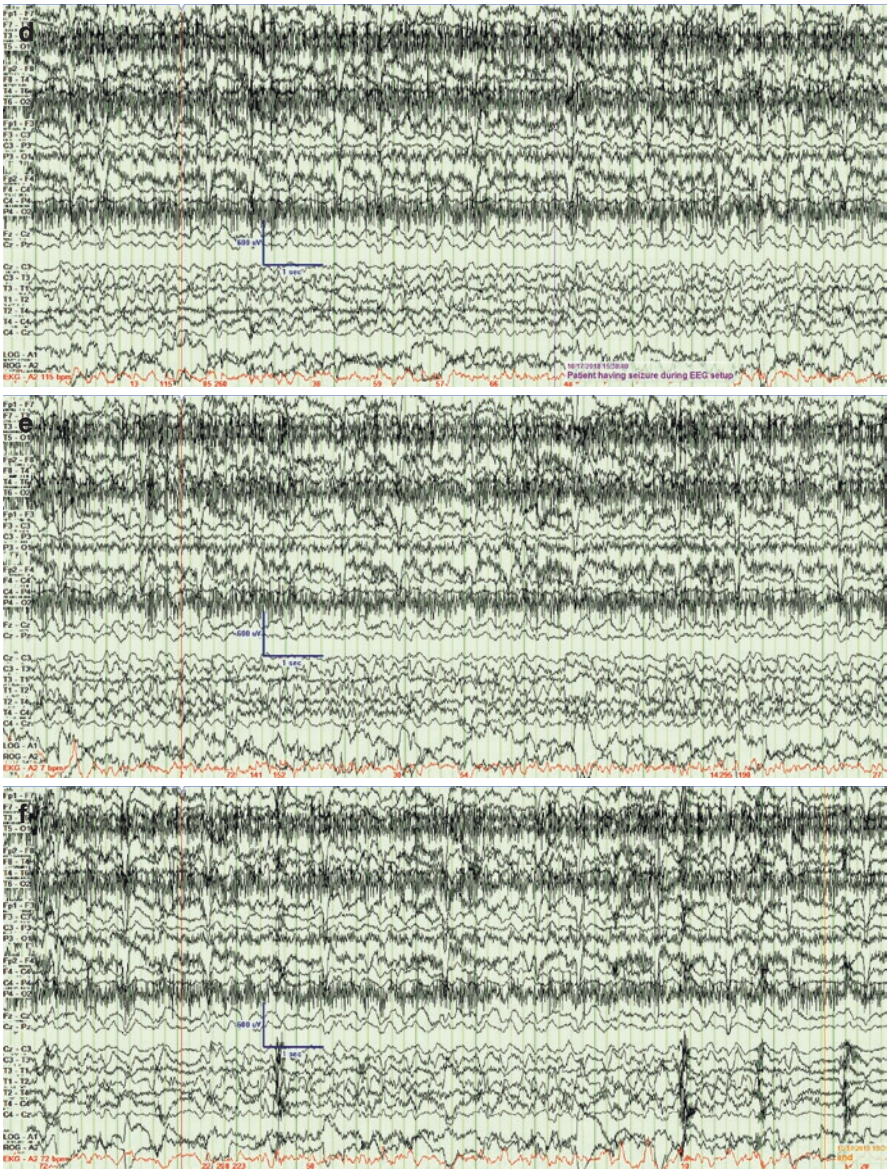



**Fig. A9** (continued)

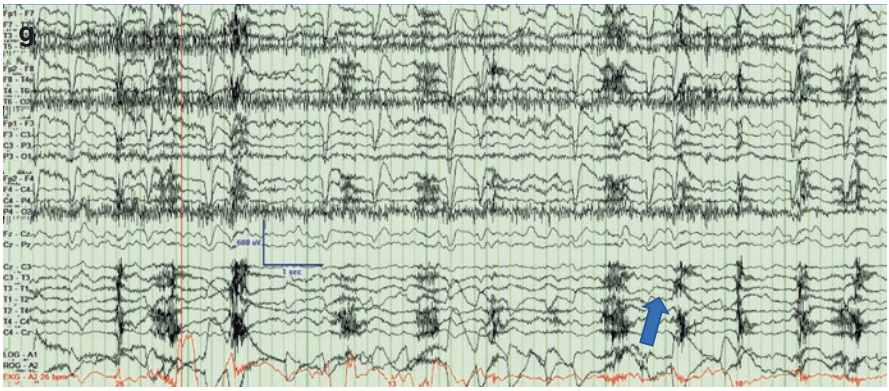


**Fig. A9** (continued)

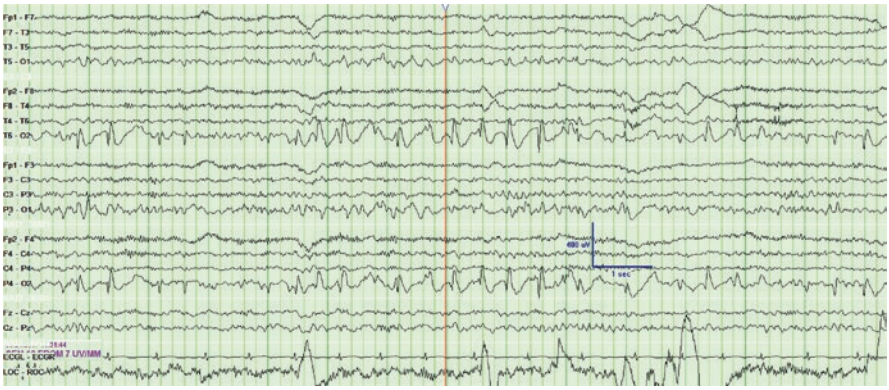


**Fig. A10** Late-onset occipital epilepsy. Note repetitive focal spike-wave discharges in the right occipital lobe

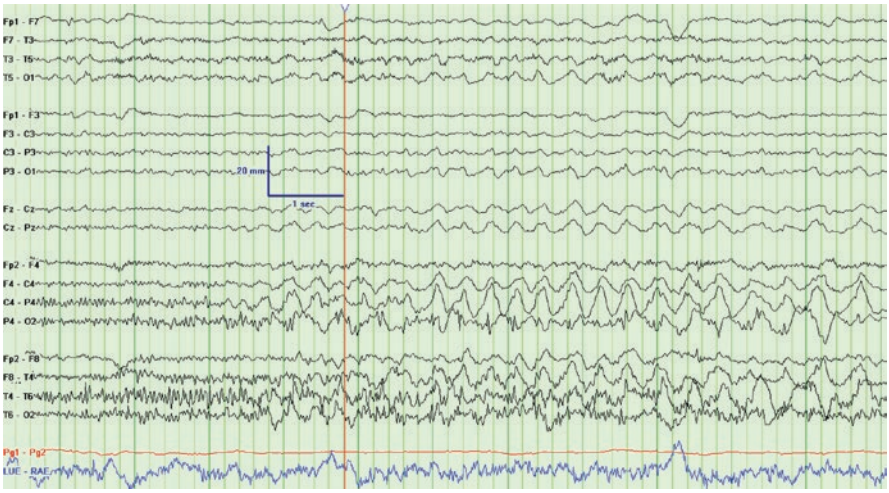



**Fig. A11** R occipital seizure. The seizure starts in the right occipital lobe with low-voltage fast spikes. As the seizure progresses, the discharges become slower and of higher amplitude

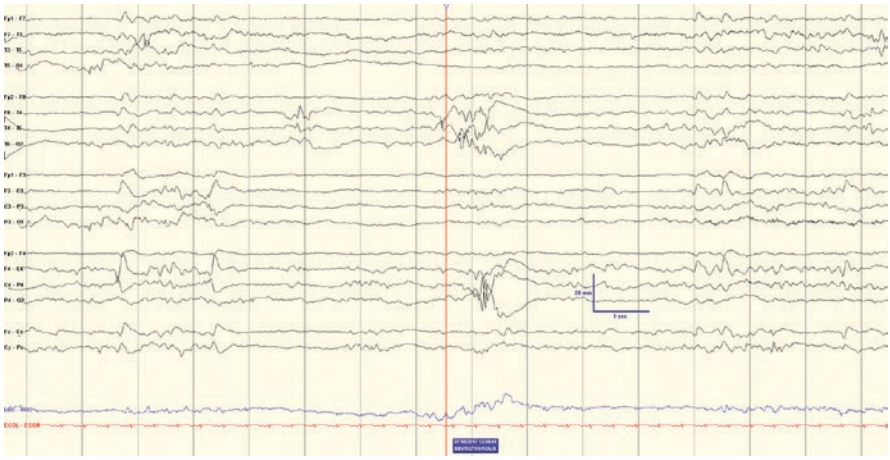


**Fig. A12** Burst suppression in a neonate: Note up to 10 seconds between bursts of acitivity

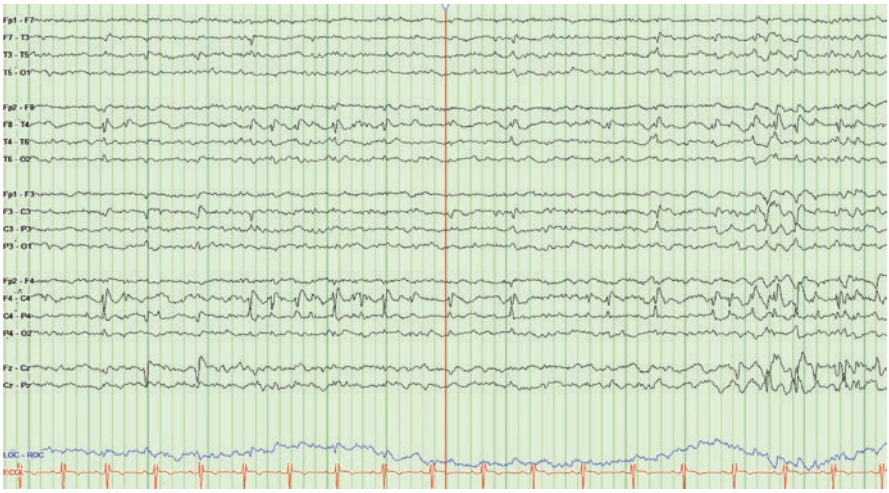


**Fig. A13** Childhood epilepsy with centrotemporal spikes: The EEG demonstrates typical centrotemporal spikes, more prominently in the right hemisphere, but also present on the left. The spikes have a diphasic morphology and phase reversal in the central leads on the bipolar montage

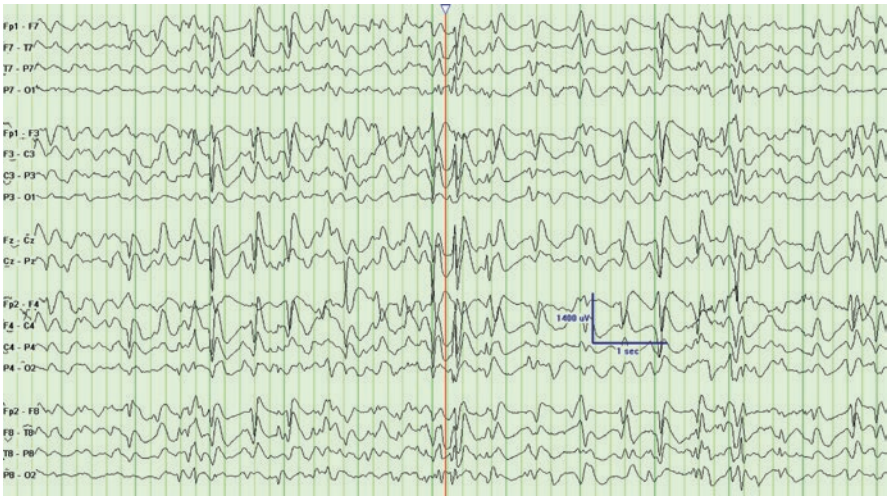


**Fig. A14** Lennox-Gastaut syndrome: Note the generalized, 2 Hz slow spike-wave pattern

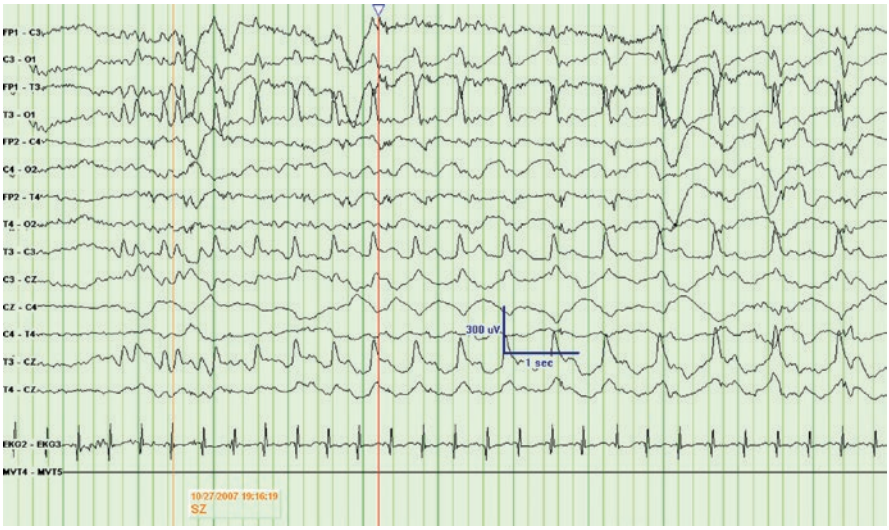



**Fig. A15** Neonatal seizure. Onset of the seizure is in the T3 lead. There is evolution in amplitude and frequency during the seizure, with lower voltage, faster activity at the beginning that slows and becomes higher amplitude. As is common with neonatal seizures, there is limited spread to other areas of cortex

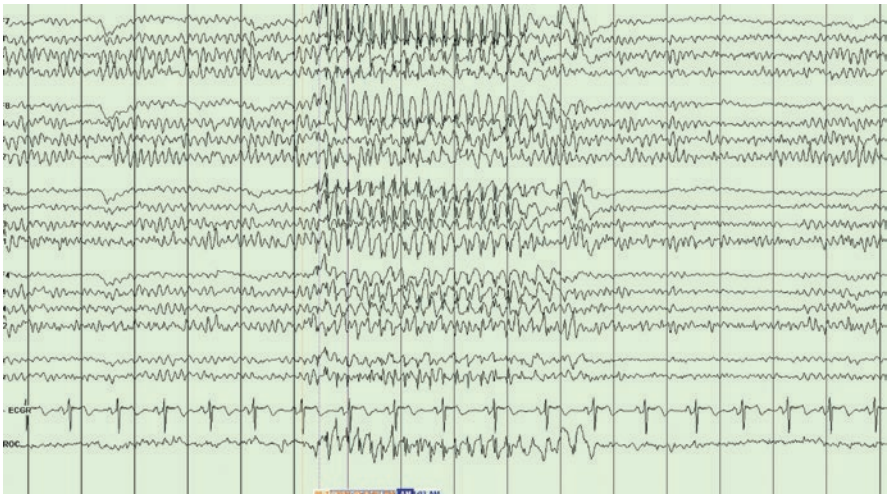


**Fig. A16** Juvenile myoclonic epilepsy. This EEG depicts the typical "fast" spike-wave discharges, about 4–5 Hz

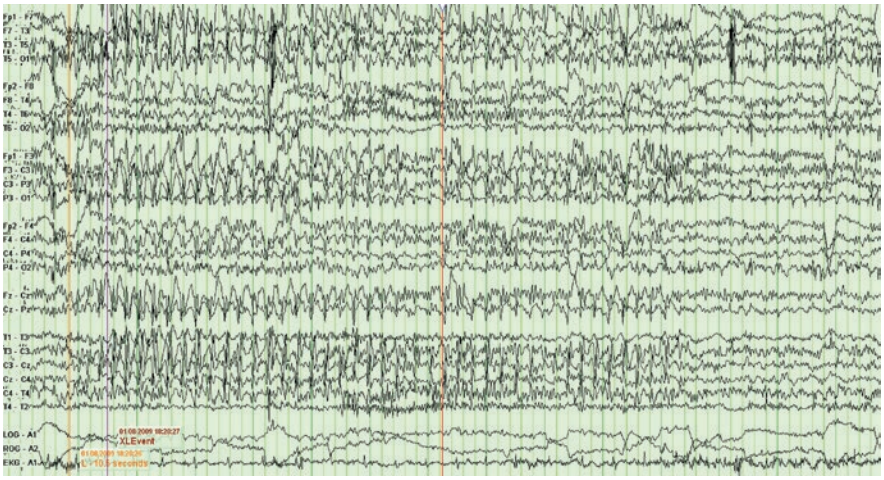


**Fig. A17** Continuous spike-wave during slow-wave sleep. 10/15 seconds of this record are dominated by generalized spike-wave discharges

# Index




D. C. Dredge (ed.), *Handbook of Pediatric Epilepsy*,
https://doi.org/10.1007/978-3-319-08290-5