Chapter

Childhood Epilepsies and When to Refer for Epilepsy Surgery Evaluation

Derryl Miller

Abstract

Many providers feel uncomfortable with the recognition of epileptic seizures, the diagnosis and classification of epilepsy syndromes, and initial treatments to offer to patients with epilepsy. Available therapies for children with epilepsy include medical management with antiseizure medications, trial of the ketogenic diet, and evaluation for epilepsy surgeries. This chapter will highlight the diagnostic criteria for epilepsy, common epilepsy syndromes according to the recent updated International League Against Epilepsy (ILAE) Classification, and when to refer to an epilepsy center for specialized treatments if not readily available such as the ketogenic diet, phase 1 presurgical evaluation, and epilepsy surgery. This chapter will also briefly highlight frequent comorbidities with epilepsy such as psychogenic nonepileptic seizures and attention deficit hyperactivity disorder and the challenges related to seizure mimics. This chapter will therefore highlight the diagnosis, workup, and management of both medically responsive epilepsy and drug resistant epilepsy (DRE) as well as its comorbidities. This chapter is a comprehensive review of the literature for the diagnosis and treatment of epilepsy and the author's experience of practice working at Riley Hospital for Children at Indiana University Health which is a National Association of Epilepsy Centers (NAEC) Level 4 Epilepsy Center.

Keywords: epilepsy, seizures, antiseizure medications, ketogenic diet, presurgical evaluation, epilepsy surgery, neuromodulation, magnetic resonance imaging, electroencephalogram, next generation sequencing

1. Introduction

Epilepsy is a syndrome of recurrent seizures with an operational definition of high risk of occurrence of seizures at or above 60% [1]. This risk of occurrence of seizures can be met several ways with the following: two unprovoked seizures which are 24 hours apart or one unprovoked seizure and a diagnostic workup placing the patient at high risk of occurrence of seizure with the Electroencephalogram (EEG), structural imaging with Magnetic Resonance Imaging (MRI) of the brain, or genetic testing [1]. Following the diagnosis of epilepsy, the clinician should initiate therapy to reduce the risk of continued seizures to prevent sudden unexplained death in epilepsy (SUDEP) [2, 3].

For most patients with epilepsy, the first two seizure medications with appropriate mechanisms for the treatment of their seizures result in seizure freedom if side effects are not encountered [4]. Despite the development of many available new antiseizure medications, rates of seizure freedom with medical management alone are not increased for those patients with drug resistant epilepsy (DRE) [5].

Given that rates of seizure freedom following the diagnosis of DRE are low with medical management alone, referral to a comprehensive epilepsy center which is capable of treatments such as the ketogenic diet, presurgical evaluation, and epilepsy surgeries such as resective, ablative, disconnective, and neuromodulation surgeries should be performed at the time of diagnosis of DRE [6].

1.1 Recognizing epileptic seizures

Epileptic seizures are paroxysmal events with discrete onset, offset, and often post ictal state [7]. The International League Against Epilepsy (ILAE), an international association of clinicians and scientists dedicated to evidence-based and efficacious practice of medicine for children and adults with epilepsy, recently released a position paper which describes epileptic seizures by semiology for identification of focal onset, generalized onset, or unknown onset [7]. Seizure classification begins with the history of the patient's description of their seizures along with visual analysis of the events by caregivers [7].

Seizures are broadly divided into generalized onset and focal onset referring to the early activation of networks in the brain, and within these two broad categories are subgroups of epileptic seizures which will be described [7].

Generalized onset seizures are subdivided into motor or nonmotor seizures with the motor features being tonic, atonic, tonic clonic, or myoclonic, while nonmotor seizures are classified as typical absence, atypical absence, absence with myoclonia or absence with eyelid myoclonia [7]. Focal onset seizures by contrast can be classified with hypermotor movements, automatic behavior, arrest of behavior, emotional response, sensory changes, or lateralized motor features such as tonic, atonic, tonic clonic, or myoclonic movements [7]. Focal onset seizures furthermore can be classified as retained awareness or impaired awareness to designate whether memory remains intact throughout the seizure or not [7]. Assessing awareness during a seizure requires delivery of a code word to determine if memory is intact throughout a seizure. At Riley Hospital for Children, code words are a color and an object such as "red truck" which, if remembered by the patient after the seizure is over, suggest focal retained awareness at the onset of the seizure symptoms. At times, seizures cannot be adequately classified as focal or generalized in onset based on the semiology alone and so are classified as unknown onset [7]. It is also possible for patients to have comorbid focal onset and generalized onset seizures [7].

One feature of seizure which highly supports focal onset by history is the patient self-reporting positive symptoms such as tastes, smells, déjà vu, visual phenomena, paresthesias, or strong emotional response which could all be auras [8]. Auras which do not progress to a secondarily generalized seizure with loss of awareness could be consistent with focal retained awareness seizures [8]. Focal retained awareness seizures can be challenging to diagnose other than by empiric treatment due to many patients with focal retained awareness seizures having negative EEG tracings during the ictus [9]. As the focal onset seizure spreads to involve both hemispheres, impacting the circuits of papez, the patient then loses awareness and an ictal pattern is seen in most cases [10, 11].

Table 1 describes the typical semiology, duration, and features of each subtype of seizure commonly experienced by the patient.

1.2 Provoked and unprovoked epileptic seizures

Epileptic seizures may be provoked or unprovoked [12–14]. A provoked epileptic seizure is a seizure with cause explaining its occurrence which is not intrinsic to the patient's brain [12, 13]. Provoked seizures have a broad differential including electrolyte abnormalities (hyponatremia, hypocalcemia, hypomagnesemia, hypoglycemia, and hyperglycemia), metabolic derangements such as hyperammonemia,

Seizure Type	Focal or Generalized Onset	Typical Duration	Semiology
Typical Absence (Petit Mal)	Generalized	5–10 seconds	Staring with behavior arrest, possibly eyelid fluttering, and loss of awareness without post ictal state
Atypical Absence	Generalized	20–60 seconds	Slowing of movement with staring and decreased responsiveness but often not clear behavior arrest
Focal Retained Awareness Seizure (Simple Partial)	Focal	60–120 seconds	Aura of tastes, smells, déjà vu, visual phenomena, paresthesia, or strong emotional response without loss of awareness
Focal Impaired Awareness Seizure (Complex Partial or Dyscognitive)	Focal	60–120 seconds	Aura of tastes, smells, déjà vu, visual phenomena, paresthesia, or strong emotional response progressing to loss of awareness and possibly secondary generalized tonic clonic seizure with post ictal state
Myoclonic Seizure	Focal or Generalized	< 1 second each	Twitching of the extremities with rapid and sudden movement which can cluster but typically are not rhythmic in a cluster
Clonic Seizure	Focal or Generalized	5–120 seconds	Rhythmic twitching of the extremities with rapid and sudden movement which clusters into rhythmic shaking
Generalized Tonic clonic Seizure (Grand Mal)	Generalized	60–120 seconds	Sudden loss of awareness with or without vocalization and stiffening of the extremities followed by rhythmic shaking and post ictal state and patients often fall
Tonic Seizure (Drop attack)	Focal or Generalized	3–10 seconds	Sudden stiffening of the extremities with or without loss of awareness and generally without post ictal state and patients often fall
Atonic Seizure (Drop attack)	Generalized	< 1–2 seconds	Sudden loss of tone with head drop and patients often will hit their head and fall without post ictal state
Infantile Epileptic Spasms Syndrome (Epileptic Spasms)	Focal or Generalized	< 3 seconds and cluster out of sleep	Stereotyped flexor or extensor clonic tonic stiffening events which each are each about 3 seconds and cluster out of sleep about every 10–15 seconds. These often disturb the patient and result in crying.

Table 1.
Seizure subtypes which are classified by onset (generalized or focal), duration in seconds, and expected semiology of each subtype.

hyperthermia seen commonly with febrile seizures between 6 months and 6 years of age, hypoxia, trauma with intracranial hemorrhage, and infectious causes such as meningitis/encephalitis [12, 13].

In the case of provoked seizures, the clinician should correct any offending provoking factor, though antiepileptics may raise the seizure threshold while the provoking factor is addressed. For example, electrolyte abnormalities which are detected should be corrected, lesions on head imaging requiring surgical management should be repaired/excised, intoxications with illicit substances should be detected and detoxified, and infectious causes ruled out with lumbar puncture or treated as appropriate [12, 13]. Patients with provoked seizures should still be treated with antiseizure medications while the provoking factor is addressed [12, 13]. Workup for provoked seizures which is generally performed in the emergency department following complete history and neurologic examination includes complete blood count (CBC), complete metabolic panel (CMP), Magnesium, and head imaging with either computed tomography (CT) or magnetic resonance imaging (MRI). Other workups to consider include Urine Drug Screen, Lactate, Pyruvate, Ammonia, Arterial Blood Gas (ABG), and lumbar puncture for total nucleated cell count, glucose, protein, and culture and stain [14].

Unprovoked seizures by contrast occur spontaneously in patients with epilepsy in the absence of provoking factors [14]. Multiple seizures which are unprovoked are highly suggestive of epilepsy as multiple unprovoked seizures constitutes high risk of recurrence of unprovoked seizures [1, 14]. Once a patient has multiple unprovoked seizures, the clinician should initiate treatment even prior to workup for the underlying cause.

1.3 Nonepileptic seizure mimics

Complicating the diagnosis of epilepsy are the many seizure mimics which include inattentiveness as is seen with attention deficit hyperactivity disorder (ADHD), sleep disturbances, autism spectrum disorder with poor social reciprocity, stereotypies, self-gratification behaviors, other subcortical movement disorders such as tic disorders, and psychogenic nonepileptic spells [15–17]. For this reason, if there is a low clinical suspicion of epileptic seizure, video EEG (VEEG) to spell capture events can be very helpful to rule out seizures, while routine EEG and head imaging are helpful for ruling in a diagnosis of epilepsy. In other words, the routine EEG and head imaging are sensitive for diagnosis of epilepsy, though they are not specific, while VEEG with characteristic events captured can both rule in and rule out epileptic seizures.

1.4 Diagnostic workup after suspected first unprovoked seizure

Diagnostic workup for epilepsy etiology in the outpatient setting after first time seizure includes imaging of the head with either CT or more ideally MRI of the brain to look for symptomatic lesions. Some of these lesions may be surgical such as hemorrhages which need to be evacuated in the case of accidental or nonaccidental trauma, supratentorial tumors, or infectious causes such as abscesses or empyema [1]. The EEG may be utilized to predict risk of occurrence of seizures as well by detecting interictal discharges or demonstrating seizure onset if seizures are captured [1, 18]. Genetic testing with chromosome microarray, epilepsy gene panels, or next generation sequencing testing, and metabolic testing can also be considered [19, 20].

Generally, the diagnosis of epilepsy is made following a first-time unprovoked seizure with rule out of provoking factors along with the detection of interictal

discharges or ictal patterns on an EEG, the detection of a lesion on the imaging of the head which indicates continued risk of occurrence of seizures, or having known genetic predisposition from testing [1, 14].

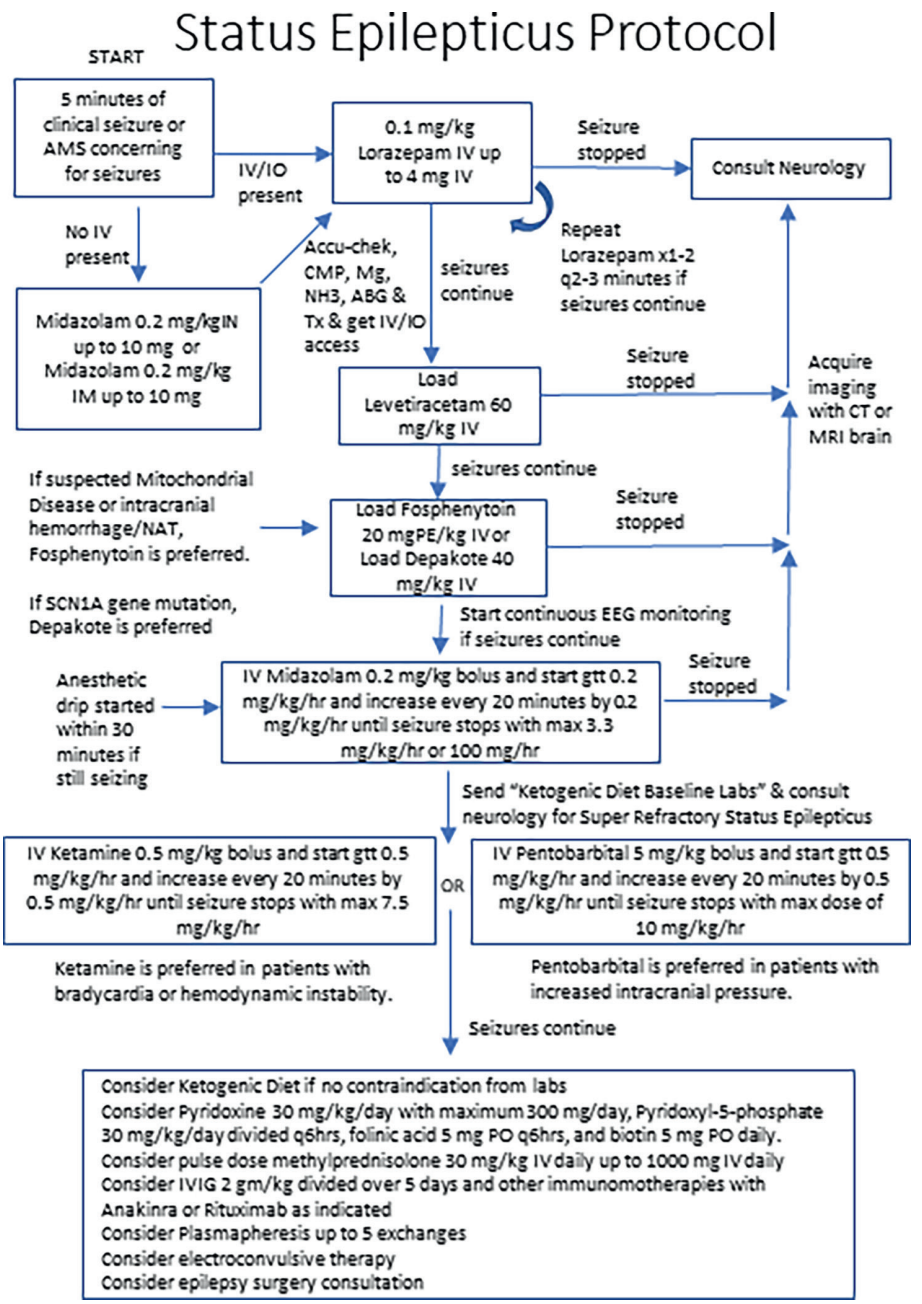

Figure 1.
Status epilepticus protocol for children beyond the neonatal period which begins at 5 minutes of clinical seizure and ends with cessation of status epilepticus. IM = intramuscular, IN = intranasal, IV = intravenous, IO = intraosseous, gtt = drip.

1.5 Protocol for status epilepticus

The first time provoked or unprovoked seizure in a patient may be consistent with status epilepticus if a seizure is longer than 5 minutes [1]. Status epilepticus as a first-time seizure is not equivalent to a diagnosis of epilepsy, though it is a medical emergency requiring urgent management with associated morbidity and mortality if not treated emergently [1, 14]. At Riley Hospital for Children, a status epilepticus protocol is utilized for the prompt and efficacious treatment of status epilepticus with concomitant diagnosis and management of the prolonged seizure (**Figure 1**).

Treatment of seizure per this protocol involves detecting and correcting provoking factors while initiating therapies for resolution of status epilepticus starting at 5 minutes [21]. Initiating treatment for status epilepticus at 5 minutes is indicated to reduce risk of physiologic loss of neurons which occurs if status is not treated quickly [21]. Refractory status epilepticus (RSE) occurs when the seizure does not stop with loads of seizure medication and super refractory status epilepticus (SRSE) is defined as continuous seizure despite initiation of anesthetic coma [21]. SRSE carries morbidity and mortality, so additional diagnostic testing to determine the underlying cause of SRSE should be conducted by the neurologist if seizures do not respond to anesthetic coma as expected.

The treatment of status epilepticus at Riley Hospital for Children in the neonatal period starts with loads of phenobarbital 20 mg/kg IV given twice followed by keppra 30 mg/kg IV given twice, while considering treatment of underlying metabolic epilepsy from inborn errors of metabolism with pyridoxine, pyridoxyl-5-phosphate, folinic acid, and biotin followed by midazolam anesthetic drip [22].

Neuronal loss and injury due to status epilepticus is seen as evidenced by cytotoxic edema seen on MRI of the brain following treatment of prolonged status epilepticus [21]. Status epilepticus should by promptly identified and the clinician should initiate an aggressive treatment protocol to avoid injury [21]. Thankfully, the majority of patients without a provoking cause of seizure which needs to be corrected do respond to appropriately dosed benzodiazepines and the first load of appropriately dosed antiseizure medications, making very prolonged status epilepticus rare if treated aggressively [21]. This protocol for treatment of status epilepticus is invaluable for the prompt treatment of status epilepticus. Involving the pediatric neurologist at the start or throughout this protocol is appropriate given that status epilepticus can cause permanent neurologic injury if not promptly treated.

2. Treatment of epileptic seizures with maintenance medications

Broadly, there are three common treatments for epileptic seizures, being antiseizure medications, the ketogenic diet, and epilepsy surgeries [4–6].

Of the available treatments, antiseizure medications are generally first line and easiest to attempt, with minimal effect on quality of life in many cases. At Riley Hospital for Children, antiseizure medications are dosed via the guidelines in **Table 2**.

Approximately 2/3 of patients with epilepsy will respond to medical management and become seizure free on an appropriate therapeutic dosing of antiseizure medications [23]. For those who are not seizure free with trial of 2 therapeutic trials of antiseizure medications for efficacy, the epileptologist should be involved for the workup and treatment of drug resistant epilepsy (DRE) as even newer medications

Generic Name (Brand Name)	**Dosing**	**Forms**	**Levels**	**Seizure Types Treated**
Brivaracetam (Briviact)	3–5 mg/kg/day	• Liquid • Tablet • Injection	0.2–2.0 mcg/mL	Broad Spectrum
Cannabidiol (Epidiolex)	2.5–20 mg/kg/day	• Liquid	300–450 ng/mL studies only	Broad Spectrum, Dravet Syndrome, Lennox Gastaut Syndrome
Carbamazepine (Tegretol, Epitol, Carbatrol, Tegretol XR)	10–20 mg/kg/day	• Liquid • Tablet • Chewable • XR capsule & tablet	4–12 mg/L of metabolite	Focal Seizures
Cenobamate (Xcopri)	1–7 mg/kg/day	• Tablet	>0.2 mcg/mL	Focal Seizures
Clobazam (Onfi)	0.3–1.3 mg/kg/day	• Liquid • Tablet	30–300 ng/mL	Broad Spectrum
Clonazepam (Klonopin)	0.01–0.05 mg/kg/day	• Tablet • Oral dissolving tablet	Not Established	Broad Spectrum
Ethosuximide (Zarontin)	10–60 mg/kg/day	• Liquid • Capsule	45–100 mcg/mL	Absence Seizures Only
Eslicarbazepine (Aptiom)	20–30 mg/kg/day	• Tablet	3–35 mg/L of metabolite	Focal Seizures
Felbamate (Felbatol)	15–45 mg/kg/day	• Liquid • Tablet	30–60 mg/L	Focal Seizures and Lennox Gastaut Syndrome
Fenfluramine (Fintepla)	0.1–0.35 mg/kg/day	• Liquid	<50 mcg/L in studies	Dravet Syndrome and Lennox Gastaut Syndrome
Gabapentin (Neurontin)	10–50 mg/kg/day	• Liquid • Tablet • Capsule	2–20 mg/L	Focal Seizures
Ganaxolone (Ztalmy)	63 mg/kg/day	• Liquid	500–900 ng/mL	CDKL5 deficiency disorder associated seizures
Lacosamide (Vimpat)	5–10 mg/kg/day	• Liquid • Tablet • Injection	5–10 mg/L	Focal Seizures
Lamotrigine (Lamictal)	1–5 mg/kg/day (On Depakote) 5–15 mg/kg/day (Not on Depakote)	• Tablet • Long acting tablet • Oral dissolving tablet • Chewable	3–14 mg/L	Broad Spectrum but may worsen Myoclonus

Generic Name (Brand Name)	**Dosing**	**Forms**	**Levels**	**Seizure Types Treated**
Levetiracetam (Keppra)	20–60 mg/kg/day	• Liquid • Tablet • Long acting tablet • Disperse tablet • Injection	12–46 mg/L	Broad Spectrum but generally ineffective for absence seizures
Pregabalin (Lyrica)	2.5–14 mg/kg/day	• Liquid • Capsule	2.8–8.3 mg/L	Focal Seizures
Oxcarbazepine (Trileptal)	20–40 mg/kg/day	• Liquid • Tablet • Long acting tablet	3–35 mg/L of metabolite	Focal Seizures
Perampanel (Fycompa)	8–12 mg/day	• Liquid • Tablet	180–610 ng/mL	Focal Seizures
Phenobarbital (Sezaby)	5–7 mg/kg/day	• Liquid • Tablet	15–40 mcg/mL	Broad Spectrum
Phenytoin (Dilantin)	5–7 mg/kg/day	• Liquid • Chewable tablet • Long acting capsule • Injection	10–20 mcg/mL	Broad Spectrum though avoided in Dravet Syndrome
Prednisolone (Rayos)	8 mg/kg/day with taper	• Liquid • Tablet • Oral dissolving tablet	Not established though can measure for compliance	Infantile Spasms
Primidone (Mysoline)	10–25 mg/kg/day	• Tablet	5–10 mg/L	Broad Spectrum
Rufinamide (Banzel)	45 mg/kg/day	• Liquid • Tablet	5–30 mcg/mL	Lennox Gastaut Syndrome
Stiripentol (Diacomit)	50 mg/kg/day	• Capsule • Powder Packet	4–22 mg/L	Dravet Syndrome
Tiagabine (Gabitril)	32 mg/day	• Tablet	0.02–0.2 mg/L	Focal Seizures
Topiramate (Topamax, Eprontia, Trokindi XR, Qudexy XR)	4–9 mg/kg/day	• Liquid, • Sprinkle Capsule • Tablet • Long acting tablet	5–20 mg/L	Broad Spectrum
Valproic Acid (Depakote, Valproate, Depakene)	15–60 mg/kg/day	• Liquid • Sprinkle Capsule • Delayed Release Tablet • Extended Release Tablet • Injectable	40–100 mcg/mL	Broad Spectrum

Generic Name (Brand Name)	Dosing	Forms	Levels	Seizure Types Treated
Vigabatrin (Sabril)	50–150 mg/kg/day	• Tablet • Packets of powder to mix with water	0.8–36 mg/L	Infantile Spasms
Zonisamide (Zonegran)	4–9 mg/kg/day	• Liquid • Capsules	10–40 mg/L	Broad Spectrum
Corticotropin injection (Acthar, ACTH Gel)	40–150 units/m^2/day	• Injectable Gel	Not established	Infantile Spasms
Diazepam (Valium)	0.1–1 mg/kg/day	• Liquid • Tablet	0.2–2.5 mcg/mL	Broad Spectrum

Table 2.
Guidelines for dosing of antiseizure medications in children utilized commonly at Riley Hospital for children including formulations of each medication, therapeutic levels of medications where appropriate, and seizure types treated.

which have been developed have not appreciably increased seizure freedom in children diagnosed with DRE [23–34].

The choice of initial antiseizure medications is based on the patient's epilepsy onset [35–38]. If a patient's epilepsy is determined to be focal, there are many choices for antiseizure medications for focal seizures and broad-spectrum agents both being efficacious [35–38]. If an epilepsy is determined to be generalized by interictal profile and semiology of seizures or unknown in onset, broad-spectrum antiseizure medications are preferentially utilized as narrow spectrum medications could worsen absence seizures and myoclonic seizures [36, 37]. Titration of monotherapy antiseizure medication to side effect or maximal therapeutic dose is generally recommended to demonstrate true medication failure before switching medications or before considering antiseizure medications in combination [39].

There are also dietary therapies with the ketogenic diet, modified Adkins diet, and low glycemic index diet [40], and many surgical options ranging from resection and ablation, disconnection such as corpus callosotomy or functional hemispherotomy, and neuromodulation techniques which are utilized in DRE which will be discussed later in this chapter [41–43].

2.1 Diagnosis and treatment of drug resistant epilepsy

Drug resistant epilepsy (DRE) is diagnosed following trials of two appropriate antiseizure medications failed for efficacy at high therapeutic doses for controlling seizures [4, 6, 18, 23, 41]. Medications can also be tried in synergistic combinations as these do exist; however, it is not necessary to prescribe medications in combination to diagnose DRE [39].

Once a child is diagnosed with DRE with focal onset, generalized onset, focal and generalized onset, or unknown onset, workup initiates to better understand the epilepsy etiology if it is incompletely understood as well as to determine if the patient would be a candidate for potentially curative epilepsy surgery [24–26]. The ILAE has

further assembled a framework for the definition of epilepsy syndromes which are clinically similar though heterogeneous by etiology [44–49]. Within each epilepsy syndrome is a wide range of etiologies with tailored medications and dietary therapy in many cases, so workup for diagnosis of etiology will be important to the neurologist to determine the cause of the drug resistant epilepsy as structural, genetic, metabolic, infectious, autoimmune, or idiopathic [44]. Structural abnormalities causing epilepsy would include cortical dysplasia, periventricular nodular heterotopia, and neoplastic processes as etiologies [44]. Genetic epilepsy is caused by either single gene disorders or is polygenic [44]. Metabolic epilepsies include mitochondrial disorders, vitamin deficiencies, and metabolite storage disorders [44]. Infectious and autoimmune causes are often diagnosed by lumbar puncture showing inflammation of the cerebrospinal fluid [44]. Furthermore, many cases of epilepsy remain idiopathic despite thorough diagnostic workup [44].

A practical example of this approach is the treatment of infantile epileptic spasms syndrome (IESS) which can present as the complete triad of developmental regression, hypsarrhythmia on the EEG, and ictal spasms captured on EEG which was originally described as West Syndrome [50]. In the patient with IESS without known etiology, available therapies include adrenocorticotropic hormone (ACTH), Vigabatrin, and high dose prednisolone [51]. In the case of patients with infantile spasms with comorbid Tuberous Sclerosis as an etiology, Vigabatrin is superior therapy to the hormonal therapies for seizure freedom [50, 51]. For this reason, a thorough physical exam looking for stigmata of tuberous sclerosis such as shagreen patches, ash-leaf macules, angiokeratomas, and imaging studies to identify cortical tubers may prompt genetic testing for the genetic causes in TSC1 and TSC2 and identification of superior therapy with Vigabatrin [50–52].

Another example of a heterogeneous etiology which is medically refractory but often responsive to tailored therapy would be the identification of early infantile developmental epileptic encephalopathies (EIDEE) [46]. EIDEE presents with global developmental delay, tone abnormalities, and seizures under 3 months old, and genetic testing and metabolic testing are high yield, resulting in guidance of therapy [46]. Such genetic mutations include SCN8A or SCN2A which generally are gain of function mutations and so respond to sodium channel blockade [46]. For this reason, early onset seizures with associated developmental delay, dysmorphism, or consanguinity history suggests that genetic testing is high yield. Available genetic testing for patients with suspected genetic epilepsies include chromosome microarray (CMA) and next generation sequencing (NGS) testing such as genetic panels, whole exome sequencing (WES), and whole genome sequencing (WGS) [19, 20]. Of these tests, NGS testing while more expensive remains higher yield than CMA with the cost per diagnosis favoring NGS testing over CMA [20]. Additionally, professional opinion suggests that NGS is very high yield in patients with global developmental delay and epilepsy of any kind.

Following the diagnosis of drug resistant epilepsy, care should be directed to an epilepsy center with pediatric neurologists with epilepsy training to assess candidacy for epilepsy surgery or for continued management through medical and dietary means [4, 6, 18, 24–26].

2.2 Phase 1 presurgical evaluation for drug resistant epilepsy

If a phase 1 presurgical evaluation cannot be performed at your center, referral to an epilepsy center is appropriate once a patient is diagnosed with DRE whether or not the etiology of their epilepsy is known [23–26]. Phase 1 presurgical evaluation

is noninvasive testing aimed at defining as precisely as possible a region of the brain called the epileptogenic zone, which is the smallest region of brain which if removed or destroyed would render the patient with DRE seizure free [18].

Phase 1 evaluation testing for DRE for epilepsy surgery generally includes high resolution MRI of the brain with 3 tesla or higher resolution if available and with thin coronal cuts to detect subtle mesial temporal lesions, prolonged video EEG monitoring with wean of antiseizure medications as needed to capture and lateralize/localize seizures with scalp electrodes, and neuropsyciatric testing if the patient may cooperate with this [26].

Discussion of these patients in multidisciplinary epilepsy committees with input from epileptologists, neurosurgeons, neuropsychologists, and neuroradiologists is critical to establish adequate concordance of the phase 1 presurgical data [25]. The committee will determine if surgery candidacy is clear, if additional phase 1 testing is required, if an invasive phase 2 monitoring will be needed, or if the patient is not a good candidate for resection or ablation [25].

If additional testing is needed to establish surgical candidacy in phase 1, interictal 18F-Fluorodeoxyglucose positron emission tomography computed tomography (FDG-PET/CT) can be utilized to determine regions of the brain where hypometabolism of glucose is noted [53]. Ictal and interictal blood flow studies with Technecium-99 m single-photon emission computed tomography (SPECT) are utilized to directly highlight the epileptogenic zone and can be co-registered with MRI of the brain for anatomic localization [54, 55]. If both interictal SPECT and ictal SPECT scans are acquired, a subtraction scan called Subtraction Ictal SPECT Coregistered to MRI (SISCOM) can be produced which highlights the epileptogenic zone with better delineation if the ictal SPECT is inconclusive [55]. In cases where nonradial dipoles are suspected, magnetoencephalography (MEG) can be utilized to anatomically localize interictal or ictal findings on the EEG by analyzing the magnetic fields detected around the head and solving the "inverse problem" to determine the most likely anatomic localization of the discharges [56].

Functional MRI of the brain, MEG, and Wada testing all are utilized to lateralize the patient's language and motor cortices to prevent injury to these eloquent regions when planning epilepsy surgery [25, 56, 57]. This evaluation is especially important in patients who are left-handed or who had injury to the suspected dominant hemisphere from stroke or other previous pathology as language lateralization is not clearly delineated in this group [58, 59]. The goal of phase 1 presurgical evaluation is definitive epilepsy surgery with ablation or resection which remain the most efficacious interventions, or lateralization or localization of the seizure focus such that a strong hypothesis for seizure localization/lateralization can prompt a phase 2 presurgical evaluation [26].

2.3 Phase 2 presurgical evaluation for drug resistant epilepsy

If lateralization is achieved but localization is unclear after comprehensive phase 1 presurgical evaluation, a decision is often made to explore the brain with phase 2 presurgical evaluation including grids, strips, depth electrodes, or stereo electroencephalography, with placement guided by the epileptologist and neurosurgeon to more accurately localize the patient's seizure onset zone for definitive surgical treatment [26]. At times during the phase 1 or phase 2 of testing for epilepsy surgery, the patient is determined not to be a candidate for resection or ablation surgery due to the epileptogenic zone being multifocal or generalized or involving eloquent cortices [18, 26]. Rather than performing disabling resective or ablative surgery in these cases, neuromodulation and

dietary management are possible for these patients [40, 43]. Cortical mapping during phase 2 evaluation can be performed by the epileptologist by delivering small shocks to each contact which is implanted to determine the location of eloquent cortices at the bedside, which is an additional advantage of phase 2 monitoring [26].

2.4 Neuromodulation

There are currently multiple devices available for neuromodulating seizures which are either placed peripherally or centrally and are open loop or closed loop for reducing seizures [43, 60].

Vagus Nerve Stimulators (VNS) are commonly placed with the generator in the left chest and leads attached to the vagus nerve (CN10) at the neck which produces open loop stimulation with afferent nerves delivering signal through the brainstem and to the cortex which reduces seizures [43]. The more modern generators also have tachycardia detection for delivering shock during a rapid rise in heart rate and comes with a magnet which the family may swipe over the generator to send a larger impulse with the goal of stopping seizures when they occur [43]. VNS has furthermore been shown to reduce risk of SUDEP in cohorts with DRE over 3–10 years of monitoring [61].

Deep Brain Stimulation (DBS) is another open loop system stimulating various nuclei of the brain with the goal of reducing seizures [62]. The anterior nucleus of the thalamus DBS has reduced seizures in patients with frontotemporal epilepsy [62]. Anterior nucleus DBS also has been shown to reduce risk of SUDEP, though it involves intracranial surgery [63]. There is evidence for DBS placement in the centromedian parafascicular nuclei complex which may show efficacy for generalized or multifocal onset seizures, though this target is being studied [60].

Reactive neurostimulation (RNS) is also approved for the treatment of focal epilepsy and is a closed loop system [60, 64]. This device is implanted within the skull and with electrodes placed on the surface of the brain or depth electrodes, which are capable of recording seizures with electrocorticography and delivering current to stop seizures [60, 64]. Like VNS and DBS, there is evidence for reduction of seizures over time and reduction in SUDEP risk as well [60, 64]. RNS can be utilized to treat two foci of seizure onset once localized and can treat seizures arising from eloquent cortex which cannot be addressed with resection or ablative surgeries [64].

2.5 Corpus callosotomy

Corpus callosotomy (CC) is a disconnection procedure which divides the hemispheres of the brain by severing the commissural white matter tract between hemispheres [65]. CC is especially effective for seizures which are generalized and result in fall injuries, such as tonic and atonic seizures [65]. CC has been used to lateralize a seizure focus that appeared bilateral on scalp and intracranial monitoring for definitive epilepsy surgery when focal semiology was suspected [66].

2.6 Ketogenic diet

For patients with drug resistant epilepsy who are not candidates for definitive surgery or if the family prefers additional nonsurgical and nonmedical therapies for epilepsy, the ketogenic diet can be utilized for both generalized and focal onset seizures [40]. Through phase 1 presurgical evaluation, many patients with drug resistant epilepsy are determined not to be effective surgical candidates and have

side effects from antiseizure medication polytherapy. Certain metabolic disorders such as patients with SLC2A1 gene mutation are also excellent candidates for the diet [40]. The ketogenic diet is a high fat and low carbohydrate diet aimed at adjusting the metabolism of the brain to reduce hyperexcitability of neurons and to reduce seizures [40]. Before starting the ketogenic diet, contraindications to its use should first be ruled out including fatty acid oxidation disorders, or other metabolic disorders which could potentially be worsened by the high fat diet [40].

At Riley Hospital for Children, baseline labs are performed with serum Complete Blood Count, Complete Metabolic Panel, Phosphorous, Magnesium, Lipid Panel, Vitamin D, Free and total carnitine, Prealbumin, Lactate, Ammonia, Uric acid, Zinc, Selenium, Amino Acid Profile, acylcarnitine analysis, and Ferritin along with urine Amino Acid Profile and Organic Acid Screen. If no contraindications to the diet are found, the ketogenic diet can be attempted with the help of a registered dietician generally titrating to a 4:1 ratio of fat to protein and carbohydrates [40].

Side effects of the ketogenic diet include weight loss, constipation, risk of kidney stones, risk of pancreatitis, and hyperlipidemia [40]. Additional considerations are that liquid medication often contains too many carbohydrates for use so families generally have to switch medications to tablet formulations [67].

3. Seizure safety and acute treatment

Even before epilepsy is diagnosed and treated, seizure precautions and first aid should be discussed with patients and families presenting for a first-time seizure, while performing diagnostic workup [68, 69]. Seizure first aid includes staying with the patient, rolling them on their side, and keeping the patient safe while timing the seizure [70]. For seizures over 5 minutes, various rescue medications are utilized which may be made available if prescribed by treating physicians, and activating emergency services is advised if a seizure is longer than 5 minutes, as this is consistent with status epilepticus which should be treated emergently (**Figure 1**). **Table 3** shows available seizure rescue medications.

Seizure precautions to prevent injuries during even brief seizures should be discussed with patients who have had even one seizure [68]. Precautions include

Medication	Sizes	Route of Administration	Dosing
Diazepam (Diastat)	2.5 mg, 10 mg, 20 mg	Rectal gel	2–5 years = 0.5 mg/kg/dose 6–11 years = 0.3 mg/kg/dose ≥12 years = 0.2 mg/kg/dose
Diazepam (Valtoco)	5 mg, 10 mg, 15 mg, 20 mg	Intranasal kit	6–11 years = 5 mg if 10–18 kg, 10 mg if 19–37 kg, 15 mg if 38–55 kg, and 20 mg if ≥56 kg ≥12 years = 5 mg if 14–27 kg, 10 mg if 28–50 kg, 15 mg if 51–75 kg, and 20 mg if ≥76 kg
Midazolam (Versed, Nayzilam)	5 mg	Intranasal kit	≥12 years = 5 mg intranasal and may repeat for 10 mg total

These are pre-dosed by the prescribing physician so can be utilized for seizure over 5 minutes or clusters of seizures over 5 minutes without return to baseline.

Table 3.
Available antiseizure medications for seizure first aid with bystanders.

swimming with only 1:1 adult supervision, avoiding baths while unattended, not climbing heights which are not enclosed, refraining from using hot objects, power tools, or other objects which may result in injury during a seizure, and generally considering the safety of an activity with the occurrence of a typical seizure [68].

Activities generally considered safe for children with epilepsy are sports without heavy contact, standing water, or heights. Photosensitive epilepsy can be ruled out by exposing the patient to various flash frequencies (1, 3, 6, 9, 12, 15, 20, and 30 Hz) while hooked to EEG. Children with epilepsy should be given autonomy to select safe activities with their peers to improve their quality of life [68–70].

4. Conclusions

For the primary care physician and other subspecialists providing care to patients with seizures, identification of epilepsy requires assessment of the complete history including number of suspected seizures that the patient has previously experienced along with the semiology of those events. If the patient has had two or more events consistent with epileptic seizures which are separated by time, the risk of recurrence is high enough to diagnose with epilepsy undetermined as to generalized or focal onset and start seizure medications, generally with broad spectrum agents as the first choice if the onset of seizures is unclear. Workup following a first-time unprovoked seizure includes an EEG and MRI of the brain with additional electrographic data or lesions contributing to the diagnosis of epilepsy after a single seizure. Drug resistant epilepsy (DRE) is diagnosed with failure of two appropriate antiseizure medications at therapeutic trials for efficacy. Patients with DRE are unlikely to achieve seizure freedom with antiseizure medications alone so should be referred to an epilepsy center for presurgical evaluation while additional medical management and the ketogenic diet can be considered. Seizure precautions and first aid education should be provided to all families with children who are diagnosed with epilepsy and for children with even one seizure to reduce risk of injuries with subsequent seizures. Rescue medication can be provided after a first unprovoked seizure in anticipation of the possibility of additional seizures.

Acknowledgements

This chapter was written without funding.

Conflict of interest

There are no conflicts of interest.

Thanks

I would like to thank my wife, Trisha Miller, who always supports me through my work and is the best spouse I could fathom. I would also like to thank all of my mentors at the Indiana University School of Medicine and Graduate Medical Education for my training and for preparing me to write this chapter.

Childhood Epilepsies and When to Refer for Epilepsy Surgery Evaluation
DOI: http://dx.doi.org/10.5772/intechopen.1005271

Author details

Derryl Miller
Riley Hospital Dr., Indiana University School of Medicine, Indianapolis, IN, USA

*Address all correspondence to: miller89@iupui.edu

References

[1] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross H, Elger CE, et al. A practical clinical definition of epilepsy. Epilepsia. 2014;**55**(4):475-482. DOI: 10.1111/epi.12550

[2] Shankar R, Donner EJ, McLean B, Nashef L, Tomson T. Sudden unexpected death in epilepsy (SUDEP): What every neurologist should know. Epileptic Disorders. 2017;**19**(1):1-9. DOI: 10.1684/epd.2017.0891

[3] Maguire M, Jackson C, Marson A, Nevitt S. Treatments to prevent sudden unexplained death in epilepsy (SUDEP). The Cochrane Database of Systematic Reviews. 2020;**4**:CD011792. DOI: 10.1002/14651858.CD011792.pub3

[4] 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):1069-1077. DOI: 10.1111/j.1528-1167.2009.02397.x

[5] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: A 30-year longitudinal cohort study. JAMA Neurology. 2018;**75**(3):279-286. Erratum in: JAMA Neurol. 2018;75(3):384. DOI: 10.1001/jamaneurol.2017.3949

[6] Jehi L, Jette N, Kwon CS, Josephson CB, Burneo JG, Cendes F, et al. Timing of referral to evaluate for epilepsy surgery: Expert consensus recommendations from the surgical therapies commission of the international league against epilepsy. Epilepsia. 2022;**63**(10):2491-2506. DOI: 10.1111/epi.17350

[7] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the international league against epilepsy: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;**58**(4):522-530. DOI: 10.1111/epi.13670

[8] Ighodaro ET, Maini K, Arya K, Sharma S. Focal Onet Seizure. In: Statpearls. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK500005/

[9] Devinsky O, Kelley K, Porter RJ, Theodore WH. Clinical and electroencephalographic features of simple partial seizures. Neurology. 1988;**38**(9):1347-1352. DOI: 10.1212/wnl.38.9.1347

[10] Bhattacharyya KB. James Wenceslaus Papez, his circuit, and emotion. Annals of Indian Academy of Neurology. 2017;**20**(3):207-210. DOI: 10.4103/aian.AIAN_487_16

[11] Kumar A, Sharma S. Focal Imparied Awareness Seizure. Treasure Island, FL: StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519030/

[12] Misra UK, Kalita J. Management of provoked seizure. Annals of Indian Academy of Neurology. 2011;**14**(1):2-8. DOI: 10.4103/0972-2327.78041

[13] Berg AT. Are febrile seizures provoked by a rapid rise in temperature? American Journal of Diseases of Children. 1993;**147**(10):1101-1103. DOI: 10.1001/archpedi.1993.02160340087020

[14] Gulati S, Kaushik JS. How I treat a first single seizure in a

child. Annals of Indian Academy of Neurology. 2016;**19**(1):29-36. DOI: 10.4103/0972-2327.173404

[15] Patel H, Blake H, Dunn D. Psychogenic nonepileptic seizures in children and adolescents. Indian Pediatrics. 2021;**58**(3):259-265. DOI: 10.1007/s13312-021-2167-9

[16] Seeber M, Cantonas LM, Hoevels M, Sesia T, Visser-Vandewalle V, Michel CM. Subcortical electrophysiological activity is detectable with high-density EEG source imaging. Nature Communications. 2019;**10**(1):753. DOI: 10.1038/s41467-019-08725-w

[17] Miller DJ, Komanapalli H, Dunn DW. Comorbidity of attention deficit hyperactivity disorder in a patient with epilepsy: Staring down the challenge of inattention versus nonconvulsive seizures. Epilepsy & Behavior Reports. 2024;**25**:100651. DOI: 10.1016/j.ebr.2024.100651

[18] Jehi L. The epileptogenic zone: Concept and definition. Epilepsy Currents. 2018;**18**(1):12-16. DOI: 10.5698/1535-7597.18.1.12

[19] Chang YT, Hong SY, Lin WD, Lin CH, Lin SS, Tsai FJ, et al. Genetic testing in children with developmental and epileptic encephalopathies: A review of advances in epilepsy genomics. Children (Basl). 2023;**10**(3):556. DOI: 10.3390/children10030556

[20] Sánchez Fernández I, Loddenkemper T, Gaínza-Lein M, Sheidley BR, Poduri A. Diagnostic yield of genetic tests in epilepsy: A meta-analysis and cost-effectiveness study. Neurology. 2019;**92**(5):e418-e428. DOI: 10.1212/WNL.0000000000006850

[21] Samanta D, Garrity L, Arya R. Refractory and super-refractory status epilepticus. Indian Pediatrics. 2020;**57**(3):239-253. DOI: 10.1007/s13312-020-1759-0

[22] Moeller AA, Stefanescu AR, Stefanescu BM, Golomb MR, Boyle FA, Buss WF, et al. A standardized, 3-tiered, seizure burden-based protocol for the treatment of neonatal seizures. Journal of Child Neurology. 2023;**38**(3-4):142-152. DOI: 10.1177/08830738231164704

[23] Moosa ANV. Antiepileptic drug treatment of epilepsy in children. Continuum (Mineap Minn). 2019;**25**(2 Epilepsy):381-407. DOI: 10.1212/CON.0000000000000712

[24] Mesraoua B, Brigo F, Lattanzi S, Abou-Khalil B, Al Hail H, Asadi-Pooya AA. Drug-resistant epilepsy: Definition, pathophysiology, and management. Journal of the Neurological Sciences. 2023;**452**:120766. DOI: 10.1016/j.jns.2023.120766

[25] Guery D, Rheims S. Clinical management of drug resistant epilepsy: A review on current strategies. Neuropsychiatric Disease and Treatment. 2021;**17**:2229-2242. DOI: 10.2147/NDT.S256699

[26] Baumgartner C, Koren JP, Britto-Arias M, Zoche L, Pirker S. Presurgical epilepsy evaluation and epilepsy surgery. F1000Res. 2019;**8**:F1000 Faculty Rev-1818. DOI: 10.12688/f1000research.17714.1

[27] Makridis KL, Bast T, Prager C, Kovacevic-Preradovic T, Bittigau P, Mayer T, et al. Real-world experience treating pediatric epilepsy patients with cenobamate. Frontiers in Neurology. 2022;**13**:950171. DOI: 10.3389/fneur.2022.950171

[28] Krasowski MD. Therapeutic drug monitoring of the newer anti-epilepsy

medications. Pharmaceuticals (Basel). 2010;**3**(6):1909-1935. DOI: 10.3390/ph30619109

[29] Shi LL, Dong J, Ni H, Geng J, Wu T. Felbamate as an add-on therapy for refractory partial epilepsy. Cochrane Database of Systematic Reviews. 2017;**7**(7):CD008295. DOI: 10.1002/14651858.CD008295.pub4

[30] Li Y, Dong N, Qin YX, Dai HR, Hu YH, Zhao YT, et al. Therapeutic drug monitoring of parampanel in children diagnosed with epilepsy: Focus on influencing factors on the plasma concentration-to-dose-ratio. Epilepsia Open. 2022;**7**(4):737-746. DOI: 10.1002/epi4.12653

[31] Bentué-Ferrer D, Verdier MC, Tribut O. Therapeutic drug monitoring of primidone and phenobarbital. Thérapie. 2012;**67**(4):381-390. French. DOI: 10.2515/therapie/2012036

[32] Singh RK, Singh R, Stewart A, Van Poppel K, Klinger S, Hulihan J, et al. Intravenous ganaxolone in pediatric super-refractory status epilepticus: A single hospital experience. Epilepsy & Behavior Reports. 2022;**20**:100567. DOI: 10.1016/j.ebr.2022.100567

[33] Vaitkevicius H, Ramsay RE, Swisher CB, Husain AM, Aimetti A, Gasior M. Intravenous ganaxolone for the treatment of refractory status epilepticus: Results from an open-label, dose-finding, phase 2 trial. Epilepsia. 2022;**63**(9):2381-2391. DOI: 10.1111/epi.17343

[34] Kanner AM, Ashman E, Gloss D, Harden C, Bourgeois B, Bautista FJ, et al. Practice guideline update summary: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new-onset epilepsy: Report of the guideline development, dissemination, and implementation Subcommittee of the American Academy of neurology and the American Epilepsy Society. Neurology. 2018;**91**(2):74-81. DOI: 10.1212/WNL.0000000000005755

[35] Gunasekera CL, Sirven JI, Feyissa AM. The evolution of antiseizure medication therapy selection in adults: Is artificial intelligence-assisted antiseizure medication selection ready for prime time? Journal of Central Nervous System Disease. 2023;**15**:1-13. DOI: 10.1177/11795735231209209

[36] Håkansson S, Wickström R, Zelano J. Selection and continuation of antiseizure medication in children with epilepsy in Sweden from 2007 to 2020. Pediatric Neurology. 2023;**144**:19-25. DOI: 10.1016/j.pediatrneurol.2023.03.016

[37] Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Chadwick D, Guerreiro C, et al. ILAE treatment guidelines: Evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2006;**47**(7):1094. DOI: 10.1111/j.1528-1167.2006.00585.x

[38] Arya R, Glauser TA. Pharmacotherapy of focal epilepsy in children: A systemic review of approved agents. CNS Drugs. 2013;**27**(4):273. DOI: 10.1007/s40263-013-0048-z

[39] Park KM, Kim SE, Lee BI. Antiepileptic drug therapy in patients with drug-resistant epilepsy. Journal of Epilepsy Research. 2019;**9**(1):14-26. DOI: 10.14581/jer.19002

[40] D'Andrea MI, Romão TT, Pires do Prado HJ, Krüger LT, MEP P, da Conceição PO. Ketogenic diet and epilepsy: What we know so far. Frontiers in Neuroscience. 2019;**13**:5. DOI: 10.3389/fnins.2019.00005

[41] Miller JW, Hakimian S. Surgical treatment of epilepsy. Continuum (Minneap Minn). 2013;**19**(3 Epilepsy):730-742. DOI: 10.1212/01.CON.0000431398.69594.97

[42] Hwang JK, Kim DS. From resection to disconnection for seizure control in pediatric epilepsy children. Journal of Korean Neurosurgical Association. 2019;**62**(3):336-343. DOI: 10.3340/jkns.2019.0031

[43] Ryvlin P, Rheims S, Hirsch LJ, Sokolov A, Jehi L. Neuromodulation in epilepsy: State-of-the-art approved therapies. Lancet Neurology. 2021;**20**(12):1038-1047. DOI: 10.1016/S1474-4422(21)00300-8. Erratum in: Lancet Neurol. 2021;20(12):e7

[44] Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for classification and terminology. Epilepsia. 2017;**58**(4):512-521. DOI: 10.1111/epi.13709

[45] Wirrell E, Tinuper P, Perucca E, Moshé SL. Introduction to the epilepsy syndrome papers. Epilepsia. 2022;**63**(6):1330-1332. DOI: 10.1111/epi.17262

[46] Zuberi SM, Wirrell E, Yozawitz E, Wilmshurst JM, Speccio N, Riney K, et al. ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE task force on nosology and definitions. Epilepsia. 2022;**63**(6):1349-1397. DOI: 10.1111/epi.17239

[47] Speccio N, Wirrell EC, Scheffer IE, Nabbout R, Riney K, Samia P, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE task force on nosology and definitions. Epilepsia. 2022;**63**(6):1398-1442. DOI: 10.1111/epi.17241

[48] Riney K, Bogacz A, Somerville E, Hirsch E, Nabbout R, Scheffer IE, et al. International league against epilepsy classification and definition of epilepsy syndromes with onset at a variable age: Position statement by the ILAE task force on nosology and definitions. Epilepsia. 2022;**63**(6):1443-1474. DOI: 10.1111/epi.17240

[49] Hirsch E, French J, Scheffer IE, Bogacz A, Alsaadi T, Sperling MR, et al. ILAE definition of the idiopathic generalized epilepsy syndromes: Position statement by the ILAE task force on nosology and definitions. Epilepsia. 2022;**63**(6):1475-1499. DOI: 10.1111/epi.17236

[50] Nelson GR. Management of infantile spasms. Translational Pediatrics. 2015;**4**(4):260-270. DOI: 10.3978/j.issn.2224-4336.2015.09.01

[51] Go CY, Mackay MT, Weiss SK, Stephens D, Adams-Webber T, Ashwal S, et al. Child neurology society, American Academy of Neurology. Evidence-based guideline update: Medical treatment of infantile spasms. Report of the guideline development Subcommittee of the American Academy of neurology and the practice Committee of the Child Neurology Society. Neurology. 2012;**78**(24):1974-1980. DOI: 10.1212/WNL.0b013e318259e2cf

[52] Miller D, Felker M, Ciccarelli M. Transitioning ambulatory medicine from pediatrics to adult care for patients with epilepsy and intellectual disability. Journal of Pediatric Epilepsy. 2020;**9**(4):172-176. DOI: 10.1055/s-0040-1717135

[53] de Laat NN, Tolboom N, Leijten FSS. Optimal timing of interictal FDG-PET

for epilepsy surgery: A systemic review on time since last seizure. Epilepsia. 2022;**7**(3):512-517. DOI: 10.1002/epi4.12617

[54] Lee WW, K-SPECT Group. Clinical applications of technetium-99m quantitative single-photon emission computed tomography/computed tomography. Nuclear Medicine and Molecular Imaging. 2019;**53**(3):172-181. DOI: 10.1007/s13139-019-00588-9

[55] Yassin A, El-Salem K, Al-Mistarehi AH, Momani A, Zein Alaabdin AM, Shah P, et al. Use of innovative SPECT techniques in the presurgical evaluation of patients with nonlesional extratemporal drug-resistant epilepsy. Molecular Imaging. 2021;**2021**:6614356. DOI: 10.1155/2021/6614356

[56] Singh SP. Magnetoencephalography: Basic principles. Annals of Indian Academy of Neurology. 2014;**17**(Suppl. 1):S107-S112. DOI: 10.4103/0972-2327.128676

[57] Somers M, Negers SF, Diederen KM, Boks MP, Kahn RS, Sommer IE. The measurement of language lateralization with functional transcranial Doppler and functional MRI: A critical evaluation. Frontiers in Human Neuroscience. 2011;**5**:31. DOI: 10.3389/fnhum.2011.00031

[58] Pritchard VE, Malone SA, Burgoyne K, Heron-Delaney M, Bishop DVM, Hulme C. Stage 1 registered report: The relationship between handedness and language ability in children. Wellcome Open Research. 2019;**4**:30. DOI: 10.12688/wellcomeopenres.15077.1

[59] Rolinski R, You X, Gonzalez-Castillo J, Norato G, Reynolds RC, Inati SK, et al. Language lateralization from task-based and resting state functional MRI in patients with epilepsy. Human Brain Mapping. 2020;**41**(11):3133-3146. DOI: 10.1002/hbm.25003

[60] Simpson HD, Schulze-Bonhage A, Cascino GD, Fisher RS, Jobst BC, Sperling MR, et al. Practical considerations in epilepsy neurostimulation. Epilepsia. 2022;**63**(10):2445-2460. DOI: 10.1111/epi.17329

[61] Ryvlin P, So EL, Gordon CM, Hesdorffer DC, Sperling MR, Devinsky O, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia. 2018;**59**(3):562-572. DOI: 10.1111/epi.14002

[62] Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia. 2010;**51**(5):899-908. DOI: 10.1111/j.1528-1167.2010.02536.x

[63] Salanova V, Sperling MR, Gross RE, Irwin CP, Vollhaber JA, Giftakis JE, et al. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. Epilepsia. 2021;**62**(6):1306-1317. DOI: 10.1111/epi.16895

[64] Bergey GK, Morrell MJ, Mizahi EM, Goldman A, King-Stephens D, Nair D, et al. Long-term treatment with responsive brain stimulation in adults with refractory and partial seizures. Neurology. 2015;**84**(8):810-817. DOI: 10.1212/WNL.0000000000001280

[65] Luat AF, Asano E, Kumar A, Chugani HT, Sood S. Corpus Callosotomy for intractable epilepsy revisited: The Children's Hospital of Michigan Series. Journal of Child

Neurology. 2017;**32**(7):624-629. DOI: 10.1177/0883073817697847

[66] Truong VT, Tayah T, Bouthillier A, Nguyen DK. Anterior corpus callosotomy in multistep invasive monitoring and surgery for atonic seizures. Epilepsy & Behavior Case Reports. 2014;**2**:11-14. DOI: 10.1016/j.ebcr.2013.12.003

[67] Feldstein TJ. Carbohydrate and alcohol content of 200 oral liquid medications for use in patients receiving ketogenic diets. Pediatrics. 1996;**97**(4):506-511. DOI: 10.1542/peds.97.4.506

[68] Nguyen R, Téllez Zenteno JF. Injuries in epilepsy: A review of its prevalence, risk factors, type of injuries and prevention. Neurology International. 2009;**1**(1):e20. DOI: 10.4081/ni.2009.e20

[69] ILAE Commission Report. Restrictions for children with epilepsy. Commission of Pediatrics of the ILAE. International league against epilepsy. Epilepsia. 1997;**38**(9):1054-1056. DOI: 10.1111/j.1528-1157.1997.tb01493.x

[70] Rank WP. Seizure first aid for bystanders. Nursing. 2020;**50**(10):11-12. DOI: 10.1097/01.NURSE.0000697196.36554.fe