Chapter 2
Seizures

James J. Riviello Jr. and Rod C. Scott

Abstract Seizures occur from excessive cortical excitation and their clinical manifestations vary depending upon the cortical areas involved. Seizures may occur in a patient with underlying epilepsy or result from an acute central nervous system (CNS) insult. This chapter defines the various terms used in describing seizures, the classification, the pathophysiology, and the various clinical manifestations of seizures. We will also describe the diagnostic studies needed for seizures, especially the electroencephalogram (EEG). The treatment of seizures and status epilepticus is reviewed in Chap. 10.

Keywords Seizures • Status epilepticus • Seizure classification

2.1 Introduction

Seizures represent a neurologic event whose clinical manifestations result from excessive CNS excitation [1]. The underlying neurophysiology of this excessive excitation is a transient hypersynchronous neuronal discharge. Seizures usually have a short duration, lasting less than several minutes. A prolonged seizure is referred to as status epilepticus (SE), and SE is more likely to occur in the critically ill. Epilepsy is defined as a condition in which there are recurrent, unprovoked seizures [2, 3].

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Table 2.1 Immediate seizure management goals

(1) Recognize the seizure May require CEEG monitoring in some patients
(2) Maintain the vital signs by ensuring the ABCs: airway, breathing, and circulation
(3) Treat the Seizure, if duration > 5 min Certain circumstances require immediate treatment
(4) Identify and treat the precipitating cause, if known
(5) Determine if an AED is needed to prevent subsequent seizure activity

AED antiepileptic drug, *CEEG* continuous EEG

The patient with epilepsy has a lowered seizure threshold, and certain factors, such as intercurrent illness or sleep deprivation, may precipitate a seizure. With a first seizure, it is important to determine if the seizure results from an acute CNS insult or it is the initial presentation of epilepsy. An acute CNS insult is more likely if the first seizure occurs during an illness, for which a specific treatment may be needed.

Seizures may occur with epilepsy or may result from an acute primary CNS insult, such as stroke, intracranial hemorrhage, or traumatic brain injury, or from a systemic disorder with secondary effects on the CNS, such as hypoglycemia, hypoxemia, or hypotension. A focal neurologic deficit is more suggestive of a primary intracranial insult, whereas global (diffuse) CNS dysfunction suggests a secondary CNS insult, such as hypoglycemia. However, focal dysfunction may occur even with global CNS dysfunction.

Subclinical seizures, also called electrographic seizures or nonconvulsive seizures, occur without obvious clinical manifestations, and EEG recording is needed to identify them. Subclinical seizures are common in a critically ill patient with an acute brain injury [4] or in a patient with epilepsy. There is a growing body of evidence that subclinical or electrographic seizures increase the risk of brain injury when they occur in conjunction with an acute CNS insult [5, 6]. The term uncoupling describes the situation when clinical seizures are controlled after the administration of an antiepileptic drug (AED) yet the electrographic seizures persist, as the clinical manifestations are "uncoupled" from the electrographic seizure. Whether clinical or subclinical, seizures represent a potential neurologic emergency, since they signify a CNS disturbance. Nonconvulsive seizures may cause altered awareness, which may be difficult to detect in the critically ill patients.

There are five immediate management goals when a patient presents with a seizure (Table 2.1). The first is to recognize the episode as a seizure. The second is to maintain the vital signs by ensuring the airway, breathing, and circulation, the ABCs. The third is to immediately treat the seizure, especially if prolonged, and the fourth is to identify and treat the precipitating cause, if possible. The last is to determine the AED needed to prevent subsequent seizure activity. Especially in regard to recognizing a seizure, it is important to know that the clinical manifestations of a seizure may vary.

The classification of seizures and the epilepsy syndromes guides management. There are three major classification systems: (1) seizure duration; (2) seizure onset,

Table 2.2 Stages of status epilepticus [7, 8]

Incipient stage (0–5 min)
Early stage (5–30 min)
Special circumstances of the early stage: situations that need immediate seizure control
Transition stage
Late stage (established) (30–60 min)
Refractory stage (>60 min)
Postictal stage

either focal or generalized; and (3) seizure etiology. The duration of seizure is important because aggressive treatment is needed for prolonged seizures. Status epilepticus, defined as a prolonged seizure lasting greater than 30 min or serial seizures without return of consciousness for 30 min, is a medical emergency and requires immediate termination. Although 30 min is the duration used to define status epilepticus, an operational definition recommends AED treatment after 5 min for a continuous seizure or serial seizures without a return of consciousness [1]. The staging of SE also guides treatment [7, 8] (Table 2.2).

The International League Against Epilepsy (ILAE) has developed an international classification of epileptic seizures which classifies seizures according to the clinical manifestations and the epilepsy syndromes associated with a constellation of signs and symptoms [2, 3]. Seizures are divided into focal or generalized according to their cortical onset. This is important because the origin in the cortex and its spread, especially how much cortex is ultimately involved, determines the clinical manifestations of the seizure. The AEDs used to prevent seizure recurrence typically have specific efficacies for either a focal or a generalized seizure. A focal seizure is defined as one whose initial clinical manifestations indicate activation of only a focal area, or one part of the cortex, or in other words, the initial activation of a focal group of neurons. A generalized seizure is one with "more than minimal involvement of both cerebral hemispheres," or in other words the initial activation of neurons throughout both hemispheres. A generalized seizure may not simultaneously involve every neuron.

The third system classifies seizures and epilepsy by their etiology, dividing them into symptomatic, cryptogenic, and idiopathic [2, 3]. A symptomatic seizure is one for which the exact cause is identified. A cryptogenic seizure is one in which an underlying specific etiology is presumed, because the neurologic state is abnormal but is not yet identified. The idiopathic seizure is one in which etiology is not known, either arises spontaneously or from an obscure unknown cause. Many of the seizures identified as idiopathic have been associated with a genetic disorder or a channelopathy. A patient presenting with a new-onset seizure or status epilepticus from a specific cause would be classified as having an acute symptomatic seizure. If a past known CNS insult had caused epilepsy, then this a remote symptomatic seizure. However, a patient with epilepsy may have a seizure precipitated by an acute illness. This is referred to as a remote symptomatic seizure with an acute precipitant [9] or an acute or chronic seizure [10].

The new classification system replaces symptomatic, cryptogenic, and idiopathic with genetic, structural/metabolic, and unknown [3]. The distinction between complex partial and simple partial seizures is also eliminated. However, these terms are still in common clinical use.

2.2 Introduction to Seizure Pathophysiology

Two levels of seizure pathophysiology are important for understanding treatment. The first is at the level of the neuronal membrane and the second is at the level of physiologic disturbances occurring in the patient.

2.2.1 Pathophysiology at the Cellular Level

Seizures result from inherent neuronal membrane instability caused by excessive CNS excitation, inadequate CNS inhibition, or a combination of the two. Simplistically, a seizure starts when CNS excitation outweighs CNS inhibition which results in prolonged membrane depolarization and ends when the CNS inhibitory systems outweigh the excitatory systems. The neuronal cell membrane is semipermeable with an intracellular to extracellular gradient maintained by osmolar differences across the membrane. The resting membrane potential (RMP) is approximately −70 uV across the membrane with ion flux across the membrane determining its discharge pattern [11]. Normally, the extracellular sodium concentration and intracellular potassium concentration are high, with the reverse for the intracellular space (low Na^+, high K^+), with this gradient maintained by a Na-K exchange pump. Cell depolarization results in sodium ion influx which lowers the RMP and causes depolarization. If depolarization is excessive, an epileptic discharge is generated. There is a high extracellular chloride ion concentration at rest. After depolarization, a chloride ion influx repolarizes the cell and reestablishes the RMP. Maintaining the RMP is dependent on the Na-K ATP pump. Acute neurologic insults, such as hypoxia, ischemia, or hypoglycemia, result in failure of the Na-K membrane pump, with the inability to restore the RMP and excessive depolarization. An excess of excitatory neurotransmitters results in excitotoxicity. Calcium and magnesium inhibit sodium influx. So excessive Na influx occurs with hypocalcemia or hypomagnesemia, resulting in increased excitability.

Understanding membrane physiology allows us to understand the relationship between electrolyte disorders and acute seizures [12] and why seizures occur with specific electrolyte disorders. CNS depression with encephalopathy is generally seen in disorders of sodium and osmolality, although increased CNS excitability may result in seizures. Hypercalcemia and hypermagnesemia produce CNS depression, whereas hypocalcemia and hypomagnesemia increase CNS excitability and

cause seizures. Disorders of potassium rarely produce seizures. In the experimental model excessive excitation itself may cause neuronal injury and cell death, referred to as excitotoxic injury.

As described above, seizures spontaneously stop when the inhibitory systems outweigh the excitatory systems. Therefore, mechanistically, a seizure develops into status epilepticus when there is a failure of the inhibitory factors [1]. In addition, status epilepticus may be more difficult to control as the duration increases and may not respond to the conventional AEDs. A rapid modification in the properties of $GABA_A$ receptors [13] through mechanisms such as altered receptor trafficking (see below) likely contributes to the reduction in inhibition.

2.2.2 Pathophysiology at the Patient Level

Lothman outlined the alterations in systemic and brain metabolism occurring with a prolonged seizure [8]: there is a decreased brain oxygen tension, with a mismatch between the sustained increase in oxygen and glucose utilization and a fall in cerebral blood flow, followed by depletion of brain glucose and oxygen. In the early stages of a seizure, brain compensatory mechanisms may protect against neuronal injury. However, as the seizure progresses, these compensatory mechanisms may become exhausted, which dramatically increase the risk of neuronal injury. This point defines the transition stage from early to late (established) SE. During all stages, the ability to compensate requires adequate airway and good breathing, circulation, and cerebral blood flow (CBF). During the early stages, blood pressure (BP) and blood lactate and glucose increase, and pH decreases [8]. The BP increases as a result of autoregulation, which increases the CBF to match the increased cerebral glucose and oxygen utilization in order to prevent neuronal exhaustion. Brain tissue oxygenation is preserved, but brain glucose stores slowly decrease. The transition stage marks the progression of the early stage to the late stage. In the late stage, BP may decrease to normal and hypotension, respiratory compromise, leading to hypercarbia, hypoxemia, decreased pH, lactate and glucose, and hyperthermia occurs. Brain parenchyma oxygen and glucose decrease, while cerebral glucose and oxygen utilization remains elevated, and CBF may decrease. Convulsive and nonconvulsive seizures increase intracranial pressure, potentially aggravating already compromised CNS compensatory mechanisms [14]. In all stages, compensatory mechanisms require adequate airway, breathing, circulation, and cerebral blood flow.

A time-dependent efficacy of treatment occurs in experimental models of SE. This decreased benzodiazepine response occurs rapidly after the onset of SE in young animals with ages corresponding to a human toddler [15]. Diazepam and the other benzodiazepines enhance the function of a subset of benzodiazepine-sensitive $GABA_A$ receptors. The surface expression of these receptors declines during SE resulting from activity-dependent trafficking of subunits of $GABA_A$ receptors [12].

Table 2.3 Seizure types

Generalized seizures
Tonic-clonic (any combination)
Absence
Typical
Atypical
Absence with special features:
Myoclonic
Myoclonic atonic
Myoclonic tonic
Clonic
Tonic
Atonic
Focal seizures
Unknown
Epileptic spasms

2.3 Presenting Acute Symptoms

The classification of the seizure starts with the seizure semiology, defined as the study of signs and symptom with seizure types divided into either focal or generalized seizures. There are as many different types of status epilepticus as there are seizure types (Table 2.3). There are three types of focal seizures, also known as partial seizures or localization-related seizures. The simple focal (partial) seizure has its clinical manifestation without altered awareness, the complex focal (partial) seizure has its clinical manifestations with altered awareness, and the focal (partial) seizure with secondary generalization starts with a focal manifestation and then evolves into a generalized tonic-clonic seizure. A simple focal (partial) seizure is really an aura, and when prolonged, is referred to as epilepsia partialis continua. The clinical manifestations of a focal seizure depend upon the origin of the discharge and the cortex involved as it propagates. The seizure semiology of the focal seizure is different in the infant. Rather than the generalized tonic-clonic seizure, the most frequent seizure types in infants are astatic, behavioral arrest, clonic, epileptic spasms, tonic seizure, and the versive seizure [16].

Generalized seizures typically have no focal features and consist of the following seizure types [2, 3]. The absence seizure or the atypical absence seizure has altered awareness, usually with eye blinking. The tonic-clonic seizure starts with initial tonic activity (a sustained posture), followed by clonic movements, or the "jerking." The myoclonic seizure differs from a clonic seizure by the duration of the movement (<100 ms). A tonic seizure occurs with mostly a sustained posture, whereas an atonic seizure consists of a loss of muscle tone, resulting in a decrease in muscle activity (may be limp). The atypical absence seizure, the tonic, and the atonic seizures typically with a neurologic disorder associated with a developmental disability or mental retardation.

Seizures and SE are also classified by semiology as convulsive or nonconvulsive, as this is what is clinically observed: whether there are convulsive movements or

only altered awareness. This scheme is more applicable in the acute setting with a critically ill child with recurrent seizures or status epilepticus. Convulsive SE (CSE) is relatively easy to identify because of the overt convulsions, whereas nonconvulsive seizures or nonconvulsive SE (NCSE) may have no outward convulsive movements, and EEG is needed to identify the electrographic seizure activity. In a study of NCSE, subtle motor activity and ocular movement abnormalities were present in 75 and 50 %, respectively, in patients with NCSE [17]. Nonconvulsive seizures or SE must also be considered in a patient with known epilepsy who presents with altered awareness.

The presence of nonconvulsive seizures or nonconvulsive status epilepticus is especially important in the patient with an acute brain injury, since electrographic seizures themselves may add to the neurological insult. In many neurological ICUs, continuous EEG monitoring is considered mandatory. Patients with CSE treated with anticonvulsants may cease their convulsive movements, yet remain in nonconvulsive status epilepticus, manifesting itself as continued altered awareness.

2.4 Diagnosis and Differential Diagnosis

The treatment of a seizure or SE starts with attention to the ABCs. The anticonvulsant treatment of status epilepticus is detailed in Chap. 10. Diagnostic studies to identify the precipitating cause must be considered as part of the treatment sequence, as an AED may control seizure activity but does not treat the underlying cause. Failure to treat the underlying cause may result in refractory SE. The appropriate diagnostic studies are done after the patient has been stabilized, and these are determined by the history, examination, and age, with a greater need to exclude treatable causes in the youngest children. Seizure classification guides management since an acute symptomatic seizure demands a complete work up to identify etiology, whereas in the patient with remote symptomatic seizures, or symptomatic epilepsy, a complete evaluation may not be needed, and the evaluation is determined by the specific history. Acute symptomatic SE is more likely in younger children. It is especially important to determine if the child has had a preceding history of seizures, or epilepsy, or if the seizure has occurred in the setting of an acute illness, even if just a nonspecific upper respiratory tract infection, and if there are any preceding psychiatric symptoms, movement disorders, or family history of autoimmune disorders. These symptoms suggest an acute autoimmune disorder (NMDA receptor encephalitis). Seizures may have an acute precipitant in a patient with epilepsy. This is referred to as remote symptomatic epilepsy with an acute precipitant or acute on remote epilepsy. In the American Academy of Neurology (AAN) practice parameter for the diagnostic assessment of the child with status epilepticus, a retrospective study, remote symptomatic SE with an acute precipitant occurred in 1 % of patient [9], whereas in the prospective North London status epilepticus surveillance study, an acute on remote cause occurred in 16 % [10].

Serum glucose should be rapidly checked to exclude hypoglycemia. CBC may be helpful for infection, although leukocytosis occurs from SE itself. Electrolytes, calcium, phosphorus, and magnesium values may be helpful in children with vomiting and diarrhea [9]. Low AED levels may be associated with SE [9]. Serum studies may be needed if there is suspicion for a specific toxin [9]. The AAN practice parameter [9] reported the following abnormalities in children undergoing acute evaluation: abnormal electrolytes (6 %), positive blood cultures (2.5 %), CNS infection (2.8 %), low AED levels (32 %,) ingestion (3.6 %), inborn error of metabolism (4.2 %), epileptiform abnormalities (43 %), and neuroimaging abnormalities (8 %). In the prospective study of new-onset SE, electrolyte abnormalities were found in 1.4 %, CNS infection in 9 %, and toxins in 1.4 % [18]. In a prospective study of new-onset seizures presenting with SE, in the acute symptomatic cases, the cause was CNS infection in 55 %, vascular in 21 %, and toxin, trauma, and electrolytes disturbances occurred in 8 % each [18]. In remote symptomatic cases, 31 % had inborn errors of metabolism, 30 % had cerebral dysgenesis, 15 % had a remote vascular cause, and a remote infection, chromosomal abnormality, or mesial temporal sclerosis occurred in 8 % each.

2.5 Assessment

In a recent review, Freilich and colleagues recommend that electrolytes, EEG, and CT/MRI are always done for new-onset SE, and if the clinical suspicion exists, urine toxicology, genetic or metabolic testing, and lumbar puncture should also be considered. For refractory SE or persistent encephalopathy, continuous EEG is recommended. For SE in a known patient with epilepsy, AED levels are always recommended, electrolytes, EEG, and CT/MRI need to be considered, and video EEG should be done when there is persistent SE or encephalopathy [19]. Lumbar puncture to exclude meningitis must be considered in the febrile child, but is not absolutely necessary in every child, depending upon the clinical situation and the ability to clinically assess the older child. If there is concern for increased intracranial pressure or a structural lesion, LP is deferred until neuroimaging is done, but antibiotics should be given prior to LP, ultimately relying on cell count and bacterial cultures. CSF pleocytosis may occur without infection, due to either an inflammatory process or breakdown in the blood-brain barrier.

Neuroimaging is indicated for new-onset SE, especially without a defined cause, or a prior history of epilepsy. The AAN practice parameter for neuroimaging in seizures recommended an emergent (scan immediately) scan for new-onset SE, or in a known epileptic not responding to treatment [20]. The child needs to be stabilized before the scan. A higher incidence of life-threatening lesions (hemorrhage, brain swelling, mass effect) occurs with a first-time seizure or in a child with epilepsy and new focal deficits, persistent altered mental status, with or without intoxication, fever, recent trauma, persistent headache, cancer, or on

Table 2.4 Conditions with a high risk for clinically significant findings on neuroimaging

New focal deficits, persistent altered awareness, persistent headaches
Sickle cell disease
Hemorrhagic disorders, anticoagulation
Cerebral vascular disease
Malignancy
HIV infection
Hydrocephalus
Travel to area endemic for cysticercosis
Closed head injury

anticoagulation [20, 21] (Table 2.4). Although MRI is more sensitive but is rarely available for emergent studies, a CAT scan will adequately identify life-threatening conditions. In our study of new-onset afebrile seizures, two criteria were associated with a high risk for a clinically significant finding: a predisposing condition and a focal seizure in a patient less than 33 months of age. Only 38/475 (8 %) had clinically significant findings and only 3 of these needed immediate intervention [21]. In the AAN practice parameter, neuroimaging abnormalities were present in 8 % [8], and with new-onset seizures presenting with SE, a diagnosis was made by neuroimaging (CT, MRI) in 30 %, with management changed in 24 % [28/143]and 20 % of cranial CAT scans were abnormal, with 14 (10 %) showing acute abnormalities, and 14 (10 %) showing chronic abnormalities [18].

An EEG is not usually needed at treatment onset for CSE, unless there is a strong suspicion for pseudoseizures or pseudostatus epilepticus, which occurs in children but is more common in adults. Lorazepam is frequently administered as first-line treatment for CSE. However, if the convulsive movements stop but there is no clinical improvement, with ongoing altered awareness, an EEG is needed to exclude NCSE. In an adult study, NCSE occurred in 14 % of patients treated for CGSE [22]. In a study in children, NCSE occurred in 5/19 following control of CSE; in 2 of these, NCSE occurred after treatment of CSE and in 3, NCSE occurred after treatment of refractory status epilepticus (RSE) [23]. In a study of all ages, NCSE was detected in 8 % of all comatose patients [24]; in children, NCSE only was detected in 2/19 children following an hypoxic-ischemic insult (Fig. 2.1) [23]. Figure 2.2 is an example of focal NCSE following a convulsive seizure with persistent altered awareness.

The indications for emergency EEG include unexplained altered awareness (to exclude NCSE); neuromuscular paralysis for SE, which eliminates the convulsive movements by neuromuscular blockade; continuous IV therapy for refractory SE, or when there is no improvement or return to baseline mental status after controlling overt convulsive movements (to exclude NCSE or nonconvulsive seizures) [25]. The EEG is useful whenever the diagnosis is in doubt, especially for pseudoseizures [26]. In a study in children, 6 of 29 children admitted with CSE had pseudostatus epilepticus [27]. There has been an increased use of continuous EEG monitoring in the critically ill patient to detect NCSE and nonconvulsive seizures as their treatment may decrease the risk of secondary brain injury.

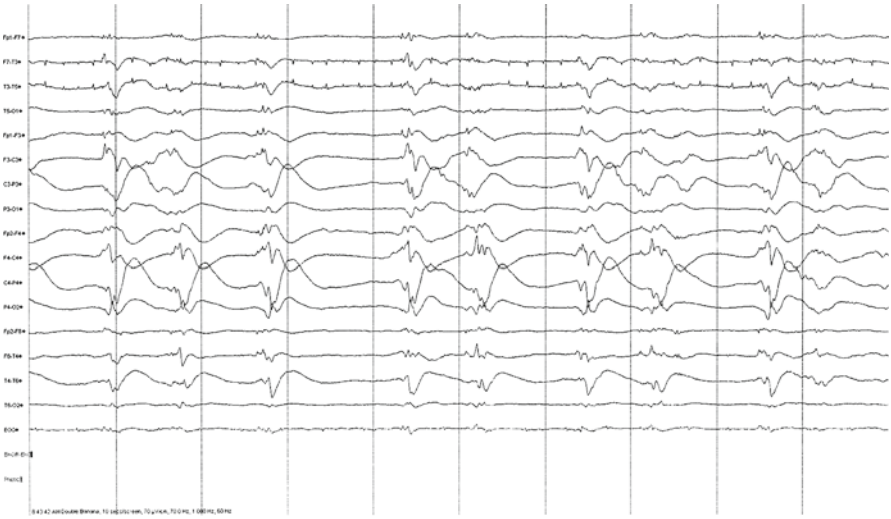

Fig. 2.1 Generalized nonconvulsive status epilepticus. EEG of generalized nonconvulsive status epilepticus. Child was comatose following a cardiac arrest. Generalized spike and slow wave discharges with a bicentral predominance

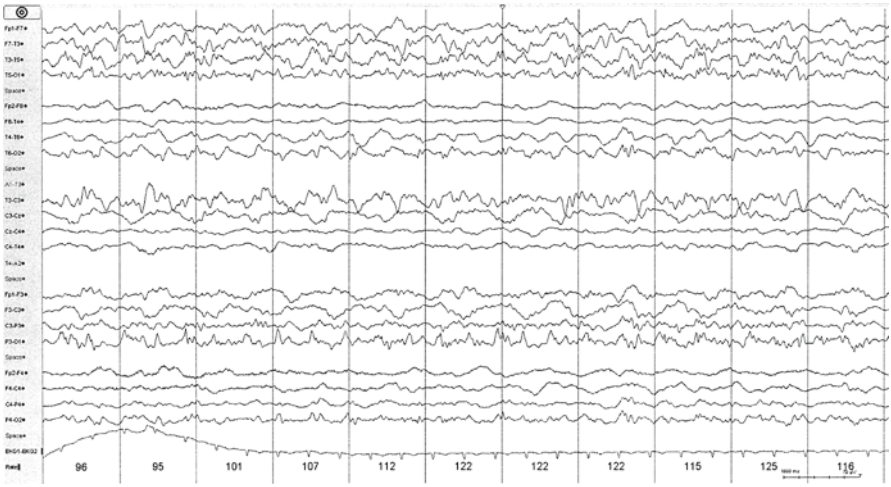

Fig. 2.2 Focal nonconvulsive status epilepticus. Child had a convulsive seizure followed by persistent altered awareness. Recurrent spikes and sharp waves in the posterior region bilaterally, left greater than right

Continuous EEG monitoring may also detect clinical activity that mimics seizure activity, which occurs frequently in this population, and unless continuous EEG monitoring is done, AEDs may be used to treat these movements. In a study of 100 children in coma, non-epileptic events were confused with seizures in 17, whereas documented epileptic seizures occurred in only 7 children [28]. In another

study of 100 children, changes were made in AED treatment in 43 children and non-epileptic events were detected in 21 children [29]. Continuous EEG monitoring is also useful in the management of refractory seizures and when the patient undergoes therapeutic neuromuscular blockade. Patients with epilepsy or with seizures immediately before the continuous EEG are at a higher risk for ongoing seizure activity [30].

Refractory Status Epilepticus (RSE): The SE is considered refractory when seizures continue despite treatment with the first two AEDs used. There are two recent reviews of the etiologies that cause RSE. The CSF examination is important in this group as unusual infections or inflammatory and autoimmune disorders may be the cause [31, 32].

2.6 Special Consideration

Some pediatric epilepsy syndromes classified under "epileptic encephalopathy (EE)" may not present with CSE, but often have brief, frequent seizures, and/or frequent abnormal epileptiform activity on EEG. It is hypothesized that the encephalopathic features (cognitive impairment, behavior problems, physical problems such as ataxia) are a direct consequence of the epileptic electrical phenomenon, and suppression of epileptic activity may improve seizure and developmental outcome [3] Although this hypothesis is still debated, there is general consensus amongst clinicians that some of these syndromes warrant early effective treatment.

West syndrome is one of the most recognized of the EEs, and often presents between 3 and 7 months of age. It is characterized by the triad of epileptic spasms (infantile spasms), psychomotor regression, and the characteristic hypsarrhythmia pattern on EEG [33]. The spasms are symmetric, brief generalized seizures (>100 ms to 1–2 s), involving flexion and/or extension of axial muscles and the extremities. Asymmetric spasms often indicate underlying structural brain pathology. Typically, the spasms occur in clusters and on awakening from sleep. The psychomotor regression usually follows onset of epileptic spasms, and visual agnosia (loss of eye contact) is often the first sign of regression. Children with symptomatic etiology of WS may have psychomotor impairment prior to the onset of the spasms.

The prognosis of WS is determined mostly by the underlying etiology. The majority of children with WS have congenital (e.g., tuberous sclerosis, genetic defects) or acquired (e.g., hypoxic-ischemic insult, brain infection) structural brain abnormalities, or neuro-metabolic disorders (e.g., pyridoxine dependency, organic aciduria) and generally have a poor prognosis (Pellock et al. 2010). They often have persistent seizures, profound cognitive impairment, and the epilepsy evolves into Lennox-Gastaut syndrome in 20–50 %. About 15 % children with WS have no identifiable etiology and tend to have a better psychomotor outcome.

2.7 Conclusion

This chapter reviews the definitions, basic concepts, and various clinical manifestations of seizures and status epilepticus as they relate to acute neurological disorders in children. It is especially important to identify the precipitating cause. Understanding the pathophysiology of seizures and reviewing the results of diagnostic studies, especially the electroencephalogram (EEG), set the stage for antiepileptic drug treatment.

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