REVIEW ARTICLE

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Neonatal Seizures

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Neonatal seizures are defined as seizures occurring within 4 weeks after birth in full-term infants or within 44 weeks of postmenstrual age in preterm infants. The estimated incidence of these seizures is 2.29 cases per 1000 live births. Higher rates have been reported among preterm neonates than among full-term neonates (14.28 cases per 1000 vs. 1.10 per 1000).[1] The International League against Epilepsy (ILAE) has developed a diagnostic framework to classify neonatal seizures,[2] which facilitates the use of common terminology and assists clinicians in making treatment decisions. Most neonatal seizures are transient and result from acute metabolic disturbances, infectious processes, or acute focal cerebral lesions. Such seizures are considered to be provoked. In full-term neonates, the most common cause of provoked seizures is hypoxic ischemic encephalopathy, followed in frequency by stroke and infection. In preterm neonates, the most common cause is intraventricular hemorrhage. Identifying the provoking event is essential for determining management.

Provoked seizures are not considered to be epilepsy, which is defined as two or more unprovoked seizures, and provoked seizures typically do not require long-term treatment with antiseizure medication.[3] Neonatal epilepsy syndromes, which are uncommon, frequently have genetic causes, and unlike provoked seizures, some of these syndromes require long-term treatment.[4]

Clinical Presentation

Neonatal seizures start focally but can spread to involve the entire body.[2] Seizures that begin in a generalized fashion are rare. Clinical seizures in neonates can be difficult to recognize because convulsive movements in babies are often complex, irregular, or subtle. Because some seizures have only an electroencephalographic (EEG) component,[5] the ILAE has emphasized the importance of EEG as essential for the identification of neonatal seizures. To address the limited availability of EEG in some settings, the Brighton Collaboration, a nonprofit global vaccine safety research network, has proposed a scheme with five levels of diagnostic certainty that can guide treatment decisions if EEG is not available (Table 1). A clinical event that occurs simultaneously with a seizure pattern on continuous EEG recording provides the highest level of certainty that the event is truly a seizure and requires treatment (level 1). When a suspected event has a focal clonic feature (rhythmic focal jerking) or tonic feature (prolonged extension of the limbs), with or without EEG corroboration, treatment is also considered to be justified (level 2). If there has been an event that could be a seizure but is not focal, clonic, or tonic and EEG is not available, treatment may be considered, but there is no clear guidance (level 3).[6] Levels 4 (suspected seizure) and 5 (not a seizure) are self-explanatory, and treatment is not required. The same approach can be applied to single or multiple seizures.

A systematic review has suggested that clinical seizure types are usually associated with specific underlying causes.[7] For example, focal clonic seizures usually signify a cerebral infarction and the need for cranial imaging to confirm the diagnosis. Tonic seizures are seen mainly with hypoxic ischemic encephalopathy but also with metabolic disorders, channelopathies, vascular disorders, or cortical malformations. When the presentation includes myoclonic seizures (sudden, brief, irregular limb contractions), metabolic disorders such as hypoglycemia or hyponatremia, amino acid disorders, or other inborn errors of metabolism are usually responsible. Sequential seizures are defined by the occurrence of more than one seizure type during an episode and are often genetically determined. Epileptic spasms (sudden flexion, extension, or mixed flexion with extension of the proximal and truncal muscles) also suggest genetic causes. Autonomic seizures are characterized by alterations in cardiovascular, vasomotor, or respiratory patterns and are typically observed in neonates with hypoxic ischemic encephalopathy or intracranial hemorrhage. Some of these etiologic associations are based on current opinion, and prospective studies with large cohorts of neonates are needed to confirm them.

Several common nonepileptic motor phenomena may be difficult to differentiate from seizures in neonates. Tremor, jitteriness, and some myoclonic movements can be mistaken for seizures. They can occur without obvious cause or as symptoms of drug withdrawal, electrolyte abnormalities, hypoglycemia, or infection. They do not have EEG correlates and are not seizures. If EEG is not available, the aforementioned levels of diagnostic certainty can be used to assess the likelihood that a paroxysmal movement is a seizure. A common self-limiting neonatal condition, benign neonatal sleep myoclonus, is characterized by myoclonic events that occur during sleep, with a normal EEG. Neonatal hyperekplexia is a rare disorder of muscle rigidity, exaggerated startle reaction, and nocturnal myoclonus, with a normal EEG, and is also not an epilepsy syndrome. The attacks can be stopped by the Vigevano maneuver, consisting of forced flexion of the head and legs toward the trunk.

Table 1. Levels of Diagnostic Certainty.*

Level	Definition	Course of Action
Level 1: Definite seizure	Suspected seizure with a continuous EEG correlate	Treat
Level 2: Probable seizure	Suspected seizure with an amplitude-integrated EEG correlate or clinically assessed focal clonic or tonic seizure	Treat
Level 3: Possible seizure	Clinical seizure other than focal tonic or clonic	Consider treatment
Level 4: Suspected seizure	Insufficient evidence to meet seizure criteria	Do not treat
Level 5: Not a seizure	Movement determined by EEG not to be a seizure	Do not treat

* Seizures defined as definite or probable should be managed with antiseizure medication. If electroencephalography (EEG) is not available, the clinician can rely on levels 3, 4, and 5, deciding whether an event is a seizure solely on the basis of clinical semiology. The levels of diagnostic certainty were proposed by the Brighton Collaboration.

EVALUATION OF NEONATAL SEIZURES

The initial steps in managing neonatal seizures are to stabilize cardiovascular and respiratory function and then to identify the cause of the seizures. Treatable medical abnormalities, such as hypoglycemia and electrolyte disorders (e.g., hyponatremia), can be rapidly detected and corrected, usually leading to cessation of seizures without the need for antiseizure medication. EEG monitoring should be initiated as early as possible to establish the presence of seizures because some types of seizures tend to peak in incidence and severity within the first 24 hours, particularly those due to hypoxic ischemic encephalopathy (Fig. 1).

Perinatal, birth, and family histories can provide clues to the underlying cause of seizures. For example, some seizures, such as those due to nonketotic hyperglycinemia, begin prenatally, and women may describe episodes of frequent, continuous, rhythmic jerking of the fetus. Certain examination findings also suggest specific causes of seizures: microcephaly may indicate cerebral dysgenesis, genetic abnormalities, or congenital infection; macrocephaly may be due to structural or genetic abnormalities; dysmorphic features suggest cerebral dysgenesis, often due to a genetic abnormality; neurocutaneous

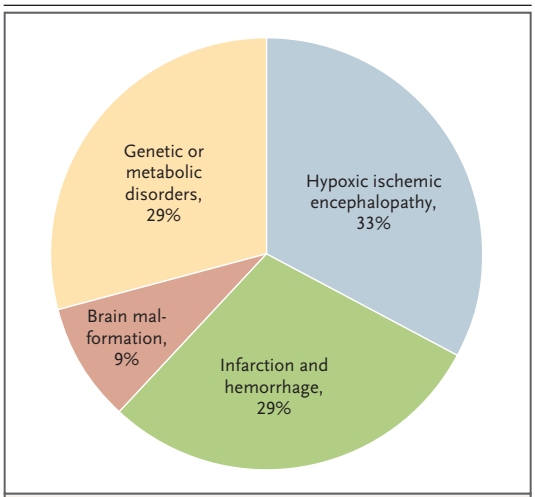

Figure 1. Causes of Acute Reactive Seizures in Term Neonates.

stigmata are indicative of specific disorders such as tuberous sclerosis or neurofibromatosis; rash suggests infection or incontinentia pigmenti; and congenital heart disease is associated with perinatal stroke.

Figure 2 outlines a proposed diagnostic pathway that leads to the possible causes of seizures, and Table 2 provides a suggested evaluation for confirming each of several common causes. A thorough evaluation might include screening for neonatal infection; toxicologic testing; metabolic testing for organic acidemias, urea cycle defects, and fatty acid oxidation defects (which may include amino acid levels, ammonia, lactate, pyruvate, very-long-chain fatty acids, urine, organic acids, biotinidase, pipecolic acid, and pyridoxal-5-phosphate); and examination of the placenta for pathological changes. If an infectious cause is suspected, serum and cerebral spinal fluid cultures are generally obtained quickly and antimicrobial treatment is promptly initiated. If the neonate's condition is not sufficiently stable for a lumbar puncture, empirical treatment for meningoencephalitis is often appropriate.

If seizures continue despite the administration of conventional antiseizure medication, a pyridoxine challenge may be attempted, since the rare condition known as pyridoxine-dependent developmental and epileptic encephalopathy responds to pyridoxine, as discussed below. This diagnosis is uncovered by intravenous administration of 100 mg of pyridoxine, followed by 30 mg of pyridoxine per kilogram of body weight per day administered intravenously or orally in two divided doses for 3 to 5 days, with EEG monitoring of the response. Close cardiopulmonary monitoring during the infusion is recommended, since there is a risk of apnea with intravenous pyridoxine. If a clear response is observed, pyridoxine administration is continued throughout the patient's lifetime.

Conventional 20-channel EEG or, if that is unavailable, amplitude-integrated EEG may be used to diagnose neonatal seizures. Amplitude-integrated EEG is a single- or double-channel EEG recorded by three to five electrodes attached to the scalp. It is readily available as a bedside test, is easy to apply with either small-needle or adhesive electrodes, and can be interpreted by neonatologists. However, amplitude-integrated EEG is less sensitive and less specific than conventional EEG for seizure detection because the limited number of electrodes makes it difficult to detect infrequent, brief, and low-amplitude seizures.[8] Amplitude-integrated EEG detected up to 38% of 851 seizures in one study.[17] Continuous and video EEG monitoring, typically performed for at least 1 hour, is a more accurate way to detect seizures than a single EEG recording.[8] Continuous EEG monitoring is suggested until the neonate has been seizure-free for 12 to 24 hours.[8]

When EEG is not available, antiseizure treatment can be initiated by determining, on the basis of the levels of diagnostic certainty described above, the likelihood that clinical events are seizures.[6] Neonates may be transferred to a neonatal intensive care unit or to a facility with EEG capability, if that testing is not readily available.

Neuroimaging is considered to be essential in the detection of possible structural abnormalities in neonates with seizure. Ultrasonography of the head is a first-line test because of its ease of use and accessibility at the bedside for acutely ill neonates who cannot be transported elsewhere. Ultrasonographic assessment has high sensitivity (100%) and specificity (93.3%) for detecting intraventricular hemorrhages with ventricular enlargement, but the sensitivity is lower in the case of normal-size ventricles or small cerebellar or extraaxial hemorrhages.[9] Additional

imaging with axial computed tomography or, preferably, magnetic resonance imaging (MRI) of the head can be performed when feasible.[10,11] Should a stroke be suspected on the basis of clinical features, magnetic resonance angiography and venography may be indicated as part of the assessment.[12]

Genetic testing is considered if there is no clear structural explanation for seizures, such as stroke, hemorrhage, or infection, or if they are sequential seizures, epileptic spasms, or tonic seizures. Although rare, some syndromes previously thought to be acquired as a result of perinatal insults have been found to be due to inherited or de novo pathogenic genetic variants. Therefore, clinicians are now testing more of their neonatal patients with undiagnosed seizures for genetic disorders and increasingly identifying these causes. Available genetic testing includes epilepsy gene panels, chromosomal microarray, targeted gene testing, and whole-exome sequencing. Knowledge of the role that genetics plays in epilepsy is rapidly evolving, with increasing numbers of pathogenic variants identified as contributing to phenotypic epilepsy syndromes. Furthermore, pathogenic variants with strikingly different epilepsy syndromes occur within the same genotype.

TREATMENT OF ACUTE SYMPTOMATIC SEIZURES

It is a generally accepted principle that all neonatal seizures with both clinical and EEG correlates and those with only EEG evidence should be treated. However, there are limited data from randomized, controlled trials to inform treatment decisions, and medications are frequently used off label. The ILAE recently provided guidelines for the management of neonatal seizures on the basis of a systematic review, a meta-analysis, and expert-based consensus.[3] Medications used in the acute care setting are typically limited to intravenous formulations. The ILAE recommends phenobarbital as the first-line antiseizure medication, regardless of the cause (e.g., hypoxic ischemic encephalopathy, stroke, hemorrhage, or genetic causes). The Levetiracetam versus Phenobarbital for Neonatal Seizures (NEOLEV2) study, a small, phase 2b, randomized, controlled trial, showed that phenobarbital was more effective than levetiracetam at 24 hours for the treatment of neonatal seizures.[13] Potential adverse effects of antiseizure medications on the developing brain are a concern. However, the risk is generally considered to be outweighed by the

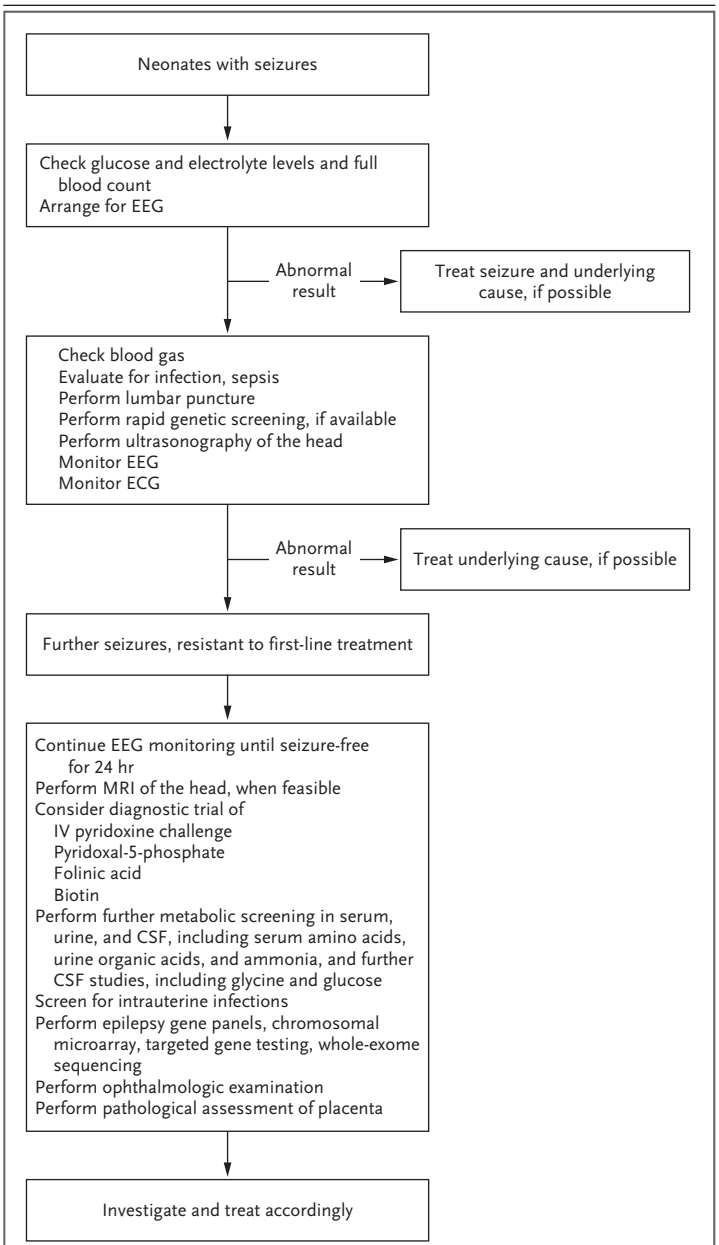

Figure 2. Proposed Diagnostic Process for Neonatal Seizures.

When lumbar puncture is performed, saving cerebrospinal fluid (CSF) for possible additional studies is good practice. ECG denotes electrocardiogram, EEG electroencephalogram, IV intravenous, and MRI magnetic resonance imaging.

Table 2. Workup for Acute Provoked Neonatal Seizures.*

Urgent Evaluation	Suspected HIE	Suspected Infection	Suspected Stroke	Suspected Metabolic Disorder
Obtain immediate laboratory measurements, including glucose, electrolytes, and full blood count; confirm with EEG or amplitude-integrated EEG	Check birth history and Apgar score; screen for other causes, depending on clinical scenario; assess need for therapeutic hypothermia	Obtain blood cultures and TORCH titers; CSF studies: glucose and protein, cell counts, PCR assay for HSV, culture; pathological assessment of placenta	Imaging: MRI with diffusion-weighted imaging; evaluate for cause (e.g., thrombophilia or vascular or cardiac cause); echocardiogram; pathological assessment of placenta	Screen for other metabolic abnormalities (screen includes amino acids, ammonia, lactate, pyruvate, very-long-chain fatty acids, urine, organic acids, biotinidase, pipecolic acid, pyridoxine, pyridoxal-5-phosphate); ophthalmologic evaluation

* CSF denotes cerebrospinal fluid, HIE hypoxemic ischemic encephalopathy, HSV herpes simplex virus, PCR polymerase chain reaction, MRI magnetic resonance imaging, and TORCH toxoplasmosis, other (syphilis, varicella, mumps, parvovirus, human immunodeficiency virus, and Zika), rubella, cytomegalovirus, and HSV.

consequences of uncontrolled seizures. It is nevertheless important to discuss the possible cause of seizures and treatment options with the family, as well as the potential duration of treatment on the basis of the neonate's response.

The goal of treatment is seizure cessation. If the neonate does not have a response to the first antiseizure medication, phenytoin, levetiracetam, midazolam, or lidocaine may be used as second-line intervention. However, there is limited evidence regarding the best medication to be used after phenobarbital has failed to control the disorder, and there are no official guidelines for selecting such a medication or determining the dose. Practice has differed among institutions.[14] Table 3 provides approximate antiseizure medication doses derived from the literature. For neonates with a cardiac disorder, levetiracetam is suggested as a potential second-line treatment over phenytoin because it is associated with fewer cardiac arrythmias and less potential cardiac toxicity. If conventional antiseizure therapies fail, one can consider trials of pyridoxine, pyridoxal phosphate, and folinic acid to correct uncommon vitamin-responsive epilepsies.

Therapeutic hypothermia for 72 hours is now used routinely for term and near-term infants with moderate-to-severe hypoxic ischemic encephalopathy in an effort to ameliorate the brain injury and improve later developmental outcomes.[20] The ILAE found that there was weak evidence, but agreement among experts, that therapeutic hypothermia may reduce the seizure burden in neonates with hypoxic ischemic encephalopathy.[3]

The consensus-based recommendation is to stop the antiseizure medication only after all provoked seizures (both seizures for which there is clinical and EEG evidence and those for which there is only EEG evidence) have ceased, regardless of the MRI or EEG findings.[21] However, this recommendation does not apply to neonatal-onset epilepsy syndromes, described below, because at least one type is likely to remit spontaneously and the other main type is typically resistant to medications. The recommendation comes from a nine-center, prospective, observational study of neonates with acute symptomatic seizures. The study considered the cause of the seizures, gestational age, status with respect to therapeutic hypothermia, EEG evidence of severity, the number of days on which EEG-confirmed seizures occurred, and findings on neurologic examination at discharge. It was further found that discontinuing medication in patients with provoked seizures that had stopped before discharge was not associated with an increased risk of postneonatal epilepsy and did not alter the risk of functional disability at 2 years of age.[21] The recurrence of seizures was not associated with medication withdrawal.

NEONATAL EPILEPSY SYNDROMES

The ILAE recently provided a position statement on the overall classification and definition of neonatal epilepsy syndromes. To some extent, these definitions incorporate previously recognized syndromes and are meant to facilitate

Table 3. Approximate Doses of the Main Antiseizure Medications for the Treatment of Neonatal Seizures.*

Medication	Loading Dose†	Maintenance Dose†	Comments
Phenobarbital	20 mg/kg of body weight; second loading dose, if required: 10–20 mg/kg, administered intravenously‡	5 mg/kg of body weight per day, administered intravenously or orally	FDA-approved; enhances GABAA inhibitory activity
Phenytoin	20 mg/kg of body weight, administered intravenously over 30-min period	5 mg/kg of body weight per day, administered intravenously in two divided doses, adjusted according to response and plasma concentration	Off-label use; voltage-gated sodium-channel blocker
Levetiracetam	40 mg/kg of body weight, administered intravenously; second loading dose, if required: 20 mg/kg	40–60 mg/kg of body weight per day, administered intravenously, or given orally in three divided doses	Off-label use; binds to SV2A and impedes synaptic vesicle trafficking
Midazolam	0.05–0.15 mg/kg of body weight	1 μg/kg of body weight per minute (60 μg/kg per hour), administered as a continuous infusion, increased in steps of 1 μg/kg per minute; maximum dose: 5 μg/kg per minute	Off-label use; GABAA agonist
Lidocaine	2 mg/kg of body weight, administered intravenously over 10-min period	7 mg/kg of body weight per hour, administered intravenously for 4 hr, then 3.5 mg/kg per hour for 12 hr, then 1.75 mg/kg per hour for 12 hr, and then stopped	Off-label use; voltage-gated sodium-channel blocker

* Information on doses is from Dehkharghani,[12] Sharpe et al.,[13] Van Den Broek et al.,[15] Pisano et al.,[16] Castro Conde et al.,[17] Sands et al.,[18] Favié et al.,[19] and Pressler et al.[3] Other agents that may be used, depending on the clinical presentation, family history, laboratory tests, and EEG findings, include pyridoxine, pyridoxal-5-phosphate, and carbamazepine. FDA denotes Food and Drug Administration, GABAA γ-aminobutyric acid type A, and SV2A synaptic vesicle protein 2A.
† Opinions about dosing vary, and the doses shown should be taken as approximate values.
‡ Higher doses of phenobarbital may be given with careful cardiorespiratory monitoring.

prognostic and treatment recommendations. They can be divided into two broad categories: self-limited epilepsies, which in turn have two subcategories, and developmental and epileptic encephalopathies (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[22] Developmental and epileptic encephalopathies are defined by intractable seizures associated with developmental impairment or regression often due to an underlying cause (which is likely to be genetic, structural, or metabolic).[23]

The self-limited neonatal epilepsy syndromes are due to pathogenic variants, either familial or de novo, most commonly in *KCNQ2* and, less commonly, in *KCNQ3*,[4] as described below, or *SCN2A*.[24] The typical self-limited epilepsy syndrome begins between 2 and 7 days after birth and remits after 6 months. Clues to this diagnosis are a family history of seizures and focal and tonic seizures at the onset of an episode, but the syndrome may sometimes include focal clonic, tonic, or sequential manifestations.[2] Sodium-channel blockers are used when seizures are due to loss-of-function *KCNQ2* and *KCNQ3* variants.[3,18]

Early infantile developmental and epileptic encephalopathy is a newly characterized entity that is manifested as medication-resistant seizures of various types in the first 3 months of life, associated with severe developmental impairment, abnormal findings on neurologic examination, and an EEG background with burst suppression (Fig. S2) or multifocal epileptiform discharges with diffuse slowing.[4] Neuroimaging, genetic testing, and metabolic studies show an underlying cause in up to 80% of infants.[25,26] These cases are rare and do not have a distinct clinical phenotype, as described below. The numbers and individual cause–specific syndromes in this group are likely to increase as more pathogenic variants are found. Currently, none of the conventional antiseizure medications, including glucocorticoids and pyridoxine, stop the seizures. Nevertheless, treatment can be targeted at an underlying metabolic disorder, if present (e.g., aminoacidopathies or organic acidemias). Surgical removal of a focal lesion

(including cortical dysplasias, hemimegaloencephaly, and cortical tubers), if present, may be considered after the failure of two or more drug trials.[27,28] These neonates may have coexisting movement disorders, cortical visual impairments, feeding difficulties, or orthopedic problems due to abnormal muscle tone and contractures.

Three additional developmental and epileptic encephalopathies have been described, with specific pathogenic variants and relatively uniform and distinct clinical phenotypes. KCNQ2-associated developmental and epileptic encephalopathy begins in the first few days of life, and the semiology is characterized by focal tonic seizures. However, focal clonic and myoclonic seizures can also occur.[29] Encephalopathy is present when the seizures begin.

Pyridoxine-dependent developmental and epileptic encephalopathy and pyridoxal phosphate deficiency–associated developmental and epileptic encephalopathy, mentioned above, are notable genetic syndromes because their treatment differs from that of other neonatal epilepsies. Patients with these disorders present within the first hours to days of life with encephalopathy and intractable seizures. Seizures are frequent, often evolving into status epilepticus with focal or multifocal myoclonic movements of the face, arms, legs, and trunk; epileptic spasms may also occur. Another disorder, CDKL5-associated developmental and epileptic encephalopathy, typically develops within the first few weeks of life, and the seizures are drug-resistant. Neonates with this disorder typically present with hypotonia and sequential seizures with hyperkinetic, tonic epileptic spasms.

PROGNOSIS AND COMPLICATIONS

The prognosis for neonatal seizures varies according to the cause, age at onset, seizure duration, and responsiveness to medication. Rapid recognition and treatment are considered the best ways to prevent adverse effects of the seizures and to improve long-term outcomes.[30] Although self-limited epilepsy syndromes, described above, are characterized by frequent seizures, they remit spontaneously, with a typically good prognosis. At the other extreme are the developmental and epileptic encephalopathies, which are due to severe, diffuse brain injury, often with a genetic cause, and have a poor overall prognosis.

Untreated seizures can cause hippocampal sclerosis and worsen the clinical outcome, regardless of the cause.[31,32] Despite this generally accepted tenet, the extent to which seizures can potentiate brain injury is unclear.[33] Analyses of data from several case series have shown that status epilepticus or seizures lasting longer than 12 to 13 minutes per hour are associated with a poor outcome, which is independent of the cause.[34-37] However, there is no definitive evidence that isolated seizures of brief duration have a negative outcome. Studies in animals suggest that the immature brain may be less susceptible to injury from seizures than the more mature brain. In two common animal models of status epilepticus, hippocampal injury was not easily induced in rats that were less than 21 days old.[33]

Certain patterns on EEG can assist in determining the prognosis for neonates with clinically confirmed EEG seizures and for those with only EEG evidence of seizure activity.[38,39] Background burst suppression and ictal activity are associated with a poor prognosis, whereas normal background activity suggests a better prognosis.[40] In a study involving neonates with hypoxic ischemic encephalopathy, normal or mildly abnormal background EEG activity was found to be predictive of a normal developmental outcome.[41] Controlling seizures before the end of the second day after delivery is also associated with a favorable outcome.[42,43]

SUMMARY

The ILAE has proposed new guidelines for defining and classifying neonatal seizures. These new syndrome definitions and classifications, along with access to genetic testing, have reshaped how clinicians view and manage neonatal seizures. Neonatal age, the age at the onset of seizures, and clinical semiology provide clues to the cause of seizures, which in turn lead to tailored treatments, and current practice stresses the importance of EEG monitoring.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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