Neonatal Seizures

5

David C. Dredge

Introduction

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

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

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

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

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

Diagnosis

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

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

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

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

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

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

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

Etiology

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

Neonatal Hypoxic/Ischemic Encephalopathy (HIE)

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

Table 5.1 Etiology of neonatal seizures [2, 9]

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

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

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

Vascular

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

Infection

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

Cerebral Malformations or Dysgenesis

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

Metabolic

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

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

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

Genetic

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

Workup

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

Table 5.3 Genes associated with neonatal seizures [15]

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

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

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

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

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

Table 5.4 Laboratory investigations for neonatal seizures

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

AASA alpha-aminoadipic semialdehyde

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

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

Treatment

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

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

First-Line Therapy

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

Second-Line Therapy

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

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

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

Neonatal Status Epilepticus

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

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

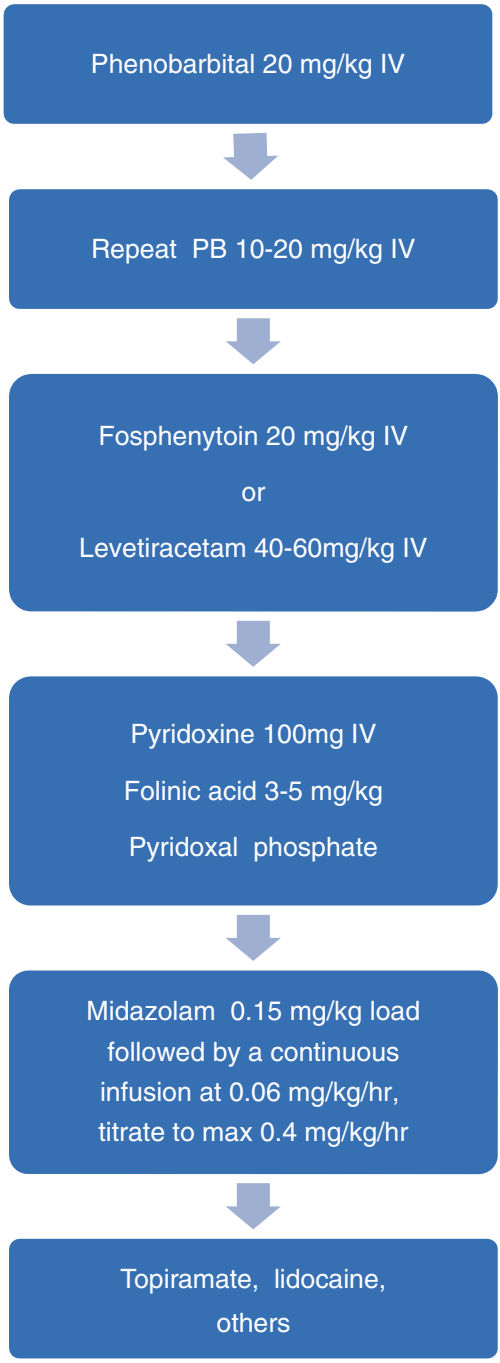

Fig. 5.1 Neonatal seizure treatment algorithm

Treatment-Related Controversy

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

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

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

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

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

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

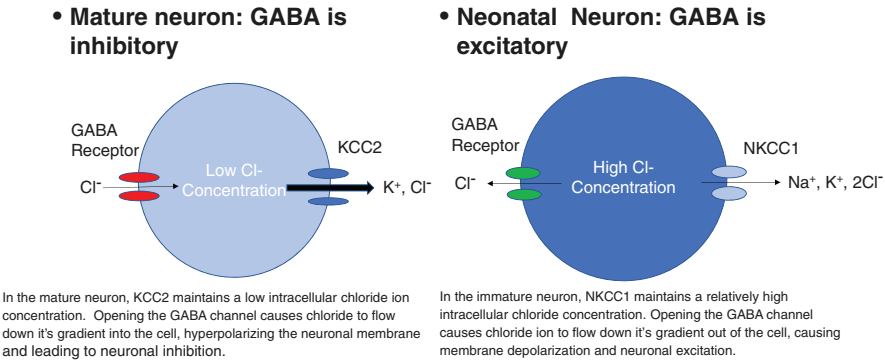

Fig. 5.2 Mature vs. immature neurons and GABA receptors

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

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

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

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

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

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

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

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

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

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

Duration of Treatment

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

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

Prognosis

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

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

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

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

Table 5.7 Outcomes of neonatal seizures, 2006 [2]

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

NDD neurodevelopmental disability

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

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

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