

Neonatal Seizures

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Abstract

The classification of neonatal seizures has been evolving since the 1960s when polygraphic monitoring of infants was introduced. During the 1970s and 1980s, the term "subtle seizure" was introduced to explain almost every sort of neonatal adventitious movement that was not clearly a focal or a multifocal clonic seizure. Video EEG, first used in the nursery in the late 1980s, revealed that most movements previously labeled *subtle seizures* usually did not have EEG correlation. Even with this evidence, the use of the term *subtle seizure* persists. This author prefers calling these phenomena simply abnormal movements until their exact genesis is known. These movements often presage a poor prognosis. Because of the uncertainties of what truly constitutes a true seizure, practitioners still rush to give immediate benefit-of-the-doubt therapy, even though there queries whether seizures themselves can cause brain injury in newborn subjects leading to subsequent neurological sequelae. The effectiveness of the two most common agents used for therapy, phenobarbital and phenytoin, is also being questioned. It is hoped that ongoing animal research and clinical trials will produce more effective agents for the pharmacological treatment of seizures. On thing seems clear: prognosis is related to the underlying cause of the seizures. *Int Pediatr.* 1999;14(4):204-207.

Key words: neonatal seizure, subtle seizure, abnormal movement, excitatory amino acid (EAA), phenobarbital

Introduction

A large number of review articles have been written in the last 3 decades on the classification, treatment, and outcome of neonatal seizures. The literature¹⁻³ of the 1960s emphasized classification of seizure types, mainly clonic and tonic varieties, and the use of polygraphy to clearly identify ictal and interictal patterns. In the 1970s, the use of the term "subtle seizure"⁴ came into vogue with the unintended result that almost all adventitious movements came to be catego-

rized as "subtle seizures" by neonatal personnel. The movements were treated in emergent fashion with anticonvulsant drugs for weeks or months in an effort to prevent or decrease acute brain damage and future seizures.

In the middle 1980s, the advent of video EEG monitoring⁵ revealed that up to 87% of the myriad of movements entitled "subtle seizures" had no electrical concomitant, although some of these movements were related to poor outcome. From that point on, a partial reclassification of neonatal seizures took place.⁶ The term "subtle seizure" was still used, but with the proviso that these might not be responsive to anti-seizure medication. The name "subtle seizure" has persisted in writings on neonatal seizures with rare exception,⁷ even though it now seems clear that the term is inappropriate regardless of the genesis of the phenomenology—frontal or brain stem release or from some other locus.

There are important nosologic disputes regarding neonatal seizures and several questions have arisen: (1) do neonatal seizures cause damage over and above the underlying injuring process; (2) do they need to be treated; and (3) is the current treatment efficacious in stopping the seizures or in preventing neurological sequelae?

Classification and Current Approach to Neonatal Seizures

Table 1 represents an updated classification to neonatal seizures. Experience has shown that uni- and multifocal clonic seizures are not only the most prevalent seizure types which occur in newborns, but are also those which are generally recognized by clinicians and nursery personnel. Clonic seizures are relatively slow (3 to 5 jerks per second), rhythmic, and need to be differentiated from clonus, called jitteriness, which is a faster tremor that can be turned on and

Neonatal Seizures Classification

Seizure Type	EEG Correlation
Unifocal clonic	++
Multifocal Clonic	++
Limb extensor posture with eye deviation	++
Eye deviation (h. nystagmus)	+
Myoclonic jerks	+/-
Tonic-clonic (rare)	+/-
Abnormal movements (i.e., mouthing, arching, pedalling, rowing)	13%

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off by stimulation or holding. Tonic seizures of one extremity, often accompanied by eye deviation, usually can be electrically verified. However, generalized tonic patterns, including opisthotonic arching, usually do not have electrical correlates, and are among those currently classified as subtle seizures. Grimacing, mouthing movements, pedaling, rowing, etc, also rarely have EEG correlates, and should simply be called abnormal movements until their origin is known (Table). Myoclonic seizures, fragmentary or more generalized jerks, may have electrical concomitants. Generalized tonic-clonic seizures are extremely rare in newborns, although they are often mistakenly reported.

Misconceptions about what should be classified as a neonatal seizure have, in the author's experience, led to an all-to-common sequence in most neonatal nurseries and neonatal intensive care units (NICUs): it starts with the immediate caretaker, often a nurse, observing an infant having unusual movements which the nurse describes as "generalized tonic-clonic." Either that, or any number of adventitious movements, thought to be "subtle seizures" are passed on to house staff and then to senior supervisors. Reaction is fast. The patient is urgently worked up for sepsis and meningitis (cultures and LP); blood glucose, electrolytes, Ca^{++} , and Mg^{++} are drawn, and the patient is usually put on antibiotics and on an anticonvulsant, usually phenobarbital. An ultrasound or computed tomography scan may be done, and a neurology consultation is requested.

When the child neurologist finally arrives on the scene, he or she usually gets a third- or fourth-hand description of the event, unless luck has it that the original observer is still at hand. He orders an EEG or possibly a polygraphic EEG, if available. A 1-hour interictal EEG may show an active seizure focus in 60% to 80% of patients,⁸ and may show background abnormalities that are sometimes helpful with prognosis. On rare occasion, video EEG is available to monitor patients at, or just after, the onset of suspicious events.

The neurologist is then asked to confirm the authenticity of the seizure(s); classify them; make further diagnostic suggestions (magnetic resonance imaging, further metabolic work-up, etc.); decide whether to continue, modify or stop treatment; and talk to the family about prognosis.

This scenario, with variations, is close to the reality of what happens in most good hospitals. It is thought to be the current best "benefit of the doubt" method to manage neonatal seizures—an approach that most neonatologists are imbued with. However, often the phenomena that are not true seizures are treated at the risk of over-sedation.

Do neonatal seizures cause brain damage?

To answer any risk-to-benefit question about current anticonvulsant therapy, one would first like to know if neonatal seizures, independent of established damage caused by the underlying process, cause pathologic alterations ca-

pable of causing subsequent seizures or any other form of developmental problem. The answer to this question has been very elusive. Most neonatal neurologists agree that outcome is usually related to underlying seizure etiology,⁹⁻¹¹ but do not know if the seizures themselves are merely epiphenomena (ie, symptoms of the underlying disease process). To answer this question, investigators have turned to animal models because human studies and rare pathological material have not been very revealing.

Animal Data

Early pioneering work of 1970s by Meldrum¹² and Wasterlain¹³ suggested that prolonged seizures and status epilepticus in mature and immature animals produced an energy failure leading to severe brain cell injury. Later experiments in the last 2 decades, however, seem to have disproved that theory by showing that 10-day-old rats (said to be equivalent to human newborns) maintain energy production in the brain by virtue of increased glycolysis and high adenosine triphosphate (ATP) release if there are no systemic complications such as hypoxia or hypotension.¹⁴ Nuclear magnetic resonance (NMR) studies, in both animals and humans, suggest that either aerobically or anaerobically, the newborn brain can maintain sufficient energy despite prolonged seizures.¹⁵

Experiments in the late 1980s and 1990s showed that the cells (particularly hippocampal cells) in the brains of mature and younger rats are susceptible to a number of convulsant agents, such as bicuculline and kainic acid, whereas those structures in 8-day-old rats show no signs of producing long seizures or status epilepticus in these rats.¹⁶ Very recent work, however, may challenge this belief. Holmes et al,¹⁷ have shown that subjecting 8-day-old rats to brief repetitive seizures using flurothyl produces subtle changes in cellular number and sprouting of mossy fibers from the CA3 area of the hippocampus become evident. These rats also show altered learning patterns as compared to controls. In addition, twice daily seizures produced with propylenetetrazol¹⁸ also produced sprouting in the dentate supragranular layer. It is conjectured that the frequent intermittent seizures produced by these methods more closely resemble the human neonatal seizure pattern than do the longer seizures produced with other proconvulsant agents. From these latest experiments, one could conclude that hippocampal circuitry is altered and that seizures in the developing brain may not be so benign after all.¹⁹ The shortcoming of these experimental studies is that they are performed in animals not subject to previous conditions such as asphyxia or meningitis.

Should neonatal seizures be treated?

It is still unclear whether seizures in experimental animal models or in human neonates induce cortical changes which

lead to subsequent seizures and altered behavior. Therefore, one needs to ask if therapy that is possibly injurious is needed to suppress them.^{20,21} Perhaps, at this time, the answer is still affirmative. Whether or not seizures cause lasting damage, one can argue that uncontrolled seizures may proceed to status epilepticus with the risk of attendant apnea, hypoxia, hypercapnea, and hypotension—any of which are probably deleterious to the brain.

Is present treatment efficacious?

Are the presently recommended treatment regimes really able to suppress seizures and avoid brain injury? It is believed that immature animals are more prone to have seizures than are mature ones, theoretically because the mechanism of seizure production in immature animals and possibly human newborns is the imbalance between excitatory and inhibitory circuits that prevails at very young ages.^{19,22} An excessive release of excitatory amino acids (EAA) would attach to their postsynaptic N-methyl-D-aspartate (NMDA) receptor and non-NMDA receptors, which are relatively uninhibited due to relatively low availability of type 2 gamma amino butyric acid (GABA₂) receptors at this stage of development. This causes an excessive amount of calcium ions to be released into neurons, which alters or destroys them. Phenobarbital is not known to act by inhibiting release of EAA, rather it may inhibit their stimulatory effects by prolonging channel flow at the GABA postsynaptic receptor. If GABA receptors are under-expressed in immature animal models, how can phenobarbital be effective in diminishing or abolishing seizures? According to Holmes (personal communication), it reduces seizure number in flurothyl-induced seizures in animals, but one still must ask whether other anticonvulsant agents might be more effective? To date, one has not been found. The experimental use of EAA inhibitors such as MK-801, an NMDA antagonist, has not decreased seizures in immature rats subjected to kainic acid induced seizures and may even exacerbate them.²³

The experience using phenobarbital to diminish or abolish seizure activity in humans has varied, with success rates ranging between 30% to 70%.²⁴⁻²⁶ Most studies are hard to compare as different doses and levels have been used to treat different types of seizures. Painter recently found (personal communication) that in babies with continuous seizures monitored by EEG for 24 hours, 43% had a complete cessation of seizures with phenobarbital administration while 45% responded to phenytoin—virtually the same percentage. The more severe and frequent the seizures at onset, the less the likelihood of success. The literature suggests that 30% to 40% of patients given intravenous dilantin may respond after phenobarbital failure.²⁷ To date, theoretically more appropriate drugs such as topiramate, an NMDA blocker, have limited use because of fear of neural and systemic side-effects.

Currently Recommended Therapy

The most commonly used treatment is intravenous phenobarbital initiated as a bolus of 20 mg/kg intravenously (usual level obtained 15-25 µg/mL). If seizures persist, then another 10 mg/kg are administered intravenously (level 25-36 µg/mL). At this point, there is a divergence in thinking about how to proceed. A minority of clinicians would give another 10 mg/kg intravenously if the baby still has seizures (level 40-90 µg/mL), which in some cases risks respiratory depression and the use of a ventilator if the baby is not already receiving artificial respiration. Having given a total of 30 mg/kg, most clinicians would opt to bolus the infant with 20 mg/kg of intravenous phenytoin given very slowly over 10 to 15 minutes.⁹ If a combination of these two drugs is ineffective, then options for achieving complete seizure cessation become limited. One can employ benzodiazepines, diazepam 0.3 mg/kg²⁸ or lorazepam 0.15 mg/kg²⁹ with success, but with awareness that an additional risk to the cardiovascular system exists when these agents are given in combination with barbiturates. Some neonatologists use an intravenous diazepam infusion as the first agent of choice.³⁰ Agents of last resort would be carbamazepine³¹ 20 mg/kg or valproate³² 20 mg/kg by nasogastric tube. A 1% paraldehyde drip titrated at a rate to stop seizures can be efficacious, but is no longer available in the United States. Lidocaine³³ and primidone³⁴ have been employed by some clinicians for the treatment of neonatal seizures.

Maintenance therapy with phenobarbital is 5 mg/kg per day in divided doses, but may have to be lowered to 4 mg/kg because of drug accumulation and drowsiness. The recommended maintenance dose for phenytoin of 5 mg/kg per day is often insufficient to maintain therapeutic levels, both by the intravenous and enteral routes. Doses up to 10-15 mg/kg per day may be needed for successful therapeutic levels.

Termination of Therapy

A 1997 poll of neonatal neurologists and neonatologists determined that the majority of experts terminate therapy with phenobarbital at an “early time,” usually while the infant is still in the nursery. This occurs for a variety of reasons³⁵: (1) evidence from experimental animals that phenobarbital reduces brain weight as well as brain DNA and RNA;³⁶ (2) tissue culture data that shows inhibition of neuronal growth and proliferation;³⁷ and (3) clinical experience that phenobarbital clouded an infant’s awareness when given as febrile seizure prophylaxis.³⁸

Prognosis

Most of the literature about neonatal seizures conclude that the prognosis of a particular baby depends upon the

etiology of the seizures. Thus one can state that certain etiologies, such as hypoxic-ischemic encephalopathy (HIE), meningitis, congenital brain abnormalities, and inborn errors of metabolism, almost uniformly have severe neurological sequelae. Patients with subarachnoid hemorrhage due to mild birth injury, certain ionic derangements in Ca^{++} , Na^{+} , and Mg^{++} , and familial neonatal seizures do well.^{5,7,9} In patients with seizures due to drug withdrawal, outlook is equivocal as many infants go home to poor environmental circumstances and developmental quotients (DQs) and intelligence quotients (IQs) are, to an extent, environmentally related.³⁹

Frequency and duration of seizures often do not correlate with outcome. Paradoxically, short, frequent events (those abnormal movements not proven to be seizures) have been correlated with poor long-term prognosis.⁵ This is because these movements are most often observed in the context, or are a product, of a severe encephalopathy such as HIE.

Conclusions

The current reality of the status of the diagnosis and management of neonatal seizures is that almost every untoward movement observed by nursery personnel is classified as a seizure, or at least is reported under the famous rubric of "rule-out seizure." Most of the movements are then treated as emergencies in the manner previously described. On occasion, treatment is postponed awaiting further thought and investigation, but most often the infant is given "benefit of the doubt" therapy hoping to avoid further damage to the infant's nervous system. It is not clear if present dogmatic regimes will achieve that much desired effect.

In a thoughtful review on the subject of neonatal seizures, Lombroso⁴⁰ observed that there was still a wide bridge between the clinic and the laboratory, but that there was much doable work that might close this gap by having animal work more closely approximate the clinical situation. It is hoped that this type of work, together with future clinical studies, will lead to the application of therapy with new anticonvulsant agents better suited to deal with the particular problems posed by neonatal seizures.

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