Improving the Treatment of Neonatal Seizures: National Institute of Neurological Disorders and Stroke Workshop Report

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In childhood, the risk of seizures is highest in the neonatal period (1.8 to 3.5/1000 live births in the United States). Neonatal seizures (NS) are associated with high mortality and morbidity rates, and their ultimate outcome is strongly influenced by their underlying cause.

Although immediate and aggressive anticonvulsant therapy would seem reasonable, animal studies suggest that the most commonly used neonatal anticonvulsants might have deleterious effects on the developing brain.[1,2] Because neonatal seizures are often self-limited, it has been reasoned that perhaps not all seizures should be treated or that anticonvulsant therapy could be discontinued quickly. Because the currently used anticonvulsants have limited efficacy and a significant fraction of survivors have adverse neurological outcomes, critical questions remain about which anticonvulsants should be used, how long the treatment should continue, and whether effective seizure cessation would improve neurodevelopmental outcome.

A workshop focusing on "Improving the Treatment of Neonatal Seizures," sponsored by the National Institute of Neurological Disorders and Stroke, was held in Bethesda, Maryland, on May 31-June 1, 2007. Participants included pediatric neurologists, neonatologists, pharmacologists, and neuroscientists with interest and expertise in pathophysiology, diagnosis and treatment of neonatal seizures, drug development, and clinical trials. This report highlights major themes that were addressed and the priorities for future research that were identified.

Three major topics were discussed: (1) recent advances in neuroscience that should guide improved treatment of NS; (2) current controversies regarding diagnosis and treatment of NS with particular attention to the use of electrographic monitoring; and (3) optimal (and feasible) design of future clinical trials (including selection of patients, candidate therapies, and meaningful short and long-term outcomes).

Several themes permeated the discussions. Many speakers emphasized that the developmental stage contributed both to the pathophysiology of seizures and responsiveness to antiepileptic drug therapy; and that conventional antiepileptic drugs had limited efficacy and possibly age-dependent risks in neonates.[1-4] Another major theme was that conventional electroencephalography (EEG) remained the "gold standard" for confirmation of NS and that it was essential to rigorously evaluate the strengths and weaknesses of current bedside brain monitoring devices for the diagnosis of NS. It was also acknowledged that the underlying cause of NS was a major determinant of neurologic outcome and required careful consideration in clinical trial design.

BASIC SCIENCE: RECENT ADVANCES AND FUTURE DIRECTIONS

Compelling evidence exists for the hypothesis that refractory seizures in neonates are due to unique mechanisms that are developmentally regulated. Most conventional antiepileptic drugs (AEDs) are developed preclinically and tested in adult animal models and human patients. However, the immature brain may contain very different targets for therapy compared with the adult brain. Major progress has been made in several areas, including delineation of the impact of neurotransmitter receptor maturation, endogenous oxidative stress signaling pathways, and inflammatory mediators in the increased seizure susceptibility, epileptogenesis, and seizure-induced cell injury in the developing brain.[2]

Animal models for neonatal seizures include chemoconvulsant administration, alone or in combination with inflammation, and physiological insults such as hypoxia or

AED	Antiepileptic drug	HIE	Hypoxic-ischemic encephalopathy
aEEG	Amplitude-integrated electroencephalogram	NICU	Neonatal intensive care unit
EEG	Electroencephalogram	NS	Neonatal seizures

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hypoxia-ischemia. Experiments in neonatal animal models have yielded a number of age-specific differences in the factors responsible for susceptibility to seizures, mechanisms of seizure induction, and mechanisms to block seizure development and long term consequences. Neurotransmitter receptor expression is developmentally regulated in such a way that excitatory mechanisms outweigh those that are inhibitory. The excitatory N-methyl-D-aspartate and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid glutamate receptors are both determined by their subunit compositions, which are developmentally regulated. The subunits that are expressed in perinatal rodent and human cortex heighten excitability. In contrast, the inhibitory gamma-amino-butyric acid receptors are expressed at low levels, and have less α1 subunit expression compared with the adult, leading to less benzodiazepine sensitivity. In addition, because of a reversal of chloride gradient, gamma-amino-butyric acid receptors are depolarizing/excitatory in the immature neuron rather than hyperpolarizing/inhibitory as in adults. This occurs because the neuronal chloride importer NKCC1 is overexpressed on immature neurons, resulting in high intracellular chloride concentrations.

This research led to the study of α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonists and NKCC1 inhibitors in animal models of neonatal seizures. The α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor antagonists topiramate and talampanel are both effective in suppressing seizures in a rodent model of neonatal hypoxia, and confer neuroprotection in models of neonatal hypoxia/ischemia. Recent studies are also demonstrating the efficacy of the NKCC1 blocker bumetanide, alone or in conjunction with phenobarbital. Bumetanide has been used safely as a diuretic in neonates, which may facilitate its translation to clinical trials in this age group. Topiramate is approved by the Food and Drug Administration as an oral anticonvulsant for children and adults; its translation to neonatal applications will require a formulation for parenteral administration. Other mechanisms for cell injury during NS include activation of oxidative stress pathways and inflammation, and agents that target these pathways may be important adjuncts to antiepileptic drugs. To replicate the complexities of seizure pathophysiology in the setting of multisystem organ dysfunction as is common in the neonatal intensive care unit (NICU), nonhuman primate studies may yield important contributions.

As pharmacologic therapies are developed, there is a need to determine their safety in animal models. A number of conventional AEDs, including phenobarbital, diazepam, and phenytoin, induce neuronal apoptosis in the normal developing rodent brain.[1] In contrast, topiramate and levetiracetam appear to not exert this effect. It is unclear, however, how any of these findings relate to the human brain, and indeed such studies have not been reported in nonhuman primates.

There was consensus that high priorities for research included investigations to understand adverse effects of AEDs on brain development, to delineate sex differences in response to seizures and to therapy, to develop combination therapies on the basis of mechanisms of seizure generation and neuronal damage, to establish reliable biomarkers of brain integrity, and to determine the relationship between efficacy for seizure suppression and long-term outcome.

DIAGNOSIS OF SEIZURES IN NEONATAL INTENSIVE CARE UNITS

Several speakers discussed the challenges inherent in the diagnosis of NS and emphasized that both underrecognition and overdiagnosis of NS occur frequently. Subclinical seizures are common in several NICU populations, including severely asphyxiated infants and preterm infants with development of intraventricular hemorrhage. Clinical correlates occur in 20% to 80% of EEG studies in neonates, and in the busy NICU setting, clinical seizure recognition may be even lower than that estimated from the review of EEG data. Conversely, video-EEG studies have shown that only two thirds of clinically recognized seizures have corresponding EEG seizures, emphasizing the clinical overestimation of seizure phenomena in infants with encephalopathy.[5] Electroclinical uncoupling is common after the administration of antiepileptic medications; that is, electroclinical seizures become clinically silent but still electrographically present,[6] and seizure duration may be shortened.[7]

The role of bedside, limited-channel amplitude-integrated electroencephalography (aEEG) in the diagnosis of neonatal seizures was a major topic of discussion. The strengths and weaknesses in the context of both clinical practice and design of future clinical trials were rigorously reviewed.[8-14] In contrast with conventional full-channel EEGs, aEEGs use fewer electrodes to create a single-channel (eg, biparietal electrodes) or two-channel recording (centroparietal or frontoparietal leads) and display aEEG tracings at the bedside. All recently developed aEEG devices also display the original EEG simultaneously; some can also record full-channel EEG and power spectral measures. The aEEG tracing is a trend measure of the EEG background amplitude, which can be used for long-term monitoring of electrocortical brain function. The aEEG has become popular in the NICU environment. Electrodes can be applied by the neonatal staff, and there is potential for interpretation of aEEG data at the bedside. This technology adds a new dimension to clinical intensive-care monitoring with continuous information about brain function.

Several investigators have undertaken comparative studies of aEEG with conventional EEG. In one study with simultaneous recordings of a single-channel EEG versus conventional EEG, there was a high rate of nondetection of seizures on the aEEG by inexperienced observers.[11] In another study, a single-channel aEEG was derived from central leads (C3-C4) and also resulted in a relatively low seizure detection rate when the aEEG was blindly evaluated.[12] In contrast, Shah (Washington University, St. Louis) presented results of a very recent unpublished study in which aEEG