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Original Article

Seizures in Preterm Neonates: A Multicenter Observational Cohort Study

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ABSTRACT

BACKGROUND: The purpose of this study was to characterize seizures among preterm neonates enrolled in the Neonatal Seizure Registry, a prospective cohort of consecutive neonates with seizures at seven pediatric centers that follow the American Clinical Neurophysiology Society's neonatal electroencephalography monitoring guideline. **STUDY DESIGN:** Of 611 enrolled neonates with seizures, 92 (15%) were born preterm. Seizure characteristics were evaluated by gestational age at birth for extremely preterm (<28 weeks, N = 18), very preterm (28 to <32 weeks, N = 18), and moderate to late preterm (32 to <37 weeks, N = 56) and compared with term neonates. **RESULTS:** Hypoxic-ischemic encephalopathy (33%) and intracranial hemorrhage (27%) accounted for the etiology in more than half of preterm neonates. Hypothermia therapy was utilized in 15 moderate to late preterm subjects with encephalopathy. The presence of subclinical seizures, monotherapy treatment failure, and distribution of seizure burden (including status epilepticus) was similar in preterm and term neonates. However, exclusively subclinical seizures occurred more often in preterm than term neonates (24% vs 14%). Phenobarbital was the most common initial medication for all gestational age groups, and failure to respond to an initial loading dose was 63% in both preterm and term neonates. Mortality was similar among the three preterm gestational age groups; however, preterm mortality was more than twice that of term infants (35% vs 15%). **CONCLUSIONS:** Subclinical seizures were more common and mortality was higher for preterm than term neonates. These data underscore the importance of electroencephalographic monitoring and the potential for improved management in preterm neonates.

Keywords: preterm, neonatal seizures, EEG, electroencephalograph, neurocritical care, neonatal encephalopathy, hypoxic-ischemic encephalopathy

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Introduction

The risk of seizures is highest in the first year after birth and especially within the first month.[1] The risk of seizures appears to be inversely related to gestational age and birth weight: the reported incidence of seizures in very low birth weight infants (less than 1500 g at birth) is approximately 1.9% to 5.8% in population-based studies[2-4] and 3.9% to 48% in single center studies.[5-8] Lloyd et al.[9] summarized 120 preterm neonates (median gestational age 29 weeks, inter quartile range 27 to 30 weeks) who were monitored using continuous electroencephalography (cEEG) for approximately 72 hours after birth. They detected seizures in only six infants (5%), suggesting that the seizure frequency in an unselected population is at the lower range of what other groups have reported.

Population-based data largely rely on reporting from vital statistics and hospital discharge diagnoses, include neonates at both low and high acuity centers, and predominantly reflect a clinical diagnosis of seizures. In contrast, the single center studies largely report the experiences of tertiary care centers with a neurological focus and higher acuity and/or standardized neurophysiology monitoring. Therefore the differences in reported rates likely reflect both the populations studied and the method of ascertainment. Of note, the highest reported rates of seizure in preterm neonates come from centers that predominantly use amplitude-integrated electroencephalography (aEEG) for seizure detection, a technique that is subject to both false-negative and false-positive results.[10]

The primary objective of this study was to characterize seizures among preterm neonates in the Neonatal Seizure Registry, a prospective cohort of neonates with seizures managed at seven US pediatric centers that follow the American Clinical Neurophysiology Society (ACNS) neonatal cEEG monitoring guideline.[11] We hypothesized that seizure etiology, response to treatment, and short-term outcome would differ by gestational age at birth.

Methods

This study was a prospective, observational cohort study of consecutive neonates with seizures treated at the seven sites of the Neonatal Seizure Registry. Each site has a level IV neonatal intensive care unit (NICU) and follows the ACNS guideline for cEEG.[11] The ACNS recommends monitoring neonates for differential diagnosis of paroxysmal events and for detection of electrographic seizures in selected high-risk populations. In neonates at risk for seizures, the ACNS guidelines recommend cEEG monitoring for a minimum of 24 hours and for 24 hours after the last electrographic seizure. In clinical practice, neonates with hypoxic-ischemic encephalopathy (HIE) who undergo therapeutic hypothermia at each of the study centers are monitored with cEEG until rewarming is complete.

All neonates with seizures diagnosed clinically and/or with EEG confirmation were enrolled from January 2013 through November 2015. Neonates with events that were determined *not* to be seizures based on clinical evaluation or EEG monitoring were not enrolled. Neonates with clinical events suspected to be seizures and treated as such with antiseizure medications were included if the clinical evaluation, event semiology, and/or outside hospital EEG supported the diagnosis of seizures, even if seizures were not identified on subsequent cEEG recordings at the study center. Indications for cEEG monitoring included differential diagnosis of clinical events concerning for seizure, encephalopathy, clinical events plus encephalopathy, or "other" indication. Details regarding seizure etiology, medical management, seizure burden, and treatment responses were recorded. The study site investigators determined primary seizure etiology based on a systematic review of the medical record. Seizure characteristics and short-term outcomes were compared within preterm gestational age groups (extremely preterm, gestational age less than 28 weeks; very preterm, gestational age 28 to less than 32 weeks; and moderate to late preterm, gestational age 32 to less than 37 weeks), and between preterm and term (gestational age 37 or more weeks) neonates. Abnormal examination was defined as any alteration in consciousness, tone, or reflexes.

For both term and preterm neonates, electrographic seizures were defined as a sudden, abnormal EEG event defined as a repetitive and evolving pattern with minimum amplitude of 2 μV and duration ≥10 seconds.[12] Seizure burden and characteristics were determined by video-EEG reports. A board-certified pediatric electroencephalographer with experience in neonatal neurophysiology reported the EEG at each site. Seizure exposure was defined as follows: no EEG seizures, isolated (fewer than seven) recorded seizures, many (seven or more) recorded seizures, frequent recurrent seizures (but not fulfilling criteria for status epilepticus), and status epilepticus (50% or more of any 60-minute EEG epoch comprising seizures). Treatment for seizures, including medication selection and duration of therapy, was at the discretion of the clinical team. No specific treatment guideline was provided to the sites as this was an observational study, although five of the seven sites had an institutional guideline, pathway, or suggested workflow for seizure management.

Descriptive statistics and results of *t* tests, ANOVA, Kruskall Wallis, Wilcoxon rank sum, and chi-square tests are presented. Analyses were performed both *within* preterm gestational age groups, as well as preterm compared with term neonates. Analyses were completed using Stata 14 (StataCorp, College Station, TX).

The local institutional review board for every site approved the study and granted a waiver of informed consent. Subjects from the Neonatal Seizure Registry were previously presented.[13,14]

Results

From January 2013 through November 2015, 611 consecutive neonates with seizures were enrolled into the Neonatal Seizure Registry. Fifteen percent (92 neonates) were born at gestational age less than 37 weeks as follows: N = 18 extremely preterm (gestational age less than 28 weeks), N = 18 very preterm (gestational age 28 to less than 32 weeks), and N = 56 moderate to late preterm (gestational age 32 to less than 37 weeks). Patient characteristics are presented in Table 1.

Seizure etiology

HIE was the most common seizure etiology among moderate to late preterm and term neonates, whereas intracranial hemorrhage was more common among extremely and very preterm neonates. Sixty percent of moderate to late preterm subjects with seizures caused by HIE were treated with therapeutic hypothermia at a median age of 36 (range $33^{1/7}$ to $36^{6/7}$) weeks. The 12 preterm survivors of HIE underwent cEEG monitoring for a median of 90 hours to include cooling and rewarming periods. Ischemic strokes and genetic epileptic encephalopathies were more commonly diagnosed in term neonates, whereas intracranial infections were a more common cause of seizures in preterm neonates ($P < 0.0005$). The proportion with an unknown etiology was similar across all gestational age groups (range 8% to 11% by gestational age group).

Monitoring and seizure characteristics

There were differences between term and preterm gestational age groups with regards to indication for