Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study

Hannah C. Glass, MDCM, MAS[1,2], Renée A. Shellhaas, MD, MS[3], Courtney J. Wusthoff, MD[4], Taeun Chang, MD[5], Nicholas S. Abend, MD[6], Catherine J. Chu, MD[7], M. Roberta Cilio, MD, PhD[1], David V. Glidden, PhD[2], Sonia L. Bonifacio, MD, MAS[8], Shavonne Massey, MD[6], Tammy N. Tsuchida, MD, PhD[5], Faye S. Silverstein, MD[3], and Janet S. Soul, MDCM[9], on behalf of the Neonatal Seizure Registry Study Group*

Objective To determine the contemporary etiology, burden, and short-term outcomes of seizures in neonates monitored with continuous video-electroencephalogram (cEEG).

Study design We prospectively collected data from 426 consecutive neonates (56% male, 88% term) ≤44 weeks' postmenstrual age with clinically suspected seizures and/or electrographic seizures. Subjects were assessed between January 2013 and April 2015 at 7 US tertiary care pediatric centers following the guidelines of the American Clinical Neurophysiology Society for cEEG for at-risk neonates. Seizure etiology, burden, management, and outcome were determined by chart review by the use of a case report form designed at study onset.

Results The most common seizure etiologies were hypoxic-ischemic encephalopathy (38%), ischemic stroke (18%), and intracranial hemorrhage (11%). Seizure burden was high, with 59% having ≥7 electrographic seizures and 16% having status epilepticus; 52% received ≥2 antiseizure medications. During the neonatal admission, 17% died; 49% of survivors had abnormal neurologic examination at hospital discharge. In an adjusted analysis, high seizure burden was a significant risk factor for mortality, length of hospital stay, and abnormal neurological examination at discharge.

Conclusions In this large contemporary profile of consecutively enrolled newborns with seizures treated at centers that use cEEG per the guidelines of the American Clinical Neurophysiology Society, about one-half had high seizure burden, received ≥2 antiseizure medications, and/or died or had abnormal examination at discharge. Greater seizure burden was associated with increased morbidity and mortality. These findings underscore the importance of accurate determination of neonatal seizure frequency and etiology and a potential for improved outcome if seizure burden is reduced. *(J Pediatr 2016;174:98-103)*.

Seizures are a common manifestation of neurologic disorders in neonates and are associated with unfavorable short- and long-term developmental outcomes.[1] More than 50% of survivors experience considerable disability across a range of developmental domains, most frequently cerebral palsy, postneonatal epilepsy, and/or intellectual disability,[1,2] and require costly, lifelong therapies and social and academic support.

Advances in the accurate diagnosis and management of seizures in neonates have been limited by several important factors: (1) seizures are difficult to diagnose because almost any abnormal movement can be attributable to seizures, yet electrographic seizures frequently do not have a clinical correlate[3,4]; (2) commonly used medications have limited efficacy[5]; and (3) the relatively rare occurrence of seizures (1-4/1000 live term births) requires multicenter collaborative efforts.[6-8] Most studies of neonatal seizures have used either single-center data or population-based information that relied primarily on observation of clinical seizures rather than seizures identified by electroencephalography (EEG).

To address these limitations, we developed the Neonatal Seizure Registry, a multicenter collaboration of tertiary centers across the US that follow the American Clinical Neurophysiology Society (ACNS) guidelines for continuous video-electroencephalogram (cEEG) monitoring for at-risk neonates.[9] The aim of this study was to use registry data to identify the contemporary profile of seizure etiologies and characteristics of seizures in a large, prospective, consecutive cohort.

ACNS	American Clinical Neurophysiology Society
cEEG	Continuous video-electroencephalogram
EEG	Electroencephalography
HIE	Hypoxic-ischemic encephalopathy
ICH	Intracranial hemorrhage

From the [1]Departments of Neurology & Pediatrics, University of California, San Francisco Benioff Children's Hospital, [2]Department of Epidemiology & Biostatistics, University of California San Francisco, San Francisco, CA; [3]Department of Pediatrics & Communicable Diseases, University of Michigan, Ann Arbor, MI; [4]Departments of Neurology & Pediatrics, Stanford University, Palo Alto, CA; [5]Department of Neurology, Children's National Health System, George Washington University School of Medicine, Washington, DC; [6]Departments of Neurology and Pediatrics, The Children's Hospital of Philadelphia and The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [7]Department of Neurology, Massachusetts General Hospital, Boston, MA; [8]Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University, Palo Alto, CA; and [9]Department of Neurology, Boston Children's Hospital, Boston, MA

*List of additional members of Neonatal Seizure Registry Study Group is available at www.jpeds.com (**Appendix**).

Supported by the Pediatric Epilepsy Research Foundation (Multi-center Neonatal Seizure Registry/A120625). H.G. is supported by the National Institutes of Health (NIH)/National Institute of Neurological Disorders and Stroke (K23NS066137) and the Neonatal Brain Research Institute at University of California, San Francisco. J.S. is supported by Boston Children's Hospital Intellectual and Developmental Disabilities Research Center (P30 HD18655). REDCap (Research Electronic Data Capture) tools is supported by University of California, San Francisco. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the NIH. The authors declare no conflicts of interest.

http://dx.doi.org/10.1016/j.jpeds.2016.03.035

Methods

Subjects were consecutive neonates (<44 weeks' postmenstrual age) with clinical events suspicious for seizures and/or confirmed EEG seizures who were admitted from January 2013 to April 2015 to 1 of the 7 participating tertiary care centers. All centers followed the 2011 ACNS guidelines for brain monitoring in neonates,[9] which recommend cEEG for the following indications: (1) to assess differential diagnosis of paroxysmal events (ie, patients with 1 or more clinical events suggestive of seizure); (2) to detect seizures in high-risk populations (ie, neonates with acute encephalopathy, need for extracorporeal membrane oxygenation, central nervous system infection, or, intracranial bleeding); and/or (3) to assess for background abnormalities during acute encephalopathy. The duration of cEEG monitoring recommended by the ACNS guidelines is until index clinical events are captured, for a minimum of 24 hours, or until at least 24 hours after resolution of electrographic seizures. All centers used cEEG for neonates treated with therapeutic hypothermia during hypothermia and rewarming. Study data were collected and managed by the use of REDCap (Research Electronic Data Capture) tools, hosted at University of California, San Francisco.[10] The local Institutional Review Board or Committee on Human Research approved a waiver of consent for data collection at each site.

Clinical data were compiled prospectively in a systematic manner by the use of predetermined variable definitions. Patient demographic characteristics, duration of monitoring, and in-hospital neurologic outcomes were extracted from medical records by a trained research assistant at each site. A study investigator at each site reviewed medical records, including clinical, laboratory, EEG, and neuroimaging results, to determine the indication for EEG monitoring, seizure etiology, and burden, as well as EEG and examination findings. Seizures were defined as repetitive, evolving patterns, with a definite beginning and end, with a minimum duration of 10 seconds and a minimum amplitude of 2 microvolts.[11,12] EEG seizure burden was defined a priori as follows: (1) none; (2) rare EEG seizures (<7); (3) many isolated EEG seizures (≥7); (4) frequent recurrent EEG seizures; (5) status epilepticus; or (6) documentation inadequate to quantify. Status epilepticus was defined as any electrographic recording with seizures lasting >50% over at least 1 hour of recording.[12,13] Seizure burden also was dichotomized to "low" (<7 seizures) or "high" (≥7). Abnormal neurologic examination was defined as abnormalities in consciousness, tone, and/or reflexes, as documented by the treating clinician(s). Antiseizure medication administration was based on local guidelines at the discretion of the treating physicians. Each site obtained a consultation from a neurologist on neonates with seizures as standard care.

To help ensure integrity of the data, the study principal investigator and coordinating center research assistant reviewed data from each site for completeness and outliers. In addition, 5 randomly chosen files from each center were re-abstracted in person by the study principal investigator and research assistant. During these study audits, data were checked for completeness and accuracy, and local investigators were asked to correct any systematic errors.

Statistical Analyses

Study results are presented as actual numbers with percentages, mean with SD, or medians with IQRs. χ^2 test was used to examine the difference between proportions. The Student *t* test was used to compare means. Statistical analyses were performed using Stata 12 (StataCorp, College Station, Texas), and *P* values <.05 were considered significant. For the adjusted analysis, variables that were significant to $P = .1$ were included in the multivariable model, which was then refined by the use of backward stepwise regression as needed.

Results

Seven sites enrolled 426 subjects who had suspected or confirmed seizures during the study period and were monitored with cEEG according to the ACNS guidelines. The indication for cEEG was a suspicion of clinical seizures in 63%, and the remaining neonates were monitored for encephalopathy with or without suspicious clinical events (15% and 19%, respectively), or other indication in 4% (during extracorporeal membrane oxygenation or postcardiac surgery in 7 subjects, abnormal neuroimaging in 5, and unspecified/other in 3). Basic demographic data are presented in **Table I**.

The most common seizure etiologies were hypoxic-ischemic encephalopathy (HIE, 38%), arterial or venous ischemic stroke (18%), and intracranial hemorrhage (ICH, 12%) (**Table I**). Neonatal-onset epilepsy was present in 13%, attributable to epileptic encephalopathy/genetic epilepsy syndrome in 6% and congenital brain malformation in 4%; benign familial neonatal epilepsy was identified in 3%. Most subjects (79%) had a single identified etiology; those with more than 1 etiology usually had a combination of acute symptomatic and/or transient metabolic etiologies.

Seizure Characteristics

Eighty-two percent of subjects had electrographic seizures detected by cEEG. The remainder had only clinical events suspicious for seizures that resolved before cEEG recording or electrographic seizures recorded at the referral hospital but no confirmed seizures on the study center cEEG. Sixty-two percent of subjects had at least 1 electrographic seizure without clinical correlate (ie, subclinical seizure), and 16% had only electrographic seizures without clinical correlate. Subclinical seizures occurred equally among neonates with at least 1 seizure captured on EEG, regardless of seizure burden.

Monitoring with cEEG was maintained for a median duration of 66 hours (IQR 40, 96 hours), with 90% of subjects monitored for ≥24 hours, and 98% monitored for >12 hours. cEEG monitoring was initiated at a median age of 50 hours