Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study

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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

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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

Table I. Clinical characteristics and seizure etiology among 426 neonates with clinically suspected and/or EEG confirmed seizures who were monitored by cEEG

	Overall, n = 426
Clinical characteristics	
Male	237 (56%)
Term (>36 wk gestation)	373 (88%)
Admission to the study center at <24 h age	222 (52%)
Medical comorbidities	
Congenital cardiac disease	60 (14%)
ECMO	27 (6%)
Dialysis	6 (1%)
Congenital diaphragmatic hernia	4 (1%)
Indication for cEEG monitoring	
Clinical event suspicious for seizure	267 (63%)
Encephalopathy	82 (19%)
Clinical event and encephalopathy	62 (15%)
Other	15 (4%)
Seizure etiology	
HIE	163 (38%)
Ischemic stroke	75 (18%)
ICH	49 (12%)
Epileptic encephalopathy/genetic epilepsy	24 (6%)
Intracranial infection	19 (4%)
Brain malformation	18 (4%)
Transient metabolic (hypoglycemia or electrolyte disturbance)	16 (4%)
Inborn error of metabolism	13 (3%)
Benign familial neonatal epilepsy	11 (3%)
Other/unknown	38 (9%)
Short-term outcomes	
Death or transfer to hospice	72 (17%)
Abnormal mental status, tone, or reflexes among survivors at discharge/transfer	173 (49%)
Length of hospital stay among survivors discharged home, d	14 (10, 28)

ECMO, extracorporeal membrane oxygenation.
Data are presented as n (%) or median (IQR).

(IQR 15 hours, 5 days) for term neonates, whose first clinically suspected seizure was reported at a median age of 27 hours (IQR 11, 80 hours). This finding was significantly different from preterm newborns for whom cEEG monitoring was initiated at a median 11 days (IQR 27 hours, 33 days, $P < .0005$ compared with term neonates), whose first suspected seizure was noted at a median of 14 days (IQR 3, 33 days). The median time to electrographic seizure detection from the onset of recording was 7 hours (IQR 3, 17 hours) and was not significantly different between term and preterm neonates ($P = .09$) or by indication for monitoring ($P = .5$).

The seizure burden was high, with 59% of subjects having ≥7 electrographic seizures and 16% having status epilepticus (**Figure**). There was no significant difference in seizure burden between preterm and term neonates or among the 3 most common causes of seizure (HIE, ischemic stroke, and ICH, $P = .9$). Term newborns with HIE treated with hypothermia showed no difference in EEG seizure frequency compared with those not treated with hypothermia (65/76, 85% vs 28/38, 74% with any EEG seizures, $P = .12$), when we excluded term newborns with other medical diagnoses and preterm newborns.

Medical Management of Seizures

Phenobarbital was the most common medication used during the hospital admission (94%) and for initial bolus dosing (93%). Forty-three percent of subjects were treated with phenobarbital before monitoring; subjects without seizures on EEG were more likely to have been treated with phenobarbital before monitoring (54/76, 71% vs 22/76, 29% $P < .001$). The next most commonly used medications were levetiracetam and fosphenytoin, followed by benzodiazepines for either intermittent or infusion dosing (**Tables II** and **III**). Topiramate, carbamazepine/oxcarbazepine, lidocaine, and lacosamide were administered to <5% of subjects.

Overall, 64% of subjects had electrographic seizures that were refractory to the initial loading dose of antiseizure medication (**Table III**). There was no significant difference in response to initial medication among term and preterm neonates. There was a significant difference in rates of refractory seizures after the initial medication given when all etiologies were compared (overall $P = .01$), but there was no significant difference among the 3 most common etiologies, where the rate of seizures refractory to initial medication was high (HIE 62%, stroke 66%, ICH 70%, $P = .3$). Neonates with inborn errors of metabolism were least likely to have refractory seizures (33% refractory), followed by neonates with benign familial neonatal seizures (40% refractory). Median loading dose with phenobarbital was 20 mg/kg (IQR 20, 20 mg/kg), and 245 of 379 subjects (65%) had subsequent electrographic seizures. Median loading dose with levetiracetam was 20 mg/kg (IQR 20, 32 mg/kg) and 14 of 22 subjects (64%) who received levetiracetam as their initial loading medication had subsequent electrographic seizures. The median loading dose of fosphenytoin was 20 mg/kg (IQR 15, 20 mg/kg) and all 4 subjects (100%) who received fosphenytoin as their initial loading medication had subsequent electrographic seizures.

Seizures were treated with at least 1 medication in >97% of subjects; and 52% were treated with ≥2 antiseizure medications during the inpatient stay (**Table III**). There was no difference in the number of medications used among term vs preterm neonates and among the 3 most common diagnoses (HIE, ICH, and ischemic stroke, $P > .3$).

Short-Term Outcomes

Overall, 72 subjects (17%) died before discharge or were transferred to hospice care, and mortality was greater for preterm compared with term neonates (32% vs 15%, $P = .002$). Seizure etiology was associated with death. Neonates with brain malformation had the greatest rate of death (33%). Among the 3 most common causes of seizure, the greatest mortality was among neonates with HIE (26%) compared with those with ICH (13%) and ischemic stroke (4%, $P < .0005$). Mortality was strongly associated with seizure burden, with greater mortality among those neonates who experienced a greater seizure burden. Neonates with <7 seizures captured on EEG at the study center had a mortality

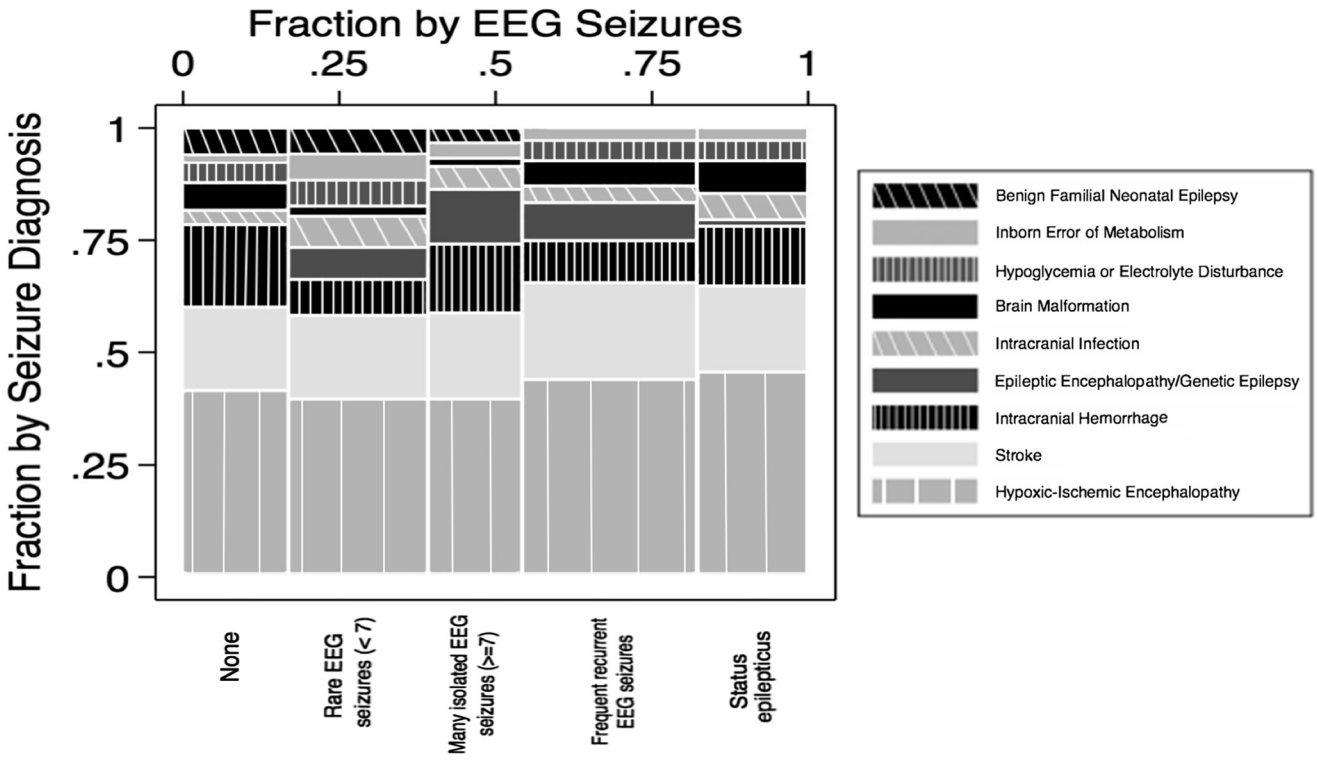

Figure. Mosaic plot of seizure burden by etiology. The proportions on the x-axis represent the number of observations for each level of seizure burden, whereas the proportions on the y-axis represent the proportion by seizure etiology.

of 6%, and those with ≥7 seizures had a 24% mortality ($P < .0005$). Similarly, neonates without status epilepticus had a mortality of 15%, and those with status epilepticus had a mortality of 26% ($P = .03$).

Neonates whose seizures were refractory to a loading dose of medication were twice as likely to die (54/264, 20%) compared with neonates whose seizures were controlled with the initial loading dose of medication (13/143, 9%, $P = .009$). Neonates who had only subclinical seizures had greater mortality (20/67, 30%) than neonates who had clinical manifestations with or without electrographic correlate (52/359, 14%, $P = .002$). In an adjusted analysis, seizure etiology, greater seizure burden, and preterm birth all remained significant risk factors for death. When we accounted for only those neonates with acute symptomatic seizures, etiology, greater seizure burden, and preterm birth remained significant risk factors for death.

Median length of hospital stay among survivors was 13 days (IQR 9, 24) for term neonates and 46 days (IQR 19, 91) for preterm neonates ($P < .0005$). Seizure etiology was associated with length of hospital stay, which was longer for subjects who had ≥7 seizures (median 16, IQR 11, 35 days) compared with those with <7 seizures (median 12, IQR 8, 27 days, $P = .02$). In an adjusted analysis, seizure

Table II. Medication use by seizure etiology among 426 neonates with clinically suspected and/or EEG confirmed seizures who were monitored by cEEG

	Phenobarbital	Levetiracetam	Fosphenytoin
Term	346 (93%)	116 (31%)	109 (29%)
Preterm	47 (89%)	18 (34%)	10 (19%)
HIE	153 (94%)	45 (28%)	44 (27%)
Ischemic stroke	71 (95%)	23 (31%)	28 (37%)
ICH	45 (92%)	19 (39%)	17 (35%)
Epileptic encephalopathy/genetic epilepsy	23 (96%)	15 (63%)	6 (25%)
Intracranial infection	18 (95%)	9 (47%)	4 (21%)
Brain malformation	18 (100%)	10 (56%)	8 (44%)
Benign familial neonatal epilepsy	9 (82%)	1 (9%)	0
Inborn error of metabolism	10 (77%)	3 (23%)	2 (15%)
Transient metabolic (hypoglycemia or electrolyte disturbance)	15 (93%)	2 (13%)	3 (19%)
Other/unknown	31 (82%)	7 (18%)	7 (18%)

Data are presented as n and row %.

Table III. Seizure management among 426 neonates with clinically suspected and/or EEG confirmed seizures who were monitored by cEEG

	Overall, n = 426
Initial loading medication and dose	
Phenobarbital (20 mg/kg, IQR 20, 20 mg/kg)	379 (89%)
Levetiracetam (20 mg/kg, IQR 20, 32 mg/kg)	22 (5%)
Fosphenytoin (20 m/kg, IQR 15, 20 mg/kg)	4 (1%)
No loading dose	18 (4%)
Seizure medications administered during the admission	
Phenobarbital	393 (92%)
Levetiracetam	134 (31%)
Fosphenytoin	119 (28%)
Benzodiazepine – intermittent doses	84 (20%)
Benzodiazepine infusion	31 (7%)
Topiramate	17 (4%)
Carbamazepine/oxcarbazepine	9 (2%)
Vitamin(s): (pyridoxine, folic acid, pyridoxal 5 phosphate)	32 (8%)
Number of antiseizure medications administered	
0	10 (2%)
1	194 (46%)
2	101 (24%)
3	68 (16%)
≥4	53 (12%)

etiology, greater seizure burden and preterm birth were all significantly associated with length of hospital stay.

When we accounted for only those neonates with acute symptomatic seizures, etiology, greater seizure burden, and preterm birth remained significant risk factors for length of stay. Among survivors, 49% had an abnormal examination (abnormality of consciousness, tone, or reflexes) at the time of discharge or transfer. There was no difference in rates of abnormal examination between term and preterm neonates ($P = .2$). Rates of abnormal examination were greatest among survivors with brain malformation (10/12, 83%), neonatal onset epileptic encephalopathies/genetic epilepsies (13/22, 59%), and HIE (69/121, 57%). Seizure burden was significantly associated with abnormal examination at the time of hospital discharge among survivors. Neonates with ≥7 electrographic seizures had a greater rate of abnormal examination at the time of hospital discharge (112/191, 59%) compared with those with <7 seizures (61/163, 37%, $P < .0005$). Among survivors of status epilepticus, 38 of 52 (73%) had a greater rate of abnormal neurological examination at the time of hospital discharge compared with those without status epilepticus 135/302 (45%). In an adjusted analysis, seizure etiology and burden remained significant for abnormal neurological examination at the time of discharge. When we accounted for only those neonates with acute symptomatic seizures, etiology was no longer a significant risk factor; however, high seizure burden remained a significant risk factor for abnormal neurologic examination.

Discussion

Our multicenter, collaborative effort from 7 tertiary centers that use cEEG according to ACNS guidelines[9] provides important data to examine and improve management of neonates with seizures. In particular, our data show that greater seizure burden is associated with mortality, longer length of hospital stay, and abnormal neurologic examination at the time of hospital discharge, independent of seizure etiology and preterm birth. This finding underscores the importance of detecting and characterizing neonatal seizures and the potential for improving outcome with better seizure control. We furthermore confirm that neonatal seizures are associated with a high need for specialized neurologic care, because more than one-half of subjects had ≥7 seizures that were refractory to initial loading doses of antiseizure medication, received ≥2 antiseizure medications, and/or were deceased or had an abnormal neurologic examination at the time of discharge.

Data from these 7 centers following ACNS guidelines add to the literature that supports the ACNS recommendations to monitor at-risk neonates with conventional video-EEG for at least 24 hours of continuous monitoring to identify subclinical seizures and confirm electrographic correlates of paroxysmal events.[9,14] A high frequency of subclinical seizures has been reported in several previous studies of neonates,[3,15,16] and our much larger study population supports and extends this finding. Furthermore, we found that seizures were detected within a median of 7 hours of cEEG monitoring onset (and more than 75% were detected within 24 hours) and that subclinical seizures were associated with high mortality.

Our data also confirm the high burden of seizures among neonates with the most common etiologies (HIE, stroke, and ICH), with >40% of these neonates having frequent recurrent seizures or status epilepticus. Notably, greater seizure burden was a significant risk factor for mortality, longer length of stay, and abnormal examination at discharge among newborns with these three acute symptomatic etiologies. This association between greater seizure burden and worse short-term outcome further supports the possibility that improved seizure control might improve neurologic outcome in these newborns. We also found that HIE remains the most common cause of seizures, despite reports suggesting a lower seizure burden among neonates treated with hypothermia.[17-19]

Similar to previous reports, we found that >50% of neonates have electrographic seizures refractory to the initial medication.[5,20] There was no significant difference in response to the 3 most common initial medications, phenobarbital, levetiracetam, and fosphenytoin. These data suggest that phenobarbital, fosphenytoin, and levetiracetam are incompletely effective for neonates with the most refractory seizures. Clinical trials are needed to determine which medication, or combination of medications, and which doses are most effective.

Although we report a large cohort from 7 pediatric centers that follow the latest ACNS guidelines for monitoring in neonates, our study has limitations. First, we relied on chart review, including EEG reports and determination of seizure etiology; however, each study center included a child neurologist and neurophysiologist with special interest in neonatal

neurology, factors that strengthen both clinical reporting and data collection for the study. Second, although study investigators regularly monitored inpatient services for eligible subjects, it is possible some at-risk patients with shorter stay or milder clinical manifestations were missed, and thus, our data might be skewed toward more severely affected subjects. Third, our large study cohort precluded collection of detailed data that would be helpful to further elucidate the etiology, characteristics, and management of neonatal seizures, such as detailed maternal and fetal data, the precise number, localization, and duration of seizures, rationale for individual medication choices, and effect of medications on EEG seizure burden. Lastly, the distribution of seizure etiology in our study may not reflect the distribution in the general population, because tertiary centers typically care for more neonates with rare neonatal-onset epilepsies and more severe and complex medical diseases. Nonetheless, our data set includes a large number of neonates with the most common seizure etiologies. This greater representation of rare etiologies is helpful to delineate differences between the rare and common seizure etiologies.

In conclusion, we have shown that seizures are a frequent manifestation of neurologic disorders in neonates and are associated with high morbidity and mortality. Optimizing seizure identification and management may improve outcome. Randomized controlled trials and large longitudinal cohort studies to examine the relationship between management and outcomes are urgently needed. The degree to which seizure burden results in or reflects a risk for increased morbidity and mortality should be addressed in future clinical trials and prospective studies that control for underlying seizure etiology. ■

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References

1. Uria-Avellanal C, Marlow N, Rennie JM. Outcome following neonatal seizures. Semin Fetal Neonatal Med 2013;18:224-32.
2. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population-based study. Neurology 2007;69:1816-22.
3. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. Epilepsia 1988; 29:256-61.
4. Biagioni E, Ferrari F, Boldrini A, Roversi MF, Cioni G. Electroclinical correlation in neonatal seizures. Europ J Paediatr Neurol 1998; 2:117-25.
5. Painter MJ, Scher MS, Stein AD, Armatti S, Wang Z, Gardiner JC, et al. Phenobarbital compared with phenytoin for the treatment of neonatal seizures. N Engl J Med 1999;341:485-9.
6. Glass HC, Pham TN, Danielsen B, Towner D, Glidden D, Wu YW. Antenatal and intrapartum risk factors for seizures in term newborns: a population-based study, California 1998-2002. J Pediatr 2009;154:24-8.e1.
7. Hall DA, Wadwa RP, Goldenberg NA, Norris JM. Maternal risk factors for term neonatal seizures: population-based study in Colorado, 1989-2003. J Child Neurol 2006;21:795-8.
8. Saliba RM, Annegers JF, Waller DK, Tyson JE, Mizrahi EM. Incidence of neonatal seizures in Harris County, Texas, 1992-1994. Am J Epidemiol 1999;150:763-9.
9. Shellhaas RA, Chang T, Tsuchida T, Scher MS, Riviello JJ, Abend NS, et al. The American Clinical Neurophysiology Society's Guideline on Continuous Electroencephalography Monitoring in Neonates. J Clin Neurophysiol 2011;28:611-7.
10. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.
11. Clancy RR, Legido A. The exact ictal and interictal duration of electroencephalographic neonatal seizures. Epilepsia 1987;28:537-41.
12. Tsuchida TN, Wusthoff CJ, Shellhaas RA, Abend NS, Hahn CD, Sullivan JE, et al. American clinical neurophysiology society standardized EEG terminology and categorization for the description of continuous EEG monitoring in neonates: report of the American Clinical Neurophysiology Society critical care monitoring committee. J Clin Neurophysiol 2013;30:161-73.
13. Abend NS, Wusthoff CJ. Neonatal seizures and status epilepticus. J Clin Neurophysiol 2012;29:441-8.
14. Wietstock SO, Bonifacio SL, Sullivan JE, Nash KB, Glass HC. Continuous video electroencephalographic (EEG) monitoring for electrographic seizure diagnosis in neonates: a single-center study. J Child Neurol 2016;31:328-32.
15. Nash KB, Bonifacio SL, Glass HC, Sullivan JE, Barkovich AJ, Ferriero DM, et al. Video-EEG monitoring in newborns with hypoxic-ischemic encephalopathy treated with hypothermia. Neurology 2011; 76:556-62.
16. Scher MS. Neonatal seizures and brain damage. Pediatr Neurol 2003;29: 381-90.
17. Low E, Boylan GB, Mathieson SR, Murray DM, Korotchikova I, Stevenson NJ, et al. Cooling and seizure burden in term neonates: an observational study. Arch Dis Child Fetal Neonatal Ed 2012;97: F267-72.
18. Orbach SA, Bonifacio SL, Kuzniewicz MW, Glass HC. Lower incidence of seizure among neonates treated with therapeutic hypothermia. J Child Neurol 2014;29:1502-7.
19. Srinivasakumar P, Zempel J, Wallendorf M, Lawrence R, Inder T, Mathur A. Therapeutic hypothermia in neonatal hypoxic ischemic encephalopathy: electrographic seizures and magnetic resonance imaging evidence of injury. J Pediatr 2013;163:465-70.
20. Boylan GB, Rennie JM, Chorley G, Pressler RM, Fox GF, Farrer K, et al. Second-line anticonvulsant treatment of neonatal seizures: a video-EEG monitoring study. Neurology 2004;62:486-8.

Appendix

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