Seizure Severity and Treatment Response in Newborn Infants with Seizures Attributed to Intracranial Hemorrhage

Emily M. Herzberg, MD[1,2], Michelle Machie, MD[4], Hannah C. Glass, MDCM, MAS[5,6,7], Renée A. Shellhaas, MD, MS[8], Courtney J. Wusthoff, MD, MS[9], Taeun Chang, MD[11], Nicholas S. Abend, MD[12], Catherine J. Chu, MD[3], M. Roberta Cilio, MD, PhD[13], Sonia L. Bonifacio, MD, MAS[10], Shavonne L. Massey, MD[12], Charles E. McCulloch, PhD[7], and Janet S. Soul, MDCM[1], on behalf of the Neonatal Seizure Registry study group*

Objective We sought to characterize intracranial hemorrhage (ICH) as a seizure etiology in infants born term and preterm. For infants born term, we sought to compare seizure severity and treatment response for multisite vs single-site ICH and hypoxic–ischemic encephalopathy (HIE) with vs without ICH.

Study design We studied 112 newborn infants with seizures attributed to ICH and 201 infants born at term with seizures attributed to HIE, using a cohort of consecutive infants with clinically diagnosed and/or electrographic seizures prospectively enrolled in the multicenter Neonatal Seizure Registry. We compared seizure severity and treatment response among infants with complicated ICH, defined as multisite vs single-site ICH and HIE with vs without ICH.

Results ICH was a more common seizure etiology in infants born preterm vs term (27% vs 10%, $P < .001$). Most infants had subclinical seizures (74%) and an incomplete response to initial antiseizure medication (ASM) (68%). In infants born term, multisite ICH was associated with more subclinical seizures than single-site ICH (93% vs 66%, $P = .05$) and an incomplete response to the initial ASM (100% vs 66%, $P = .02$). Status epilepticus was more common in HIE with ICH vs HIE alone (38% vs 17%, $P = .05$).

Conclusions Seizure severity was greater and treatment response was lower among infants born term with complicated ICH. These data support the use of continuous video electroencephalogram monitoring to accurately detect seizures and a multistep treatment plan that considers early use of multiple ASMs, particularly with parenchymal and high-grade intraventricular hemorrhage and complicated ICH. *(J Pediatr 2021;■:1-8)*.

Intracranial hemorrhage (ICH) is an important cause of neonatal morbidity and one of the most common etiologies of neonatal seizures.[1] Among neonates born term with acute provoked seizures, ICH is the third most common seizure etiology, reported in 9%-17% of patients.[1-4] ICH as a cause of seizures is more common in infants born preterm (27%-33%) than in infants born term, and ICH is the most common reported cause of seizures in infants born at ≤32 weeks of gestation.[5,6]

Whereas ICH has been established as an important etiology of seizures in infants born term and preterm, the types and sites of ICH contributing to seizures have not been studied in detail. Parenchymal and subarachnoid hemorrhages are thought to cause seizures based on their direct contact with neurons,[7,8] whereas subdural hemorrhage is often asymptomatic in neonates.[7,9] Although intraventricular hemorrhage (IVH), especially when associated with periventricular hemorrhagic infarction (PVHI), has been reported frequently in infants born preterm with seizures, less is known about its role as a seizure etiology in infants born

aEEG	Amplitude-integrated electroencephalogram
ASM	Antiseizure medication
cvEEG	Continuous video electroencephalogram
EEG	Electroencephalogram
HIE	Hypoxic–ischemic encephalopathy
ICH	Intracranial hemorrhage
IVH	Intraventricular hemorrhage
NSR	Neonatal Seizure Registry
PVHI	Periventricular hemorrhagic infarction

From the [1]Department of Neurology, Boston Children's Hospital, Boston, MA; [2]Division of Newborn Medicine, Department of Pediatrics, and [3]Department of Neurology, Massachusetts General Hospital, Boston, MA; [4]Departments of Neurology and Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX; [5]Department of Neurology and Weill Institute for Neuroscience, [6]Department of Pediatrics, Benioff Children's Hospital, and [7]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA; [8]Department of Pediatrics, University of Michigan, Ann Arbor, MI; [9]Departments of Neurology & Pediatrics and [10]Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University, Palo Alto, CA; [11]Department of Neurology, Children's National Hospital, George Washington University School of Medicine, Washington, DC; [12]Departments of Neurology and Pediatrics, Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; and [13]Division of Pediatric Neurology, Department of Pediatrics, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium

*List of additional Neonatal Seizure Registry investigators and contributors available at www.jpeds.com (**Appendix**).

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Portions of this study were presented at the Child Neurology Society annual meeting, October 23-26, 2019, Charlotte, NC; and the Pediatric Academic Societies annual meeting, May 1-5, 2020 (virtual). Additionally, our group has published several manuscripts using data from this multicenter neonatal cohort (PMIDs: 27106855, 28558955, 28733343, and 30790268), that include overlapping patients. However, this is our study group's first description of intracranial hemorrhage as a seizure etiology on its own.

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term.[8,10] In addition, there are few data regarding seizure characteristics or management for infants born term or preterm whose seizures are caused by ICH.

The objective of this study was to characterize ICH as a seizure etiology among prospectively enrolled infants born term and preterm with respect to ICH location, seizure severity, and treatment response. We hypothesized that infants with complicated ICH would have greater seizure severity and less response to antiseizure medication (ASM). Elucidating the contribution of ICH to neonatal seizure severity will inform the need to identify seizures using continuous video electroencephalogram (cvEEG) as a management strategy to optimize care of infants with complicated ICH.

Methods

We performed a secondary analysis of a prospective, observational, consecutive cohort of neonates with seizures enrolled from January 2013 through November 2015 at 7 sites of the Neonatal Seizure Registry (NSR). Each site followed the 2011 American Clinical Neurophysiology Society guidelines for brain monitoring in neonates.[11] The institutional review boards approved the study and a waiver of informed consent was granted at each site.

Infants were enrolled in the NSR cohort if they were ≤44 weeks of postmenstrual age at the time of seizure onset and had seizures that were clinically suspected and/or electroencephalogram (EEG)-confirmed. Infants were identified by prospective review of clinical admission data through the electronic health record at each institution. Infants meeting the inclusion criteria were consecutively enrolled. Infants with clinical events suspected to be seizures and treated with ASMs were enrolled if the clinical evaluation and/or referring hospital EEG supported the diagnosis of seizures, even if the subsequent cvEEG at the study center did not identify seizures. All infants had cvEEG monitoring. Infants with clinical events that were determined not to be seizures (ie, had no cvEEG correlate) were excluded. Infants from the NSR cohort were included in the present study if ICH was listed as a primary or secondary seizure etiology, or if hypoxic–ischemic encephalopathy (HIE) was listed as a primary seizure etiology for infants born term. Infants were excluded if their gestational age was not available. The types of ICH included IVH with and without associated infarction (PVHI, ie, "grade 4 IVH"), parenchymal hemorrhage, subarachnoid hemorrhage, and subdural hemorrhage. High-grade IVH was defined as grade 3 or 4 IVH.

Study data were collected prospectively using REDCap (Research Electronic Data Capture).[12,13] The study definitions of seizures, EEG seizure burden, and status epilepticus were published previously.[1] For purposes of this study, a high seizure burden was defined as frequent recurrent EEG seizures or status epilepticus. Incomplete response to initial ASM was defined as electrographic seizures documented >30 minutes after the initial load of ASM was complete.

For the infants with ICH, we first determined whether ICH was a primary vs secondary seizure etiology and next determined whether there were any other seizure etiologies. The primary seizure etiology was defined as the diagnosis thought to be primarily responsible for seizures, determined by seizure location by cvEEG together with ICH location by neuroimaging. The secondary seizure etiology was defined as any additional diagnosis that likely contributed to seizures, also determined by cvEEG and neuroimaging data, particularly for multifocal seizures or multiple neurologic conditions (eg, HIE and ICH). Determination of whether a seizure etiology was primary or secondary was made by a study investigator with neonatal neurology expertise at each site after review of the clinical, neuroimaging, and EEG reports. The intracranial compartment and specific site of ICH were determined by review of all available neuroimages and imaging reports (including head ultrasound, brain magnetic resonance imaging, and computed tomography of the head) by the study site investigators, including a child neurologist with a special interest in neonatal neurology. Because subdural hemorrhage is more commonly an incidental finding than a cause of seizures, seizure etiologies were re-evaluated by review of neuroimaging and EEG reports by the site investigator in cases in which subdural hemorrhage was listed as a seizure etiology. Subdural hemorrhage was considered a seizure etiology when it was large, located in the region of a seizure focus by cvEEG, and there was not another more likely seizure etiology. A PVHI (ie, "grade 4 IVH") was defined as an IVH with associated periventricular hemorrhagic infarction, whereas an isolated parenchymal hemorrhage without an associated IVH was classified as a parenchymal hemorrhage.

The primary outcome of seizure severity was determined by measures of seizure burden and documentation of subclinical seizures. The secondary outcome of treatment response was determined by measures of incomplete response to the initial ASM and the number of ASMs administered. Given the small number of infants born preterm (<37 weeks of gestation) with ICH in the cohort, analyses of multisite vs single-site ICH and HIE with ICH vs HIE alone were completed only in infants born term.

Statistical Analyses

Demographic and clinical characteristics were summarized with frequency and percentage for categorical variables. Numeric continuous variables were described with mean and SD or median and IQR. Differences in the primary and secondary outcomes between groups were analyzed using the Student t test for continuous outcome variables and the Pearson χ^2 and the Fisher exact test for categorical outcome variables. Analyses were completed using SPSS 24 (IBM Corp). P values <.05 were considered significant.

Results

The NSR cohort included 513 infants born term and 92 infants born preterm. ICH was identified as a seizure etiology in 113 infants, but 1 was excluded due to unknown gestational age; these 112 infants (80 term, 32 preterm) were included in the present study (Table I). We also included 201 infants born term with a primary seizure etiology of HIE, of whom 13 (6%) had a secondary diagnosis of ICH contributing to seizures and 188 (94%) had no ICH or small ICH that did not contribute to seizures, eg, small parturitional subdural hemorrhage in the posterior fossa. The infants in the present study have been included in previous publications of the NSR study group.[1,5,14,15]

Among infants born at term, ICH was the primary seizure etiology in 52 of 513 (10%). No other seizure etiology was identified in 31 (60%) of these infants. Additional seizure etiologies included other ICH in ≥1 separate intracranial compartments (n = 16, 76%), arterial or venous stroke (n = 7, 33%), HIE (n = 4, 19%), infection (n = 1, 5%), and hypoglycemia (n = 1, 5%). There were 28 of 513 (5%) term neonates with ICH as a secondary seizure etiology whose primary seizure etiology was HIE in 13 (46%), arterial or venous stroke in 9 (32%), infection in 3 (11%), brain malformation in 2 (7%), and cerebral contusion in 1 (4%).

Among infants born preterm, ICH was the primary seizure etiology in 25 of 92 (27%); 20 (80%) had no other seizure etiology identified. Additional seizure etiologies for the remaining 5 (20%) patients included: other ICH in ≥1 intracranial compartments (2), infection (1), brain malformation (1), electrolyte disturbance (1), and genetic syndrome (1). There were 7 of 92 (8%) infants born preterm with ICH as a secondary seizure etiology whose primary seizure etiology was HIE (4), brain malformation (1), venous stroke (1), and infection (1).

ICH was a more common primary seizure etiology among infants born preterm compared with term (27% vs 10%, $P < .001$). However, among neonates with ICH as a primary or secondary seizure etiology, there were no significant differences in other seizure etiologies by gestational age.

The Figure summarizes the types of ICH and their specific locations. The most common sites of ICH were parenchymal hemorrhage in infants born both term (46%) and preterm (44%), and IVH, which was significantly less frequent in infants born term (30%) compared with preterm (53%, $P = .03$). Similarly, PVHI (ie, "grade 4 IVH") was more common among infants born preterm (38%) than those born term (9%, $P = .001$). In addition, most infants born term and preterm with IVH as a seizure etiology (excluding those with PVHI) had grade 3 IVH (67% and 59%, respectively). Lastly, subarachnoid and subdural hemorrhages were the least common seizure etiologies in all neonates.

Next, we evaluated the primary outcome of seizure severity among infants born term and preterm with seizures caused by ICH. High seizure burden and subclinical seizures were common (Table I). Of those neonates with ICH as a primary seizure etiology, only 10 of 52 (19%) infants born term compared with 8 of 25 (32%, $P = .26$) born preterm had cvEEG monitoring initiated for seizure screening in high-risk clinical scenarios (eg, encephalopathy, abnormal imaging, extracorporeal membrane oxygenation), rather than for clinical events suspicious for seizures.

Concerning the secondary outcome of treatment response, most infants born term with ICH (70%) had an incomplete response to the initial ASM, as did 63% ($P = .81$) of infants born preterm. Despite similar treatment responses, neonates born term showed a trend of receiving more ASMs to control seizures than infants born preterm (2 vs 1, $P = .06$). Overall, 36% of infants born term and 41% of infants born preterm had 0-6 EEG-confirmed seizures (no seizures: 14 term and 6 preterm; 1-6 seizures: 15 term and 7 preterm). Whereas 14 of 28 (50%) neonates born term with 0-6 seizures received phenobarbital before cvEEG monitoring, only 5/13 (38%) of those born preterm with 0-6 seizures received phenobarbital before cvEEG monitoring.

Table I. Characteristics of neonates with ICH as a primary or secondary seizure etiology

Characteristics	Term (N = 80)	Preterm (N = 32)
Clinical characteristics		
Male sex	43 (54)	16 (50)
Birth weight, kg	3.48 [3.15, 3.71]	1.40 [0.80, 2.20]
Gestational age, wk	39.4 [38.6, 40.3]	30.1 [26.9, 33.1]
Mode of delivery		
Vaginal	50 (63)	8 (25)
Operative vaginal (vacuum/forceps)	5 (6)	1 (3)
Scheduled cesarean delivery	7 (9)	4 (13)
Emergent cesarean delivery	17 (21)	19 (60)
Apgar score at 1 min	7 [2, 8]	4 [2, 7]
Apgar score at 5 min	8 [7, 9]	7 [5, 9]
Seizure characteristics		
Indication for EEG monitoring		
Clinical events suspicious for seizures	51 (64)	19 (59)
Encephalopathy	15 (19)	5 (16)
Clinical events and encephalopathy	9 (11)	2 (6)
Abnormal imaging	2 (3)	4 (13)
Presence of subclinical seizures	59 (74)	24 (75)
Seizure burden (EEG seizures)		
None	14 (18)	6 (19)
Rare EEG seizures (<7)	15 (19)	7 (22)
Many isolated EEG seizures (≥7)	13 (18)	4 (13)
Frequent recurrent EEG seizures/status epilepticus	38 (48)	14 (44)
Treatment characteristics		
Incomplete response to initial ASM	56 (70)	20 (63)
Number of ASMs administered	2 [1, 3]	1 [1, 2.75]
Outcome		
Abnormal examination at discharge	19 (24)	6 (19)
Disposition		
Home	60 (75)	13 (41)
Transfer to another hospital/long-term care facility	10 (13)	8 (25)
Deceased/hospice	10 (13)	11 (34)

Data are presented as No. (%) or median [IQR].

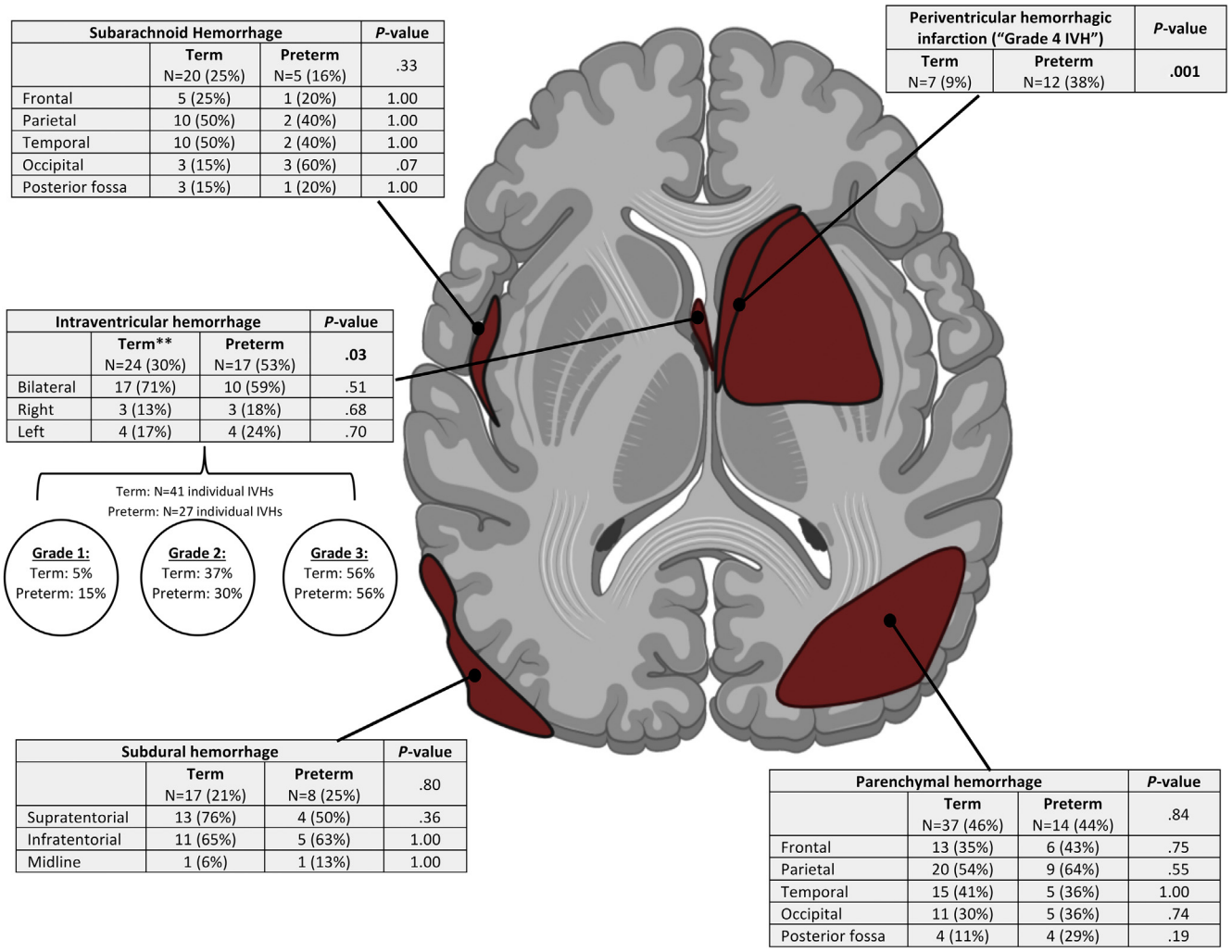

Figure. Locations of ICH in 80 infants born at term and 32 infants born preterm with ICH as a seizure etiology. Percentages do not add up to 100%, as neonates may have more than 1 location of each type of hemorrhage.

Among neonates born term with ICH as a primary seizure etiology, we compared primary and secondary outcomes between infants who had ICH in multiple vs a single site(s) (**Table II**). There were no significant differences in secondary seizure etiologies of HIE or stroke between infants with ICH in multiple vs a single site(s). More neonates born term with seizures attributed to multisite vs single-site ICH had subclinical seizures (93% vs 66%, $P = .05$), a greater seizure frequency/burden ($P = .03$), and an increased rate of incomplete response to the initial ASM (100% vs 66%, $P = .02$).

Lastly, we compared outcomes in neonates born term with HIE and ICH vs HIE alone (**Table III**). Status epilepticus was more common among neonates born term with HIE and ICH vs HIE alone (38% vs 17%, $P = .05$). There were no differences between these groups regarding incomplete response to the initial ASM or the number of ASMs administered.

Discussion

In this report of neonatal seizures attributed to ICH, we provide a detailed description of the type and site of ICH causing seizures, from data derived from a prospective, multicenter cohort of infants born term and preterm. In particular, although ICH was a more common seizure etiology in infants born preterm than term, we demonstrate that parenchymal and IVH most commonly caused seizures in infants born term and preterm (vs subarachnoid or subdural hemorrhage). These detailed data show that across the gestational age spectrum, seizures caused by ICH have high seizure severity and poor treatment response, similar to those neonates with focal or diffuse ischemic brain injury, ie, ischemic stroke or HIE as their primary seizure etiology.[1,5]

These data add to the existing literature describing seizures caused by ICH in infants born term and preterm, which currently consists of case reports and small

Table II. Seizure characteristics, management, and outcome in neonates born at term with ICH in multiple sites vs a single site

Characteristics	Single ICH site (N = 38)	Multiple ICH site (N = 14)	*P* value
Seizure characteristics			
Presence of subclinical seizures	25 (66)	13 (93)	**.05**
Seizure burden (EEG seizures)			
None	10 (26)	0 (0)	.16
Rare EEG seizures (<7)	6 (16)	3 (21)	
Many isolated EEG seizures (≥7)	8 (21)	1 (7)	
Frequent recurrent EEG seizures/Status epilepticus	14 (37)	10 (71)	**.03**
Treatment characteristics			
Incomplete response to initial ASM	25 (66)	14 (100)	**.02**
Number of ASMs administered	2 [1, 3]	2.5 [1.75, 3]	.51
Outcome			
Abnormal examination at discharge	7 (18)	2 (14)	.74
Disposition			
Home	29 (76)	14 (100)	.14
Transfer to another hospital/long-term care facility	4 (11)	0 (0)	
Deceased/hospice	5 (13)	0 (0)	

Data are presented as No. (%) or median [IQR].
P values in bold indicate statistical significance.

retrospective series.[16-18] Previous reports have suggested seizures were the most common presentation of ICH in neonates and pediatric patients, with an incidence of 40%-72%.[17,19,20] However, this incidence varies by the type of ICH included, with a greater incidence of seizures reported in those with parenchymal and IVHs.[17,20] These previous findings are further enhanced by our data demonstrating that parenchymal and IVHs are the most common types of ICH contributing to seizures.

Our findings also confirm previous reports that ICH is a more common seizure etiology among infants born preterm compared with term, likely attributable to the greater incidence of IVH (with and without associated infarction) in infants born preterm vs term.[5,10,21] Although our study is relatively large, it likely underestimated the incidence of seizures related to ICH in infants born preterm, as seizure detection in this population can be challenging.[22] In particular, the reported incidence of seizures among infants born preterm is

Table III. Seizure characteristics, management, and outcome in neonates born at term with HIE and ICH vs HIE alone

Characteristics	HIE with ICH (N = 13)	HIE without ICH (N = 188)	*P* value
Clinical characteristics			
Apgar score at 1 min	2 [0.5, 3]	2 [1, 4]	.72
Apgar score at 5 min	4 [2, 6]	5 [3, 7]	.49
Mode of delivery			
Vaginal	6 (46)	69 (37)	.56
Instrumented vaginal (vacuum or forceps)	1 (8)	14 (7)	
Scheduled cesarean delivery	2 (15)	14 (7)	
Emergent cesarean delivery	4 (31)	91 (48)	
Received therapeutic hypothermia	8 (62)	107 (57)	.75
Seizure characteristics			
Presence of subclinical seizures	11 (85)	123 (65)	.16
Seizure burden (EEG seizures)			
None	1 (8)	34 (18)	.37
Rare EEG seizures (<7)	2 (15)	45 (24)	
Many isolated EEG seizures (≥7)	2 (15)	26 (14)	
Frequent recurrent EEG seizures	3 (23)	51 (27)	
Status epilepticus	5 (38)	32 (17)	**.05**
Treatment characteristics			
Incomplete response to initial ASM	9 (69)	113 (60)	.35
Number of ASMs administered	2 [1, 3]	2 [1, 2]	.39
Outcome			
Abnormal examination at discharge	6 (46)	63 (34)	.23
Abnormal consciousness	7 (54)	41 (22)	**.01**
Assisted ventilation at discharge	6 (46)	41 (22)	**<.05**
All oral feeds at discharge	4 (31)	98 (52)	.14
Disposition			
Home	6 (46)	120 (64)	.33
Transfer to another hospital/long-term care facility	2 (15)	28 (15)	
Deceased/hospice	5 (38)	40 (21)	

Data are presented as No. (%) or median [IQR].
P values in bold indicate statistical significance.

highly variable depending on the type and timing of EEG monitoring and the selection of neonates for monitoring, with a reported incidence of 4%-48% in single-center studies of amplitude-integrated electroencephalogram (aEEG) or cvEEG in the first days after birth.[21,23-25] A greater seizure incidence has been reported in studies using aEEG compared with cvEEG monitoring in infants born preterm,[22,23,25] raising questions about the accuracy of aEEG vs cvEEG for seizure detection in this population. In addition, variations in inclusion criteria (all infants born preterm vs those with a clinical indication for cvEEG monitoring such as IVH) and infant gestational age (≤30 weeks vs <37 weeks) likely contribute to large variability in reported seizure incidence. Lastly, variable cvEEG monitoring timing and duration, ranging from 3 to 72 hours of continuous monitoring initiated at different time points over the first week after birth, may affect reported seizure incidence.

One systematic study found that only 5% of 120 infants with gestational ages ≤32 weeks who were screened with cvEEG monitoring in the first 72 postnatal hours after birth had electrographic seizures.[22] Notably, those infants born preterm with seizures were more likely to have a grade 3 or 4 IVH in the first 72 hours compared with those without seizures (33% vs 4%, $P = .04$). Therefore, although the prevalence of early-life seizures may be low among unselected infants born preterm, those with severe IVH are a high-risk population who would likely benefit from cvEEG screening. Our data further support this recommendation, given that among 25 infants born preterm with ICH as the primary seizure etiology, 32% had cvEEG monitoring initiated based on encephalopathy or abnormal head imaging rather than suspected seizures, and had seizures that could have been missed without a screening cvEEG approach. Experimental and clinical data also support seizure screening in high-risk neonates, given the association between seizure burden and adverse outcomes. Although this relationship has been most rigorously studied in infants born term with perinatal asphyxia,[26-28] a similar relationship has been described in infants born preterm.[29] Furthermore, new data suggesting a shorter time to seizure treatment increases the odds of successful seizure control further support a screening cvEEG approach in high-risk neonates.[30] Although our data showed high seizure burden and frequent subclinical seizures in infants born both term and preterm, 38% of neonates in the study had low seizure burden (0-6 EEG-confirmed seizures). Among these neonates with low seizure burden, 1 of 2 of infants born term but only ~1 of 3 of infants born preterm received phenobarbital before cvEEG monitoring. These data show that some term neonates do respond to an initial ASM and do not require additional ASMs. In contrast, infants born preterm may not respond as well to the initial ASM or may benefit from more screening cvEEG for earlier detection and treatment of seizures, because more infants born preterm with seizures had cvEEG monitoring initiated for reasons other than suspected seizures.

Another finding of this study was that infants with complicated ICH have greater seizure severity and poorer treatment response. Specifically, the presence of multiple sites of ICH was associated with a greater seizure burden compared with a single site of ICH. Even more striking, all infants with multiple sites of ICH had a poor response to the initial ASM, compared with ~2 of 3 of those with single-site ICH. Furthermore, almost all infants (93%) with multisite ICH had subclinical seizures. Multisite ICH likely increases the risk of multiple seizure origins, which may contribute to greater seizure severity and poorer response to treatment. Therefore, neonates with multisite ICH may benefit particularly from routine cvEEG monitoring and more aggressive seizure management.

Our data showed that neonates with HIE complicated by secondary ICH tended to have greater seizure severity compared with those with HIE alone. The occurrence of ICH in neonates with HIE is multifactorial, potentially involving a progression of hypoxia-related endothelial dysfunction leading to increased permeability of cerebral vessels and ultimately vascular leakage that occurs with reperfusion injury.[8] The increased cerebral venous pressure in the setting of perinatal asphyxia also may play a role in the development of IVH, as demonstrated in animal studies of preterm fetal sheep.[8,31] In term neonates, venous thrombosis is thought to be a common mechanism leading to IVH.[32] However, it is unclear whether the greater seizure severity in neonates with HIE and ICH (vs HIE alone) is related to more severe ischemic brain injury or the additive effect of the ICH. Investigators in our study specifically noted ICH as a secondary seizure etiology in these neonates. Thus, it is more likely that ICH itself contributed to the higher seizure severity rather than more severe ischemic brain injury in neonates with HIE complicated by ICH.

The literature evaluating ICH as a complication of HIE is limited. One study of 138 neonates with HIE found that 18% had concomitant ICH, which is 3 times greater than our reported rate of ICH complicating HIE, but the authors found no difference in seizure incidence in neonates with HIE and ICH vs isolated HIE.[18] The difference in ICH incidence between studies may be related to the inclusion of all types of ICH regardless of potential contribution to seizures in the study of 138 neonates, particularly because they reported subdural hemorrhage as the most common site of ICH complicating HIE (34%). In contrast, our cohort likely includes neonates with HIE and ICH whose ICH was not thought to contribute to seizures and therefore not reported, which could explain why our study showed a lower rate of ICH complicating HIE. Our data suggest that neonates with seizures caused by both HIE and ICH are a high-risk population with regard to seizure severity, and the reasons for this finding deserve further study.

Although this is a large, multicenter, prospective cohort of neonates with seizures caused by ICH, our study has several limitations. First, some subgroup analyses were limited by small sample sizes, such as infants born preterm with ICH and those with both HIE and ICH or multisite ICH. Second, the study relied on the determination of seizure etiologies by study investigators from available neuroimaging and EEG

data. Although all data were interpreted by specialists with expertise (neonatal neurologists, pediatric neurophysiologists and neuroradiologists), the lack of a central review of data may have led to variability in assigning seizure etiologies among centers. Third, in some neonates without an available magnetic resonance imaging of the brain, ICH type and location were determined by ultrasonography of the head only, which might have limited the ability to distinguish PVHI from isolated parenchymal hemorrhage. Fourth, we did not include a specific category for subpial hemorrhages, which were likely included in the subarachnoid hemorrhage category.[33] Lastly, we were unable to determine potential contributors to the differences between neonates with HIE and ICH vs HIE alone (eg, coagulopathy/bleeding risk or other potential risk factors for ICH).

Our report provides evidence that ICH is an important seizure etiology in infants born both term and preterm with regard to seizure severity and management. These findings support the recommendation for routine cvEEG monitoring in neonates with ICH, as recommended by American Clinical Neurophysiology Society guidelines,[11] as the time to seizure treatment may improve outcome.[34] Clinicians should consider initiating cvEEG monitoring for infants with parenchymal hemorrhage and high-grade IVH, even in the absence of clinical seizures, as our data show high seizure severity with frequent subclinical seizures in this population. We also identify several particularly high-risk groups of neonates with ICH, including infants born preterm with parenchymal hemorrhage or high-grade IVH and neonates born term with multisite ICH or HIE and ICH, and suggest they may benefit from both a screening cvEEG approach to improve seizure detection and a multistep treatment plan that considers early use of ASMs. ■

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Reprint requests: Janet S. Soul, MDCM, Department of Neurology, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115. E-mail: janet.soul@childrens.harvard.edu

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Appendix

List of additional Neonatal Seizure Registry investigators and contributors:

Donna M. Ferriero, MD, MS
UCSF Benioff Children's Hospital
University of California San Francisco School of Medicine
San Francisco, CA
Contributed to study design, data analysis, and interpretation

Kevin J. Staley, MD
Massachusetts General Hospital
Harvard Medical School
Boston, MA
Contributed to study design, data analysis, and interpretation

Ann Marie Bergin, MB, ScM, MRCP (UK)
Boston Children's Hospital
Harvard Medical School
Boston, MA
Contributed to neurophysiology data analysis and interpretation

Dennis Dlugos, MD, MSCE
Children's Hospital of Philadelphia
University of Pennsylvania School of Medicine
Philadelphia, PA
Contributed to neurophysiology data analysis and interpretation

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