Pediatric Neurology 137 (2022) 54–61

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Research Paper

Seizure Burden, EEG, and Outcome in Neonates With Acute Intracranial Infections: A Prospective Multicenter Cohort Study

Nehali Mehta, MD [a], Renée A. Shellhaas, MD, MS [b], Charles E. McCulloch, PhD [c], Taeun Chang, MD [d], Courtney J. Wusthoff, MD, MS [e, f], Nicholas S. Abend, MD, MSCE [g, h, i], Monica E. Lemmon, MD [j], Catherine J. Chu, MD, MMSc [k], Shavonne L. Massey, MD, MSCE [g, h], Linda S. Franck, RN, PhD, FAAN [l], Cameron Thomas, MD, MS [m], Janet S. Soul, MDCM [n], Elizabeth Rogers, MD [o], Adam Numis, MD [a, o], Hannah C. Glass, MDCM, MAS [a, c, o, *]

[a] Department of Neurology and Weill Institute for Neuroscience, University of California San Francisco, San Francisco, California
[b] Department of Pediatrics, University of Michigan, Ann Arbor, Michigan
[c] Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California
[d] Department of Neurology, Children's National Hospital, George Washington University School of Medicine, Washington, District of Columbia
[e] Department of Neurology, Stanford University, Palo Alto, California
[f] Division of Neonatal and Developmental Medicine, Department of Pediatrics, Stanford University, Palo Alto, California
[g] Department of Neurology, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania
[h] Department of Pediatrics, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania
[i] Department of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania
[j] Departments of Pediatrics and Population Health Sciences, Duke University School of Medicine, Durham, North Carolina
[k] Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts
[l] Department of Family Health Care Nursing, University of California San Francisco, San Francisco, California
[m] Division of Neurology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio
[n] Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts
[o] Department of Pediatrics, UCSF Benioff Children's Hospital, University of California San Francisco, San Francisco, California

ARTICLE INFO

Article history:
Received 2 June 2022
Accepted 9 September 2022
Available online 19 September 2022

Keywords:
Meningitis
Encephalitis
Seizures
Epilepsy
Neurocritical care
Central nervous system
Neonates

ABSTRACT

Background: Limited data exist regarding seizure burden, electroencephalogram (EEG) background, and associated outcomes in neonates with acute intracranial infections.
Methods: This secondary analysis was from a prospective, multicenter study of neonates enrolled in the Neonatal Seizure Registry with seizures due to intracranial infection. Sites used continuous EEG monitoring per American Clinical Neurophysiology Society guidelines. High seizure burden was defined a priori as seven or more EEG-confirmed seizures. EEG background was categorized using standardized terminology. Primary outcome was neurodevelopment at 24-months corrected age using Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS). Secondary outcomes were postneonatal epilepsy and motor disability.
Results: Twenty-seven of 303 neonates (8.9%) had seizures due to intracranial infection, including 16 (59.3%) bacterial, 5 (18.5%) viral, and 6 (22.2%) unknown. Twenty-three neonates (85%) had at least one subclinical seizure. Among 23 children with 24-month follow-up, the WIDEA-FS score was, on average, 23 points lower in children with high compared with low seizure burden (95% confidence interval, [−48.4, 2.1]; $P = 0.07$). After adjusting for gestational age, infection etiology, and presence of an

Funding: This work was supported by the Patient-Centered Outcomes Research Institute, United States (grant number 2015C2-1507-31187).

Disclosures: Dr. Mehta has no disclosures. Dr. Shellhaas receives research support from NIH, the Pediatric Epilepsy Research Foundation, and the University of Michigan. She receives royalties from UpToDate for authorship of topics related to neonatal seizures, serves as a consultant for the Epilepsy Study Consortium, and is an Associate Editor for *Neurology*. Dr. McCulloch has no disclosures. Dr. Chang has no disclosures. Dr. Wustoff has no disclosures. Dr. Abend has no disclosures. Dr. Lemmon receives salary support from NIH (K23NS116453). Dr. Chu receives research support from Biogen Inc, NIMH, and NINDS. She consults for Ovid Pharmaceuticals and Biogen Inc. Dr. Massey has no disclosures. Dr. Franck has no disclosures. Dr. Thomas receives research support through NIH and UCB. Dr. Soul has no disclosures. Dr. Rogers has no disclosures. Dr. Numis has no disclosures. Dr. Glass receives research support from NIH.

* Communications should be addressed to: Dr. Glass; Department of Neurology; University of California, San Francisco, 675 Nelson Rising Ln, PO Box 0663; San Francisco, CA 94143.
E-mail address: hannah.glass@ucsf.edu (H.C. Glass).

https://doi.org/10.1016/j.pediatrneurol.2022.09.001

additional potential acute seizure etiology, the effect size remained unchanged ($\beta = -23.8$, $P = 0.09$). EEG background was not significantly associated with WIDEA-FS score. All children with postneonatal epilepsy (n = 4) and motor disability (n = 5) had high seizure burden, although associations were not significant.

Conclusion: High seizure burden may be associated with worse neurodevelopment in neonates with intracranial infection and seizures. EEG monitoring can provide useful management and prognostic information in this population.

Introduction

Acute intracranial infections are important causes of morbidity and mortality in neonates. The incidence of neonatal meningitis is estimated to be 0.39 per 1000 births,[1] which is a higher incidence than at any other time of life. Although the incidence of bacterial meningitis has been declining in older age groups, it has remained steady in neonates.[2] Additionally, acute neonatal encephalitis—typically secondary to viral infections acquired postnatally—is uncommon, but often results in severe adverse neurological outcomes.[3-5] Seizures are a frequent manifestation of acute neonatal meningitis and encephalitis,[6] but little is known about the relationship between seizure burden, electroencephalogram (EEG) background, and developmental outcome in neonates with seizures due to intracranial infection.

Studies have reported that seizures are a potential risk factor for adverse outcome in neonates with bacterial meningitis and viral encephalitis,[7,8] and that abnormal EEG background is associated with poor prognosis following neonatal bacterial meningitis and herpes simplex virus (HSV) encephalitis.[9-14] Prior studies are limited by single-center data, retrospective cohorts, lack of continuous electroencephalography (cEEG) monitoring, and lack of standardized measures and outcomes. In addition, most studies of encephalitis include children over a broad age range that can make it challenging to provide tailored counseling to families of newborns with seizures due to intracranial infection.

The objective of this study was to characterize seizures, EEG background, and outcomes among neonates with seizures due to acute intracranial infections enrolled in the *Neonatal Seizure Registry-II (NSR-II)* cohort.[15] We hypothesized that neonates with a high burden of acute symptomatic seizures or worse EEG background features would be more likely to have unfavorable neurodevelopmental outcomes and a higher incidence of postneonatal epilepsy compared with neonates with a low seizure burden or normal EEG background features.

Methods

Study design

This was a secondary analysis from a prospective multicenter cohort study (NCT02789176) of neonates with acute symptomatic seizures born between July 2015 and March 2018 and treated at one of the nine centers of the *NSR-II*.[15] Each center has a level IV neonatal intensive care unit, a level IV comprehensive pediatric epilepsy program, and follows the American Clinical Neurophysiology Society (ACNS) guidelines for cEEG monitoring.[16] Management of seizures and epilepsy occurred at the discretion of the clinical teams at each institution; there was no study-specific treatment pathway or protocol. The study was approved by the local institutional review board at each site, and written informed consent was obtained from parents of enrolled neonates.

Inclusion criteria

Neonates ≤44 weeks postmenstrual age at the time of seizure onset were enrolled into the *NSR-II* cohort if they either (1) had seizures confirmed on EEG or (2) were treated with an antiseizure medication (ASM) for a clinical event suspicious for seizure and had an acute symptomatic etiology to explain the seizure (e.g., hypoxic-ischemic encephalopathy [HIE], stroke, intracranial hemorrhage, or infection).[17] Neonates were not enrolled into the *NSR-II* cohort if they had (1) events that were determined not to be seizures by history, semiology, or EEG; (2) transient causes for seizures (such as electrolyte disturbances) without brain injury; or (3) neonatal-onset epilepsy.

Seizure etiologies were determined by the principal investigator at each site. This secondary analysis included neonates if infection was listed as an etiology of seizures, specifically neonates with meningitis, encephalitis, or meningoencephalitis. Some neonates had an additional potential acute seizure etiology listed (i.e., HIE, ischemic stroke, or intracranial hemorrhage) along with infection. Similar to previous studies, neonates were included in this study even if an organism was not identified, as long as neuroimaging, cerebrospinal fluid (CSF) studies, and the clinical presentation were indicative of an acute intracranial infection.[1,11,18] Neonates with congenital infections such as syphilis or systemic infections without intracranial involvement were excluded. Charts were reaudited specifically for the present study by the local principal investigator and research coordinators to confirm neonates in the cohort met all the inclusion criteria.

Measurements

Study data were collected and managed using REDCap electronic data capture tools hosted at University of California, San Francisco.[19] Data collected included clinical characteristics and details regarding the infection, EEG and seizure data, and outcome data.

EEG and seizure data

EEG background during the first 24 hours of monitoring was categorized as (1) normal, (2) mild-moderately abnormal (not normal but not severe), (3) severely abnormal (flat trace, severe discontinuity, or burst suppression), (4) electrographic status epilepticus at the onset of recording (within the first hour), or (5) cannot assess.[16] A seizure was defined as an abnormal, sudden event of at least 10 seconds with an amplitude ≥2 μV that demonstrated a repetitive and evolving pattern on EEG.[16] Seizure burden was categorized as (1) none, (2) rare EEG seizures (less than seven), (3) many isolated EEG seizures (greater than or equal to seven), (4) frequent recurrent EEG seizures, (5) status epilepticus, or (6) documentation inadequate to quantify.[20] Status epilepticus was defined as any electrographic recording with seizures lasting >50% over at least one hour of recording. All ASMs administered

during the duration of hospitalization were recorded. The initial loading ASM was defined as the first ASM administered as a loading dose bolus. Children were considered to have an incomplete response to the initial loading dose if they had one or more EEG-proven seizures more than 30 minutes after a minimum initial loading dose of phenobarbital (20 mg/kg), fosphenytoin/phenytoin (15 mg/kg), or levetiracetam (40 mg/kg).

Outcomes

The primary outcome was functional development evaluated using the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS) at 24 months corrected age. The WIDEA-FS is a 50-item questionnaire administered via telephone by a trained research team member who was unaware of the patient's history. WIDEA-FS evaluates self-care, motor, communication, and social learning skills.[21] The total score ranges from 50 to 200 points. WIDEA-FS has demonstrated concurrent validity with the Bayley Infant and Toddler Scales of Development, Third Edition (Bayley-III).[22] A child was considered functionally impaired if the total WIDEA-FS score was greater than 2 S.D. below the mean for typically developing children. The average WIDEA-FS score and S.D. in typically developing children is 172 [±10] points at 24 months.

Secondary outcomes were (1) a diagnosis of postneonatal epilepsy, as defined by the International League Against Epilepsy criteria,[23] which was determined by telephone interviews conducted at age 12, 18, and 24 months and corroborated by chart review, and (2) motor disability, defined as modified Gross Motor Function Classification System≥II at 24 months corrected age.[24] All discrepancies were adjudicated by a study investigator.[25] The presence of infantile spasms, as well as intractable epilepsy, which was defined as ongoing seizures despite administration of more than two ASMs, was also noted.

Analysis

Stata (StataCorp LLC, College Station, TX, USA) version 17.0 was used to perform all statistical analysis. Percentages, median, and interquartile ranges were calculated for descriptive statistics. The etiology of infection was dichotomized into bacterial or viral/unknown, given most "unknown" intracranial infections are suspected to be viral in nature.[26] EEG background was dichotomized into normal/mild-moderate abnormalities (including normal and mild-moderately abnormal background) and severe abnormalities (including severely abnormal background and electrographic status epilepticus at the onset of recording) for outcome analysis.[16] Seizure burden was dichotomized into low (including none and rare seizures) and high (many isolated seizures, frequent recurrent seizures, or status epilepticus) for outcome analysis, as we have done in the past.[20]

Linear regression analysis (with robust standard errors to allow for unequal variance) was used to determine whether seizure burden and EEG background were each associated with WIDEA-FS score. An adjusted model also included gestational age, etiology of infection, and presence of an additional potential acute seizure etiology as potential confounders. Bootstrap analysis with 10,000 repetitions was used to assess sensitivity to the non-normality of the WIDEA-FS scores and gave virtually identical results.

The associations between the exposure variables and epilepsy and motor disability were determined using Fisher exact test. P values <0.05 were considered significant.

Results

Of the 303 children in the *NSR-II* cohort, 27 neonates (8.9%) met inclusion criteria for the current study. Sixteen neonates (16 of 27, 59.3%) had a bacterial intracranial infection, five neonates (five of 27, 18.5%) had a viral intracranial infection, and six (six of 27, 22.2%) of the infections were categorized as unknown. Of the bacterial infections, Group B *Streptococcus* (10 of 16, 62.5%) and *Escherichia coli* (three of 16, 18.8%) were the most common organisms, whereas HSV was the most common virus (four of five, 80.0%) (Table 1).

Thirteen neonates (13 of 27, 48.1%) had an additional potential acute seizure etiology listed along with infection, including HIE in four neonates (four of 27, 14.8%), periventricular hemorrhagic infarction in one neonate (one of 27, 3.7%), intraventricular hemorrhage in three neonates (three of 27, 11.1%), and ischemic stroke in five neonates (five of 27, 18.5%).

EEG, seizure characteristics, and seizure treatment

All neonates had an abnormal EEG background. Twenty-three (23 of 27, 85.2%) neonates had EEG-only seizures at some point during the recording, including four children (four of 27, 14.8%) with exclusively EEG-only seizures (Table 1). All but one neonate (26 of 27, 96.3%) had seizures recorded on EEG. The neonate without confirmed EEG seizures had clinical seizures that were treated and resolved before EEG initiation. One neonate had seizures captured on EEG only at the referring institution; therefore, two neonates (two of 27, 7.4%) had no seizures captured on EEG at the study institution.

All but one neonate (26 of 27, 96.3%) were treated with an initial load of an intravenous ASM. Sixteen neonates (16 of 27, 59.3%) had ongoing seizures after the initial medication load (see Table 2 for details of ASM management).

Outcome

During the follow-up period, 18 neonates (18 of 27, 66.7%) were discharged home, seven neonates (seven of 27, 25.9%) were transferred to another hospital for ongoing care, two neonates (two of 27, 7.4%) were discharged to a long-term care facility, and none died.

WIDEA-FS score at 24 months was available for 23 of 27 children (85.2%) at a mean [S.D.] of 24.0 [± 0.7] months of age. The median 24-month total WIDEA-FS score was 157 (interquartile range, 138 to 176), which was 1.5 S.D. below the normal mean. Seven children (seven of 23, 30.4%) had scores that were above the normal mean.

Unadjusted analysis

Compared with children with low seizure burden, children with high seizure burden scored an average of 23 points lower on their WIDEA-FS score ($\beta = -23.2$, 95% confidence interval [−48.4, 2.1], $P = 0.07$) (Table 3). Figure graphically represents the distribution of WIDEA-FS scores among neonates with low and high seizure burden. EEG background was not significantly associated with WIDEA-FS score.

Of the 24 children in the cohort for whom follow-up data were available for secondary outcomes, four of 24 (16.7%) were diagnosed with postneonatal epilepsy by 24 months. Table 4 provides the clinical characteristics of the children with epilepsy. Four children with high seizure burden developed epilepsy (four of 19, 21.1%), whereas none of the children with low seizure burden developed epilepsy (zero of five, 0%), but this was not significantly different ($P = 0.5$). Four children with mild-moderately abnormal EEG background developed epilepsy (four of 19, 21.1%), and no

TABLE 1
Clinical, EEG, and Seizure Characteristics of 27 Neonates With Acute Symptomatic Seizures Secondary to Acute Intracranial Infection

Variable	N = 27
Clinical characteristics	
Female sex	12 (44)
Age at admission, hours	215 [41, 356]
Gestational age, weeks	38.6 [34.1, 39.3]
Delivery mode	
Vaginal	18 (66.7)
Caesarean section	8 (29.6)
Unknown	1 (3.7)
Therapeutic hypothermia	2 (7.4)
Organism	
Bacteria	16 (59.3)
Group B *Streptococcus*	10 (37)
Escherichia coli	3 (11.1)
Haemophilus influenzae	1 (3.7)
Citrobacter koseri	1 (3.7)
Staphylococcus	1 (3.7)
Viral	5 (18.5)
HSV 1 and 2	4 (14.8)
Parechovirus	1 (3.7)
Unknown	6 (22.2)
Additional potential seizure etiologies	
HIE	4 (14.8)
Intracranial hemorrhage	4 (14.8)
Ischemic stroke	5 (18.5)
EEG characteristics	
Worst EEG background in the first 24 hours	
Normal	0 (0)
Mild/moderately abnormal	21 (77.8)
Severely abnormal	2 (7.4)
Electrographic status epilepticus at the onset of recording	3 (11.1)
Cannot assess	1 (3.7)
Seizure characteristics	
Age at first clinical seizure, hours	254 [52, 382]
Neonates with seizures captured on EEG	26 (96.3)
Neonates with subclinical seizures	23 (85.2)
Seizure burden	
None	2 (7.4)
Rare EEG seizures	5 (18.5)
Many isolated EEG seizures	9 (33.3)
Frequent recurrent EEG seizures	6 (22.2)
Status epilepticus	5 (18.5)
Number of days of seizures on EEG	2 [1, 3]

Abbreviations:
EEG = Electroencephalogram
HIE = Hypoxic-ischemic encephalopathy
HSV = Herpes simplex virus
IQR = Interquartile range
Data are presented as N (%), median [IQR].

children with severely abnormal background developed epilepsy (zero of four, 0%) ($P > 0.99$). None of the children for whom follow-up data were available developed infantile spasms or drug-resistant epilepsy.

Motor disability occurred in five children, and only in those with high seizure burden (five of 19, 26.3%) and in those with mild-moderately abnormal EEG background (five of 19, 26.3%), but the difference was not significant in either group ($P = 0.5$).

Adjusted analysis

After adjusting for gestational age, etiology of infection, and presence of an additional potential acute seizure etiology, children with high seizure burden had, on average, a WIDEA-FS score that was 23 points lower than that of children with low seizure burden ($\beta = -23.8$, 95% confidence interval [−51.7, 4.1], $P = 0.09$, Table 3). Gestational age, etiology of infection, and presence of an additional potential acute seizure etiology were not associated with WIDEA-FS in the adjusted model.

Discussion

In this multicenter, prospective cohort study, acute intracranial infection was the cause of seizures in 9% of neonates. More than half the neonates with intracranial infection had a bacterial infection, and a minority of neonates had a viral infection or no definite pathogen identified. High seizure burden trended toward an association with worse neurodevelopmental outcome, whereas EEG background did not. These data demonstrate the importance of cEEG monitoring in neonates with intracranial infections given the high rate of subclinical seizures, which would not have been detected without EEG. This finding is consistent with that of previous reports of neonates with acute symptomatic seizures of various different etiologies[20,27] and is supportive of guidelines from the ACNS[28] and the International League Against Epilepsy,[29] which recommend cEEG in all neonates at risk for seizures, including those with intracranial infections. Larger studies are necessary to confirm these preliminary findings and fully understand prognostic utility of cEEG monitoring in neonates with intracranial infection.

Previous studies report a high incidence of acute symptomatic seizures in neonates with acute intracranial infections. Up to 60% of children with acute bacterial meningitis[8,18,30,31] or HSV encephalitis[32-34] have seizures. Although acute symptomatic seizures associated with intracranial infections are generally thought to be difficult to manage,[6] limited data are available regarding seizure treatment in this population.[35] We report that approximately 60% of neonates had an incomplete response to the initial loading dose of ASM (most commonly phenobarbital), which is similar to previously reported response to treatment of neonates with acute symptomatic seizures of all causes.[36] In addition, most in this cohort of neonates with acute intracranial infections also required more than one ASM for seizure control. These data do not suggest that seizures secondary to neonatal intracranial infections are more refractory than other causes of neonatal seizures, but rather underscore the need for novel therapeutic approaches to treat neonatal seizures resulting from all etiologies.[36]

Several studies have reported that the presence of acute symptomatic seizures is a poor prognostic indicator in meningitis[8,37,38] and, to a lesser extent, in encephalitis.[7] Prior studies are limited by heterogeneous patient populations, inclusion of both neonates and children, and “unfavorable outcomes” grouped to include multiple outcomes such as death, deafness, blindness, focal neurologic deficits, and cognitive dysfunction.[8,37-39] Furthermore, most previous studies reported only presence or absence of seizures rather than seizure burden. One study determined seizure duration greater than 12 hours was a predictor of adverse outcome in neonatal bacterial meningitis, but seizure frequency or concomitant EEG data were not reported.[8] Our data build on previous studies and suggest an association between seizures and worse developmental outcomes. Using prospectively collected data and a validated neurodevelopmental measure, we found that children who experienced a high seizure burden as neonates had developmental test scores that were nearly 2.5 S.D. lower than those of children who experienced a low seizure burden.

The underlying pathogenesis of seizures in children with intracranial infection may depend on the timing. In the early phase of the disease, seizures are thought to reflect autonomic dysfunction from hyperthermia, hypotension, hypoxia,[40,41] or a response to injury sustained by the cerebral cortex from the infection.[18] Seizures that occur more than a week into the infection are likely the result of complications such as hydrocephalus, subdural empyema, or stroke.[6,40] Investigators have speculated that the poorer prognosis in neonates with acute intracranial infections who developed seizures when compared with neonates who did not develop seizures is due to a more severe clinical condition in the former.[41] Our

TABLE 2
Antiseizure Medication Treatment Profile in Neonates With Acute Symptomatic Seizures Secondary to Acute Intracranial Infections

Variable	ASM	N = 27
Initial loading ASM	Phenobarbital	22 (81.5)
	Levetiracetam	4 (14.8)
	No load	1 (3.7)
Initial loading dose, mg/kg	Phenobarbital	20 [19.9, 20.2]
	Levetiracetam	25 [20, 35]
ASM administered	Benzodiazepine*	6 (22.2)
	Phenobarbital	24 (88.9)
	Phenytoin/fosphenytoin	15 (55.6)
	Levetiracetam	16 (59.2)
	Topiramate	3 (11.1)
	Oxcarbazepine	2 (7.4)
	Other†	2 (7.4)
Total number of ASMs administered during hospitalization	1 ASM	8 (29.6)
	2 ASMs	5 (18.5)
	3 ASMs	10 (37)
	4+ ASMs	4 (14.8)

Abbreviations:
ASM = Antiseizure medication
Data are presented as N (%), median [IQR].
* Benzodiazepine category included both intermittent benzodiazepines such as lorazepam (18.5%) and diazepam (3.7%) and midazolam infusion (3.7%).
† Other medications used included pyridoxine (3.7%) and a study drug (3.7%).

findings that a higher seizure burden may be associated with lower performance on developmental assessment at 24 months may be due to worse clinical severity in the neonates with higher seizure burden or an independent effect of the seizures themselves leading to additional brain injury, similar to what has been hypothesized for HIE and stroke.[42] Our data support a cumulative effect of seizures on initial brain injury in neonates with acute intracranial infections, given a trend of higher seizure burden with worse neurodevelopmental outcome despite adjusting for variables that are typically associated with adverse neurodevelopmental outcome in this population. Ongoing studies in larger cohorts are warranted.

Epilepsy is a known consequence of intracranial infection; however, few studies have prospectively studied the relationship to better understand risk factors and natural history.[43] The rate of epilepsy following pediatric bacterial meningitis ranges from 4% to 7%.[18,44] In our study, approximately 17% of children developed postneonatal epilepsy by age two years. There are several reasons that may explain the higher incidence of epilepsy in our cohort. First, our study was restricted to the neonatal population with seizures. Age may play a role in the risk of seizures due to the hyperexcitability of the immature brain in the setting of a developmental mismatch of excitatory and inhibitory neurotransmitter systems.[45] This finding has been demonstrated in other mechanisms of brain injury such as arterial ischemic stroke, where younger age is associated with a higher rate of subsequent epilepsy.[46] The risk of developing epilepsy in our cohort of neonates with intracranial infection was similar to the risk of developing epilepsy in the cohort of neonates with acute symptomatic seizure of all causes,[47] which further suggests that age may play a dominant role. Second, our cohort included both bacterial meningitis and viral encephalitis. The reported rate of pediatric postencephalitic epilepsy is higher, ranging from 9% to 27%.[7,13] However, these studies included autoimmune as well as infectious encephalitides and longer follow-up. Therefore, they are difficult to compare directly with our cohort. Third, all neonates in the current cohort had acute symptomatic seizures during the acute intracranial infection. Several studies of both viral and bacterial intracranial infections have found that acute symptomatic seizures were strongly associated with postinfectious epilepsy.[7,13,18] Therefore, our cohort consisted of neonates who were likely at the highest risk of developing epilepsy. Lastly, two of the four children who developed epilepsy also had additional potential acute seizure etiologies, namely, intraventricular hemorrhage and stroke. It is possible that the additional brain injury contributed to the development of epilepsy in these patients. Further data are needed to examine the development of specific types of postneonatal epilepsy following neonatal intracranial infection.

Unlike previous studies, we did not find an association between EEG background and outcome. There are several possible reasons. First, our sample size may have been too small to detect a significant relationship between EEG background and outcome. Second, EEG background classification differs between studies, with

TABLE 3
Unadjusted and Adjusted Regression Analyses of the Relationship Between Seizure Burden, EEG Background, Etiology of Infection, Gestational Age, Presence of Additional Potential Acute Seizure Etiology, and Neurodevelopmental Outcome (WIDEA-FS Score)

Variable	Unadjusted		Adjusted*	
	β Coefficient [95% CI]	*P* Value	β Coefficient [95% CI]	Adjusted *P* Value
High seizure burden	−23.2 [−48.4, 2.1]	0.07	−23.8 [−51.7, 4.1]	0.09
Abnormal EEG background	5.4 [−12.6, 23.4]	0.54	−4.5 [−39.7, 30.8]	0.79
Etiology of Infection	−7.1 [−38.0, 23.7]	0.64		
Gestational age	0.8 [−2.9, 4.5]	0.66		
Presence of additional potential acute seizure etiology	9.8 [−20.0, 39.5]	0.50		

Abbreviations:
CI = Confidence interval
EEG = Electroencephalogram
WIDEA-FS = Warner Initial Developmental Evaluation of Adaptive and Functional Skills
* Adjusted model includes gestational age at birth, etiology of infection (bacterial vs viral/unknown), and presence of additional potential acute seizure etiology.

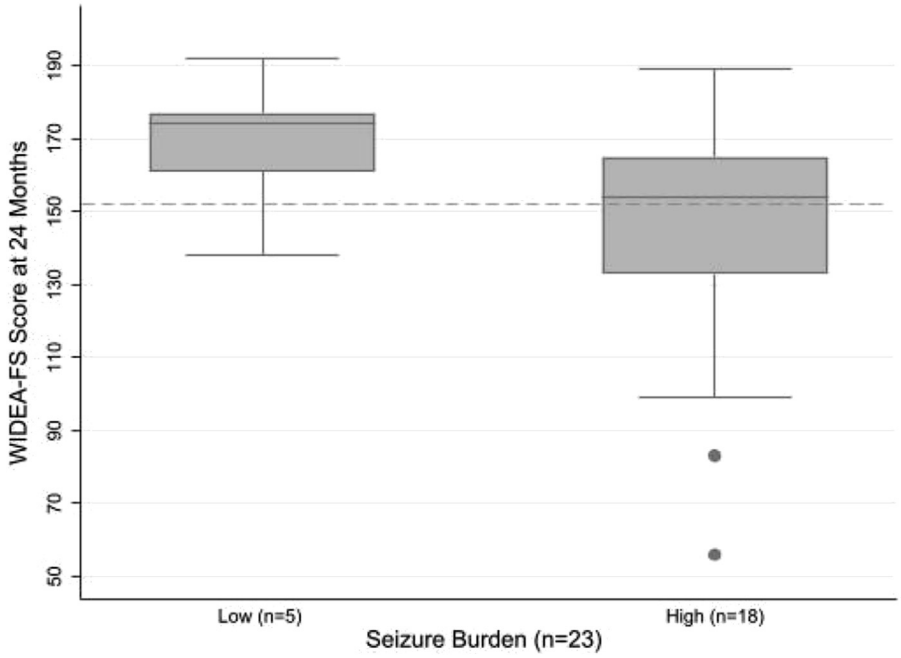

FIGURE. Distribution of Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS) scores among 23 children with low and high seizure burden. WIDEA-FS score for typically developing population is 172 [10]. Dashed line represents WIDEA-FS score of functional impairment (2 S.D. below the mean). The color version of this figure is available in the online edition.

broader definitions of "severely abnormal" used in other studies compared with this study.[9,10] Third, EEGs in this cohort were performed during the acute illness, whereas EEGs in other studies were performed at variable or unknown times. Fourth, it is possible that the acute seizures or other factors related to the underlying infection and its treatment have a greater impact on neurological outcome than severity of acute encephalopathy measured by EEG background. Lastly, unlike other studies, our cohort was assembled based on the diagnosis of acute symptomatic neonatal seizures rather than the diagnosis of intracranial infection. Thus, we have complete EEG data, whereas others did not. More standardization and larger cohort studies are necessary to understand the relationship between EEG background abnormalities and prognosis in neonates with acute intracranial infections.

Our work has several limitations—most notable is its small sample size. With a cohort of 27 patients and four lost to follow-up, we only detected a trend toward association between high seizure burden and worse performance on a standardized neurodevelopmental assessment. We did not detect a significant association between EEG background and outcome or an association between seizure burden or EEG background and our secondary outcomes. Second, although we focused on neonates, our cohort was heterogeneous as we included neonates of all gestational ages and with all types of acute intracranial infections. We addressed

TABLE 4
Clinical Characteristics of Neonates With Acute Symptomatic Seizures Secondary to Acute Intracranial Infections Who Developed Postneonatal Epilepsy by 24 Months

Patient	Sex	Gestational Age (Weeks)	Etiology of Infection (Organism)	Additional Potential Acute Seizure Etiologies	EEG Background	Seizure Burden	Epilepsy Diagnosis	Epilepsy Management	WIDEA-FS Score*	GMFCS Score*
1	F	38.5	HSV	N/A	Mild-moderate abnormalities	High	Focal epilepsy	LEV, PHB	56	V
2	M	31	*Escherichia coli*	IVH	Mild-moderate abnormalities	High	Unknown	OXC	112	III
3	M	39	GBS	N/A	Mild-moderate abnormalities	High	Focal epilepsy	LEV, OXC	148	0
4	F	40.3	GBS	Ischemic stroke	Mild-moderate abnormalities	High	Focal epilepsy	LEV	99	IV

Abbreviations:
EEG = Electroencephalography
F = Female
GBS = Group B *Streptococcus*
GMFCS = Gross Motor Function Classification System Score
HSV = Herpes simplex virus
IVH = Intraventricular hemorrhage
LEV = Levetiracetam
M = Male
OXC = Oxcarbazepine
PHB = Phenobarbital
WIDEA-FS = Warner Initial Developmental Evaluation of Adaptive and Functional Skills
* Obtained at 24 months corrected age.

this heterogeneity by adjusting for gestational age and infection type as possible confounders in our analysis. Third, we did not have important clinical data such as temperature, blood pressure, CSF profile, and white blood cell count, which have also been reported as prognostic factors.[8,37] In addition, we did not have information about the initiation, type, or duration of antimicrobial therapies that were used in this cohort, which could also have influenced outcome. Finally, our cohort included some neonates with intracranial infections that also had an additional potential etiology of acute seizures, such as stroke, hemorrhage, or HIE. Although we adjusted for the presence of an additional potential acute seizure etiology, we are unable to definitively distinguish whether the intracranial infection alone or additional potential seizure etiologies—which include complications of infection—affected outcome. This is a general limitation to studying children with intracranial infection and seizures. Nonetheless, strengths of this study include prospective enrollment of patients, evaluation at centers that provide cEEG monitoring per ACNS guidelines,[28] and follow-up using standardized measures of neurodevelopment.

Conclusion

In this multicenter cohort of neonates with acute symptomatic seizures due to intracranial infection, we show that EEG seizure burden—a potentially modifiable risk factor—may provide important prognostic information on neurodevelopmental outcome. Our data demonstrate that cEEG monitoring is beneficial for neonates with acute intracranial infection given high rates of subclinical seizures and high overall seizure burden. Future studies should determine whether timely antimicrobial treatment or use of adjunctive therapies may also play a role in reducing seizure burden and improving subsequent long-term outcomes. Understanding the optimal treatment approach for seizures as well as additional prognostic factors using neuroimaging, EEG, and long-term follow-up will allow us to provide evidence-based care and novel interventions to this population.

Acknowledgments

Thank you to all the NSR clinical research coordinators across all sites for all their support.

References

1. Holt DE. Neonatal meningitis in England and Wales: 10 years on. Arch Dis Child Fetal Neonatal Ed. 2001;84:85F–89F.
2. Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States, 1998–2007. N Engl J Med. 2011;364:2016–2025.
3. Volpe JJ. Neonatal encephalitis and white matter injury: more than just inflammation? Ann Neurol. 2008;64:232–236.
4. Verboon-Maciolek MA, Groenendaal F, Hahn CD, et al. Human parechovirus causes encephalitis with white matter injury in neonates: WM Injury Caused by HPeVs. Ann Neurol. 2008;64:266–273.
5. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. N Engl J Med. 2009;361:1376–1385.
6. Volpe JJ, ed. Volpe's Neurology of the Newborn. 6th ed. Philadelphia, PA: Elsevier; 2018.
7. Cooray G, Ygberg S, Fowler Å, Wickström R. Post-encephalitic epilepsy in childhood: results from a prospective cohort study. Epileptic Disord. 2021;23:133–142.
8. Klinger G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. Pediatrics. 2000;106:477–482.
9. Chequer RS, Tharp BR, Dreimane D, Hahn JS, Clancy RR, Coen RW. Prognostic value of EEG in neonatal meningitis: retrospective study of 29 infants. Pediatr Neurol. 1992;8:417–422.
10. Klinger G, Chin CN, Otsubo H, Beyene J, Perlman M. Prognostic value of EEG in neonatal bacterial meningitis. Pediatr Neurol. 2001;24:28–31.
11. Watanabe K, Hara K, Hakamada S, Kuroyanagi M, Kuno K, Aso K. The prognostic value of EEG in neonatal meningitis. Clin Electroencephalogr. 1983;14:67–77.
12. Fister P, Peček J, Jeverica S, Primec ZR, Paro-Panjan D. Neonatal group B streptococcal meningitis: predictors for poor neurologic outcome at 18 months. J Child Neurol. 2022;37:64–72.
13. Yoshioka M, Kuroki S, Mizue H. Clinical and electroencephalographic studies of postencephalitic epilepsy. Pediatr Int. 1989;31:480–483.
14. Sainio K, Grandström ML, Pettay O, Donner M. EEG in neonatal herpes simplex encephalitis. Electroencephalogr Clin Neurophysiol. 1983;56:556–561.
15. Glass HC, Soul JS, Chang T, et al. Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures. JAMA Neurol. 2021;78:817.
16. Tsuchida TN, Wusthoff CJ, Shellhaas RA, 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;30:161–173.
17. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE commission for classification and terminology. Epilepsia. 2017;58:512–521.
18. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. N Engl J Med. 1990;323:1651–1657.
19. 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;42:377–381.
20. Glass HC, Shellhaas RA, Wusthoff CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. J Pediatr. 2016;174:98–103.e1.
21. Peyton C, Wroblewski K, Park J, et al. Validity of the warner initial developmental evaluation of adaptive and functional skills (WIDEA-FS): a daily activity criterion checklist for infants and toddlers. Pediatr Res. 2021;90:1052–1057.
22. Peyton C, Msall ME, Wroblewski K, Rogers EE, Kohn M, Glass HC. Concurrent validity of the Warner Initial Developmental Evaluation of Adaptive and Functional Skills and the Bayley Scales of Infant and Toddler Development, Third Edition. Dev Med Child Neurol. 2021;63:349–354.
23. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE Official Report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475–482.
24. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 2008;39:214–223.
25. Shellhaas RA, Soul JS, Chang T, et al. Looking at the effect of treatment duration for newborn infants who have seizures. Patient-Centered Outcomes Research Institute (PCORI); 2021 https://doi.org/10.25302/07.2021.CER.150731187. Accessed May 28, 2022.
26. McGuire JL, Tuite NV, Swami SK, Avery RA. Assessment of diagnostic yield of nonculture infection testing on cerebrospinal fluid in immune-competent children. JAMA Netw Open. 2019;2, e197307.
27. Clancy RR, Legido A, Lewis D. Occult neonatal seizures. Epilepsia. 1988;29:256–261.
28. Shellhaas RA, Chang T, Tsuchida T, et al. The American clinical Neurophysiology society's guideline on continuous electroencephalography monitoring in neonates. J Clin Neurophysiol. 2011;28:611–617.
29. Pressler RM, Cilio MR, Mizrahi EM, et al. The ILAE classification of seizures and the epilepsies: modification for seizures in the neonate. Position paper by the ILAE Task Force on Neonatal Seizures. Epilepsia. 2021;62:615–628.
30. Overall JC. Neonatal bacterial meningitis. J Pediatr. 1970;76:499–511.
31. Pike MG, Wong PKH, Bencivenga R, et al. Electrophysiologic studies, computed tomography, and neurologic outcome in acute bacterial meningitis. J Pediatr. 1990;116:702–706.
32. Kimberlin DW, Lin CY, Jacobs RF, et al. Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics. 2001;108:223–229.
33. Toth C, Harder S, Yager J. Neonatal herpes encephalitis: a case series and review of clinical presentation. Can J Neurol Sci. 2003;30:36–40.
34. Mikati MA, Feraru E, Krishnamoorthy K, Lombroso CT. Neonatal herpes simplex meningoencephalitis: EEG investigations and clinical correlates. Neurology. 1990;40:1433.
35. ter Horst H, van Olffen M, Remmelts H, de Vries H, Bos A. The prognostic value of amplitude integrated EEG in neonatal sepsis and/or meningitis. Acta Paediatr. 2010;99:194–200.
36. Glass HC, Soul JS, Chu CJ, et al. Response to antiseizure medications in neonates with acute symptomatic seizures. Epilepsia. 2019;60:e20–e24.
37. Kaaresen P, Flaegstad T. Prognostic factors in childhood bacterial meningitis. Acta Paediatr. 1995;84:873–878.
38. Grimwood K, Nolan T, Bond L, Anderson V, Catroppa C, Keir E. Risk factors for adverse outcomes of bacterial meningitis. J Paediatr Child Health. 1996;32:457–462.
39. Wald ER, Bergman I, Taylor HG, Chiponis D, Porter C, Kubek K. Long-term outcome of group B streptococcal meningitis. Pediatrics. 1986;77:217–221.
40. Chang CJ, Chang HW, Chang WN, et al. Seizures complicating infantile and childhood bacterial meningitis. Pediatr Neurol. 2004;31:165–171.
41. Paul Rosman N, Peterson DB, Kaye EM, Colton T. Seizures in bacterial meningitis: prevalence, patterns, pathogenesis, and prognosis. Pediatr Neurol. 1985;1:278–285.
42. Glass HC, Grinspan ZM, Shellhaas RA. Outcomes after acute symptomatic seizures in neonates. Semin Fetal Neonatal Med. 2018;23:218–222.

43. Murthy JMK, Prabhakar S. Bacterial meningitis and epilepsy. Epilepsia. 2008;49:8–12.
44. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. Pediatr Infect Dis J. 1993;12:389–394.
45. Holmes GL, Ben-Ari Y. The neurobiology and consequences of epilepsy in the developing brain. Pediatr Res. 2001;49:320–325.
46. Fox CK, Mackay MT, Dowling MM, et al. Prolonged or recurrent acute seizures after pediatric arterial ischemic stroke are associated with increasing epilepsy risk. Dev Med Child Neurol. 2017;59:38–44.
47. Shellhaas RA, Wusthoff CJ, Numis AL, et al. Early-life epilepsy after acute symptomatic neonatal seizures: a prospective multicenter study. Epilepsia. 2021;62:1871–1882.