Received: 7 May 2021 | Revised: 9 June 2021 | Accepted: 10 June 2021

DOI: 10.1111/epi.16978

Epilepsia®

FULL-LENGTH ORIGINAL RESEARCH

Early-life epilepsy after acute symptomatic neonatal seizures: A prospective multicenter study

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Funding information
Pediatric Epilepsy Research Foundation; Patient-Centered Outcomes Research Institute, Grant/Award Number: 1507-31187

Abstract

Objective: We aimed to evaluate early-life epilepsy incidence, seizure types, severity, risk factors, and treatments among survivors of acute neonatal seizures.

Methods: Neonates with acute symptomatic seizures born 7/2015-3/2018 were prospectively enrolled at nine *Neonatal Seizure Registry* sites. One-hour EEG was recorded at age three months. Post-neonatal epilepsy and functional development (Warner Initial Developmental Evaluation of Adaptive and Functional Skills – WIDEA-FS) were assessed. Cox regression was used to assess epilepsy-free survival.

Results: Among 282 infants, 37 (13%) had post-neonatal epilepsy by 24-months [median age of onset 7-months (IQR 3–14)]. Among those with post-neonatal epilepsy, 13/37 (35%) had infantile spasms and 12/37 (32%) had drug-resistant epilepsy. Most

children with post-neonatal epilepsy had abnormal neurodevelopment at 24-months (WIDEA-FS >2SD below normal population mean for 81% of children with epilepsy vs 27% without epilepsy, RR 7.9, 95% CI 3.6–17.3). Infants with severely abnormal neonatal EEG background patterns were more likely to develop epilepsy than those with mild/moderate abnormalities (HR 3.7, 95% CI 1.9–5.9). Neonatal EEG with ≥3 days of seizures also predicted hazard of epilepsy (HR 2.9, 95% CI 1.4–5.9). In an adjusted model, days of neonatal EEG-confirmed seizures (HR 1.4 per day, 95% CI 1.2–1.6) and abnormal discharge examination (HR 3.9, 95% CI 1.9–7.8) were independently associated with time to epilepsy onset. Abnormal (vs. normal) three-month EEG was not associated with epilepsy.

Significance: In this multicenter study, only 13% of infants with acute symptomatic neonatal seizures developed post-neonatal epilepsy by age 24-months. However, there was a high risk of severe neurodevelopmental impairment and drug-resistant seizures among children with post-neonatal epilepsy. Days of EEG-confirmed neonatal seizures was a potentially modifiable epilepsy risk factor. An EEG at three months was not clinically useful for predicting epilepsy. These practice changing findings have implications for family counseling, clinical follow-up planning, and future research to prevent post-neonatal epilepsy.

KEYWORDS

anti-seizure medication, electroencephalogram, epilepsy, hypoxic-ischemic encephalopathy, infantile spasms, neonatal encephalopathy, neonatal seizures, neurocritical care, seizure

1 | INTRODUCTION

Most seizures in newborns are caused by acute brain injury (e.g. hypoxic-ischemic encephalopathy, ischemic stroke, or intracranial hemorrhage).[1] These acute symptomatic seizures are distinct from the recurrent unprovoked seizures that are the hallmark of epilepsy. While people with epilepsy often have a history of pre-natal or perinatal brain injury and neonatal seizures[2,3] and clinical neonatal seizures are a risk factor for non-remitting epilepsy,[4,5] prior studies of risk factors for epilepsy after acute provoked neonatal seizures are limited by lack of modern diagnostic technology, retrospective design, or single center cohorts.

Older, population-based studies relied on clinical seizure diagnosis in neonates,[5,6] or ICD9 diagnosis.[7] As most neonatal seizures are subclinical and many abnormal movements are not seizures,[8] research using EEG diagnosis of neonatal seizures is necessary. Recent studies of epilepsy after neonatal seizures included EEG diagnosis of neonatal seizures; however, these often relied upon single center cohorts, or focused solely on neonates with hypoxic-ischemic encephalopathy.[9–12] Some forms of post-neonatal epilepsy, e.g. infantile spasms, require distinct treatments or have specific prognostic significance. While some studies report that 10%–16% of children with clinical neonatal seizures developed infantile spasms and others report >20% of survivors developed epilepsy,[6,13,14] few investigations provide the necessary detail regarding epilepsy syndromes or seizure types to adequately counsel families about future risk. These evidence gaps

Key Points

- Post-neonatal epilepsy after acute symptomatic neonatal seizures is uncommon (13%); severity ranges from relatively infrequent to intractable daily seizures.
- One third of children with epilepsy following neonatal seizures develop drug-resistant epilepsy.
- The risk of abnormal neurodevelopment is three times higher for children with versus without epilepsy following acute symptomatic neonatal seizures.
- Overall duration of EEG seizures (in days) is a potentially modifiable risk factor for post-neonatal epilepsy.
- Routine EEG at three months of age is not helpful to identify children at highest risk for epilepsy.

present a challenge when counseling families of neonates with seizures and in planning post-neonatal care.

Broad understanding of the profile of post-neonatal epilepsy after acute symptomatic neonatal seizures is clinically relevant, and necessary to inform clinical trial design for studies that aim to prevent post-neonatal epilepsy or mitigate neurodevelopmental risk. We aimed to fill these gaps with a multicenter, prospective observational study. We hypothesized that clinical features of the neonatal course, neonatal EEG, and follow-up EEG at three-months corrected age would be useful clinical predictors of post-neonatal epilepsy.

2 | METHODS

2.1 | Study design

This is a pre-specified secondary outcome analysis from a prospective, observational, multicenter study of infants with acute symptomatic neonatal seizures born between 7/2015 and 3/2018 who were enrolled at one of nine *Neonatal Seizure Registry (NSR)* sites (prospectively registered at NCT02789176; primary outcomes were reported previously[15,16]). Approximately half of the participants (150/303) were enrolled during the neonatal seizure admission; the remainder were recruited prior to age 24 months from the first *NSR* cohort[1,17,18] or from outpatient clinics at a *NSR* study center.

Each *NSR* site has a level IV neonatal intensive care unit (NICU) and a level IV comprehensive pediatric epilepsy program. All sites followed the American Clinical Neurophysiology Society (ACNS) guidelines for continuous electroencephalography (cEEG) in neonates.[19] No study-specific neonatal seizure treatment pathway or epilepsy evaluation or treatment protocols were mandated. For this observational study, seizure treatment including antiseizure medication (ASM) selection, dosing, and treatment duration, was at the discretion of the clinical teams. The *NSR* Parent Advisory Panel contributed to the design and interpretation of results from this study. This panel consisted of representatives from family advocacy groups and at least one parent of a child with neonatal seizures (not enrolled in this study) from each study site. At each site, the local institutional review board approved the study. All participating infants were enrolled following written, informed consent from parents. Demographic and clinical data were determined by chart review.

2.2 | Inclusion and exclusion criteria

Inclusion criteria: Preterm and full term neonates with (1) EEG-confirmed neonatal seizures at the study site or referring hospital, or (2) treatment with ASM for clinical events suspected to be neonatal seizures, if the clinical history, including event semiology, strongly supported the diagnosis of seizures, and (3) the neonatal seizures had an acute symptomatic etiology (i.e., hypoxic-ischemic encephalopathy, ischemic stroke, intracranial hemorrhage, or other brain injury).

Exclusion criteria: Infants were excluded if they had clinical events that were determined *not* to be seizures based on history, semiology, or cEEG. Neonates with seizures due to readily reversible metabolic abnormalities (e.g., hyponatremia, hypocalcemia, or hypoglycemia without brain injury), or neonatal onset epilepsy syndromes were also excluded.

2.3 | Neonatal clinical data

Neonatal clinical data were extracted from the medical records by a clinical research coordinator at each site and confirmed by the site investigator. The discharge neurological examination was defined as abnormal if consciousness, reflexes, or tone were clearly documented as abnormal in the medical record within three days of hospital discharge.

2.4 | EEG data

Neonatal EEG results were obtained from the clinical reports for all participants. The most abnormal neonatal EEG background was classified as: (1) normal, (2) mildly or moderately abnormal (excessive negative sharp waves, positive sharp waves, excessive discontinuity or asynchrony), or (3) severely abnormal (burst-suppression, flat trace, depressed and undifferentiated, or electrocerebral inactivity). Seizures were defined as sudden, abnormal EEG events with repetitive and evolving pattern with amplitude $\geq$2 μV and duration $\geq$10 s, with or without a clinical correlate.[20] Neonatal seizure burden was extracted as seizure counts from cEEG reports at the study center. Cumulative recorded seizure counts during cEEG monitoring were categorized as follows: status epilepticus, frequent recurrent seizures, $\geq$7 isolated seizures, <7 seizures, or none.[1] Status epilepticus was defined as >30 min of seizures within any 1-h epoch.[20]

A 1-h follow-up EEG at three months corrected age was offered to each of the 150 infants who enrolled prior to discharge from the neonatal seizure admission. These EEGs were centrally reviewed by two clinical neurophysiologists and differences in scoring were resolved through consensus reviews. Epileptiform abnormalities were defined as any ($\geq$1) sharp wave or spike. Multifocal spikes were defined as three or more independent, non-contiguous foci over both hemispheres.[20] Hypsarrhythmia was defined as a "Burden of Amplitudes and Epileptiform Discharges" (BASED) score of

4 or 5.[21] Persistent hemispheric asymmetry was defined as continuous unihemispheric/lateralized suppression or high amplitude slowing with sharp waves or spikes confined to one hemisphere with preserved normal EEG patterns over the contralateral hemisphere.

2.5 | Outcome measures

Standardized telephone interviews were conducted when the children reached 12, 18, and 24 months corrected age. In each interview, parents were asked whether their child had post-neonatal epilepsy, and if so, when the first unprovoked seizure occurred. The responses were corroborated by review of medical records. Post-neonatal epilepsy was defined using the 2014 ILAE criteria[22]: (1) At least two unprovoked seizures occurring >24 h apart; or (2) one unprovoked seizure and a probability of further seizures similar to the recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years; or (3) diagnosis of an epilepsy syndrome after 44 weeks post-menstrual age (PMA). Epilepsy was classified as focal (exclusively focal seizure semiologies), generalized (exclusively bilateral symmetric, or generalized, seizure semiologies), mixed (combination of focal and either generalized or unclassifiable onset seizures), or unclassified (based on ambiguities in medical records).[23] Drug-resistant epilepsy was defined as continued seizures despite trials of >2 appropriate ASMs.[24]

Functional neurodevelopment was measured via the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS), administered at 24 months corrected age.[25–28] Trained research team members who were blinded to neonatal history administered the WIDEA-FS by telephone. Functional impairment was operationally defined as total WIDEA-FS score >2 standard deviations below the normal population mean.

Motor outcome was assessed via telephone administration of a modified Gross Motor Function Classification System at 24 months corrected age.[29] Functional motor disability was defined as GMFCS ≥II at 24 months corrected age. Cerebral palsy diagnoses were identified through parent interview and corroborated by chart review.

2.6 | Analysis

Risk for epilepsy or abnormal neurodevelopment: Chi square, risk ratio, and t-tests were used to compare children with and without epilepsy. The sensitivity, specificity, and positive and negative predictive values of abnormal findings on three-month follow-up EEGs for post-neonatal epilepsy prediction were also calculated.

To determine independent risk factors for post-neonatal epilepsy, we built a Cox regression model including all neonatal variables with unadjusted association with post-neonatal epilepsy at $p \leq .1$ and using backwards, stepwise regression retaining variables with adjusted $p \leq .1$.

Time to epilepsy diagnosis: Cox proportional hazards was used to examine epilepsy-free survival by risk groups identified in the unadjusted analysis. Kaplan Meier curves were generated to visualize differences in epilepsy-free survival. Participants were censored at loss to follow-up or 24 months corrected age (end of study period).

All analyses were conducted using SAS version 9.4 (SAS Institute Inc.). All tests were set at a significance level of $p < .05$.

3 | RESULTS

We enrolled 305 infants. Two were excluded – one due to a subsequently diagnosed genetic syndrome and one because acute seizure onset was later than 44 weeks postmenstrual age (Figure 1). Neonatal seizure etiology was hypoxic-ischemic encephalopathy for 130 (43%), ischemic stroke for 79 (26%), intracranial hemorrhage for 55 (18%), and other acute brain injury in 39 (13%; intracranial infection in 24, hypoglycemia with brain injury in four, and uncategorized in 11). Phenobarbital was the first loading ASM in 90%; 53% received ≥2 ASM to treat the neonatal seizures. Follow-up data were available for 282 children (93%; three died prior to age 12 months, one parent withdrew consent, and 17 did not have any follow-up data available).

3.1 | Profile of post-neonatal epilepsy

Among 282 children with follow-up at one or more time points, 37 (13%) developed epilepsy before 24 months corrected age. The median age of epilepsy onset was 7 months (IQR 3, 14) (as reported in Ref.15). The risk of epilepsy was not different for the 238 term infants compared with the 44 preterm infants (Table 2).

Epilepsy types were: focal epilepsy (19/37, 51%), generalized epilepsy (2/37, 5%), mixed epilepsy (both focal and generalized features; 6/37, 16%), and unclassified epilepsy type (10/37, 27%). Infantile spasms developed in 13/37 (35%). Among children with infantile spasms, six never had any other documented seizure semiology before age 24 months, two had other seizure types before they developed infantile spasms, and five developed additional seizure semiologies after the infantile spasms were diagnosed.

At last follow-up (parent interview or medical record report, whichever was later), 20/37 (54%) children with epilepsy had been seizure-free for ≥6 months, 12/37(32%) had

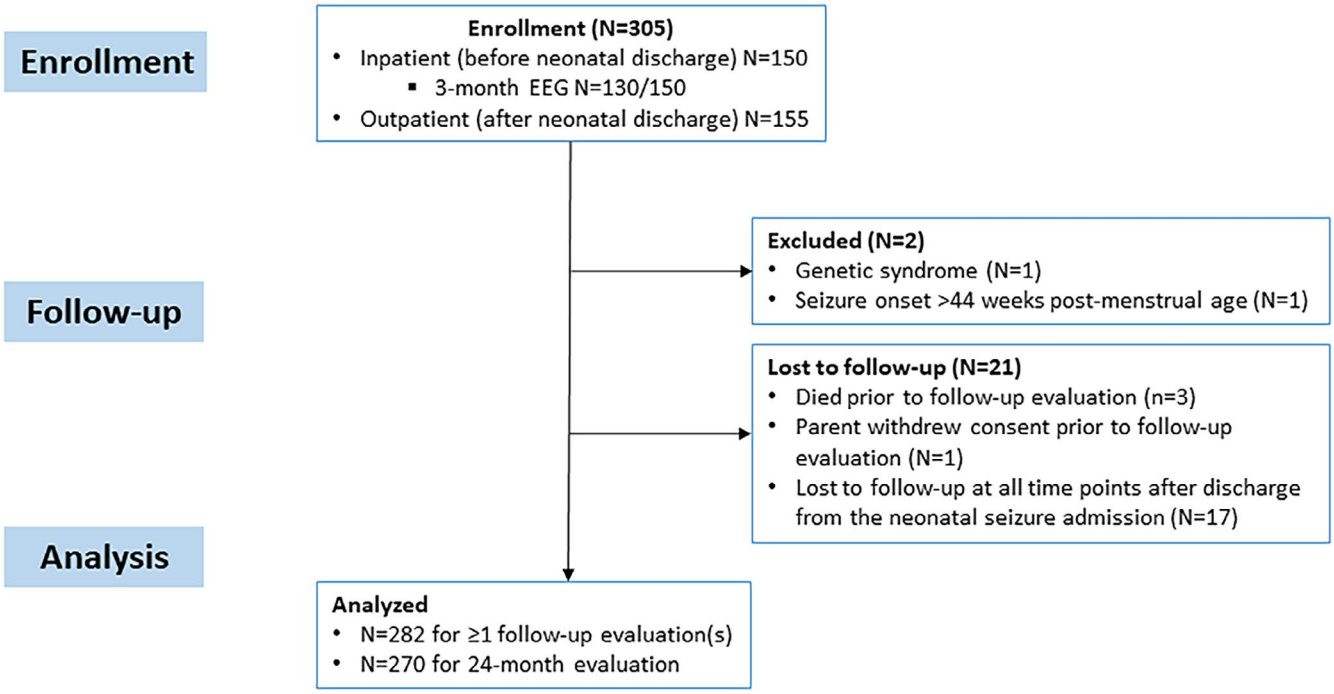

FIGURE 1 Flow diagram

TABLE 1 Epilepsy treatments prescribed after hospital discharge for 37 infants with post-neonatal epilepsy

Antiseizure medications	*N* (%)
Levetiracetam	24 (65%)
Topiramate	8 (22%)
Prednisolone	8 (22%)
Vigabatrin	7 (19%)
Oxcarbazepine	6 (16%)
ACTH	5 (14%)
Clobazam	3 (8%)
Clonazepam	3 (8%)
Lacosamide	3 (8%)
Cannabidiol	2 (5%)
Ketogenic Diet	1 (3%)
Zonisamide	1 (3%)
Number of ASMs for post-neonatal epilepsy	*N* (%)
0[a]	3 (8%)
1	15 (41%)
2	7 (19%)
>2[b]	12 (32%)

[a]Among the three infants with epilepsy who were not treated with additional ASM, one had two focal seizures and the clinician advised that the child receive ASM, but parents declined, one had suspected unprovoked seizures one month after hospital discharge and then a focal seizure at age 17 months but no ASM was prescribed, and one was continued on phenobarbital for the post-neonatal epilepsy.
[b]Infants who were prescribed >2 ASMs for post-neonatal epilepsy (i.e., after resolution of acute symptomatic neonatal seizures) were considered to have treatment-resistant epilepsy.

less than one seizure per month, but 4/37(11%) reported daily seizures. Twelve (32%) had treatment-resistant epilepsy (two or more ASMs initiated *after* discharge from the neonatal seizure admission) by 24 months corrected age. Most of the children with post-neonatal epilepsy were receiving ASM at the time of last follow-up (31/37, 84%). Treatments children received for epilepsy are outlined in Table 1.

Most children with post-neonatal epilepsy had abnormal neurodevelopment, defined as WIDEA-FS >2SD below normal population mean at corrected age 24 months (81% of children with epilepsy vs 27% without epilepsy, RR 7.9, 95% CI 3.6–17.3, $p < .0005$). Children with epilepsy were also at elevated risk for functional motor disability (GMFCS ≥2) at age 24 months (67% with epilepsy compared with 9% without epilepsy; RR 7.5, 95% CI 4.7–12.0, $p < .0001$).

3.2 | Neonatal risk factors for post-neonatal epilepsy

There was no difference in risk of epilepsy based on gestational age, sex, family history of epilepsy, or neonatal seizure etiology (Table 2). In the unadjusted analysis, neonatal risk factors for epilepsy included: severely abnormal EEG background, higher number of days with EEG-confirmed seizures, higher seizure burden, need for ≥2 ASMs for neonatal seizure control, and abnormal discharge neurologic examination (Table 2). The risk of epilepsy before 24 months was 10% for children with one calendar day of EEG seizures, 13%

TABLE 2 Clinical characteristics of 282 infants who survived acute symptomatic neonatal seizures

	Total	Epilepsy	No epilepsy	
	N = 282	37 (13%)	245 (87%)	*p*-Value
Clinical characteristics				
Gestational age at birth				
<28 weeks	9 (3%)	2 (5%)	7 (3%)	.13
28 to <32 weeks	5 (2%)	2 (5%)	3 (1%)	
32 to <37 weeks	30 (11%)	6 (16%)	24 (10%)	
≥37 weeks	238 (84%)	27 (73%)	211 (86%)	
Male	156 (55%)	21 (57%)	135 (55%)	.9
5-min Apgar score	8 (5, 9)	8 (5, 9)	8 (5, 9)	1
Family history of febrile seizures (*N* = 245 with data)	22 (9%)	5 of 35 (14%)	17 of 210 (8%)	.24
Family history of epilepsy (*N* = 245 with data)	30 (12%)	4 of 35 (11%)	26 of 210 (12%)	.87
Neonatal seizure and EEG characteristics				
Seizure etiology				
Hypoxic-ischemic encephalopathy	124 (44%)	18 (49%)	106 (43%)	.7
Ischemic stroke	75 (27%)	8 (22%)	67 (27%)	
Intracranial hemorrhage	47 (17%)	5 (14%)	42 (17%)	
Other	36 (13%)	6 (16%)	30 (12%)	
Worst EEG background during the 1st 24 h at study center[a]				
Normal	23 (8%)	0 (0%)	23 (9%)	.003
Mild/moderately abnormal	186 (66%)	20 (54%)	166 (68%)	
Severely abnormal (burst suppression, depressed/undifferentiated, flat tracing)	47 (17%)	14 (38%)	33 (13%)	
Electrographic status epilepticus at onset of recording	24 (9%)	3 (8%)	21 (9%)	
Cannot assess	2 (1%)	0 (0%)	2 (1%)	
EEG seizure burden at the study center				
None[b]	51 (18%)	4 (11%)	47 (19%)	.04
Few (<7)	76 (27%)	10 (27%)	66 (27%)	
Many isolated (≥7)	53 (19%)	4 (11%)	49 (20%)	
Frequent recurrent	61 (22%)	12 (32%)	49 (20%)	
Status epilepticus	40 (14%)	6 (16%)	34 (14%)	
Documentation inadequate	1 (<1%)	1 (<1%)	0 (0%)	
Days of EEG seizures	1 (1, 2)	2 (1, 3)	1 (1, 2)	.01
Initial loading anti-seizure medication (ASM)				
Phenobarbital	254 (90%)	35 (95%)	219 (89%)	.6
Levetiracetam	15 (5%)	2 (5%)	13 (5%)	
Fosphenytoin	3 (1%)	0	2 (1%)	
No loading dose	10 (4%)	0	10 (4%)	
Incomplete response to initial loading dose of medication	174 (62%)	27 (73%)	147 (60%)	.3
Received ≥2 ASM to treat neonatal seizures	150 (53%)	27 (73%)	123 (50%)	.01
Neonatal clinical course				
Complex medical diagnosis (congenital heart disease, ECMO, congenital diaphragmatic hernia)	33 (12%)	4 (11%)	29 (12%)	.9

(Continues)

TABLE 2 (Continued)

	Total	Epilepsy	No epilepsy	
	N = 282	37 (13%)	245 (87%)	*p*-Value
Therapeutic hypothermia	84 (30%)	9 (24%)	75 (31%)	.4
Abnormal neurologic exam at discharge	88 (31%)	24 (65%)	64 (26%)	<.0005

[a]Using the clinical report.

[b]Neonates with no recorded EEG seizures had received treatment with ASM for clinical events suspected to be neonatal seizures, and had a clinical history, including event semiology, that strongly supported the diagnosis of seizures.

for two days of EEG seizures, and 28% for three or more days of EEG seizures.

In an adjusted model, days of neonatal EEG-confirmed seizures (HR 1.4 per day of seizures, 95% CI 1.2–1.6, $p < .0001$) and abnormal discharge exam (HR 3.9, 95% CI 1.9–7.8, $p = .0001$) were independently associated with time to post-neonatal epilepsy onset.

3.3 | Neonatal predictors of time to post-neonatal epilepsy onset

The neonatal seizure etiology was not associated with age of post-neonatal epilepsy onset ($p = .74$). However, infants with three or more days of EEG seizures (vs. fewer days) had earlier onset of epilepsy than those with fewer days of seizures (HR 2.9, 95% CI 1.4–5.9). Infants with severely abnormal (vs. mildly/moderately abnormal) EEG backgrounds in the first 24 h of EEG monitoring had earlier epilepsy diagnosis (HR 3.7, 95% CI 1.9–7.3; Figure 2). An abnormal neurological examination, compared with a normal examination, at hospital discharge was also associated with earlier onset of epilepsy (HR 4.7, 95% CI 2.4–9.3).

3.4 | Three-month EEG and risk for post-neonatal epilepsy

Three-month EEG was completed at a median age of 2.8 months (IQR 2.3, 3.4) for 130 of the 149 infants (86.7%) who were enrolled during the neonatal seizure admission, and 123 of these children (94.6%) had subsequent follow-up evaluations. There was no difference in neonatal characteristics between children with and without three-month EEG (Table S1).

Among 123 infants with three-month follow-up EEG and subsequent follow-up, four had post-neonatal epilepsy before the three-month EEG was recorded. All had been maintained on ASMs at the time of discharge from the neonatal seizure admission and three held a diagnosis of cerebral palsy by 24 months corrected age. Five of the 123 (4%) had hypsarrhythmia on the 3-month EEG. Two of the five (40%) with hypsarrhythmia already had a post-neonatal focal epilepsy diagnosis at the time of EEG and all five were diagnosed with epilepsy before 24 months corrected age. Only one of the five (20%) was later diagnosed with infantile spasms. All five children with hypsarrhythmia at three months corrected age had cerebral palsy by age 24 months.

A distinct and persistent hemispheric asymmetry on the three-month EEG was associated with post-neonatal epilepsy risk (4/103, 4%, vs. 3/16, 19%, $p = .050$). Presence of epileptiform abnormalities, however, was not associated with post-neonatal epilepsy risk. Overall, most children who had an abnormality on three-month EEG did not develop post-neonatal epilepsy (Tables 3 and 4).

The three-month EEG results were not independently associated with risk of epilepsy in the multivariable regression model. The sensitivity, specificity, positive predictive value, and negative predictive value of abnormal three-month EEG as a predictor of post-neonatal epilepsy are displayed in Table 4.

Presence of multifocal sharp waves or spikes on the three-month EEG was associated with lower 24-month WIDEA-FS scores (113.2 ± 40.2 with vs. 155.5 ± 31.4 without, $p < .0001$), and the association persisted among children who did not develop epilepsy before 24 months corrected age (126.1 ± 39.9 with vs. 160.0 ± 24.8 without, $p = .07$); this association was not significant for infants who developed epilepsy (100.3 ± 38.9 with vs. 123.7 ± 51.5, $p = .31$). Unifocal sharp waves or spikes were not associated with WIDEA-FS scores ($p > .4$ for all tests of association).

4 | DISCUSSION

In this large, multicenter, prospective study of infants who survived acute symptomatic neonatal seizures, the proportion of children who developed post-neonatal epilepsy by age 24 months was relatively small (37/282, 13%). However, there was a range of post-neonatal epilepsy severity – while most (20/37) were seizure-free for at least six months by age 24 months, a third (12/37) had treatment-resistant epilepsy and frequent daily seizures. Furthermore, compared with children without epilepsy, children with epilepsy were three times more likely to have neurodevelopmental impairment. Our results also suggest that a routine EEG at age

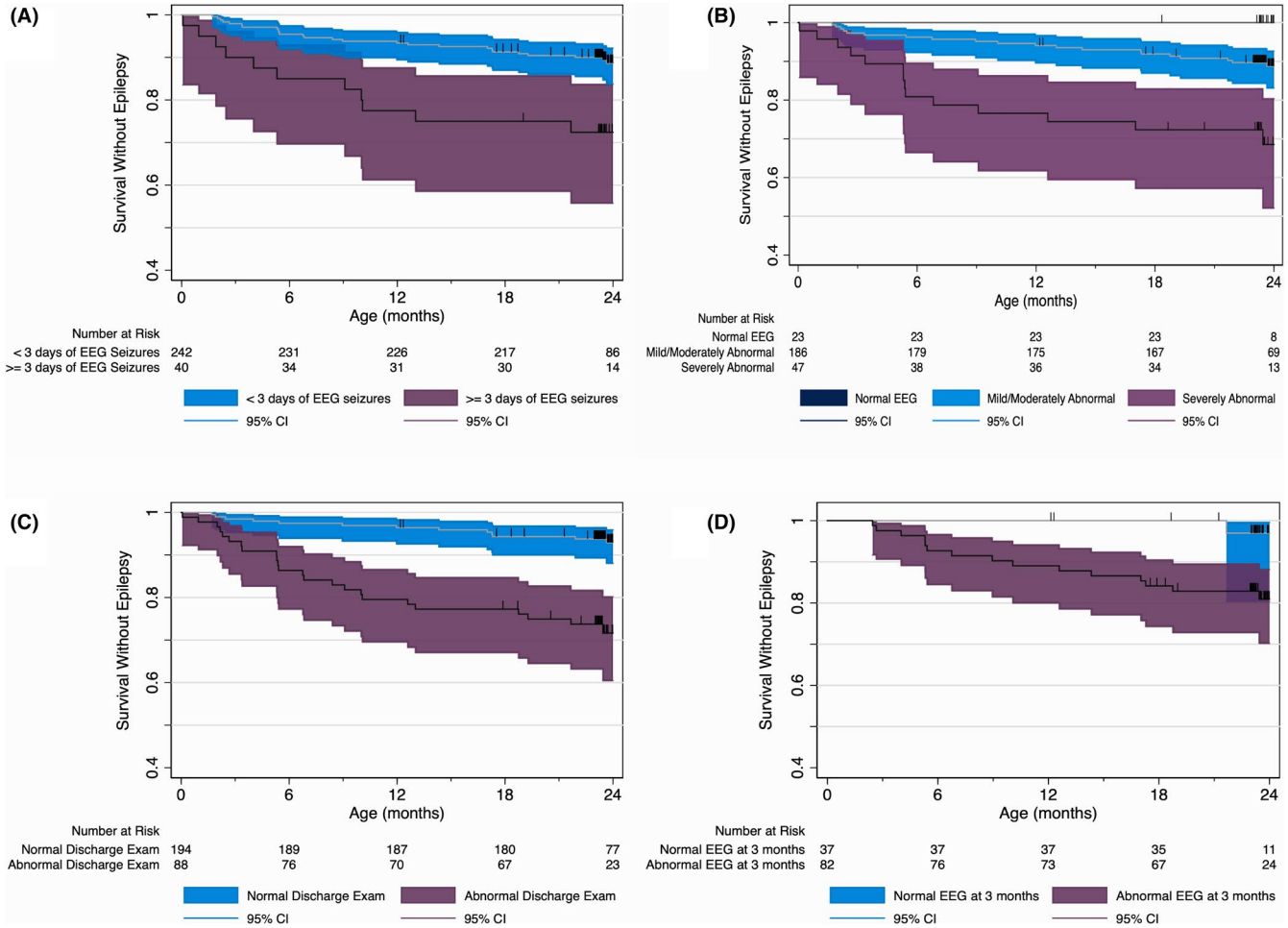

FIGURE 2 Survival without post-neonatal epilepsy among 270 infants with acute symptomatic neonatal seizures. Having >3 days of EEG-confirmed neonatal seizures (Panel A), abnormal neurological examination at the time of hospital discharge (Panel B), or severely abnormal neonatal EEG background (Panel C) was associated with earlier onset post-neonatal epilepsy. However, the risk of epilepsy was not predicted by the results of a routine EEG at three months corrected age (Panel D)

three months did not improve prediction of epilepsy by age 24 months. An important subset of infants (7/37, 19%) developed epilepsy before three months, a common time point for clinical follow-up, and most children with an abnormal EEG at 3-months did not develop epilepsy (positive predictive value of abnormal EEG was 16%).

Previous studies of children with clinical neonatal seizures reported higher rates of post-neonatal epilepsy (20%–30%[13,14,30]) and studies of EEG-confirmed neonatal seizures have reported post-neonatal epilepsy rates of nearly 50%.[31] There are several potential reasons for the difference. First, some studies that reported a higher risk of epilepsy had longer follow-up intervals.[14,31] Population-based studies suggest that although the risk of epilepsy is highest in the first two years, the risk continues at least throughout childhood.[32] We are currently following the *NSR* cohort for early school-age outcomes (NCT04337697). Second, prior studies may be subject to bias toward more severe cases because of recruitment from specialty clinics. Third, we speculate that implementation of therapeutic hypothermia as a neuroprotective strategy for neonates with hypoxic-ischemic encephalopthy[33] may have reduced the risk of epilepsy in our study participants. Finally, comprehensive neurocritical care[34–38] including conventional EEG monitoring[19] for all neonates with seizures in our patient cohort, may have facilitated prompt seizure detection and treatment which might also have contributed to lower rates of post-neonatal epilepsy.

While others have reported infantile spasms as a separate outcome,[13,14,30] our study adds information about the range of epilepsy types and severity within the first two years after neonatal seizures. Importantly, we show a range of severity of epilepsy outcomes: while one third (12/37) had drug-resistant epilepsy, more than half (20/37) had good seizure control (no seizures for at least six months) before age 24 months. Understanding the range of possible epilepsy outcomes is important for counseling parents and planning clinical follow-up care. It also has implications for research protocols designed to study potential interventions to decrease the risk

TABLE 3 EEG patterns at three-months did not clearly distinguish infants who later developed post-neonatal epilepsy

3-month EEG characteristics for infants without hypsarrhythmia[a]	Total, $N = 119$	Epilepsy, $N = 16$	No epilepsy, $N = 103$	p-Value
Normal EEG	37 (31%)	1 (6%)	36 (35%)	.02
Abnormal EEG				
Abnormal without epileptiform discharges	50 (42%)	6 (38%)	44 (43%)	.13
Focal epileptiform discharges	20 (17%)	5 (31%)	15 (15%)	
Multifocal epileptiform discharges	12 (10%)	4 (25%)	8 (8%)	
Hemispheric asymmetry	7 (6%)	3 (19%)	4 (4%)	.05

[a]Follow-up EEG was available for 123 infants. Four infants already had diagnosed epilepsy at the time of this EEG (three-months corrected age).

TABLE 4 Predictive value of abnormal EEG patterns at three months for post-neonatal epilepsy[a]

	Sensitivity	Specificity	PPV	NPV
Abnormal EEG	94% (70%–99%)	35% (26%–45%)	18% (11%–28%)	97% (85%–99%)
Abnormal EEG with any epileptiform features	56% (30%–80%)	78% (68%–85%)	28% (14%–47%)	92% (84%–97%)
Abnormal EEG with multifocal spikes	25% (7%–52%)	92% (85%–97%)	33% (10%–65%)	89% (81%–94%)

[a]Data are presented as: point estimate (95% confidence interval).

of post-neonatal epilepsy and its severity following neonatal seizures.

These data also confirm previous findings that post-neonatal epilepsy is often associated with neurodevelopmental impairment,[13,39,40] and add that neurodevelopmental impairment was not confined to children with treatment-resistant epilepsy or high post-neonatal seizure burden. In fact, 81% of children with epilepsy had abnormal neurodevelopment although only 32% of those with epilepsy had treatment-resistant seizures and 54% of children with epilepsy had been seizure-free for >6 months at their last follow-up.

Neonatal status epilepticus has previously been identified as a risk factor for post-neonatal epilepsy.[41–43] Although we did not replicate that result, we identified the number of days with neonatal seizures as a potentially modifiable risk factor for post-neonatal epilepsy. Not only was having more than three days of EEG confirmed seizures associated with increased risk for epilepsy, but it was also associated with a risk for earlier age of epilepsy onset. This finding is important for counseling families of infants with one or two days of seizures that their children are at lower risk for epilepsy and highlighting the need for early follow-up for high-risk infants (those with three or more EEG seizure days are at high risk for epilepsy with onset in the first few months of life). It also raises the possibility that early, effective identification and treatment of neonatal seizures could be a strategy to lower the rate of post-neonatal epilepsy. Additional considerations of risk for post-neonatal epilepsy include genetic or epigenetic predisposition. Of note, >10% of children in our study had a family history of epilepsy, but this did not differentiate those who developed post-neonatal epilepsy. This observation is in contrast to the significantly increased risk of epilepsy after traumatic brain injury among people with a family history of epilepsy.[44]

Our data demonstrate an important limitation of the common clinical practice to advise survivors of neonatal seizures to undergo an EEG at around age three months to inform decisions regarding safety of weaning ASM after acute symptomatic neonatal seizures and assessment of the risk of future epilepsy.[45] We previously showed in this cohort that it is safe to discontinue ASM prior to discharge home from the neonatal seizure admission.[15] Given that result, we do not advocate waiting for the results of an EEG at age three months to inform decisions about weaning ASM. Furthermore, four infants developed epilepsy before the three-month EEG and among those who went on to develop epilepsy after age three months, the EEG results did not meaningfully inform the risk for incident epilepsy. Moreover, 85% of children with an abnormal EEG at age three months did not develop epilepsy, and the positive predictive value of any abnormality, or even of any epileptiform abnormality, was low (18%–33%). Together, these results suggest limited clinical value of a routine EEG at three months of age.

Our data also demonstrate a key limitation of the three-month follow-up interval: five infants had already developed hypsarrhythmia by the time of their three-month assessment, and two of these five infants already had diagnosed focal epilepsy. We previously showed that children with (1) severely abnormal EEG background or three or more days of EEG seizures, (2) basal ganglia or brainstem injury, and (3) abnormal tone on neurologic examination at discharge have more than 50% risk of infantile spasms.[16] We suggest that families of children with these epilepsy risk factors should be carefully advised to watch for focal seizures or infantile spasms, to

contact their pediatrician or neurologist immediately should they see possible signs of epilepsy, and to have neurology follow-up before three months. The role of an EEG at three months – or earlier – to screen for hypsarrhythmia and infantile spasms for children with all three risk factors is not known and merits further investigation. Additionally, pediatricians should query parents of infants who survived neonatal seizure about possible infantile spasms and other seizure types during health maintenance appointments in early infancy.

Our multicenter study included children recruited from centers that follow American Clinical Neurophysiology Society guidelines for neonatal EEG monitoring[19] and have comprehensive pediatric epilepsy programs. Yet, some limitations must be acknowledged. First, we chose two, clinically relevant time-points to examine EEG. Whether EEG background at hospital discharge, one month, or two months corrected age would have better predictive power to assess early post-neonatal epilepsy risk was not examined. Second, three-month EEG was performed for only 43% of the children in this cohort (81% of those eligible), which limits interpretation regarding its use. Third, to maximize clinical applicability of this study, we relied on standard qualitative EEG interpretation rather than advanced quantitative EEG analyses and included seizure counts and days of EEG-confirmed seizures rather than more detailed seizure burden measurements. Similarly, we report practical results that can inform clinical counseling (e.g., none of the neonates with normal interictal neonatal EEG backgrounds developed epilepsy; continued EEG-confirmed seizures for three or more days was a risk factor for epilepsy). Nonetheless, our results using EEG results from the neonatal admission and at three months are broadly applicable to clinical practice and generalizable to most centers. Whether serial EEGs for high-risk infants could guide early treatment, akin to the emerging strategy for infants with tuberous sclerosis complex,[46] could be an area for future study. Fourth, we were also unable to include centrally reviewed MRI data to determine whether the pattern, location, or severity of neonatal brain injury is associated with post-neonatal epilepsy. Finally, our follow-up so far has been limited to age 24-months. We expect that additional children in this cohort will develop epilepsy at later ages and school-age follow-up is underway in order to address this important knowledge gap.

5 | CONCLUSIONS

Post-neonatal epilepsy after acute symptomatic neonatal seizures is a potential outcome that is worrisome to families and clinicians. In this large, prospective, and multicenter cohort of infants who survived acute symptomatic neonatal seizures, the majority (87%) did not develop post-neonatal epilepsy before age 24 months, and among those that did, more than half were seizure-free for at least six months.

At the same time, among 13% of infants who did develop post-neonatal epilepsy, there was a range of severity and epilepsy types, and three times the risk of neurodevelopmental impairment. Particularly notable was the early onset of epilepsy, including infantile spasms, prior to age three months in a small number of infants. Infants were at higher risk for post-neonatal epilepsy if they had experienced three or more days of neonatal seizures or had documented abnormal neurologic exams at discharge, indicating that infants with these risk factors warrant close clinical follow up. A follow-up EEG at three months did not help predict which infants would subsequently develop epilepsy. Taken together, these findings have practical clinical implications: clinical follow-up and outpatient EEG after acute neonatal seizures can be tailored based on risk of post-neonatal epilepsy. Infants who had >3 days of neonatal seizures, a severely abnormal neonatal EEG background, or an abnormal neurological examination at the time of hospital discharge should be evaluated frequently during the first two years for incident epilepsy.

ACKNOWLEDGEMENTS

The study investigators would like to thank the *Neonatal Seizure Registry* Parent Advisory Panel members for their invaluable guidance, as well as the clinical research coordinators at each site for their tireless work enrolling and following study participants. This study was supported by the Patient Centered Outcomes Research Institute (1507-31187) and the Pediatric Epilepsy Research Foundation.

CONFLICT OF INTEREST

Renée A. Shellhaas, MD, MS serves as associate editor for *Neurology*, receives royalties from UpToDate for authorship of topics related to neonatal seizures, and is a consultant for The Epilepsy Study Consortium; Courtney J. Wusthoff MD, MS serves as associate editor for the Journal of Clinical Neurophysiology, has received payment as a consultant for Persyst, and has received payment for expert testimony; Nicholas S. Abend, MD MSCE has received consulting payment (Epilepsy Foundation), royalties (Demos), and payment for legal consulting; Nancy A. McNamara MD has received royalties for articles for Medlink for authorship of topics related to pediatric epilepsy; Cameron Thomas, MD, MS has received payment for legal consulting; Hannah C. Glass, MDCM, MAS has received payment for legal consulting. The remaining authors have no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Shellhaas RA, Wusthoff CJ, Numis AL, Chu CJ, Massey SL, Abend NS, et al. Early-life epilepsy after acute symptomatic neonatal seizures: A prospective multicenter study. *Epilepsia*. 2021;62:1871–1882. https://doi.org/10.1111/epi.16978