Sleep Disorders Five Years After Acute Provoked Neonatal Seizures

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Objective To evaluate whether abnormal sleep is associated with adverse outcomes for children who survived acute provoked neonatal seizures, and their parents.

Study design This 9-center study prospectively followed newborns with acute provoked seizures. When children reached age 5 years, parents completed the Children's Sleep Habits Questionnaire (CSHQ), the Pediatric Sleep Questionnaire–Sleep Related Breathing Disorders (PSQ-SRBD) subscale, the Vineland Adaptive Behavior Scales–3, and the Hospital Anxiety Depression Scale. Children were also assessed with the Wechsler Preschool and Primary Scale of Intelligence-IV (WPPSI-IV). Spearman correlations and multivariable analyses were used to evaluate risk factors for sleep problems.

Results The mean CSHQ score was 45 ± 7; 77 of 118 children (65%) had an abnormal score (above the healthy sleep threshold of 41). On the PSQ-SRBD, 32 of 119 children (27%) screened positive for sleep-disordered breathing (SDB). SDB symptoms were more common among children with cerebral palsy (42% with vs 22% without; P = .03) and epilepsy (54% with vs 24% without; P = .02). Children with lower scores on the Vineland-3 (*rho* = −0.25; P = .01) and WPPSI-IV (*rho* = −0.31; P = .004) at 5 years of age were more likely to have symptoms of SDB. Worse CSHQ and PSQ-SRBD scores were associated with higher parental anxiety (*rho* = 0.28 [P = .002] and *rho* = 0.34 [P = .0002], respectively) and depression scores on the Hospital Anxiety Depression Scale (*rho* = 0.16 [P = .08] and *rho* = 0.17 [P = .07], respectively).

Conclusions Two-thirds of early school-aged survivors of acute provoked neonatal seizures had parent-reported sleep abnormalities and one-quarter screened positive for SDB. Early screening and effective treatment for sleep disorders could be an innovative, practice-changing approach to improve outcomes after neonatal seizures. *(J Pediatr 2025;278:114412)*.

Children who survive acute provoked neonatal seizures are at risk for neurodevelopmental consequences that include epilepsy and cerebral palsy, as well as cognitive and behavioral challenges.[1] Novel interventions are needed to improve the developmental trajectories of these at-risk children.

Sleep problems and sleep disorders are common in childhood, yet clinicians and families may not realize that effective treatment is possible.[2-4] Among healthy children, symptoms of sleep-disordered breathing (SDB) have been shown to predict subsequent development of hyperactivity and other behavior problems as much as 7 years later, even after SDB symptoms have resolved.[5,6] Two randomized controlled trials have demonstrated a robust impact from treatment for childhood SDB, even when mild, on subsequent neurobehavioral outcomes and quality of life.[7,8] Indeed, the American Academy of Pediatrics recommends that pediatricians screen all children for obstructive sleep apnea

CP	Cerebral palsy
CSHQ	Children's Sleep Habits Questionnaire
HADS	Hospital Anxiety and Depression Scale
OSA	Obstructive sleep apnea
PSQ-SRBD	Pediatric Sleep Questionnaire–Sleep Related Breathing Disorders subscale
SDB	Sleep-disordered breathing
Vineland-3	Vineland Adaptive Behavior Scales
WPPSI-IV	Wechsler Preschool and Primary Scale of Intelligence-IV

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(OSA) syndrome, because it is a highly prevalent condition and the "identification and treatment can result in alleviation of current symptoms, improved quality of life, prevention of sequelae, education of parents, and decreased health care utilization."[9]

We hypothesize that the consequences of sleep disorders are heightened among children with acute provoked neonatal seizures because these children are also at an increased risk for neurobehavioral problems. We also hypothesize that children's sleep problems are associated with parent well-being. If so, early screening and effective treatment could provide a novel mechanism to improve outcomes for these children and families. As a first step toward evaluating sleep as a modifiable risk factor for adverse neurobehavioral outcomes, we screened a multicenter, longitudinal cohort of 5-year-old survivors of neonatal seizures for sleep problems.

Methods

Children born between July 2015 and March 2018 who were enrolled in a prospective multicenter cohort study (NCT02789176) of neonates with acute provoked seizures were invited to participate in a school-aged follow-up study (NCT04337697), which was conducted from 2020 to 2024. Participants were treated at 1 of the 9 centers of the *Neonatal Seizure Registry*.[10,11] Each center has a level IV neonatal intensive care unit and a level IV comprehensive pediatric epilepsy program that follows the 2011 American Clinical Neurophysiology Society guidelines for continuous electroencephalography monitoring.[12] The study questions, design, outcome measures, and analyses were informed by a parent advisory panel. The local institutional review board at each site approved the study, and parents provided written informed consent.

Eligible participants for this study had seizures due to an acute provoked etiology with onset at <44 weeks postmenstrual age, parents who were able to participate in English or Spanish (professional interpreters were available), and had completed the 24-month follow-up protocol. Excluded were infants who had a transient underlying cause of neonatal seizures (eg, mild hypoglycemia, hyponatremia, hypocalcemia with normal neuroimaging), neonatal-onset epilepsy syndromes, risk for adverse outcome independent of the neonatal seizures and underlying brain injury (eg, inborn errors of metabolism, fetal infection, brain malformation), or death during the neonatal seizure admission.

When the children reached 5 years of age, families completed validated instruments to measure sleep behaviors, risk for SDB, child development, and parent mental health. Parents either completed the surveys online or could opt to have a study coordinator read the questions verbatim and record their responses.

Sleep

The Children's Sleep Habits Questionnaire (CSHQ) is a widely used, broad sleep assessment that has been applied successfully to children with diverse neurodevelopmental diagnoses.[13] The abnormal threshold score for CSHQ is 41 (higher scores are more abnormal). In a cohort of healthy school-aged children, 23% scored >41.[14]

The Pediatric Sleep Questionnaire—Sleep-Related Breathing Disorders (PSQ-SRBD) Scale is the most commonly used symptom inventory for OSA, and reflects risk for polysomnogram-confirmed diagnoses.[15,16] Multiple studies have identified the PSQ-SRBD as an effective instrument for assessment of childhood risk for OSA.[17,18] The threshold score for PSQ-SRBD is 0.33 (higher scores are more abnormal). This screening test has approximately 85% sensitivity and specificity for polysomnogram-defined SDB in school-aged children.[15]

Development

The Vineland Adaptive Behavior Scales, 3rd edition (Vineland-3) is a validated tool to assess adaptive behavior for people at risk for intellectual, developmental, and other disabilities.[19] Standard scores have a mean of 100 ± 15. We considered scores of <70 to indicate functional impairment.

The Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV), measures cognitive development for children ages 2-6 years. Standard scores have a mean of 100 ± 15.

Parent Mental Health

The Hospital Anxiety and Depression Scale (HADS) is a well-validated measure of symptoms of anxiety and depression.[20] The HADS has been used extensively to characterize the impact of neonatal intensive care unit hospitalization or childhood illness on parent psychological well-being.[10,21-25] On the HADS Anxiety and Depression subscales, scores of 8-10 are considered borderline abnormal and scores >10 are abnormal.

Epilepsy and Cerebral Palsy

Epilepsy was defined as recurrent unprovoked seizures after the neonatal period as determined through parent report and corroborated by medical record review.[26] Similarly, cerebral palsy diagnosis and severity (Gross Motor Function Classification System), were reported by parents and confirmed in the medical records.[27]

Statistical Analysis

Univariable statistics were used to describe the overall sample, as well as the subgroups of children with epilepsy or cerebral palsy. Spearman correlations, 2-sample *t* tests, and 1-way analysis of variance were calculated to assess relationships between clinical variables and sleep questionnaire results. Linear regression was used to test the association

between child development (Vineland-3, WPSSI) and parent-reported child sleep problems (CSHQ, PSQ-SRBD).

Multivariable models were developed to test the hypothesis that children with more severe neurodevelopmental disabilities have more sleep problems. We adjusted for preterm birth (<37 weeks' gestation), Gross Motor Function Classification System at 24 months, epilepsy, Vineland-3, and WPPSI scores. Secondary analyses examined children with vs without cerebral palsy because of the hypothesis that the abnormal tone associated with cerebral palsy may predispose children to OSA. These models were built using backwards stepwise selection, removing predictors with highest *P* value until only predictors with a *P* value of <.05 were retained. To assess for independent associations between parents' mental health and children's sleep problems, multivariable models for parent mental health (HADS scores) included the child's diagnosis of epilepsy, cerebral palsy, and impaired functional development (Vineland-3 < 70).

All analyses were completed using SAS 9.4 (Carey, NC) with a two-tailed *P* value of .05 considered statistically significant.

Results

A total of 188 children were enrolled in the school-aged follow-up study, and the parents of 119 of the 158 children (75%) with assessments at age 5 years completed sleep surveys. These 119 children form the cohort for the current study. Children included in the present analysis had similar clinical profiles to the full cohort in which they were originally enrolled (**Table I**, online; available at www.jpeds.com). Approximately one-half were boys (64/119 [54%]), most were born at full term (103/119 [87%]), and nearly one-half had hypoxic-ischemic encephalopathy as the cause of their neonatal seizures (56/119 [47%]) (**Table II**). The mean CSHQ score was 45 ± 7, and 77 of 118 (65%) scored above the healthy threshold of 41 (1 parent did not complete the CSHQ). On the PSQ-SRBD, 32 of 119 children (27%) screened positive for SDB. CSHQ and PSQ-SRBD were positively correlated with each other (*rho* = 0.47; *P* < .0001) and did not differ significantly by gestational age or neonatal seizure etiology (**Table II**).

Univariable Analyses

CSHQ scores were not significantly different among children with or without cerebral palsy or epilepsy (**Figure 1**). Abnormal PSQ-SRBD scores were more common among children with cerebral palsy (13/31 [42%] with cerebral palsy vs 19/87 [22%] without; *P* = .03) and epilepsy (7/13 [54%] with epilepsy vs 25/103 24% without; *P* = .02) (**Figure 2**).

Children with lower scores on the Vineland-3 (*rho* = −0.25; *P* = .01) and WPPSI-IV (*rho* = −0.30; *P* = .004) at 5 years of age were more likely to have higher (more abnormal) PSQ-SRBD scores.

Worse (higher) CSHQ and PSQ-SRBD scores were both associated with parental symptoms of anxiety (*rho* = 0.28 [*P* = .002] and *rho* = 0.34 [*P* = .0002]) and depression on the HADS (*rho* = 0.16 [*P* = .08] and *rho* = 0.17 [*P* = .07]).

Multivariable Models

In the multivariable model, none of the neonatal or follow-up clinical variables were associated with the CSHQ. However, children who were born preterm had significantly lower (better) PSQ-SRBD scores (model coefficient estimate −0.11 [SE, 0.05] *P* = .02) and those who had Vineland <70 had significantly higher (worse) PSQ-SRBD scores (estimate, 0.19; SE, 0.05; *P* = .0003).

In multivariable models of *children with cerebral palsy*, prematurity was associated with lower (better) CSHQ (estimate, −8.7; SE, 3.1; *P* = .009) and PSQ-SRBD scores (estimate, −0.2; SE, 0.08; *P* = .05). Epilepsy was associated with higher (worse) CSHQ scores (estimate, 6.6; SE, 2.6; *P* = .02) and having a Vineland score of <70 was associated with higher (worse) PSQ-SRBD scores (estimate, 0.14; SE, 0.07; *P* = .04). Among *children without cerebral palsy*, neither the multivariable model for CSHQ nor the model for PSQ-SRBD had any significant clinical predictors.

In multivariable analyses (**Table III**, online; available at www.jpeds.com), parental HADS-anxiety scores were associated with CSHQ and cerebral palsy, but not epilepsy or Vineland-3 of <70. Parental HADS-anxiety scores were also associated with higher PSQ-SRBD scores, but neither cerebral palsy nor epilepsy or Vineland-3 of <70 contributed to the model. Parental HADS-depression scores were associated with CSHQ, but cerebral palsy, epilepsy, and Vineland of <70 did not contribute to the model. We found no association between HADS-depression scores and PSQ-SRBD scores.

Discussion

In this prospective, multicenter study, approximately two-thirds of 5-year-old survivors of acute provoked neonatal seizures had parent-reported sleep abnormalities and one-quarter screened positive for symptoms of SDB. These results suggest that sleep disorders are far more common among children with a history of neonatal seizures than the healthy pediatric population. Although epilepsy and cerebral palsy were associated with symptoms of SDB, only 14% of participating children carried either of these diagnoses; thus, many children without epilepsy or cerebral palsy also had parent-reported sleep problems.

Sleep disorders in infancy and childhood can contribute to adverse neurobehavioral outcomes and parental anxiety and depression.[28,29] Because sleep disorders are readily treatable, they may be modifiable risk factors for adverse child and parent outcomes, such as those seen in survivors of acute provoked neonatal seizures. Thus, early screening and effective treatment for sleep disorders may be a novel approach to improve childhood outcomes after neonatal seizures. The treatment of sleep disorders in children can range from behavioral interventions to manage chronic insomnia

Table II. Associations between clinical and demographic characteristics and sleep scale scores for 119 five-year-old survivors of acute provoked neonatal seizures

Characteristics	N = 119	Association with CSHQ score	Association with PSQ-SRBD score
Neonatal characteristics			
Gestational age, weeks	38.8 ± 2.9	*rho** = −0.09	*rho* = −0.002
		P = .34	*P* = .99
Preterm birth	17 (14)	*P* = .32	*P* = .20
Male sex	64 (54)	*P* = .49	*P* = .45
Neonatal seizure etiology		*P* = .80	*P* = .58
Hypoxic-ischemic Encephalopathy	56 (47)		
Ischemic stroke	34 (29)		
Hemorrhages	17 (14)		
Other	12 (10)		
Outcome at age 2 years			
Cerebral palsy	31 (26)	*P* = .52	*P* = .003
Epilepsy	13 (11)	*P* = .30	*P* = .01
Outcome at age 5 years			
Vineland-3, score	90.4 ± 18.6	*rho* = −0.05	*rho* = −0.25
		P = .59	*P* = .01
WPPSI-IV score	92.8 ± 23.7	*rho* = −0.12	*rho* = −0.30
		P = .28	*P* = .004

Values are mean ± SD or number (%).
*rho derived from Spearman correlation.

disorder to supplemental oxygen, adenotonsillectomy, or positive airway pressure for SDB.

The American Academy of Pediatrics' technical report for diagnosis and management of OSA highlights that early diagnosis and treatment of SDB may improve long-term cognitive, social, and academic outcomes.[30] Emerging evidence suggests, for example, that early treatment of SDB in infants with trisomy 21 may result in improved cognitive development by 3 years of age.[31] Conversely, there are risks of not treating children with SDB, including long-term consequences on cognitive development, executive function, and social interactions.[30] Given the increased risk for abnormal cognitive and neurobehavioral outcomes among children with neonatal seizures and our finding that most of these children may have a sleep disorder by 5 years of age, our study suggests an urgent need to (1) begin routinely screening such children for sleep disorders, and (2) conduct additional research to assess whether early diagnosis and treatment of sleep disorders can alter the trajectory of neurobehavioral outcomes in this patient population.

How early to begin screening for sleep problems remains an open question. Assessment at school age may miss early SDB that, although resolved, may have contributed to impaired brain development. A cohort study of children aged 2-13 years found that SDB symptoms at baseline, compared with 4 years later, were a stronger predictor of newly emerged hyperactive behavior at study end.[5] Others

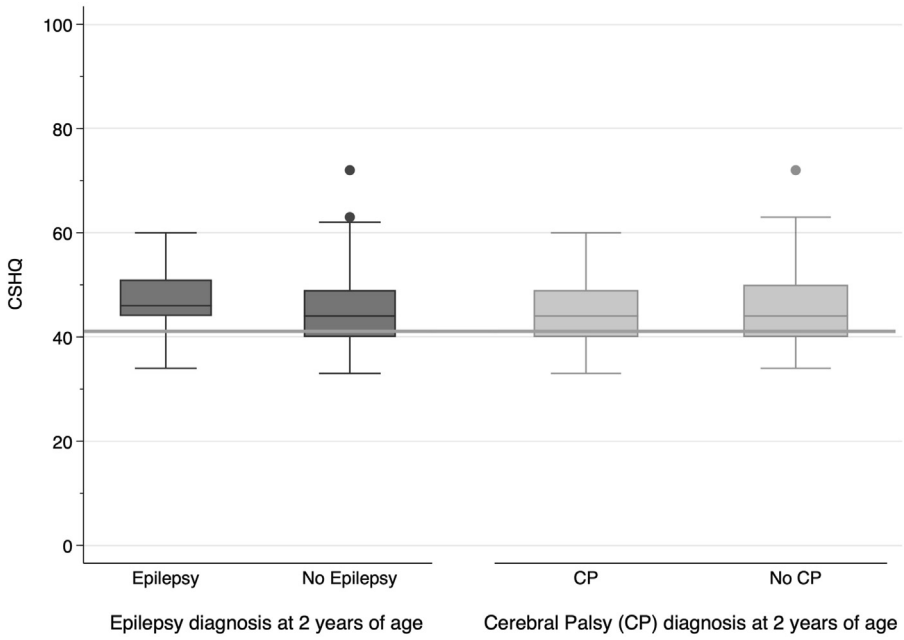

Figure 1. Among 118 survivors of neonatal seizures, 77 (65%) scored above the healthy sleep threshold of 41. Abnormal CSHQ scores were not different for children with epilepsy (11/13 with epilepsy vs 66/105 without; *P* = .3) or cerebral palsy (19/31 with cerebral palsy vs 58/86 without; *P* = .52). Boxplot legend: middle line = median, box ends = 25th and 75th percentiles, whiskers = (25th or 75th percentile)*1.5 × IQR. Dots = outliers; horizontal line = abnormal CSHQ threshold score (41).

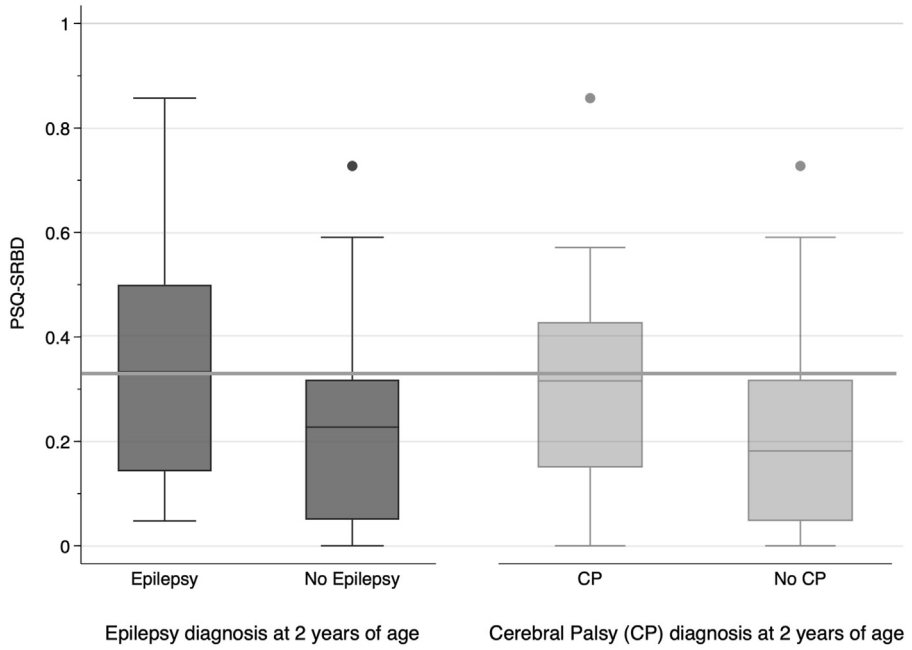

Figure 2. Among 119 survivors of neonatal seizures, abnormal PSQ-SRBD scores were associated with epilepsy (7/13 [54%] with epilepsy vs 25/105 [24%] without; $P = .02$) and with cerebral palsy 13/31 [42%] with cerebral palsy vs 19/84 [22%] without; $P = .03$). Boxplot legend: middle line = median, box ends = 25th and 75th percentiles, whiskers = (25th or 75th percentile)*1.5 × IQR. Dots = outliers; horizontal line = abnormal PSQ-SRBD threshold score (0.33).

reported that SDB symptoms as early as ages 6 or 18 months, even when the symptoms resolved by the time of assessments at older ages, were associated with a 40%-50% increased odds of behavior problems, including hyperactivity, at age 7 years.[6] These results suggest that harm to the developing brain caused by SDB may occur within the first 2 years, with substantive impact on behavior and development, only to emerge years later when these phenotypes typically become readily distinguishable from age-appropriate behavior.[6] These findings, combined with evidence that early treatment improves outcomes for infants with trisomy 21, indicate that future studies should evaluate screening paradigms to identify and treat sleep problems earlier.[31]

Multiple factors likely contribute to an increased risk for sleep disorders among survivors of neonatal seizures. Abnormal tone, as manifest by cerebral palsy, may increase the risk for OSA.[32] Brain injury may also alter central regulation of respiratory drive and result in central sleep apnea or hypoventilation. Meanwhile, many sleep issues in the earliest years are behavioral. For example, chronic insomnia disorder (formerly subcategorized as sleep-onset association disorder and limit-setting disorder) often arises from remediable interactions between well-meaning parents and their children.[33,34] Vulnerable child syndrome, commonly experienced after critical neonatal illness, may exacerbate these behavioral sleep challenges. Appropriate screening, referral to sleep medicine clinicians, and definitive testing (eg, with polysomnography) may result in effective treatment and mitigation of negative neurodevelopmental consequences.[35]

Our study's strengths include the longitudinal follow-up of children recruited as neonates at 9 US children's hospital, with careful characterization of the neonatal seizures, neurodevelopment, parent well-being, and symptoms of sleep disorders assessed with validated instruments. School-aged follow-up began in 2020 (during the COVID-19 pandemic). Thus, owing to stay-at-home orders, limitations on clinical research protocols at study centers, and other pandemic-related challenges, not all families in the original cohort were able or willing to return for testing. Nevertheless, the clinical profiles of children who participated in the present analysis were very similar to those of the originally enrolled cohort. It is possible that the pandemic had an impact on the children's sleep; an increase in parent-reported sleep problems was reported in the context of the pandemic.[36,37] We did not enroll a healthy control group, because our study focused on discerning the detailed outcomes of children who experienced neonatal seizures.

Additional limitations include the small sample size in key subgroups, particularly children with postneonatal epilepsy. Subgroup analyses are, therefore, subject to a lack of precision. We did not confirm diagnoses of sleep disorders through chart review, formal sleep medicine evaluations, or polysomnography; rather, we tested the hypothesis that widely used screening surveys would identify many children

who are at high risk for sleep disorders. Screening instruments do not obviate the need for diagnostic testing (eg, polysomnography). Future work should include systematic screening for other SDB risk factors (eg, obesity) and formal evaluations for behavioral sleep disorders and diagnostic testing for SDB and other sleep-related diagnoses. The parents of children with abnormal CSHQ and PSQ-SRBD scores often reported symptoms of anxiety and depressions on the HADS. It is possible that more anxious or depressed parents will report problems on a validated survey more readily. It is also possible that children's abnormal sleep has direct impact on their parents' mental health. The interactions between sleep, neurodevelopment and behavior, and parental mental health are complex. Our results demonstrate associations among these domains. Further work is needed to identify the causal pathways.

In conclusion, this study's results suggest that most 5-year-old children who had acute provoked neonatal seizures are at high risk for sleep disorders. Assessment and treatment for sleep disorders, starting at the earliest ages, for survivors of neonatal seizures could be highly impactful during childhood and, by extension, throughout the lifespan. Systematic screening, and referral of children with abnormal CSHQ and PSQ-SRDB scores for formal sleep evaluations and subsequent treatment, could be an innovative and practice-changing approach to optimizing long-term outcomes. ■

CRediT authorship contribution statement

Renée A. Shellhaas: Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Linda S. Franck:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Betsy Pilon:** Writing – review & editing, Methodology, Conceptualization. **Courtney J. Wusthoff:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Shavonne L. Massey:** Writing – review & editing, Investigation, Data curation. **Catherine J. Chu:** Writing – review & editing, Investigation, Conceptualization. **Janet S. Soul:** Writing – review & editing, Investigation, Data curation. **Monica E. Lemmon:** Writing – review & editing, Methodology, Investigation, Data curation. **Adam L. Numis:** Writing – review & editing, Investigation, Conceptualization. **Julie S. Sturza:** Writing – review & editing, Formal analysis, Data curation. **Cameron Thomas:** Writing – review & editing, Investigation, Data curation. **Giulia M. Benedetti:** Writing – review & editing, Investigation, Data curation. **Stephanie M.D. Rau:** Writing – review & editing, Project administration, Investigation, Data curation. **Tayyba Anwar:** Writing – review & editing, Investigation, Data curation. **Madison M. Berl:** Writing – review & editing, Investigation, Data curation. **Charles E. McCulloch:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Hannah C. Glass:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

Renée Shellhaas reports financial support for this study was provided by National Institute of Neurological Disorders and Stroke and the Patient-Centered Outcomes Research Institute. Renée Shellhaas reports a relationship with Pediatric Epilepsy Research Foundation that includes: board membership and employment. Renée Shellhaas reports a relationship with The Epilepsy Study Consortium that includes: consulting or advisory. Renée Shellhaas reports a relationship with UptoDate Inc that includes: royalties for authorship of topics related to neonatal seizures. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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