Pediatric Neurology 163 (2025) 76–81

Contents lists available at ScienceDirect

Pediatric Neurology

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

Research Paper

# Neonatal Seizures and Associated Neurobehavioral Profiles in Preschool Age Children

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## ARTICLE INFO

*Article history:*
Received 6 May 2024
Accepted 22 November 2024
Available online 28 November 2024

*Keywords:*
Neonatal seizure
Epilepsy
Neurobehavioral profiles
Adaptive functioning
Social skills
Behavior
Development

## ABSTRACT

*Background:* Neonatal seizures are common with acute brain injury. Up to 25% of survivors develop postneonatal epilepsy. We hypothesized postneonatal epilepsy diagnosed by age 24 months would increase risk for early markers of neurobehavioral disorders than acute provoked neonatal seizures alone.
*Methods:* Neonates with acute provoked seizures born from July 2015 to March 2018 were enrolled at nine *Neonatal Seizure Registry* sites. Composite scores from parent-completed standardized ratings assessed Adaptive, Social, Externalizing, Internalizing, Self-Regulation, and Sensory Seeking domains. Linear regression demonstrated relationships between composite scores for children who developed postneonatal epilepsy compared with those who did not. Results were adjusted for seizure etiology, sex, gestational age, and cerebral palsy (CP) severity.
*Results:* A total of 151 children ($n = 20$, 13% with postneonatal epilepsy), 4.1 years median age, participated. Children with epilepsy had impaired adaptive (Cohen $d = 1.62$, $P < 0.0001$), social (Cohen $d = 0.86$, $P = 0.004$), and executive functioning (Cohen $d = 0.56$, $P = 0.06$) compared with children without

Original research statement: The material presented here is original research, has not been previously published, and has not been submitted for publication elsewhere while under consideration. An abbreviated version of some of the content of the current manuscript was also presented to the Pediatric Academic Society annual conference in April 2023.

Consent statement: Participant consent required, with the study approved by the University of California San Francisco IRB of Record (HUM00177193).

Funding: This study was supported by the Pediatric Epilepsy Research Foundation; Patient-Centered Outcomes Research Institute, Grant/Award Number: 1507-31187. NIH, grant/award number R01NS111166.

Disclosures: The content is solely the responsibility of the authors and does not necessarily represent the official views of the Pediatric Epilepsy Research Foundation.

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https://doi.org/10.1016/j.pediatrneurol.2024.11.008

epilepsy. Mean scores for children without epilepsy were within average range. Risk for impairment among children with epilepsy persisted after adjusting for neonatal seizure etiology, sex, and gestational age, but not when adjusting for CP severity.

*Conclusions:* There was higher incidence of adverse neurobehavioral outcomes among preschool children diagnosed with postneonatal epilepsy compared with those without epilepsy. CP severity was associated with greater impairment; results also suggest that epilepsy is an independent predictor of adaptive functioning. Children with postneonatal epilepsy should be screened for neurobehavioral problems to facilitate early identification and developmental support.



## Introduction

Seizure risk is greatest in the first week after birth, and risk remains high throughout the neonatal time period.[1] Neonatal seizures are defined as occurring within the first four weeks after delivery for term-born children and up to 44 weeks postmenstrual age for preterm children[2] and have an incidence of between 1.6 and 5 per 1000 live births.[3] Neonatal seizures often reflect underlying brain pathology associated with, or caused by, other complex perinatal and neonatal conditions.[4] The most common cause of neonatal seizures is hypoxic-ischemic encephalopathy, followed by intracranial hemorrhage and ischemic stroke.[5] Although acute provoked neonatal seizures resolve, some survivors develop subsequent recurrent, unprovoked seizures (postneonatal epilepsy).

Specific postneonatal epilepsy syndromes present with certain behavioral profiles[6–10]; however, few studies evaluate the relationship between neonatal seizures and childhood behavior. Existing literature characterizing outcomes after neonatal seizures have prioritized outcomes related to cognitive or sensorimotor functioning.[11] Animal models demonstrate that recurrent seizures in the neonatal time period result in both cognitive and behavioral impairment.[12,13] Studies of newborn infants indicate an increased risk for autism spectrum disorder among infants who experienced birth asphyxia, a common underlying etiology for neonatal seizures.[14] One longitudinal study[15] indicated that children born in 1970 to 1972 with a history of seizures restricted to the neonatal time period had increased incidence of behavioral disorders (including externalizing and internalizing behaviors) at age six years, as well as social challenges into early adulthood. However, the participants' seizures were diagnosed clinically (without electroencephalographic confirmation). Direct study of associations between neonatal seizures and child behavior has been limited.

Neonatal seizures, regardless of the underlying etiology, may serve as a unifying early risk factor for the development of maladaptive behavioral patterns. Although specific patterns of behavior may depend on postneonatal epilepsy syndrome or particular patterns of brain injury, general themes include problems with attention, social competence, and both internalizing (i.e., withdrawn, anxious) and externalizing (i.e., disruptive) behaviors in school-aged children.[16–18] In children with epilepsy, earlier age at onset of seizures is associated with greater parent-rated social challenges.[19] The overarching aim of the current study was to evaluate the relationship between postneonatal epilepsy and adverse neurodevelopmental outcomes at preschool age among children with a history of provoked neonatal seizures. We hypothesized that development of postneonatal epilepsy is associated with worse behavioral outcomes.

## Methods

### *Participants*

Neonates (N = 151) with acute provoked seizures born from July 2015 to March 2018 were re-enrolled at nine *Neonatal Seizure Registry* sites at preschool age (three to five years), median age of 4.1 (interquartile range 3.5, 5.0) years. Testing was completed at the time of enrollment (e.g., age at testing was the same as age at enrollment).

Inclusion criteria for enrollment were <44 weeks postmenstrual age at seizure onset, seizures due to an acute provoked cause, parents who were English or Spanish literate (with assistance of interpreter), and completion of a 24-month follow-up protocol (including Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS) and assessment of postneonatal epilepsy).[20] Children were excluded from the study if they did not survive the neonatal admission, if they had a transient cause of seizures (e.g., mild hypoglycemia, hyponatremia, hypocalcemia with normal neuroimaging), if they experienced neonatal-onset epilepsy syndromes, or if they had risk for adverse outcome of independent seizures and underlying brain injury (including but not limited to inborn errors of metabolism, fetal infection, brain malformation).

Approximately 13% (n = 20) of participating children were diagnosed with postneonatal epilepsy by age 24 months.[20] Postneonatal epilepsy was defined using the 2014 International League Against Epilepsy criteria: (1) at least two unprovoked seizures occurring >24 hours apart; (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 postmenstrual age.[20]

### *Study measures and variables*

Composite and index scores from standardized, norm-referenced, parent rating forms were used to assess behavioral outcomes in the following domains.

#### *Adaptive Functioning*

Adaptive skills were assessed using the Vineland Adaptive Behavior Scale, 3rd edition, (VABS-3)[21] Parent/Caregiver report form. VABS-3 consists of 502 Likert scale questions and produces the following domain composite scores: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior. The domain composite scores for Communication, Daily Living, and Socialization combine to form the Adaptive Behavior Composite score (mean = 100; S.D. = 15). This composite score was used for analyses.

#### *Emotional functioning*

Emotional functioning was assessed using the Behavior Assessment System for Children, 3rd edition, preschool (BASC-3)[22] parent form. BASC-3 consists of 139 Likert scale questions that produce the following domain composite scores: Internalizing Problems, Externalizing Problems, Adaptive Skills, and Behavioral Symptoms. Both the Internalizing Problems (i.e., depression, anxiety, and somatization) and Externalizing Problems (i.e.,

hyperactivity and aggression) composite scores (mean = 50; S.D. = 10) were used for analyses.

*Executive functioning*

Emerging executive functioning was assessed using the Behavior Rating Inventory of Executive Function—Preschool Version (BRIEF-P)[23] parent report form. This form consists of 63 Likert scale questions that produce the following domain scores: Inhibit, Shift, Emotional Control, Working Memory, and Plan/Organize. The Global Executive Composite (mean = 50; S.D. = 10) represents a composite of the individual domain scores, which was used in analyses.

*Social functioning*

Social functioning was assessed using the Social Responsiveness Scale, 2nd edition, (SRS-2)[24] parent report form. This form consists of 65 Likert scale questions that produce the following domain scores: Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted and Repetitive Behaviors. A Total Composite Score (mean = 50; S.D. = 10), formed from the five domain scores, was used in analyses.

*Sensory processing*

Sensory processing was assessed using the Sensory Profile, 2nd edition, (SP-2)[25] parent report form. This form consists of 86 Likert scale questions that produce the following scores: Seeking/Seeker, Avoiding/Avoider, Sensitivity/Sensor, and Registration/Bystander.

Consistent with published protocols in the scoring manuals, outcome scores were considered within the clinically "at-risk" range if they fell within 1 to 1.5 S.D. above the age-adjusted normative mean score on the BRIEF-P and SRS-2, 1 to 2 S.D. above the age-adjusted normative mean score on the BASC-3, and 1 to 2 S.D. below the age-adjusted normative mean score on the VABS-3. Outcome scores were considered in the "clinically significant" range if they were above 1.5 S.D. from the age-adjusted normative mean on the BRIEF-P and SRS-2, 2 S.D. above the age-adjusted normative mean score on the BASC-3, and 2 S.D. below the age-adjusted normative mean score on the VABS-3. For the SP-2 clinically "at-risk" scores are those that fall 1 point to either side of the mean (i.e., 2 or 4) and "clinically significant" scores are those that fall 2 points to either side of the mean (i.e., 1 or 5).

*Procedure*

Parents completed five standardized rating forms online or in person: VABS-3, BASC-3, BRIEF-P, SRS-2, and the SP-2. If the parent was unable to complete the forms independently, a research assistant read the forms aloud to the parent and recorded their responses. Research assistants were instructed not to interpret the questions or answers or to assist parents in their replies.

*Statistical analyses*

Univariate statistics were used to describe the overall sample, as well as the subgroups of participants who were or were not diagnosed with epilepsy by age 24 months. Chi-square tests and Wilcoxon two-sample test were used to check for differences in demographics and clinical characteristics between the two groups.

Linear regression was used to test the association between postneonatal epilepsy diagnosis and composite behavior scores. Models were adjusted for seizure etiology, sex, preterm birth, and child's age at testing (given that a range of ages were tested). To examine the contribution of cerebral palsy (CP) to the outcomes, the models were adjusted again to include all of the above, plus CP severity (i.e., Gross Motor Function Classification System [GMFCS]). We also examined seizure frequency at enrollment and completed Spearman correlations to evaluate for any association between frequency of seizures and neurobehavioral outcomes.

Percentage of missing data for child demographic and clinical course variables was miniscule (0 to 1%). For the neurobehavioral outcomes, values were missing from 11% to 19% of the sample. Multivariate normal imputation with 10 imputations was used to address missing data; results are shown for complete case analysis. Imputation results were qualitatively similar.

All analyses were completed using SAS 9.4 with a two-tailed $P$ value of 0.05 considered statistically significant.

## Results

A total of 151 children were enrolled. The children with postneonatal epilepsy (n = 20) did not differ from those without epilepsy (n = 131) in terms of child sex, preterm birth status, age at re-enrollment, or neonatal seizure etiology (Table 1). As previously described,[20] there was a higher prevalence of CP among children with epilepsy compared with participants without epilepsy (80% vs 20%, $P < 0.0001$).

The mean behavioral scores for children without epilepsy were, on average, within normal limits across all domains (Table 2, Fig). In contrast, among children with epilepsy, mean adaptive functioning fell within the impaired range (66.6, S.D. 22.3) and was significantly lower than that of children without epilepsy (unadjusted mean difference 26.3, 95% confidence interval [CI] 17.8 to 34.8, $P < 0.0001$). Among children with epilepsy, the mean for Adaptive Skills fell more than 2 S.D. below the age-adjusted normative mean, which is in the significantly impaired range.

Across other neurobehavioral measures, although social functioning was in the average range for both groups, children with epilepsy had significantly worse SRS-2 scores than those without epilepsy (unadjusted mean difference 9.1, 95% CI 3.0 to 15.3), $P = 0.004$) and were more likely to have scores in the "at-risk" or "clinically significant" range (54% of children with epilepsy compared with 21% of children without epilepsy, $P = 0.01$). Similarly, there was a trend toward worse BRIEF-P Global Executive Composite scores (unadjusted mean difference −7.1, 95% CI −14.4 to 0.3, $P = 0.06$) and a greater percentage of children with epilepsy had "at-risk" or "clinically significant" scores (54% with epilepsy vs 31% without epilepsy, $P = 0.10$) suggesting potentially worse executive function (i.e., self-regulation). Regarding sensory processing, children with epilepsy were found to have greater variability in certain types of processing with a significant effect of Registration/Bystander processing (unadjusted mean difference 0.5, 95% CI 0.2 to 0.9, $P = 0.004$) and a trend toward an effect of Avoiding/Avoider processing (unadjusted mean difference −0.4, 95% CI −0.7 to 0.0, $P = 0.06$). This finding suggests that children with epilepsy are more likely to process certain sensory information differently (i.e., at the extremes) compared with those without epilepsy. There were no significant differences between children with or without epilepsy for emotional functioning.

Differences between children with and without epilepsy were similar after adjusting for seizure etiology, sex, preterm birth, and age at testing. However, after adjusting the model to include CP severity, as indicated by GMFCS scores, we found that for children with CP, there was a significant difference in GMFCS in the epilepsy versus no epilepsy groups ($P = 0.01$). Those with epilepsy had higher GMFCS scores, median (interquartile range) 3.5 (1.5, 4) vs 1.[1,2] Higher GMFCS was associated with poorer adaptive functioning, but the results also suggest that epilepsy is an independent predictor of adaptive functioning ($P = 0.09$) beyond CP severity.

As a marker of epilepsy severity, we evaluated for associations between unprovoked seizure frequency at the time of enrollment

**TABLE 1.**
Clinical Characteristics of 151 Children With Acute Provoked Neonatal Seizures With and Without Postneonatal Epilepsy Followed to Preschool Age

| Clinical Characteristic | Total N = 151 | Postneonatal Epilepsy N = 20 | No Epilepsy N = 131 | *P* Value for Test of Difference |
|---|---|---|---|---|
| Male, n (%) | 79 (52%) | 12 (60%) | 67 (52%) | 0.46 |
| Preterm, n (%) | 24 (16%) | 5 (25%) | 19 (14%) | 0.23 |
| Seizure etiology, n (%) | | | | 0.70 |
| Hypoxic-ischemic encephalopathy | 72 (48%) | 8 (40%) | 64 (49%) | |
| Ischemic stroke | 37 (24%) | 5 (25%) | 32 (24%) | |
| Intracranial hemorrhage | 23 (15%) | 3 (15%) | 20 (15%) | |
| Other | 19 (13%) | 4 (20%) | 15 (11%) | |
| Age at enrollment, median (IQR) | 4.1 (3.5, 5.0) | 3.8 (3.4, 5.4) | 4.2 (3.5, 5.0) | 0.80 |
| Cerebral palsy diagnosis at age 24 months, n (%) | 42 (28%) | 16 (80%) | 26 (20%) | <0.0001 |

Abbreviation:
IQR = Interquartile range
"Other" category for seizure etiology includes infection (n = 14), hypoglycemia (n = 1), kernicterus (n = 1), and unknown cause of seizures (n = 4).

and neurobehavioral outcomes. Seizure frequency was not associated with the measured outcomes, with the exception of Sensory Profile Sensitivity/Sensor (higher seizure burden was associated with higher [worse] scores, $P = 0.4$).

## Discussion

In this prospective, multicenter study, preschool children who developed postneonatal epilepsy after surviving acute provoked neonatal seizures were at risk for adverse outcomes in adaptive, social, and executive functioning. These findings support the hypothesis that a diagnosis of postneonatal epilepsy among neonatal seizure survivors is associated with a greater risk for adverse outcomes than a history of acute provoked neonatal seizures alone. Preschool children with postneonatal epilepsy showed parent-rated difficulties across several domains, particularly in adaptive and social functioning, as well as in emerging executive functioning/self-regulation and aspects of sensory processing. Functioning across other domains was within age-normed expectations and not significantly different between children with or without epilepsy for these preschool age children.

Adaptive functioning was, on average, within the impaired range in the postneonatal epilepsy group, whereas other measured behavioral domains fell on average within the typically developing range. This finding was largely driven by the severity of CP, with a higher proportion of children with postnatal epilepsy also having

**TABLE 2.**
Neurobehavioral Outcomes of 151 Children With Acute Provoked Neonatal Seizures With and Without Postneonatal Epilepsy Followed at Preschool Age

| Domain | Epilepsy Diagnosed by 24 Months N = 20 | No Epilepsy Diagnosed by 24 Months N = 131 | Mean (95% CI) Difference*P* Value | Adjusted Mean (95% CI) Difference Adjusted *P* Value* | Adjusted Mean (95% CI) Difference Adjusted *P* Value† |
|---|---|---|---|---|---|
| Adaptive Functioning | | | | | |
| VBAS-3 ABC, mean (S.D.) | 66.6 (22.3) | 92.9 (15.2) | −26.3 (−34.8 to −17.8) <0.0001 | −22.8 (−31.2 to −14.4) <0.0001 | −7.5 (−16.2 to 1.2) 0.09 |
| Emotional Functioning | | | | | |
| BASC-3 Externalizing, mean (S.D.) | 47.0 (10.2) | 51.4 (8.3) | −4.4 (−9.0 to 0.2) 0.06 | −4.6 (−9.3 to 0.1) 0.06 | 1.1 (−4.7 to 6.9) 0.71 |
| BASC-3 Internalizing, mean (S.D.) | 49.1 (10.2) | 50.7 (7.9) | −1.5 (−6.0 to 2.9) 0.50 | −1.6 (−6.2 to 3.0) 0.49 | 3.0 (−2.7 to 8.7) 0.30 |
| Executive Functioning | | | | | |
| BRIEF-P GEC, mean (S.D.) | 61.1 (13.5) | 54.1 (12.6) | 7.1 (−0.3 to 14.4) 0.06 | 6.8 (−0.8 to 14.5) 0.08 | 0.6 (−8.5 to 9.7) 0.90 |
| Social Functioning | | | | | |
| SRS-2 Total Composite Score, mean (S.D.) | 59.0 (10.5) | 49.9 (10.6) | 9.1 (3.0 to 15.3) 0.004 | 8.9 (2.6 to 15.2) 0.006 | 1.0 (−6.5 to 8.6) 0.79 |
| Sensory Processing | | | | | |
| SP-2 Seeking/Seeker, mean (S.D.) | 3.1 (0.8) | 3.0 (0.6) | 0.1 (−0.3 to 0.4) 0.87 | 0.1 (−0.3 to 0.4) 0.76 | 0.2 (−0.3 to 0.6) 0.47 |
| SP-2 Avoiding/Avoider, mean (S.D.) | 2.7 (0.7) | 3.1 (0.7) | −0.4 (−0.7 to 0.0) 0.06 | −0.3 (−0.7 to 0.1) 0.12 | −01 (−0.6 to.3) 0.35 |
| SP-2 Sensitivity/Sensor, mean (S.D.) | 3.3 (0.9) | 3.1 (0.6) | 0.2 (−0.1 to 0.5) 0.23 | 0.2 (−0.1 to 0.6) 0.20 | 0.1 (−0.3 to 0.5) 0.68 |
| SP-2 Registration/ Bystander, mean (S.D.) | 3.5 (0.6) | 3.0 (0.6) | 0.5 (0.2 to 0.9) 0.004 | 0.5 (0.2 to 0.9) 0.006 | 0.4 (0.0 to 0.9) 0.04 |

Abbreviations:
ABC = Adaptive Behavior Composite
BASC-3 = Behavior Assessment System for Children, 3rd edition (mean = 50; S.D. = 10)
BRIEF-P = Behavior Rating Inventory of Executive Function–Preschool Version (mean = 50; S.D. = 10)
CI = Confidence interval
GEC = Global Executive Composite
GMFCS = Gross Motor Function Classification System
SP-2 = Sensory Profile (mean = 3; S.D. 0.6)
SRS-2 = Social Responsiveness Scale, 2nd edition (mean = 50; S.D. = 10)
VABS-3 = Vineland Adaptive Behavior Scale, 3rd edition (mean = 100; S.D. = 15).
* Adjusted for preterm birth, seizure etiology, sex, and age.
† Adjusted for preterm birth, seizure etiology, sex, age, and GMFCS score.

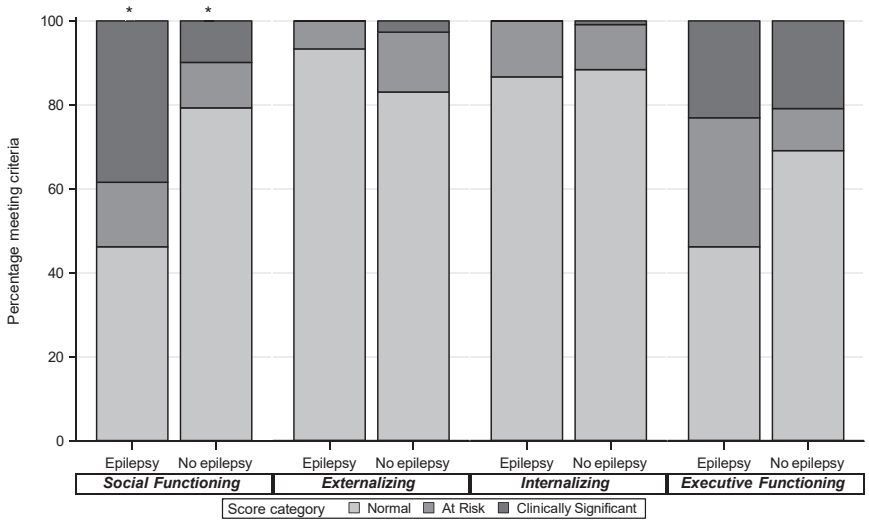


**FIGURE.** "At-risk" and "clinically significant" neurobehavioral outcomes by domain among 151 children with a history of acute provoked neonatal seizures; *$P < 0.01$.

more severe motor impairment from CP (i.e., higher GMFCS). This is consistent with prior research that has also found that higher GMFCS is associated with poorer adaptive functioning,[26] and with related impairments in motor functioning, social functioning, and communication impacting practical daily living skills. Age at testing, sex, neonatal seizure etiology, and unprovoked post-neonatal seizure frequency were not contributors to neurobehavioral outcomes assessed here.

Neurobehavioral problems are a significant challenge in children with early-onset epilepsies and contribute to a negative effect on quality of life above and beyond the seizures themselves.[27,28] A recent study of preschoolers found significantly more neurobehavioral problems in children with early-onset epilepsy compared with age-matched controls; nearly two-thirds of the children with early-onset epilepsy had a behavioral problem in at least one domain (i.e., adaptive, executive functioning, internalizing, externalizing, social, and autism risk), and many showed impairments across multiple domains.[27] Similar to our findings, adaptive behavior and social functioning were impaired in preschoolers with early-onset epilepsy. Unlike our findings, the study also revealed notable concerns for internalizing behavior such as withdrawal or anxiety, which was not present in our cohort. Increased neurobehavioral problems have also been seen in school-aged children with epilepsy, which suggests that these impairments persist and may become more apparent with age.

Adaptive functioning describes behaviors that are necessary to adequately function in day-to-day activities that are expected for one's age. Adaptive scores can be used to help identify children with global developmental delay, and low adaptive scores at preschool are correlated with later intellectual impairment and poorer school achievement.[29] We examined whether seizure etiology was an independent risk factor for behavioral outcomes at preschool age and found no difference between groups after also adjusting for sex, gestational age, and age at examination. This finding is consistent with a recent study examining children with early-onset epilepsy (not after specifically neonatal seizures) that found that the epilepsy etiology was not strongly associated with impairment.[27]

Given the high risk for abnormal behavior and development among the study participants with postneonatal epilepsy,[20] our findings support the need for early screening and intervention for all children with a history of neonatal seizures and particularly those with subsequent postneonatal epilepsy and those with co-occurring CP. Our study supports the importance of assessing for neurobehavioral impairments in this population before starting school, especially in children who develop postneonatal epilepsy. There is much literature to support early intervention, particularly during early development to mitigate and alter long-term developmental trajectories. Although direct early intervention for the child is helpful, there is also literature to support education, parent management training, and other parenting interventions in preschool populations to improve long-term neurobehavioral outcomes.[30]

### *Limitations and future directions*

Behavioral ratings were supplied by a single parent rater, as opposed to multiple parent or teacher raters. Parent ratings are known to differ from teacher assessments,[23] likely attributable to differences in available observations. Importantly, parent ratings ultimately provide a critical snapshot of functioning in the daily environment that may best predict overt behavioral problems[31] and have been found to be reliable estimates of early development. Although there are inherent problems with informant reports due to indirect observational methods,[32,33] parent report of behavior in very young children is often most meaningful given that children in this age range are less likely to have other major environmental influencers. Second, it was also beyond the scope of this study to directly assess neurobehavioral and cognitive correlates of parent-rated behavior, which may provide a more robust investigation into behavioral outcomes in future study. Third, the comparison between groups was limited by the small size of the neonatal epilepsy group. More robust conclusions might be drawn from a larger sample size, but the abnormal scores in our participants with epilepsy reflect challenges known to affect children with other early-life epilepsies. This strengthens confidence in our findings. Finally, the preschool age sample included here was somewhat broad. There are important differences in the three- to four-year age range in terms of environmental influences, as some children attend preschool, whereas others remain at home and are most closely influenced by caregivers. Also, the potential influence of the coronavirus disease 2019 pandemic cannot be understated, as it may have led some children in the cohort staying home when they might otherwise have attended school, potentially impacting opportunities for early socialization and learning, particularly in those who are medically complex.[34] Future research involving a larger sample size to facilitate clearer age delineation at this essential early educational stage may elicit more precise results.

Behavioral patterns in the preschool age range (three to four years) can respond well to intervention.[35] Addressing behavioral concerns, particularly executive function and behavioral regulation, is important for school readiness[16] and ongoing academic achievement.

## Conclusion

In summary, in this multicenter cohort of children who survived provoked neonatal seizures, those who developed epilepsy by 24 months corrected age and who had more severe CP showed higher incidence of adverse neurobehavioral outcomes at preschool age compared with those who did not develop epilepsy or CP (or who had less severe CP). Identifying children at risk for challenges with executive function, adaptive function, and socialization is key to optimize developmental support, especially as children graduate from early intervention programs and enter formal schooling.

## CRediT authorship contribution statement

**Allyssa M. Mattes:** Writing – review & editing, Writing – original draft. **Renée A. Shellhaas:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization. **Hannah C. Glass:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Conceptualization. **Julie Sturza:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Stephanie Rau:** Project administration. **Monica Lemmon:** Writing – review & editing, Methodology, Investigation. **Elizabeth E. Rogers:** Writing – review & editing, Methodology, Investigation. **Adam Numis:** Project administration. **Janet S. Soul:** Writing – review & editing, Methodology, Investigation. **Madison Berl:** Writing – review & editing. **Courtney J. Wusthoff:** Writing – review & editing, Investigation. **Catherine J. Chu:** Writing – review & editing, Investigation. **Shavonne L. Massey:** Writing – review & editing, Investigation. **Cameron Thomas:** Writing – review & editing, Investigation. **Linda S. Franck:** Writing – review & editing, Investigation. **Charles E. McCulloch:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Guilia M. Benedetti:** Writing – review & editing, Investigation. **Justin Means:** Writing – review & editing. **Katie Means:** Writing – review & editing. **Tayyba Anwar:** Writing – review & editing, Investigation. **Jennifer C. Gidley Larson:** Writing – review & editing, Writing – original draft, Methodology.

## Declaration of competing interest

Dr. Shellhaas receives royalties from UpToDate for authorship of topics related to neonatal seizures, serves as a consultant for the Epilepsy Study Consortium, and receives a stipend for her role as president-elect of the Pediatric Epilepsy Research Foundation. The other authors declare no competing interests.

## Acknowledgments

The authors would like to acknowledge the research coordinators at each study site and sincerely thank all participating families.

## References

1. Mahmood A, Zaman SQ, Mahmud S. Neonatal seizures. Prof Med J. 2014;21:1048–1053.
2. Dlugos DJ. The nature of neonatal status epilepticus–a clinician's perspective. Epilepsy Behav. 2015;49:88–89.
3. Oh A, Thurman DJ, Kim H. Independent role of neonatal seizures in subsequent neurological outcomes: a population-based study. Dev Med Child Neurol. 2019;61:661–666.
4. Tekgul H, Gauvreau K, Soul J, et al. The current etiologic profile and neurodevelopmental outcome of seizures in term newborn infants. Pediatrics. 2006;117:1270–1280.
5. Vasudevan C, Levene M. Epidemiology and aetiology of neonatal seizures. Semin Fetal Neonatal Med. 2013;18:185–191.
6. Cetin OE, Korkmaz B, Alev G, Demirbilik V. EEG abnormalities and long term seizure outcome in high functioning autism. Acta Neurol Belg. 2017;117:729–732.
7. Austin JK, Dunn DW. Progressive behavioral changes in children with epilepsy. Prog Brain Res. 2002;135:419–427.
8. Dunn DW, Austin JK, Caffrey HM, Perkins SM. A prospective study of teachers' ratings of behavior problems in children with new-onset seizures. Epilepsy Behav. 2003;4:26–35.
9. Schacter S, Holmes G, Trenite D. Behavioral aspects of epilepsy: principles and practice. Epilepsy Behav. 2008;16:184–185.
10. Austin JK, Perkins SM, Johnson CS, et al. Behavior problems in children at time of first recognized seizure and changes over the following 3 years. Epilepsy Behav. 2011;21:373–381.
11. Painter MJ, Sun Q, Scher MS, Janosky J, Alvin J. Neonates with seizures: what predicts development? J Child Neurol. 2012;27:1022–1026.
12. Holmes GL. Effects of early seizures on later behavior and epileptogenicity. Ment Retard Dev Disabil Res Rev. 2004;10:101–105.
13. Holmes GL. The long-term effects of neonatal seizures. Clin Perinatol. 2009;36:901–914. vii-viii.
14. Hisle-Gorman E, Susi A, Stokes T, Gorman G, Erdie-Lalena C, Nylund CM. Prenatal, perinatal, and neonatal risk factors of autism spectrum disorder. Pediatr Res. 2018;84:190–198.
15. Temple CM, Dennis J, Carney R, Sharich J. Neonatal seizures: long-term outcome and cognitive development among 'normal' survivors. Dev Med Child Neurol. 1995;37:109–118.
16. Elkinci O, Titus J, Rodopman A, Berkem M, Trevathan E. Depression and anxiety in children and adolescents with epilepsy: prevalence, risk factors, and treatment. Epilepsy Behav. 2009;14:8–18.
17. Almane D, Jones JE, Jackson DC, Seidenberg M, Hermann BP. The social competence and behavioral problem substrate of new- and recent-onset childhood epilepsy. Epilepsy Behav. 2014;31:91–96.
18. Dal Canto G, Pellacani S, Valvo G, Masi G, Ferrari AR, Sicca F. Internalizing and externalizing symptoms in preschool and school-aged children with epilepsy: Focus on clinical and EEG features. Epilepsy Behav. 2018;79:68–74.
19. Freilinger M, Reisel B, Reiter E, Zelenko M, Hauser E, Seidl R. Behavioral and emotional problems in children with epilepsy. J Child Neurol. 2006;21:939–945.
20. 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.
21. Sparrow SS, Cicchetti DV, Saulnier CA. Vineland adaptive behavior scales. 3rd ed (Vineland-3). Bloomington: NCS Pearson; 2016.
22. Reynolds CR, Kamphaus RW. Behavior Assessment for Children: Third Edition (BASC-3). Bloomington, MN: Pearson; 2015.
23. Goia G, Espy KA, Isquith PK. Behavior Rating Inventory of Executive Functioning - Preschool Version. Lutz, FL: Psychological Assessment Resources; 2003.
24. Constantino JN, Gruber CP. Social Responsiveness Scale. 2nd ed (SRS-2). Torrance, CA: Western Psychological Services; 2012.
25. Dunn W. Sensory Profile: Second edition (SP-2). Bloomington, MN: Pearson; 2014.
26. Bartlett DJ, Chiarello LA, McCoy SW, et al. Determinants of gross motor function of young children with cerebral palsy: a prospective cohort study. Dev Med Child Neurol. 2014;56:275–282.
27. Hunter MB, Yoong M, Sumpter RE, et al. Neurobehavioral problems in children with early-onset epilepsy: a population-based study. Epilepsy Behav. 2019;9:87–93.
28. Ferro MA, Camfield CS, Levin SD, et al. Trajectories of health-related quality of life in children with epilepsy: a cohort study. Epilepsia. 2013;54:1889–1897.
29. Berg AT, Caplan R, Baca CB, Vickrey BG. Adaptive behavior and later school achievement in children with early-onset epilepsy. Dev Med Child Neurol. 2013;55:661–667.
30. Rimestad ML, Lambek R, Zacher Christiansen H, Hougaard E. Short- and long-term effects of parent training for preschool children with or at risk of ADHD: a systematic review and meta-analysis. J Atten Disord. 2019;23:423–434.
31. Miranda A, Colomer C, Mercader J, Fernandez MI, Presentacion MJ. Performance-based tests versus behavioral ratings in the assessment of executive functioning in preschoolers: associations with ADHD symptoms and reading achievement. Front Psychol. 2015;6:545.
32. Berg AT, Altalib HH, Devinsky O. Psychiatric and behavioral comorbidities in epilepsy: a critical reappraisal. Epilepsia. 2017;58:1123–1130.
33. Vandenbroucke L. Family demographic profiles and their relationship with the quality of executive functioning subcomponents in kindergarten. Br J Dev Psychol. 2016;34:226–244.
34. Sato K, Fukai T, Fujisawa KK, Nakamuro M. Association between the COVID-19 pandemic and early childhood development. JAMA Pediatr. 2023;177:930–938.
35. Arpi E, Ferrari F. Preterm birth and behaviour problems in infants and preschool-age children: a review of the recent literature. Dev Med Child Neurol. 2013;55:788–796.