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ORIGINAL ARTICLE

Neurodevelopmental outcomes at 9–14 months gestational age after treatment of neonatal seizures due to brain injury

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Abstract

Purpose Infants with brain injury are susceptible to developmental delays. Survivors of neonatal seizures are at risk for developmental delay, epilepsy, and further neurological comorbidities. Despite advances in neonatal critical care, the prevalence of adverse long-term outcomes and seizure recurrence remains unchanged. Our goal is to determine if early treatment of neonatal seizures with phenobarbital or levetiracetam is associated with worse neurodevelopmental outcomes in brain-injured infants.

Methods We conducted a retrospective cohort study of 119 infants admitted between 2013 and 2017 who were at risk for developmental delay and assessed in our clinic. We compared brain injury infants with neonatal seizures to brain injury infants without neonatal seizures using Bayley scores (BSID III) at 9–14 months gestational age. A comparison of Bayley scores between those exposed to phenobarbital and levetiracetam was conducted.

Results Twenty-two children with neonatal seizures scored lower than 53 children without seizures in all domains with significant values in composite scores for cognitive function ($p = 0.003$) and language ($p = 0.031$). We found no difference in scores at 9–14 months between infants exposed to phenobarbital versus levetiracetam.

Conclusions Our results suggest that in infants with brain injury, the occurrence of neonatal seizures has an adverse effect on neurodevelopmental outcomes. The choice of antiseizure medication may not play a significant role in their outcomes.

Keywords Developmental delay · Levetiracetam · Bayley Scale · Phenobarbital

Introduction

Neonatal seizures occur in one to four out of 1000 live births in North America and are a major predictor of future neurodevelopmental outcomes [1]. The incidence of ongoing epilepsy after neonatal seizures has been estimated to be 17.6–21.0% [2, 3]. Several antiseizure medications are used in the neonatal ICU. These include phenobarbital, fosphenytoin, clonazepam, topiramate, and levetiracetam. Phenobarbital is the most commonly used antiseizure drug for neonatal seizures [4]. Levetiracetam is another antiseizure drug available in intravenous and oral form that is used off-label for the treatment of neonatal seizures [5]. Analysis of current prescribing trends across the USA continues to show high utilization of phenobarbital but with an increase in levetiracetam use [6]. Unfortunately, neither drug is sufficiently effective at treating neonatal seizures. A comparative study of phenobarbital and phenytoin found both drugs equally ineffective at treating neonatal seizures [7]. Levetiracetam was associated with seizure improvement within 24 h for 8 out of 23 neonates in a retrospective cohort study [8]. Another recent study showed levetiracetam stopped seizures in 27 of 32 neonates with hypoxic ischemic encephalopathy who failed to respond to phenobarbital [9]. Although this data is promising, prospective studies are needed to compare efficacy at stopping neonatal seizures.

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Phenobarbital, a gamma aminobutyric acid (GABA) receptor agonist, has been associated with apoptotic neurodegeneration in infant rats at plasma concentrations between 25 and 35 μg/L. These concentrations are routinely achieved in humans with neonatal seizures [10]. The long-term effects of phenobarbital on neurodevelopment are heavily debated. Antenatal exposure to phenobarbital before delivery was found not to impact neurodevelopmental outcomes compared with unexposed infants at 36 months of life [11]. A study measuring developmental delay in children with neonatal seizures using the Functional Independence Measure for Children (WeeFIM) score found similar degrees of delay in children sent home from the neonatal ICU on phenobarbital (58%) compared with children sent home without (52%) [12]. Levetiracetam is a second-generation antiseizure medication that targets the SV2 protein of the synaptic vesicle fusion complex, inhibiting neurotransmitter release. It is structurally related to the neuroprotective pyrrolidone compound piracetam. In rat models, it was found to reduce ischemic damage and suppress non-convulsive seizures [13]. A retrospective study of infants who received antiseizure medications for neonatal seizures showed increased exposure to phenobarbital is associated with worse neurodevelopmental outcomes than levetiracetam at their 24-month assessment [14]. However, many infants in this study were exposed to both medications and the severity of epilepsy after discharge from the NICU was not established.

Infants with brain injury are susceptible to developmental delays. Survivors of neonatal seizures are at risk for developmental delay, epilepsy, and further neurological comorbidities [15]. Despite advances in neonatal critical care, the prevalence of adverse long-term outcomes and seizure recurrence remains unchanged [3]. Our goal is to determine if early treatment of neonatal seizures with phenobarbital or levetiracetam is associated with worse neurodevelopmental outcomes in brain-injured infants. We hypothesize that the choice of initial treatment with phenobarbital or levetiracetam does not influence neurodevelopmental outcomes in infants with brain injury.

Methods

Study design and subject enrollment This is a retrospective case-controlled cohort design approved by the Institutional Review Board of the University of Florida (UF). We reviewed the medical records of all patients admitted to the Neonatal Intensive Care Unit of UF Health Shands Children's Hospital from January 1, 2013 through September 1, 2016 who were assessed through the Early Developmental Assessment Clinic (EDAC) based in the Division of Pediatric Neurology at the UF College of Medicine. Patients were included in the brain injury with neonatal seizure group if they were assigned the ICD-9 code diagnosis of neonatal seizures (779.0), epilepsy (345.0–9), or other convulsions (780.39). Infants whose charts were coded with ICD-10 were included using the following codes: convulsions in the newborn (P90) or other convulsions (R56.9). All remaining charts were assigned to the brain injury group.

Inclusion/exclusion criteria Each chart was manually reviewed to screen for inclusion/exclusion criteria. All infants assessed in this study had brain injury. This included neonates who suffered intraventricular hemorrhage, ischemic and hemorrhagic stroke, or some form of encephalopathy (anoxic brain injury, hypoxic ischemic encephalopathy, cardiopulmonary arrest, renal or metabolic encephalopathy) in the neonatal intensive care unit. Infants were included in the brain injury with neonatal seizure group if the chart review confirmed a diagnosis of neonatal seizures, and if the initial seizure treatment consisted of phenobarbital and/or levetiracetam. Exclusion criteria for the brain injury with neonatal seizure group included early infantile epileptic encephalopathies, congenital cerebral abnormalities, channelopathies, inborn errors of metabolism, initial treatment with any other antiseizure medication, hypsarrhythmia on EEG, and/or a burst suppression pattern on EEG for term infants. Brain injury group without neonatal seizures included subjects with the same inclusion/exclusion criteria as above and were not exposed to antiseizure medications (phenobarbital or levetiracetam). Matched controls without risk factors for developmental delay were not obtained. This study reflects our experience with neonatal brain injury.

Seizure characterization and treatment All neonates with brain injury were placed on continuous EEG monitoring either at the time of concern for brain injury, identification of brain injury, or clinical events concerning for seizures. EEG leads were placed in this study using the international 10–20 system of electrode placement with silver chloride EEG electrodes. Five patients had abrupt discontinuation of EEG monitoring due to high frequency oscillatory ventilation or at the discretion of the treating physician. Seizures were identified as clinical only, clinical with electrographic correlate, or electrographic only. If clinical seizures were present, a continuous video EEG was obtained for 24–72 h to evaluate for significant interictal discharges or electrographic seizures. All seizures (clinical, clinical with electrographic correlate, or electrographic) were treated with either phenobarbital 20 mg/kg IV bolus followed by maintenance dosing of 5 mg/kg/day divided every 12 h or levetiracetam 20–30 mg/kg IV bolus followed by maintenance dosing of 20–30 mg/kg/day divided every 12 h. If seizures continued despite treatment with either antiseizure drug, additional boluses of phenobarbital or levetiracetam were administered. For the purposes of this study, if a child received both medications in the process of treating a seizure, the medication the child was on for the longest duration and quantity was deemed their primary antiseizure medication. Patients were weaned off antiseizure medications at the time of discharge or soon after if they remained seizure free. This was done at the discretion of the neonatologist or pediatric neurologist.

Seizure and neurodevelopmental outcomes After discharge, patients were monitored for ongoing seizures by a board-certified pediatric neurologist (SG) in the EDAC. The presence of ongoing seizures was determined by parental reporting. If an infant was discharged on antiseizure medications and became seizure free, he/she was weaned off the antiseizure drug by 6 months of life. Infants were evaluated for developmental delays in the EDAC by board-certified attending pediatric neurologists and an occupational therapist (JB) trained to administer the Bayley Scales of Infant and Toddler Development®, Third Edition (Bayley-III®). Evaluations of premature infants were corrected for gestational age and were performed between 9- and 14-month gestation age. Developmental delay was defined as a Bayley-III composite score two standard deviations below the mean. Composite scores for motor and language as well as the scaled subset scores in each domain (cognitive, fine motor, gross motor, expressive language and receptive language) were used for analysis. Only infants who were seen in follow-up were included in the analysis.

Data management Study data were collected and managed using REDCap electronic data capture tools hosted at the University of Florida [16]. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources.

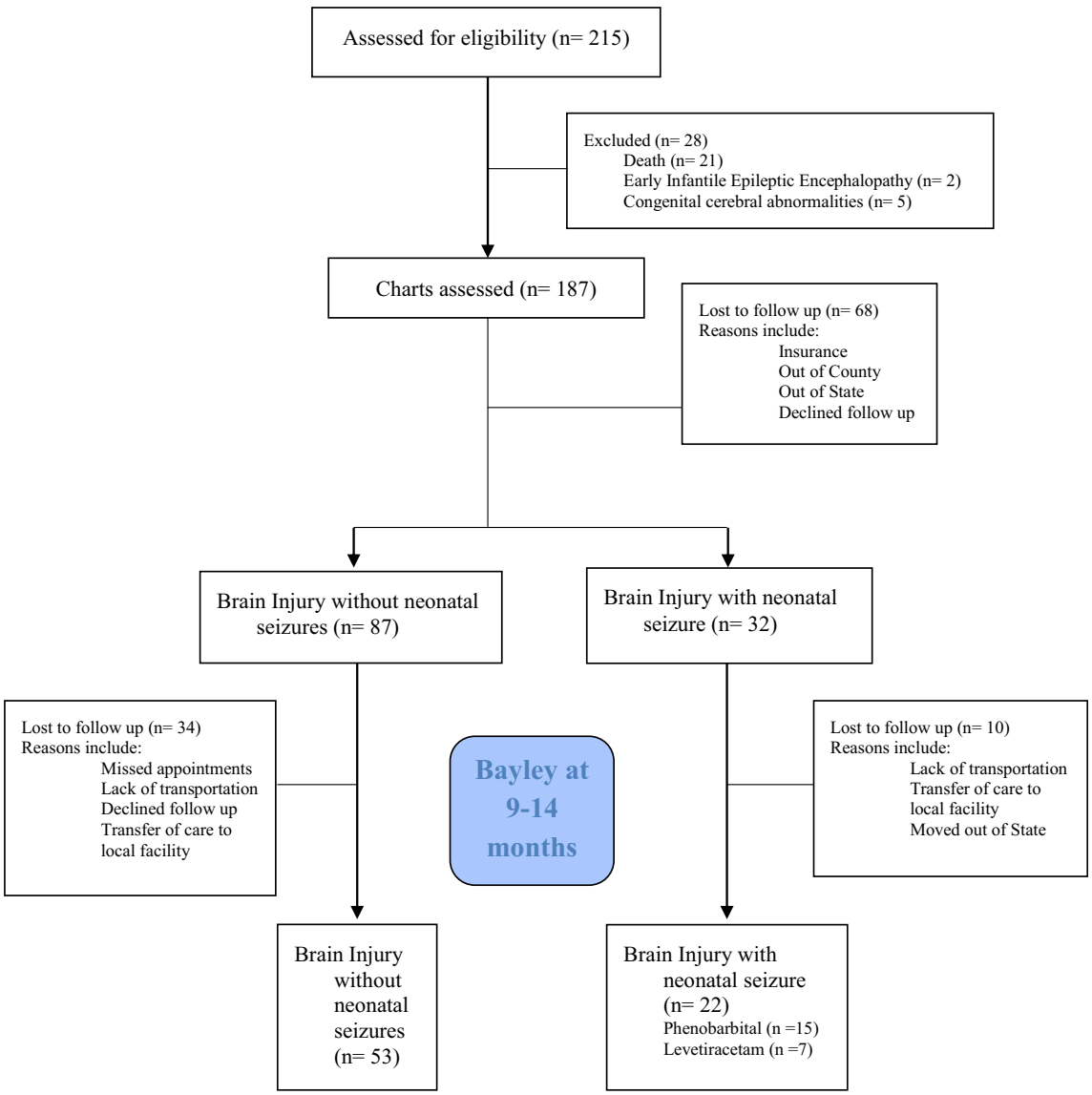

Fig. 1 Flow diagram of patient selection

Table 1 Baseline maternal and neonatal characteristics were similar between the brain injury neonatal seizure group and brain injury no seizures group except Apgar scores at 5 min, pH on venous or cord blood gas, and base deficit

	Brain injury with neonatal seizure (mean ± SD)	Brain injury without neonatal seizure (mean ± SD)	*p* value*
Number of patients	22	53	
Characteristics			
Maternal			
Age	27.8 ± 6.9	28.0 ± 5.4	
Gravida	2.7 ± 4.2	2.8 ± 1.9	
Para	2.0 ± 2.0	1.7 ± 1.2	
Caucasian (no. (%))	10 (52)	28 (53)	
Neonatal			
Gestational age	35.2 ± 6.4	32.5 ± 5.6	
Female (no. (%))	10 (45)	23 (43)	
Apgar at 5 min	4.0 ± 2.6	7.7 ± 1.8	< 0.01
Cord or VBG pH	7.2 ± 0.18	7.3 ± 0.13	< 0.01
Base deficit (mmol/l)	12.4 ± 7.8	5.0 ± 5.8	< 0.01
Birth weight (grams)	2418 ± 1514	1827 ± 1048	
Intubation (%)	19 (86)	36 (68)	
Ventilation (%)	19 (86)	47 (89)	
Length of stay	56.5 ± 58.1	56.8 ± 40.5	
Type of brain injury (%)			
Hypoxic ischemic encephalopathy/ anoxic brain injury	14 (64)	22 (42)	
Mild	3	13	
Moderate	4	6	
Severe	7	3	
Intraventricular hemorrhage (grades III–IV)	5 (23)	18 (34)	
Ischemic/hemorrhagic stroke	2 (9)	6 (11)	
Other causes of encephalopathy (metabolic, renal, sepsis, hypovolemic shock)	2 (9)	10 (19)	

*Only significant *p* values are reported

Statistical analysis The statistical analysis of the data was performed by using the open source statistical software package R (version 3.3.3) with different statistical analysis methods including independent *t* test and the non-parametric Mann-Whitney *U* test. Specifically, in the descriptive analysis of continuous variables of demographics data, an independent *t* test was used. Categorical demographic data is reported as total number and percentage. Two sample comparisons for the 9–14 months' group were conducted with a Mann-Whitney *U* test. A *p* value less than 0.05 was regarded as significant in hypothesis testing.

Results

Patient characteristics Figure 1 outlines the eligibility and selection for analysis of subjects for this study. One hundred and eighty-seven patients met eligibility criteria. A total of 119 patients were enrolled based on the inclusion criteria and availability of data. Eighty-seven infants with brain injury without seizures were included in the control group. Fifty-three infants in this group completed follow-up at 9–14 months corrected gestational age. Thirty-two infants with brain injury and seizures were initially included in the neonatal seizure group. Twenty-two of these patients completed follow-up at 9–14 months corrected gestational age. Analysis of baseline characteristics (Table 1) indicates that subjects in the neonatal seizure group are more likely to have a lower Apgar score at 5 min, lower pH, and high base deficits on venous or cord blood gas. Seizure characteristics such as etiology, number of clinical seizures, number of electrographic seizures, total duration of seizures in minutes, medications utilized, and number of seizures after discharge are shown in Table 2. Two patients required the use of both medications. One neonate required the addition of phenobarbital which was continued at the time of discharge. One required the addition of levetiracetam but remained on phenobarbital at the time of discharge. Maximal seizure burden was calculated as the maximal hourly seizure burden within continuous EEG recording and is measured in minutes of seizure per hour of video EEG monitoring [17]. There were no significant hospitalizations or surgeries after discharge in patients seen at 9–14 months. Baseline characteristics were similar between the levetiracetam and phenobarbital patients.

Neurodevelopmental outcomes at 9–14 months Differences are present at 9–14 months between the brain injury without neonatal seizure group and brain injury with neonatal seizure group in language and cognition scores with the neonatal seizure group having significantly worse scores. Table 3 shows the divergence between the groups. The composite cognitive scores were lower for the brain injury with neonatal seizure group with a median score of 77.5 compared with the brain injury group with a median score of 90 ($p = 0.002$). Similar differences were found in the composite language scores for the brain injury with neonatal seizure group with a median score of 86 compared with the brain injury without neonatal seizure group with a mean score of 100 ($p = 0.01$). There was no difference in scores between patients exposed to phenobarbital or levetiracetam, as shown in Table 4.

Discussion

It is known that neonatal seizures in brain-injured patients correlate with unfavorable cognitive outcome and that this

Table 2 This describes the baseline characteristics of the 22 patients selected for the neonatal seizure group

	Brain Injury with neonatal seizure
Number of patients	22
Clinical seizures per patient*	1 (1–2.5)
Total minute duration of clinical seizures*	0.5 (0.2–4)
Electrographic seizures per patient*	2 (1.75–4)
Total minute duration of electrographic seizures*	4 (0.42–15.75)
Total minute duration of clinical and electrographic seizures*	4.17 (0.75–15.5)
Maximal seizure burden in minutes/h*	0.12 (0.02–0.46)
Etiology	
Hypoxic ischemic encephalopathy	13
Infectious	2
Hemorrhage	5
Unknown	2
First antiseizure drug	
Phenobarbital	15
Levetiracetam	7
Not responding to 1st drug	2
Second antiseizure drug	
Phenobarbital	1
Levetiracetam	1
Discharged with antiseizure drug	10
Phenobarbital	10
Levetiracetam	0
Seizures at 6 months	2
Antiseizure drug at 6 months	4
Seizures at 12 months	1
Antiseizure drug at 12 months	1
Phenobarbital	1
Levetiracetam	0

*Values presented as median (interquartile range)

may very well be driven by extent of injury leading to an increased likelihood of seizures, and not by the seizures themselves. We observed similar findings in our cohort. We also found that the initial choice of antiseizure medication, phenobarbital or levetiracetam, was not associated with worse long-term developmental outcomes. Although the study is not powered to find a significant difference, it does lead to further questions regarding the choice of antiseizure medications for this population.

Several studies have shown the effects of neonatal seizures on brain injury and long-term outcomes. A prospective randomized control trial evaluated treatment of clinical and subclinical seizure identified by amplitude EEG versus treatment of clinical seizures without amplitude EEG. There was a correlation between duration of seizures and worsening changes on MRI of the brain. Patients in this study were full-term neonates with hypoxic ischemic encephalopathy. A similar study using continuous EEG monitoring for neonates with hypoxic ischemic encephalopathy found increasing seizure burden correlated significantly with lower performance scores in cognition, language, and motor skills on the Bayley-III [18]. A recent population-based retrospective study based on claims data in the USA analyzed a cohort from 2009 and followed them up to 6 years. Of the 800 subjects with neonatal seizures in a cohort of 490,071 patients, 39.3% of them had some form on intellectual disability and 47.4% developed epilepsy. Data was based on claims reporting. Etiology for neonatal seizures in this study included other forms of brain injury besides hypoxic ischemic encephalopathy such as perinatal complications, congenital infections, brain malformations, metabolic disturbances, cerebrovascular disease, and hydrocephalus [19]. Our data supports these prior studies and shows a correlation between neonatal seizures and worsening cognitive and language outcomes assessed by the Bayley-III in neonatal brain injury patients from a variety of etiologies.

Our institution adopted a treatment algorithm allowing the neurologist or neonatologist to use either drug at a prescribed

Table 3 Bayley scores at 9–14 months gestational age showing infants with neonatal seizures having worse outcomes

Bayley scores for 9–14 months gestational age	Brain injury with neonatal seizure	Brain injury without neonatal seizures	*p* value
Composite score cognitive	77.5 (57.5–85)	90 (80–95)	0.001
Composite score language	86 (77–99.25)	100 (86–106)	0.012
Composite score motor	74.5 (47.5–88)	82 (64–91.75)	0.066
Scaled score cognitive	6 (3–7.75)	8 (6–9)	0.012
Scaled score receptive language	7 (5.25–9)	9 (7–10.25)	0.043
Scaled score expressive language	8 (6–10)	10 (9–12)	0.007
Scaled score fine motor	6 (3–8)	7 (5–8)	0.364
Scale score gross motor	3.5 (1–9)	7 (2–9)	0.252

All numbers are presented as median (interquartile range)

dose. Providers can choose either phenobarbital 20 mg/kg IV bolus followed by maintenance dosing of 5 mg/kg/day divided every 12 h or levetiracetam 30–60 mg/kg IV bolus followed by maintenance dosing of 30 mg/kg/day divided every 12 h. We recently changed our algorithm to reflect a recent study [9] and findings at our institution showing seizure cessation at higher doses of levetiracetam in neonates with hypoxic ischemic encephalopathy [8, 20].

A recent study compared the effectiveness of levetiracetam and phenobarbital for the treatment of seizures during infancy. Children treated with levetiracetam were free from monotherapy failure compared with phenobarbital. The findings suggest levetiracetam is superior to phenobarbital for infant seizures. Neonatal seizures were not included in this analysis. The choice of antiseizure medication was not randomized in the study. A higher proportion of infants in the phenobarbital group had developmental structural brain abnormalities [21]. Our study focuses on neonatal seizures in a population with brain injury and suggests no difference in treatment failure or neurodevelopmental outcomes for these infants.

The study is based on our experience with antiseizure medications in a population at risk for developmental delays. A major limitation of this study is not having matched groups for comparison. This includes matched controls without brain injury and within our two groups. Thus, it is difficult to determine the effects of the individual medication on normal developmental in children seen in in the NICU or between types of brain injury. Matched control studies would be needed to further test this hypothesis. There are likely many confounding variables that and biases within our study due to the small sample size, retrospective nature of the study, and lack of randomization. Five neonates in our study did not complete continuous EEG monitoring. In some cases, EEG monitoring was initiated at the time of discovery of the injury. Seizures that occurred prior to identification of brain injury would have been missed.

Lower Apgar's, lower pH, and higher base deficits have all previously been associated with poor outcomes [15]. In our study, subjects within the neonatal seizure group were more likely to have a lower Apgar score at 5 min, lower pH, and high base deficits on venous or cord blood gas. However, this may reflect the design of our study to include different types of brain injury that may not have alterations in Apgar, pH, and base deficits. In addition, some of our patients had multiple types of injury. Brain injury often does not fit clear diagnostic definitions or patterns. This study reflects the "real world" problem when treating brain injury and its outcomes.

We observed a trend in our data that suggests the presence of neonatal seizures may be a factor for

Table 4 Bayley scores at 9–14 months gestational age of infants with neonatal seizures treated with phenobarbital or levetiracetam. We found no significant difference between the two groups

Bayley scores for 9–14 months gestational age	Phenobarbital	Levetiracetam	*p* value
Composite score cognitive	70 (60–83.75)	85 (65–90)	0.530
Composite score language	86 (77–97)	86 (72.5–94.5)	1
Composite score motor	61 (49–92.5)	82 (58–86.5)	1
Scaled score cognitive	6 (3–7.75)	7 (3–8)	0.733
Scaled score receptive language	7 (5.5–9.75)	8 (5.5–8.5)	0.536
Scaled score expressive language	8 (6.5–9.75)	8 (5.5–10.5)	0.911
Scaled score fine motor	7 (3–9)	6 (2.5–6.5)	0.462
Scale score gross motor	4 (1–9.75)	3 (1–6)	0.953

All numbers are presented as median (interquartile range)

neurodevelopmental impairments rather than the selection of two commonly used antiseizure medications. However, a future prospective study could be more definitive regarding this point. The somewhat high dropout rate between eligible subjects and those who underwent analysis was due to multiple reasons including availability of follow-up data on some patients. This led to a smaller number of subjects in the neonatal seizure group than anticipated, representing a limitation of this study. It would be helpful to continue following this cohort over time to assess longer-term developmental outcomes. The overall interpretation of these results is confined to looking at what was observed, and what factors were associated with these observations. There are many confounding factors, both measured and unmeasured, that may be responsible for any differences or lack thereof. We view this report as hypothesis generating, rather than hypothesis testing.

Conclusion

We observed that brain injury infants with neonatal seizures had worsening of neurodevelopmental outcomes at 9–14 months gestational age irrespective of the antiseizure medication used. Larger studies are needed to determine if this observation is significant.

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Authors' contribution Suman Ghosh: Dr. Ghosh conceptualized and designed the study, designed data collection instruments, supervised data collection, and drafted and revised the manuscript.

Andrea C Cabassa Miskimen: Ms. Miskimen helped design data collection instruments, collected data, and reviewed and revised manuscript.

Matthew A Robinson: Mr. Robinson carried out the initial data analyses, provided statistical analysis and graphics, and contributed and reviewed the manuscript.

Baiming Zou: Dr. Zou carried out the initial data analyses, provided statistical analysis and graphics, and contributed and reviewed the manuscript.

Janet Brady: Ms. Brady collected data, performed diagnostics for the study, reviewed data, and contributed to the draft of the manuscript.

Michael Weiss: Dr. Weiss provided interpretation of data and critical review of the manuscript.

Peter B. Kang: Dr. Kang conceptualized and designed the study, reviewed and revised the manuscript, and provided senior mentorship.

Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to disclose.

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