Annals of the Child Neurology Society
Open Access

RESEARCH ARTICLE

Feeding and developmental outcomes after neonatal seizures—A prospective observational study

Katelyn H. Roberts[1], John D. E. Barks[1], Hannah C. Glass[2,3,4], Janet S. Soul[5], Taeun Chang[6], Courtney J. Wusthoff[7,8], Catherine J. Chu[9], Shavonne L. Massey[10], Nicholas S. Abend[10,11], Monica E. Lemmon[12], Cameron Thomas[13], Ronnie Guillet[14], Elizabeth E. Rogers[3], Linda S. Franck[3,15], Harlan McCaffery[16], Yi Li[17], Charles E. McCulloch[4] & Renée A. Shellhaas[1]

[1]Department of Pediatrics, University of Michigan, Ann Arbor, Michigan, USA
[2]Department of Neurology and Weill Institute for Neuroscience, University of California San Francisco, San Francisco, California, USA
[3]Department of Pediatrics, UCSF Benioff Children's Hospital, University of California San Francisco, San Francisco, California, USA
[4]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California, USA
[5]Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[6]Department of Neurology, Children's National Hospital, George Washington University School of Medicine, Washington, District of Columbia, USA
[7]Department of Neurology, Stanford University, Palo Alto, California, USA
[8]Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University, Palo Alto, California, USA
[9]Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts, USA
[10]Departments of Neurology and Pediatrics, Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA
[11]Departments of Anesthesia and Critical Care Medicine, Children's Hospital of Philadelphia and Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA
[12]Departments of Pediatrics and Population Health Sciences, Duke University School of Medicine, Durham, North Carolina, USA
[13]Department of Pediatrics, Division of Neurology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio, USA
[14]Department of Pediatrics, Division of Neonatology, Golisano Children's Hospital, University of Rochester, Rochester, New York, USA
[15]Department of Family Health Care Nursing, University of California San Francisco, San Francisco, California, USA
[16]Department of Pediatrics, University of Michigan, Michigan, Ann Arbor, USA
[17]Department of Radiology and Biomedical Imaging, University of California San Francisco, San Francisco, California, USA

Correspondence
Renée A. Shellhaas, Washington University School of Medicine, MSC 8091-29-12400, 660S. Euclid Ave, St. Louis, Missouri 63110, USA. Email: rshellhaas@wustl.edu

Funding Information
Patient-Centered Outcomes Research Institute, Grant/Award Number: 1507-31187; National Institute of Neurological Disorders and Stroke, Grant/Award Number: K02NC102598 (to Dr. Wusthoff) and K23NS116453 (to Dr. Lemmon)

Received: 15 August 2022; Accepted: 27 November 2022

Annals of the Child Neurology Society **2022; 00(00): 1–9**

doi: 10.1002/cns3.6

Abstract

Objective: Among neonates with acute symptomatic seizures, we evaluated whether the inability to take full feeds at the time of hospital discharge from neonatal seizure admission is associated with worse neurodevelopmental outcomes, after adjusting for relevant clinical variables. **Methods:** This prospective, nine-center study of the Neonatal Seizure Registry (NSR) assessed characteristics of infants with seizures, including evidence of brainstem injury on magnetic resonance imaging (MRI), mode of feeding upon discharge, and developmental outcomes at 12, 18, and 24 months. The inability to take oral feeds was identified through a review of medical records. Brainstem injury was identified through a central review of neonatal MRIs. Developmental outcomes were assessed with the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS) at 12, 18, and 24 months corrected age. **Results:** Among 276 infants, inability to achieve full oral feeds was associated with lower total WIDEA-FS scores (160.2 ± 25.5 for full oral feeds vs. 121.8 ± 42.9 for some/no oral feeds at 24 months, $p < 0.001$). At 12 months, a gastrostomy tube was required for 23 of the 49 (47%) infants who did not achieve full oral feeds, compared with 2 of the 221 (1%) who took full feeds at discharge ($p < 0.001$). **Conclusions:** The inability to take full oral feeds upon hospital discharge is an objective clinical sign that can identify infants with acute symptomatic neonatal seizures who are at high risk for impaired development at 24 months.

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.
This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Introduction

Symptomatic seizures due to acute brain injury occur in 1–4 per 1000 live births.[1–5] While acute symptomatic seizures are generally a transient symptom, neurodevelopment is closely linked with the location and extent of the underlying brain injury. Oral feeding is a critical early neonatal milestone that is likely to be affected by neonatal brain injury. For example, 29% of infants in a single-center study who survived neonatal stroke were reported to require gastrostomy tube (G-tube) feeding at 1 year of age.[6] In a single-center study, neonates with hypoxic–ischemic encephalopathy (HIE) with brainstem injury were at increased risk for needing a G-tube or nasogastric (NG) tube at the time of hospital discharge.[7,8] Feeding milestones are also associated with neurodevelopment and feeding technology needs for preterm infants.[9–11]

We hypothesized that the presence of brainstem injury on neonatal magnetic resonance imaging (MRI) would be associated with the inability to achieve full oral feeds by the time of hospital discharge. We also hypothesized that infants with acute provoked neonatal seizures, regardless of seizure etiology, commonly have feeding difficulties and that inability to take full oral feeds at hospital discharge is an early indication of risk for abnormal neurodevelopment.

We also sought to understand (1) whether the inability to achieve oral feeds at the time of discharge from the neonatal seizure admission is associated with a long-term need for feeding technology and (2) the impact of outpatient feeding therapy on the continued need for feeding technology. We hypothesized that not achieving full oral feeds at the time of discharge from the neonatal seizure admission would be associated with a later need for G-tube placement and that involvement in outpatient feeding therapy would be associated with decreased reliance on feeding technology for nutrition.

To explore these associations, we analyzed data from a multicenter, prospective observational study of neonates with acute provoked seizures, to determine whether achieving full oral feeds by the time of hospital discharge was associated with neurodevelopmental outcomes and/or the need for long-term feeding technology.

Methods

This was a secondary analysis of a prospective, nine-center study of the Neonatal Seizure Registry (NSR) (NCT02789176), which enrolled and followed infants with acute symptomatic neonatal seizures of varying etiologies (including, but not limited to, HIE, stroke, and intracranial hemorrhage). Details regarding the primary study design and primary outcomes are reported elsewhere.[12–17] Each NSR site follows the American Clinical Neurophysiology Guidelines for neonatal electroencephalogram (EEG) monitoring.[12] EEG monitoring results were incorporated in this study as the worst EEG background included the following categories: normal, mild/moderately abnormal, severely abnormal, and status epilepticus at EEG onset. The local institutional review board at each of the nine sites approved the protocol (e.g., HUM00114541 at the University of Michigan Medical School Institutional Review Board), and a parent of every enrolled infant provided written informed consent.

Participants

Inclusion criteria for the present analyses were: (1) acute symptomatic neonatal seizures (onset <44 weeks post-menstrual age), (2) survival to hospital discharge, and (3) available follow-up data. Infants with neonatal-onset epilepsy were excluded from the main NSR study. For the present analysis, we also excluded neonates with complex congenital heart disease since they are known to be at risk for poor oral feeding skills.[18–20]

Neonatal data collection

Infants were classified based on site investigators' assessment of seizure etiology as having HIE, stroke, hemorrhage, or other etiology (e.g., infection, severe hypoglycemia, etc.). Feeding at the time of discharge from the neonatal seizure admission was dichotomized: (1) full oral feeds and (2) some/no oral feeds if the infant required a feeding tube for any percentage of their nutrition. Neonatal MRIs were reviewed by a central neuroradiologist with expertise in neonatal imaging who was blinded to clinical details including feeding. Brainstem injury was defined by the presence of signal abnormality on diffusion-weighted imaging and T1- or T2-weighted imaging in the brainstem, which could either be from a primary injury or a secondary Wallerian injury. To extract additional detail on feeding outcomes at 12–24 months corrected age and to assess participation in outpatient feeding therapies (e.g., participation in outpatient occupational or speech feeding therapy) not available in the original NSR data set, a focused chart review was undertaken at each NSR site.

Outcomes

For all outcome measures, the ages reported are corrected for prematurity. Feeding outcomes at 12, 18, and 24 months were defined by the continued need for feeding technology, such as NG tube or G-tube feeding, for any portion of feeds as reported in follow-up visit documentation. Developmental outcomes at ages 12, 18, and

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

24 months were assessed by the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS). WIDEA-FS is a 50-item questionnaire used to evaluate a child's adaptive skills in daily situations in the areas of mobility, communication, social, cognitive, and self-care. WIDEA-FS has been shown to have concurrent validity with Bayley-III and can be used to determine intervention strategies for children at high risk for neurodevelopmental disabilities.[21–23]

Analysis

To assess the association between brainstem injury on MRI and the inability to achieve full oral feeds at the time of discharge, Fisher's exact test was used for bivariate comparisons. To assess the association between the inability to achieve oral feeds and longitudinal neurodevelopmental outcomes, univariate analysis was performed to test associations with "full oral feeds," with Fisher's exact test performed for categorical variables and Wilcoxon's rank-sum test performed for continuous variables.

Linear mixed models with a random intercept at the patient level were used to model WIDEA total score, WIDEA total *Z*-score, and WIDEA subscale outcomes at 12, 18, and 24 months, with "full oral feeds" and its interaction with the three follow-up time points (12, 18, and 24 months) as the primary predictors. Through expert consensus, potentially relevant demographic and clinical variables were selected to be included in the multivariable analysis. The WIDEA total score final model was selected in a backward stepwise fashion, retaining fixed-effect covariates with $p < 0.05$. These covariates were then used in all other multivariable models in this study.

Logistic regression models of the outcome "full oral feeds" were fit with brainstem injury as the primary predictor for the full sample and then for each subgroup of seizure etiology (HIE, perinatal ischemic stroke, intracranial hemorrhage, and other etiology). Firth's bias-reduced logistic regression (R package *logistf*) was used in cases where brainstem injury cell counts were excessively low.

Bivariate analyses were conducted using Fisher's exact test to evaluate the association between the inability to achieve oral feeds at the time of discharge and the need for G-tube at 12, 18, and 24 months. As an exploratory analysis, we evaluated whether receiving outpatient feeding therapy in those who were not able to achieve full oral feeds at the time of initial hospital discharge led to an improvement in oral feeds to the point of no longer requiring a G-tube.

Analyses were conducted using R version 4.0.5 and the package *nlme* was used for the mixed-model analyses.

Results

Data were available for 276 infants. Of these, 53 (19%) infants did not take full oral feeds at the time of hospital discharge (Table 1).

Brainstem injury and ability to achieve full oral feeds at discharge

For the full cohort with MRI data available ($N = 216$), the presence of brainstem injury on MRI was associated with the inability to achieve full oral feeds by the time of discharge from the initial hospital admission for neonatal seizures but was no longer significant after adjustment in multivariable analysis (Table 2). However, for the subset of neonates with seizures due to HIE, even after adjustment, brainstem injury was significantly associated with the inability to take oral feeds (7/80, 8.8% who took full oral feeds vs. 7/16, 30.8% who did not take full oral feeds had brainstem injuries, adjusted $p = 0.03$).

Inability to achieve full oral feeds at discharge as a predictor of neurodevelopmental outcome

Inability to achieve full oral feeds at the time of discharge from the neonatal seizure admission was associated with lower total WIDEA-FS scores at 12, 18, and 24 months (Table 1 and Figure 1) and in five of the six WIDEA-FS subscales at most time points, the exception being diapering (Supporting Information: Table 1).

In multivariate analysis (Table 3 and Supporting Information: Table 2), oral feeds, gestational age at birth, the most abnormal neonatal EEG background, and tone on exam at discharge were independently associated with total WIDEA-FS scores. The difference in developmental outcome scores between the two feeding groups was more than twice as large at 18 months as at 12 months and was stable from 18 to 24 months (Supporting Information: Table 3).

In addition, *Z*-scores for total WIDEA-FS scores at 12, 18, and 24 months were compared across the two feeding groups. Children who did not achieve full oral feeds by the time of discharge from the neonatal seizure admission had significantly lower total WIDEA-FS scores (normalized to the population norm) at each time point (Table 1 and Supporting Information: Table 4).

Inability to achieve full oral feeds at discharge as a predictor of future feeding technology needs

Long-term feeding outcomes and the need for permanent feeding technology were available for 270 infants. A G-tube

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 1. Clinical and demographic profile and oral feeding at the time of discharge from the neonatal seizure admission[a]

	Full oral feeds ($n = 223$)	Some/no oral feeds ($n = 53$)	Univariate analysis p value
Male sex	125 (56.1%)	31 (58.5%)	0.76
Gestational age (weeks)	39.7 [38.6; 40.6]	38.7 [35.3; 39.6]	0.001
Birthweight (kg)	3.2 [2.9; 3.6]	3.1 [2.4; 3.6]	0.03
5-min Apgar score	7.0 [5.0; 9.0]	6.5 [3.0; 8.0]	0.04
Primary seizure etiology			0.02
Hypoxic–ischemic encephalopathy	98 (43.9%)	26 (49.1%)	
Perinatal ischemic stroke	63 (28.3%)	6 (11.3%)	
Intracranial hemorrhage	34 (15.2%)	15 (28.3%)	
Other	28 (12.6%)	6 (11.3%)	
Age at admission to *NSR* site (h)	16.4 [4.0; 51.3]	7.9 [1.9; 46.2]	0.40
Race			0.38
White	142 (63.7%)	31 (58.5%)	
Black/African American	30 (13.5%)	5 (9.4%)	
Other	51 (22.8%)	17 (32.1%)	
Hispanic ethnicity	34 (15.2%)	10 (18.9%)	0.27
Maternal education			0.62
High school or less	48 (22.6%)	14 (27.5%)	
Any college	114 (53.8%)	28 (54.9%)	
Graduate study	50 (23.6%)	9 (17.6%)	
Age at hospital discharge (days)	12.0 [8.0; 20.0]	33.0 [16.0; 58.0]	0.001
Tone on discharge exam			0.001
Abnormal	54 (25.5%)	29 (60.4%)	
Worst EEG background			0.001
Normal	20 (9.0%)	1 (1.9%)	
Mild/moderately abnormal	157 (70.7%)	26 (49.1%)	
Severely abnormal	27 (12.2%)	21 (39.6%)	
Status epilepticus at EEG onset[b]	18 (8.1%)	5 (9.4%)	
WIDEA-FS scores			
12 months	114.9 ± 18.5	85.7 ± 25.8	0.001
18 months	145.0 ± 23.2	102.6 ± 38.0	0.001
24 months	160.2 ± 25.5	121.8 ± 42.9	0.001
WIDEA-FS total *Z*-score >2 SDs below the normal population mean			
12 months	6 (2.6%)	13 (24.5%)	0.001
18 months	22 (9.9%)	18 (34.0%)	0.001
24 months	52 (23.3%)	28 (52.8%)	0.001

[a]Data are represented as *N* (%) or median [interquartile range].
[b]Status epilepticus was one of the four categories within the "worst EEG background" clinical variable.
EEG, electroencephalogram; NSR, Neonatal Seizure Registry; WIDEA-FS, Warner Initial Developmental Evaluation of Adaptive and Functional Skills.

was placed by age 12 months for 23 of the 49 (46.9%) infants who did not achieve full oral feeds at discharge from the neonatal seizure admission, compared with 2 of the 221 (0.9%) who took all feeds by mouth by hospital discharge ($p < 0.001$). The results were similar at 18 and 24 months (Table 4), although most infants who required a G-tube at any time point had the tube placed by 12 months. Of note, some children who previously required placement of a G-tube for a portion of their nutrition were able to have the G-tube removed by 24 months if full oral feeds were achieved.

Outpatient feeding therapy as a predictor of decreased reliance on feeding technology

Among infants with the inability to take full oral feeds by the time of hospital discharge, information on long-term outpatient feeding therapy was available for 40 infants (75.5% of infants) and 33/40 (82.5%) received outpatient feeding therapy by 24 months. None of the seven infants who did not receive outpatient feeding therapy versus 20/33 (60.6%) of infants who did receive outpatient feeding therapy required a G-tube by 24 months. Half of the infants

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 2. Association between brainstem injury and ability to take oral feeds by the time of discharge from the neonatal seizure admission

Seizure etiology	Number with brainstem injury with full oral feeds	Number with brainstem injury with some/no oral feeds	OR (95% CI)	*p* value (unadjusted)	OR (95% CI)[a]	*p* value (adjusted)[a]
All etiologies	23/182 (12.6%)	9/34 (18.9%)	0.40 (0.17, 0.97)	0.04	0.56 (0.18, 1.77)	0.32
HIE ($n = 96$)	7/80 (8.8%)	7/16 (30.8%)	0.12 (0.04, 0.43)	0.001	0.14 (0.02, 0.81)	0.03
Stroke ($n = 52$)[b]	14/47 (29.8%)	0/5 (0.0%)	4.76 (0.25, 91.87)	0.30	4.07 (0.25, 66.53)	0.33
Intracranial hemorrhage ($n = 40$)[b]	1/32 (3.1%)	1/15 (6.7%)	0.24 (0.02, 2.62)	0.24	0.83 (0.01, 63.01)	0.93
Other ($n = 28$)[b]	1/22 (4.3%)	1/5 (20.0%)	0.20 (0.02, 2.39)	0.20	0.18 (0.005, 6.92)	0.36

[a]Adjusted for gestational age, worst EEG background documented in EEG report during first 24 h, and tone on exam at discharge.
[b]Firth's bias-reduced logistic regression applied due to low cell frequencies of brainstem injury, using R package *logistf*.
CI, confidence interval; EEG, electroencephalogram; HIE, hypoxic–ischemic encephalopathy; OR, odds ratio.

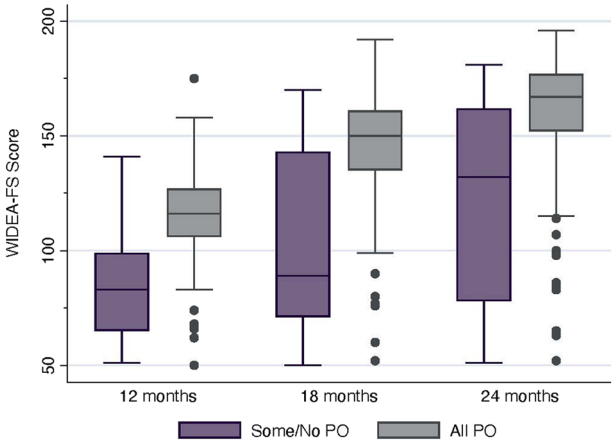

Figure 1. Boxplots of WIDEA-FS at 12, 18, and 24 months corrected age by oral feeding status at hospital discharge among 276 survivors of acute symptomatic neonatal seizures. The average total WIDEA-FS in a typically developing population is 172 ± 10 points at 24 months. The horizontal line within the box represents the median. The top and bottom of the boxes represent the 25th and 75th percentiles (IQR) and whiskers extend to the smallest and largest value that is no more than 1.5 times the IQR. IQR, interquartile range; PO, oral feeds; WIDEA-FS, Warner Initial Developmental Evaluation of Adaptive and Functional Skills.

Table 3. Multivariable analysis of neonatal predictors of total WIDEA-FS scores

Variable	β-coefficient	SE	*p* value
Full oral feeds upon neonatal discharge	11.31	4.02	0.005
Gestational age	1.85	0.40	<0.001
Abnormal tone	–11.65	3.001	<0.001
Worst EEG background: mild/moderately abnormal compared to normal	–7.82	4.72	0.10
Worst EEG background: severely abnormal compared to normal	–20.04	5.74	0.001
Worst EEG background: status epilepticus at onset compared to normal	–9.57	6.46	0.14
Interaction: change from 12–18 months by full oral feeds	13.71	3.14	<0.001
Interaction: change from 18–24 months by full oral feeds	12.69	3.95	0.001

EEG, electroencephalogram; WIDEA-FS, Warner Initial Developmental Evaluation of Adaptive and Functional Skills.

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Table 4. Inability to take full oral feeds by the time of discharge from the neonatal seizure admission was associated with the need for G-tube placement by age 24 months

	Full oral feeds at neonatal discharge ($n = 221$)	Some/no oral feeds at neonatal discharge ($n = 49$)	p value
Feeding outcome at 12 months			
Full oral feeds	219 (99.1%)	26 (53.1%)	<0.001
G-tube present	2 (0.9%)	23 (46.9%)	
Feeding outcome at 18 months			
Full oral feeds	218 (98.6%)	29 (59.2%)	<0.001
G-tube present[a]	3 (1.4%)	20 (40.8%)	
Feeding outcome at 24 months			
Full oral feeds	218 (98.6%)	31 (63.3%)	<0.001
G-tube present[a]	3 (1.4%)	18 (36.7%)	

[a]Some children had G-tube removed when no longer clinically indicated.
G-tube, gastrostomy tube.

who participated in outpatient feeding therapy (17/33, 51.5%) were able to achieve full oral feeds by 24 months. Some children who initially required a G-tube were able to achieve full oral feeds with feeding therapy by 24 months.

Discussion

In this secondary analysis of a prospective, multicenter study of infants who survived acute symptomatic neonatal seizures, the inability to take full oral feeds by the time of hospital discharge was a risk factor for abnormal neurodevelopment. Total WIDEA-FS score and five of the six WIDEA-FS subscales showed significant and increasing differences over time between the infants who took full oral feeds by the time of hospital discharge and those who did not. This finding is consistent with reports that lack of oral feeding is an early neonatal marker of adverse developmental milestone achievement among premature infants.[24–26] For the primary analysis of the parent NSR study, a 12-point (0.5 SD) reduction in WIDEA-FS scores was considered clinically significant by our stakeholder partners; the differences found between our two feeding groups were more than triple this difference (38.4 points).[13,27]

Parents of neonates with seizures report that uncertainty about the future is a major stressor.[16,28,29] We provide a new, objective predictor of outcome: the ability to take oral feeds. Early identification of infants who are at risk for a long transition time to oral feeds could provide early opportunities for oral motor intervention before feeding issues develop,[30] and distinguish infants who are at high risk for impaired functional development.

It is intuitive that infants who were unable to achieve full oral feeds at the time of discharge are more likely to need a G-tube later in their clinical course compared with infants who were taking full oral feeds at discharge. However, it was noteworthy that fewer than half of infants who initially did not achieve full oral feeds required G-tube placement at 12 months of age. This finding has important implications for parent counseling and underscores the potential role of early intervention to support infants as feeding skills evolve.

A G-tube was placed by age 12 months in about half of the infants who did not achieve full oral feeds by the time of discharge from the neonatal seizure admission. However, half of the infants who participated in outpatient feeding therapy were able to achieve full oral feeds by 24 months. A direct comparison cannot be made between premature infants with feeding difficulties and infants with seizures with feeding difficulties, as the reasons for the feeding difficulties may differ. For example, in infants with seizures, feeding difficulties may be related to underlying brain injury, but in infants with prematurity, feeding difficulties may be related to other factors, such as prolonged intubation and oral aversion. However, the result of our study supports existing data that feeding outcomes continue to improve into a child's second year of life. For example, in an analysis of extremely low birthweight infants from 25 centers, among infants who required a G-tube, 32% eventually achieved full oral feeds at the time of follow-up.[31] In another study, 40% of preterm infants that were referred to a neonatal feeding program were discharged home from the neonatal intensive care unit on G-tube feeds with 22% achieving full oral feeds by 1 year of age, with the authors suggesting that a feeding intervention after G-tube placement improves long-term feeding outcomes.[11] Of note, in a retrospective review of infants requiring NG tube feeds in the first 6 months of life, medical complications were significantly correlated with a longer time to transition from NG tube feeding to full oral feeding.[30]

In prior single-center studies, infants with HIE and stroke who had brainstem injury were more likely to need G-tube feeding later in life than those without brainstem injury.[6–8,32] We replicated this finding in a subgroup

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

analysis of neonates with HIE. Although the presence of brainstem injury on MRI was associated with the inability to achieve full oral feeds by the time of discharge from the initial hospital admission for neonatal seizures across all etiologies on initial analysis, the association was no longer significant after adjustment in multivariable analysis, which may be related to the large number of patients with HIE in our study and fewer patients with other etiologies.

Our study is strengthened by the prospective, multicenter enrollment of infants who survived acute symptomatic neonatal seizures due to a range of etiologies. However, the long-term feeding outcomes were gathered retrospectively. This limitation prohibited the collection of more detailed information that might differentiate the severity of feeding dysfunction (e.g., percentage of nutrition delivered via feeding tube vs. by mouth at the determined time points). In addition, the study was not designed to determine the influence of outpatient feeding therapy on the ability to achieve full oral intake given that therapies themselves, and access to those services, may differ across centers. Finally, small subgroup sizes or heterogeneity of imaging protocols and timing of MRI across sites may have limited our ability to detect associations between brainstem injury and abnormal feeding in some etiologic subgroups.

Conclusion

The inability to take full oral feeds by the time of initial hospital discharge is a marker for future neurodevelopmental challenges and the likelihood of needing feeding technology for neonates with acute symptomatic seizures. Brainstem injury was associated with feeding dysfunction in infants with HIE; about one-third of infants with brainstem injury in the setting of HIE did not achieve full oral feeds before discharge. This information will be helpful for counseling parents regarding developmental outcomes. Infants who did not achieve full oral feeds at the time of discharge were more likely to need long-term feeding technology in the future, with half requiring placement of a G-tube at 24 months corrected age. Future directions may include a trial of intensive feeding therapy for this population of children.

Author Contributions

Katelyn H. Roberts: Conceptualization; methodology; writing – original draft. **John D. E. Barks**: Conceptualization; methodology; writing – review and editing. **Hannah C. Glass**: Funding acquisition; writing – review and editing. **Janet S. Soul**: Writing – review and editing. **Taeun Chang**: Writing – review and editing. **Courtney J. Wusthoff**: Writing – review and editing. **Catherine J. Chu**: Writing – review and editing. **Shavonne L. Massey**: Writing – review and editing. **Nicholas S. Abend**: Writing – review and editing. **Monica E. Lemmon**: Writing – review and editing. **Cameron Thomas**: Writing – review and editing. **Ronnie Guillet**: Writing – review and editing. **Elizabeth E. Rogers**: Writing – review and editing. **Linda S. Franck**: Writing – review and editing. **Harlan McCaffery**: Formal analysis; writing – review and editing. **Yi Li**: Methodology; writing – review and editing. **Charles E. McCulloch**: Methodology; writing – review and editing. **Renée A. Shellhaas**: Conceptualization; funding acquisition; methodology; resources; writing – review and editing.

Acknowledgments

The Neonatal Seizure Registry research team is grateful to the children and families who participated in this study, our dedicated parent partners, and the hardworking clinical research coordinators at every study site. This work was supported by the Patient-Centered Outcomes Research Institute under contract number 2015C2-1507-31187. Dr. Wusthoff, a coauthor of this work, was supported by the National Institute of Neurological Disorders and Stroke under Grant 5K02NS102598. Dr. Lemmon, a coauthor of this work, was supported by the NIH under Grant K23NS116453.

Conflicts of Interest

John D. E. Barks and Hannah C. Glass receive research support from NIH. Catherine J. Chu receives research support from Biogen Inc. and NIH. Monica E. Lemmon receives research support from NIH (K23NS116453). Cameron Thomas receives research support through NIH and UCB. Renée A. Shellhaas receives research support from NIH. She receives royalties from UpToDate for authorship of topics related to neonatal seizures, serves as a consultant for the Epilepsy Study Consortium, and is president-elect of the Pediatric Epilepsy Research Foundation. The remaining authors declare no conflict of interest.

ORCID

Janet S. Soul http://orcid.org/0000-0001-6998-7753
Monica E. Lemmon http://orcid.org/0000-0001-6253-775X
Renée A. Shellhaas http://orcid.org/0000-0002-3175-3908

References

1. Saliba RM, Annegers JF, Waller DK, Tyson JE, Mizrahi EM. Incidence of neonatal seizures in Harris County, Texas, 1992–1994. *Am J Epidemiol*. 1999;150(7):763-769.
2. Glass HC, Shellhaas RA, Wusthoff CJ, et al. Contemporary profile of seizures in neonates: a prospective cohort study. *J Pediatr*. 2016;174:98-103.e1.

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3. Shellhaas RA. Seizure classification, etiology, and management. *Handb Clin Neurol*. 2019;162:347-361.
4. Lanska MJ, Lanska DJ, Baumann RJ, Kryscio RJ. A population-based study of neonatal seizures in Fayette County, Kentucky. *Neurology*. 1995;45(4):724-732.
5. Ronen GM, Buckley D, Penney S, Streiner DL. Long-term prognosis in children with neonatal seizures: a population-based study. *Neurology*. 2007;69(19):1816-1822.
6. Barkat-Masih M, Saha C, Hamby DK, Ofner S, Golomb MR. Feeding problems in children with neonatal arterial ischemic stroke. *J Child Neurol*. 2010;25(7):867-872.
7. Gupta S, Bapuraj JR, Carlson G, Trumpower E, Dechert RE, Sarkar S. Predicting the need for home gavage or g-tube feeds in asphyxiated neonates treated with therapeutic hypothermia. *J Perinatol*. 2018;38(6):728-733.
8. Sarkar S, Bhagat I, Bapuraj JR, Dechert RE, Donn SM. Does clinical status 1 week after therapeutic hypothermia predict brain MRI abnormalities? *J Perinatol*. 2013;33(7):538-542.
9. Wolthuis-Stigter MI, Luinge MR, da Costa SP, Krijnen WP, van der Schans CP, Bos AF. The association between sucking behavior in preterm infants and neurodevelopmental outcomes at 2 years of age. *J Pediatr*. 2015;166(1):26-30.e1.
10. Patra K, Greene MM. Impact of feeding difficulties in the NICU on neurodevelopmental outcomes at 8 and 20 months corrected age in extremely low gestational age infants. *J Perinatol*. 2019;39(9):1241-1248.
11. Jadcherla SR, Khot T, Moore R, Malkar M, Gulati IK, Slaughter JL. Feeding methods at discharge predict long-term feeding and neurodevelopmental outcomes in preterm infants referred for gastrostomy evaluation. *J Pediatr*. 2017;181:125-130.e1.
12. Shellhaas RA, Chang T, Tsuchida T, et al. The American Clinical Neurophysiology Society's Guideline on continuous electroencephalography monitoring in neonates. *J Clin Neurophysiol*. 2011;28(6):611-617.
13. Glass HC, Soul JS, Chang T, et al. Safety of early discontinuation of antiseizure medication after acute symptomatic neonatal seizures. *JAMA Neurol*. 2021;78(7):817-825.
14. Shellhaas RA, Wusthoff CJ, Tsuchida TN, et al. Profile of neonatal epilepsies: characteristics of a prospective US cohort. *Neurology*. 2017;89(9):893-899.
15. Lemmon ME, Bonifacio SL, Shellhaas RA, et al. Characterization of death in infants with neonatal seizures. *Pediatr Neurol*. 2020;113:21-25.
16. Lemmon M, Glass H, Shellhaas RA, et al. Parent experience of caring for neonates with seizures. *Arch Dis Child Fetal Neonatal Ed*. 2020;105(6):634-639.
17. Glass HC, Grinspan ZM, Li Y, et al. Risk for infantile spasms after acute symptomatic neonatal seizures. *Epilepsia*. 2020;61(12):2774-2784.
18. Jadcherla SR, Vijayapal AS, Leuthner S. Feeding abilities in neonates with congenital heart disease: a retrospective study. *J Perinatol*. 2009;29(2):112-118.
19. Natarajan G, Reddy Anne S, Aggarwal S. Enteral feeding of neonates with congenital heart disease. *Neonatology*. 2010;98(4):330-336.
20. Hsieh A, Tabbutt S, Xu D, et al. Impact of perioperative brain injury and development on feeding modality in infants with single ventricle heart disease. *J Am Heart Assoc*. 2019;8(10):e012291.
21. Peyton C, Wroblewski K, Park J, et al. Validity of the Warner Initial Developmental Evaluation of Adaptive and Functional Skills (WIDEA-FS): a daily activity criterion checklist for infants and toddlers. *Pediatr Res*. 2021;90(5):1052-1057.
22. Msall ME. Measuring functional skills in preschool children at risk for neurodevelopmental disabilities. *Ment Retard Dev Disabil Res Rev*. 2005;11(3):263-273.
23. Peyton C, Msall ME, Wroblewski K, Rogers EE, Kohn M, Glass HC. Concurrent validity of the Warner Initial Developmental Evaluation of Adaptive and Functional Skills and the Bayley Scales of Infant and Toddler Development, Third Edition. *Dev Med Child Neurol*. 2021;63(3):349-354.
24. Dodrill P, McMahon S, Ward E, Weir K, Donovan T, Riddle B. Long-term oral sensitivity and feeding skills of low-risk pre-term infants. *Early Hum Dev*. 2004;76(1):23-37.
25. Jadcherla SR, Wang M, Vijayapal AS, Leuthner SR. Impact of prematurity and co-morbidities on feeding milestones in neonates: a retrospective study. *J Perinatol*. 2010;30(3):201-208.
26. DeMauro SB, Patel PR, Medoff-Cooper B, Posencheg M, Abbasi S. Postdischarge feeding patterns in early- and late-preterm infants. *Clin Pediatr*. 2011;50(10):957-962.
27. Shellhaas RA, Soul JS, Chang T, et al. *Looking at the Effect of Treatment Duration for Newborn Infants Who Have Seizures*. Patient-Centered Outcomes Research Institute (PCORI); 2021. Accessed December 5, 2022. Available online at: www.pcori.org/sites/default/files/ShellhaasGlass374-Final-Research-Report.pdf
28. Hill E, Glass HC, Kelley K, et al. Seizures and antiseizure medications are important to parents of newborns with seizures. *Pediatr Neurol*. 2017;67:40-44.
29. Lemmon ME, Glass HC, Shellhaas RA, et al. Family-centered care for children and families impacted by neonatal seizures: advice from parents. *Pediatr Neurol*. 2021;124:26-32.
30. Bazyk S. Factors associated with the transition to oral feeding in infants fed by nasogastric tubes. *Am J Occup Ther*. 1990;44(12):1070-1078.
31. Warren MG, Do B, Das A, et al. Gastrostomy tube feeding in extremely low birthweight infants: frequency, associated comorbidities, and long-term outcomes. *J Pediatr*. 2019;214:41-46.e5.

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

32. Martinez-Biarge M, Diez-Sebastian J, Wusthoff CJ, et al. Feeding and communication impairments in infants with central grey matter lesions following perinatal hypoxic–ischaemic injury. *Eur J Paediatr Neurol*. 2012;16(6):688-696.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

© 2022 The Authors. *Annals of the Child Neurology Society* published by Wiley Periodicals LLC on behalf of the Child Neurology Society.

28313267, 0, Downloaded from https://onlinelibrary.wiley.com/doi/10.1002/cns3.6, Wiley Online Library on [04/01/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License