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Primary care developmental screening of term and late preterm nicu graduates

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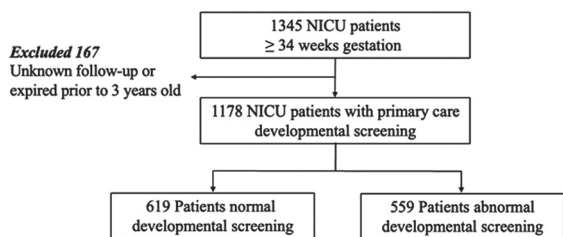
BACKGROUND: Infants ≥ 34 weeks gestation are at relatively low-risk for developmental delay and do not qualify for high-risk infant follow-up based on prematurity alone. However, with prolonged neonatal intensive care unit (NICU) hospitalization and life-sustaining interventions, there is an increased risk for neurodevelopmental impairment in this population. Currently, there is no standardized risk stratification to predict which infants ≥ 34 weeks gestation are at highest risk for delays. We aim to compare key clinical characteristics of infants with normal vs. abnormal developmental screening in the primary care setting. Our secondary aim is to identify which infants in this cohort would benefit most from early developmental intervention.

We hypothesize that gestational age alone is not predictive of normal development.

METHODS: We performed a retrospective cohort study of infants born ≥ 34 weeks gestation between 1/2013-12/2015, admitted to the Children's Wisconsin (CW) NICU, and followed by a Wisconsin-based primary care provider for routine developmental screening at 3-6 years of age. Developmental screening results reported either in the primary care visit note or any CW subspecialty clinic note were included for analysis. Screening was considered abnormal if developmental concerns in cognition, motor, language, and/or social domains were documented. In addition, neonatal diagnoses, procedures, and clinical characteristics were extracted. Mann Whitney, Chi-Square, and Fisher's exact tests were used to compare patients with normal vs. abnormal preschool age development.

RESULTS: We screened 1345 NICU infant charts, and 88% received primary care developmental screening (Figure 1). We identified 559 (47%) infants with abnormal

Figure 1. Study cohort



developmental screening results. Infants with abnormal developmental screens were more likely to have an antenatal congenital anomaly (32% vs. 54%, $p<0.001$), NICU surgical procedure (26% vs. 38%, $p<0.001$), prolonged length of NICU stay (6 days vs. 11 days, $p<0.001$), or more than one subspecialist appointment after discharge (1 vs. 2, $p<0.001$) (Table 1). The most common diagnoses in patients with abnormal development were congenital heart disease and ventriculomegaly. At discharge, only 15% of infants with abnormal developmental screens were referred to NICU follow-up clinic and only 22% were referred to physical, occupational, speech, or NICU follow-up services.

CONCLUSION: NICU characteristics negatively impact developmental screening in a presumed low-risk population. These results can be used to revise current

NICU follow-up inclusion criteria and improve developmental outcomes through early intervention services.

Parental holding of infants with Hypoxic Ischemic Encephalopathy (HIE) during therapeutic hypothermia

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BACKGROUND AND PURPOSE: Therapeutic hypothermia (TH) is the only treatment shown to reduce mortality and disability in affected infants and improves neurologic outcome for term and near-term infants with moderate to severe HIE. Historically, parents have not held their infants during TH for a variety of reasons including the potential to warm the infant, extra efforts required to securely transfer infant from the bed to the parent, and due to safety concerns related to possible equipment dislodgement. Simultaneously, parents may feel a loss of normalcy and have an impaired ability to bond with their infant. The purpose of this study was to determine the feasibility of parental holding during TH by monitoring vital sign stability and to assess parental attitudes around holding.

Table 1. Infant diagnoses, procedures, and characteristics compared between normal vs. abnormal developmental screening.

	Normal Developmental Screening (n= 619)	Abnormal Developmental Screening (n= 559)	P-value
Gestation Age at Delivery (weeks)	38 [36, 39]	38 [36, 39] [^]	0.505
Birthweight (grams)	3100 [2565.0, 3550.0]	3040 [2592, 3485] [^]	0.415
Male Sex	334 (54%)	320 (57%) ⁺	0.290
Apgar Scores			
1 Minute	8 [5, 8]	7 [5, 8] [^]	0.255
5 Minute	9 [8, 9]	9 [7, 9] [^]	0.106
Antenatal congenital anomaly identified (n)	194 (32%)	296 (54%) ⁺	<0.001
Primary NICU Diagnosis			
Hypoxic Ischemic Encephalopathy	14 (2%)	15 (3%) [#]	0.781
Neonatal Seizures	24 (4%)	42 (8%) [#]	0.010
Ventriculomegaly	6 (1%)	30 (5%) [#]	<0.001
Myelomeningocele	6 (1%)	19 (2%) [#]	0.007
Congenital Heart Disease	74 (12%)	194 (35%) [#]	<0.001
Surgical Procedure while in the NICU (n)	163 (26%)	210 (38%) ⁺	<0.001
Ambulatory Subspecialist Appointments at Discharge (n)	1 [0, 1]	2 [1, 4] [^]	<0.001
NICU Follow Up Clinic appointment scheduled (n)	54 (9%)	82 (15%) ⁺	0.002
Physical, Occupational, Speech Therapy, Birth-to-3, or Developmental Follow-up at Discharge (n)	72 (12%)	125 (22%) ⁺	<0.001
Length of Hospital Stay (days)	6 [3, 15]	11 [3, 26] [^]	<0.001

[^] indicates Mann Whitney test, ⁺ indicates Chi-Square test, [#] indicates Fisher's exact test.

Data is presented as median [IQR] or count (%).

MATERIALS OR METHODOLOGIES: From 2018 until 2021 we used an algorithm to determine holding eligibility of infants. Written informed parental consent was obtained for all patients. Parents of enrolled subjects were encouraged to commit a minimum of 1 consecutive hour of holding. During the maintenance phase of TH heart rate, core temperature, oxygen saturations and regional saturations (cerebral) were recorded for one hour before holding, during the holding experience, and for one hour after holding. Synchronized data were collected from the Philips bedside monitor, INVOS NIRS monitor, and Blanketrol III using the Moberg Component Neuromonitoring System (CNS). Infants remained on the cooling blanket atop of a pillow in the parent's lap during holding. After the holding event(s) a parent survey was administered, and responses were deidentified to encourage candid feedback.

RESULTS: We enrolled 24 infants in our study and recorded 40 holding events during the maintenance phase of TH. Eleven infants were held more than once. Five infants had seizures during TH but none while being held. There were no adverse events and no significant vital sign disturbances associated with holding during TH. While 11% of parents reported anxiety about potentially adversely affecting their infants during holding, 88% of respondents felt it was very important to hold their infant at least once per day/visit if deemed medically safe to do so. Furthermore, 86% reported holding their infant significantly improved their emotional and/or physical well-being. 100% of respondents indicated that the holding experience had a significant positive impact or some positive effect on their infant. 8% of mothers even reported an associated increase in milk production.

CONCLUSIONS/IMPACT: This study found holding infants during therapeutic hypothermia can be done safely for infants with HIE and can provide feelings of emotional well-being to NICU parents.

REFERENCES

- [1] Craig, Alexa K. et al. Maternal Holding During Therapeutic Hypothermia for Infants with Neonatal Encephalopathy is Feasible. *Acta Paediatrica*. 2019; 108 (9):1597-1602.

Neonatal imitation of late preterm infants and its prognostic value

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Newborn infants can imitate the modeled gesture even within the first hours of life following birth. This mimicry mechanism is called neonatal imitation (NI). Imitation of an action that was not learned indicates that newborns can see and demonstrate proprioception and perceptual-motor coordination and match it with the model. In this study, we investigated the presence of NI in healthy late-preterm newborns, compared their NI responses with healthy term infants, and explored its prognostic value with follow-up visits. 36 term and 36 late preterm infants were included. NI responses were tested within 12-72 hours after birth. Babies with congenital anomalies and infants hospitalized and lost interest during the study period were excluded from the study. The test was performed in a quiet, adequately lit environment when the infants were awake, fed, and calm. The model showed gestures to the infants for 20 seconds, then stood with a neutral face for 20 seconds. The test continued for 4 minutes for each gesture. A researcher scored the video recordings according to the criteria specified in the literature³. 23 late preterm and 27 term infants were tested for two facial gestures: Mouth opening (MO) and tongue protrusion (TP) (Figure 1). Infants were followed-up until postmenstrual 51 weeks and evaluated twice at postmenstrual 45th and 51st weeks for Prechtl's General Movements Assessment. Both groups yielded a significantly higher number of TP responses following the TP gesture of the model ($p < 0.001$, $p = 0.017$). (Table 1). The TP responses of late preterm and term infants were 19(82%) and 20 (74%), respectively, whereas only 9 out of 23 (39%) preterm infants and 15 out of 27 (55%) term infants displayed NI responses for MO. In the follow-up, one of the preterm infants displayed poor repertoire movement, and one of the term infants had cramp synchronized pattern general movements; nevertheless, both had a positive response for TP in the neonatal period. In conclusion, late preterm displayed similar NI responses compared to term newborns. NI scores did not show a correlation with GM assessments in our study. The differences in NI and its prognostic significance can be better understood through longitudinal follow-up and further studies in larger patient groups.



Figure 1. Late preterm infant response to modeling gesture (TP, MO, and Neutral face)

	Response	Model Gesture		P	Model Gesture		P
		TP	MO		M	SD	
Late	TP	11,13	8,813	<0,001	6,35	5,416	0,170
preterm	MO	3,30	2,687		4,48	3,436	
Term	TP	9,93	9,261	0,017	6,81	8,663	0,570
	MO	4,93	4,755		5,70	4,983	

Table 1. Comparison of NI responses to the model gesture

REFERENCES

- [1] Heimann M, Nelson Ke, Schaller J. Neonatal Imitation Of Tongue Protrusion And Mouth Opening: Methodological Aspects And Evidence Of Early Individual Differences. *Scand J Psychol.* 1989;30(2):90-101. Doi:10.1111/J.1467-9450.1989.Tb01072.X
- [2] Einspieler C, Prechtl Hfr. Prechtl's Assessment Of General Movements: A Diagnostic Tool For The Functional Assessment Of The Young Nervous System. *Ment Retard Dev Disabil Res Rev.* 2005;11(1):61-67. Doi:10.1002/Mrdd.20051
- [3] Meltzoff An, Moore Mk. Imitation In Newborn Infants: Exploring The Range Of Gestures Imitated And The Underlying Mechanisms. *Dev Psychol.* 1989;25(6):954-962. Doi:10.1037/0012-1649.25.6.954

Challenges in recruitment for an acute neonatal seizure trial

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BACKGROUND: Newborns have one of highest rates of seizures across childhood, which can put them at risk for epilepsy and neurodevelopmental disabilities later in life.¹ Despite this, neonatal seizure treatment trials are rarely conducted due to ethical considerations, difficulties in trial design, and limited hospital resources and personnel.²⁻⁴ We highlight a single center's experience and the challenges encountered in screening, enrolling, and consenting for an acute neonatal seizure treatment trial.

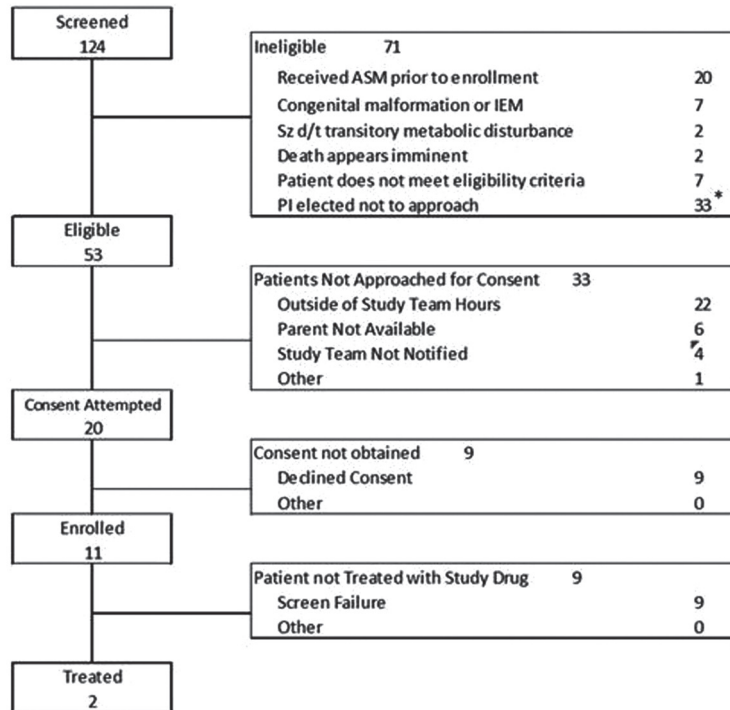
METHODS: Children's National (CN) is the lead site of an acute symptomatic neonatal seizure trial for a new

formulation of phenobarbital. Two physician investigators and two study coordinators at CN screened patients being transferred for continuous video electrographic encephalography (EEG) in the NICU between 1/24/2022 and 9/12/2022. Starting July 1st, the study team implemented updated consenting methods by presenting patients' parents with condensed study information. The study team recorded each patient's date and time of arrival, eligibility status, reason consent was declined, and reasons eligible patients were not approached (study team unavailable, parent or guardian not available, the study team not notified, or other). Study team screening hours were between 6:00 and 23:00 including weekends and holidays. Eligible patients were tracked for date and time of first EEG seizure.

RESULTS: Of the 124 patients screened, 53 were eligible for the study (Fig 1). 53% (28/53) arrived at CN NICU between 18:00 and 6:00 (Fig 2). Twenty of those eligible were approached for consent, 11 consented and 2 patients received study drug (Fig 1). The reasons eligible patients were not enrolled are as follows: patient arrived outside of study team hours (22/42=52%); parent declined consent (9/42=21%); unavailable parent (6/42=14%); lack of study team notification of patient (4/42=10%); and expiration of study drug (1/33=3%) (Fig 3). Some of these patients went on to have seizures within the time they would have been eligible to receive study drug (Fig 3). Study team availability was 76% on weekdays and 64% during off hours (weekends and holidays). 67% of the time the team was unavailable due to Investigational Drug Services restricting screening to business hours for the first 28 days of the study and unexpected death of one of the co-investigators pausing screening for 16 days. These 44 days account for 17 out of the 22 patients that arrived outside of study team hours. Condensing the consent script in July increased our study enrollment from 45% to 71%. There was no correlation in the consent rate between consent conducted in-person compared to consent conducted over the phone.

CONCLUSION: Limited availability of study staff after hours (18:00-6:00) is a major impediment to enrolling neonates in an acute seizure trial. A shorter, focused consent script increased study enrollment both in person and over the phone.

CONSORT Diagram (1/24/2022-9/12/2022)



*Low likelihood of developing seizures or high likelihood to need a benzodiazepine for sedation

Figure 1. The flow chart of patients screened to treated.

REFERENCES

- [1] Uria-Avellanal C., Marlow N., Rennie J. M. Outcome following neonatal seizures. Semin. Fetal Neonatal Med. 2013; 18, 224–232.
- [2] Laventhal N., Tarini B. A., Lantos J. Ethical issues in neonatal and pediatric clinical trials. Pediatr. Clin. North Am. 2012; 59, 1205–1220.
- [3] Amin S. B., McDermott M. P., Shamoo A. E. Clinical trials of drugs used off label in neonates: ethical issues and alternative study designs. Account. Res. 2008; 15, 168–187.
- [4] Soul JS, Pressler R, Allen M, Boylan G, Rabe H, Portman R, Hardy P, Zohar S, Romero K, Tseng B,

Bhatt-Mehta V, Hahn C, Denne S, Auvin S, Vinks A, Lantos J, Marlow N, Davis JM; International Neonatal Consortium. Recommendations for the design of therapeutic trials for neonatal seizures. Pediatr Res. 2019; 85(7), 943-954.

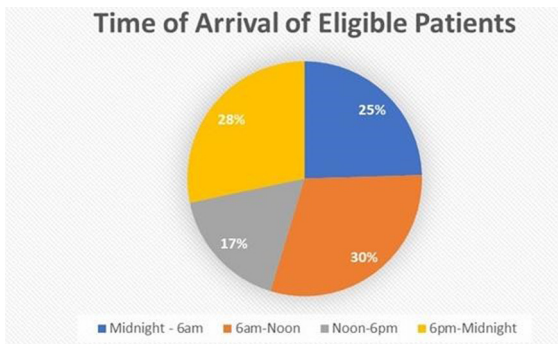


Figure 2. Time of arrival of all eligible patients from 1/24/2022 – 9/12/2022 (n=53)

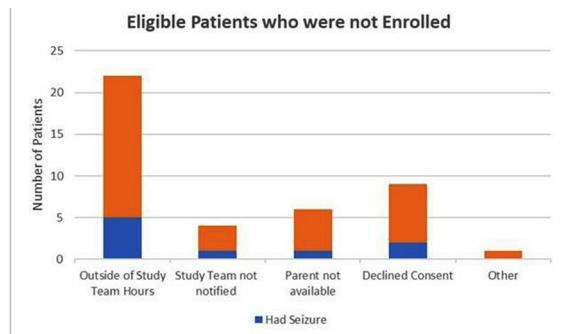


Figure 3 . 42 total eligible patients were not enrolled in the study, and 9 of them went on to have seizures within 24 hours of EEG placement. 22 patients arrived outside of study team hours, and 5 of those patients had seizures. The study team was not notified for 4 patients, and 1 of those patients had a seizure. The parent was not available for 6 patients, and 1 of those patients had a seizure. 9 parents were approached for consent by the study team, and 2 of those patients had seizures. Finally, 1 patient who did not seize arrived when there was expired study drug and did not end up having seizures.

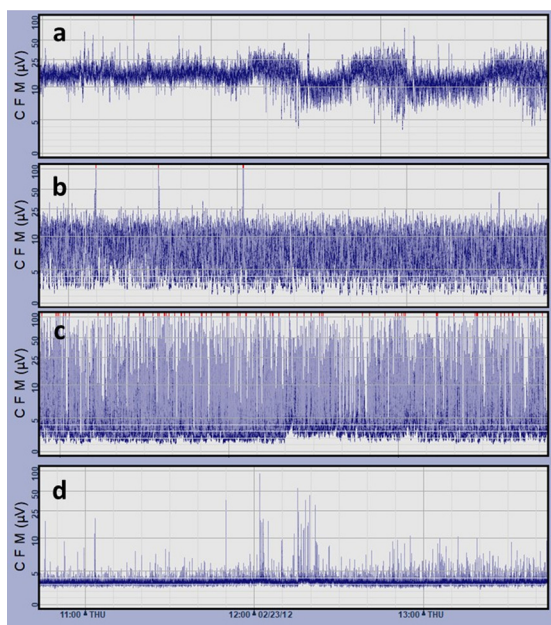
Long term neurodevelopment and predictors of outcome in a single center cohort of infants with neonatal encephalopathy

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BACKGROUND AND PURPOSE: Neonatal encephalopathy (NE) is a leading cause of mortality and morbidity worldwide. Throughout the years different bio and electrophysiological markers such as amplitude integrated EEG (aEEG), conventional EEG, evoked potentials, magnetic resonance imaging (MRI) and physical examination were found to have significant predictive ability for long term neurodevelopmental outcome. The purpose of this study was to assess the distinct and combined contribution of different markers for prediction of long-term outcome.

MATERIALS OR METHODOLOGY: Infants born after 35 weeks of gestation, between November 2014 and May 2019 in Soroka medical Center, Beer-Sheva, Israel, diagnosed with moderate to severe NE of presumed hypoxic ischemic origin, monitored with aEEG and with brain MRI before 10 days of age were included in the study. Infants with cerebral malformations/hemorrhage/infection/stroke, inborn error of metabolism or genetic disorder were excluded.



Early life demographic and clinical data were prospectively collected. Continuous neuromonitoring with aEEG (figure 1) during the first 4 days of life was assessed for seizures and daily background activity was dichotomized to:

1. Normal/near normal: Continuous or discontinuous background
2. Abnormal: Burst suppression, low voltage or isoelectric background Early life MRI (table 2) was scored according to a modified Rutherford et al. scoring that included diffusion sequences and dichotomized to:
3. Normal/mild abnormalities
4. Moderate to severe abnormalities

Outcome after 2 years of age was assessed using data collected from the child developmental center, medical records and personal communication with parents and dichotomized to: 1. Normal/mildly abnormal, 2. Moderately/severely abnormal. Clinical data as described in table 3 was used to categorize outcome. Multivariable binary logistic regression was performed on the basis of univariable analysis to develop the best predictive model for long term outcome.

RESULTS: Sixty-three out of 76 infants were included in the study. Eleven (17.5%) and 29 (46%) had good or mildly impaired outcome respectively, 3 (4.8%) and 20 (31.77%) had moderate or severe outcome respectively (including 9 (24.3%) who died). Univariable model is presented in table 4. In multivariable models, best combined predictors of outcome were: 5 minutes Apgar score ($p=0.004$), aEEG at the second day of life ($p<0.001$) and MRI ($p<0.001$).

CONCLUSION AND IMPACT: Despite improvement in intensive care and the advent of hypothermia, early biomarkers are significantly associated with outcome. International and national registries of neonatal encephalopathy with long term outcome are important tools for monitoring trends, changes and new therapies.

REFERENCES

- [1] Hamelin S et al. *Neurophysiol Clin.* 2011 Feb;41(1):19-27.
- [2] Kontio T et al. *Clin Neurophysiol.* 2013 Jun;124(6): 1089-94.
- [3] Shankaran S et al. *J Pediatr.* 2015 Nov;167(5):987-93.
- [4] Rutherford M et al. *Lancet Neurol.* 2010;9(1):39-45
- [5] Okerefor A, et al. *Pediatrics.* 2008;121(5):906-14.

Table 1: Modified Rutherford score

Score	0	1	2	3
White Matter	Normal	Abnormal signal in periventricular white matter	Abnormal signal extending to subcortical regions or focal punctuate lesions/infarcts	Severe widespread abnormal signal, overt infarct or hemorrhage
Grey Matter	Normal	Abnormal signal intensity, including highlighting in no more than two regions	Abnormal signal intensity, including highlighting in 3 regions	Abnormal signal intensity, including highlighting in more than 3 regions
Basal Ganglia	Normal	Focal abnormal signal intensity	Multi-focal abnormal signal intensity	Widespread abnormal signal intensity
Posterior limb of internal capsule (PLIC)	Normal	Reduced/ asymmetrical signal intensity	Reversed or abnormal signal intensity bilaterally	Abnormal signal intensity extending outside the PLIC
Corpus Callosum	Normal	Focal signal abnormality in no more than two sites	Extensive signal abnormalities	
Cerebellum	Normal	Focal signal abnormality in no more than two sites	Multifocal signal abnormalities in more than two sites	Severe widespread abnormal signal, overt infarct or hemorrhage
Brain stem	Normal	Abnormal signal restricted to the pyramids	loss of anatomical details, excessive differentiation between anterior and posterior pons, mild/focal	Widespread abnormal signal intensity, abnormal myelination, marked asymmetries
			areas of abnormality, mild asymmetries	

Table 2: scoring system used in assessing neurodevelopmental outcome at the age of two

Variable	Mild	Moderate	Severe
Death before 2y	Alive		Dead
General health	NORMAL	Orthopedic intervention	Respiratory Support
vision	Normal/glasses/squint	Blind one eye	Blind both eyes
hearing	NORMAL/hearing aid		Deaf
Gastrostomy	No		Yes
Weight centile	>10%	3-10%	<3%
Height centile	>10%	3-10%	<3%
Head circumference centile	>10%	3-10%	<3%
Placement	Home/normal nursery	Special education	Institution
Medications	None	Anticonvulsant	
Neurological examination	Normal/mild	Moderate	Severe
GMFCS level	1, 2	3	4, 5
Gross motor	NORMAL	Delayed	Abnormal
Fine motor	Normal \ delayed	Abnormal	
Language	NORMAL	Delayed	Abnormal
Bayley screening test	Competent	Emerging	At risk
Cognitive Tests			

GMSCF: Gross Motor Function Classification System

Table 4: Univariable analysis of predictors for long term outcome

	Moderate/Severe abnormal MRI	Male sex	1 min Apgar ≤3	5 min Apgar ≤5	Depressed aEEG				
					0-6h	6-12h	12-24h	24-48h	48-72h
Good/Mildly Impaired Outcome (n=40)	8 (20%)	32 (80%)	26 (65%)	18 (45%)	28 (70%)	15 (38%)	8 (20%)	6 (15%)	3 (8%)
Moderately/Severely Impaired Outcome (n=23)	20 (87%)	21 (91%)	18 (78%)	19 (82%)	21 (91%)	22 (96%)	20 (87%)	19 (83%)	14 (67%)
Sensitivity/Specificity	91/71%	80/40%	74/41%	84/51%	86/43%	96/60%	91/71%	90/76%	83/82%
P Value	<0.001	0.302	0.394	0.004	0.063	<0.001	<0.001	<0.001	<0.001

Functional brain networks after perinatal stroke: Results from a pilot study

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BACKGROUND AND PURPOSE: An increasing number of studies facilitates functional brain networks to analyze cognitive function in diverse neurological conditions. Focal brain injury seems to impact functional brain networks on a local and a global scale. Long term changes of functional brain networks after perinatal stroke have not been studied extensively so far. Our aim was to explore functional brain networks after perinatal stroke with EEG-based functional connectivity. We were interested in whole brain and intra-hemispheric functional network characteristics.

METHODOLOGY: A test-control pilot study was conducted in a total number of 27 individuals. Inclusion criteria for the test group were: a history of perinatal stroke – either arterial ischemic or hemorrhagic stroke, term delivery, age at inclusion 5-18 years and absence of other neurological disabilities. Inclusion criteria for the control group were: healthy children and adolescents, with no history of brain injury or known neurologic conditions, term delivery and age at inclusion 5-18 years. We recorded a 64-channel resting-state EEG in 27 participants (13 from the test group and 14 from the control group). Individuals from the control group were matched to the test group by age and gender. We processed EEG data and calculated functional connectomes for each participant and analyzed differences in connectome graph metrics between the two groups. Several metrics reflecting network properties were investigated. We were interested in whole brain networks and intra-hemispheric networks (ipsilesional and contralesional). The strength of the inter-hemispheric connections was also studied. We used characteristic path

as a metric reflecting the level of synchronization, clustering coefficient as a metric of network segregation, small-worldness and modularity as metrics of network organization and degree variance as an indirect metric of network topology.

RESULTS: Test group functional networks had indices of higher segregation with increased clustering coefficient and increased small-worldness on both whole brain and intra-hemispheric scale. A more regular topology with lower degree variance was present in functional brain networks of the test group compared to the control group. Ipsilesional hemisphere of the test group also had a more regular topology with lower degree variance compared to the contralesional hemisphere. A total number of inter-hemispheric links was higher in the test group.

CONCLUSION/IMPACT: Our study suggests that perinatal stroke impacts functional brain networks organization and topology in a long term. According to our results, indices of functional brain network disruption persist years after initial brain injury. Our pilot study shows that high-density EEG can be used for investigating functional networks after perinatal stroke. Future studies should focus on exploring the options of using this method for prognostication, especially with trying to find the correlation between functional brain networks characteristics and cognitive outcome in children and adolescents with perinatal stroke.

REFERENCES

- [1] Aerts H, Fias W, Caeyenberghs K, Marinazzo D. Brain networks under attack: Robustness properties and the impact of lesions. *Brain*. 2016;139(12):3063-3083. doi:10.1093/brain/aww194
- [2] Stam CJ. Modern network science of neurological disorders. *Nat Rev Neurosci*. 2014;15(10):683-695. doi:10.1038/nrn3801
- [3] Alstott J, Breakspear M, Hagmann P, Cammoun L, Sporns O. Modeling the impact of lesions in the human brain. *PLoS Comput Biol*. 2009;5(6):e1000408.
- [4] Ilves N, Ilves P, Laugesaar R, et al. Resting-State Functional Connectivity and Cognitive Impairment in

- Children with Perinatal Stroke. *Neural Plast.* 2016;2016. doi:10.1155/2016/2306406
- [5] Saunders J, Carlson HL, Cortese F, Goodyear BG, Kirton A. Imaging functional motor connectivity in hemiparetic children with perinatal stroke. *Hum Brain Mapp.* 2019;40(5):1632-1642.
- [6] van Diessen E, Numan T, van Dellen E, et al. Opportunities and methodological challenges in EEG and MEG resting state functional brain network research. *Clin Neurophysiol.* 2015;126(8):1468-1481. doi:10.1016/j.clinph.2014.11.018
- [7] Haartsen R, van der Velde B, Jones EJH, Johnson MH, Kemner C. Using multiple short epochs optimises the stability of infant EEG connectivity parameters. *Sci Rep.* 2020;10(1):1-13. doi:10.1038/s41598-020-68981-5
- [8] Carvalhaes C, De Barros JA. The surface Laplacian technique in EEG: Theory and methods. *Int J Psychophysiol.* 2015;97(3):174-188. doi:10.1016/j.ijpsycho.2015.04.023
- [9] Vinck M, Oostenveld R, Van Wingerden M, Battaglia F, Pennartz CMA. An improved index of phase-synchronization for electrophysiological data in the presence of volume-conduction, noise and sample-size bias. *Neuroimage.* 2011;55(4):1548-1565. doi:10.1016/j.neuroimage.2011.01.055
- [10] Sporns DO. *Networks of the Brain.*; 2015. doi:10.1017/CBO9781107415324.004
- [11] Rubinov M, Sporns O. Complex network measures of brain connectivity: Uses and interpretations. *Neuroimage.* 2010;52(3):1059-1069. doi:10.1016/j.neuroimage.2009.10.003
- [12] Bullmore E, Sporns O. Complex brain networks: Graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci.* 2009;10(3):186. doi:10.1038/nrn2575

Cerebral Sinovenous thrombosis in the term neonates: Diagnostic and prognostic challenges

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BACKGROUND AND AIM: Our case series represent the experience of one maternity hospital and a referral neonatal neurology centre in the diagnosis and follow up of the cases of cerebral sinovenous thrombosis (CSVT) in term neonates.

MATERIAL AND METHODS: During a 4 years interval, there were diagnosed 4 cases of neonatal CSVT in patients born in the hospital and another 6 cases were referred to our follow up centre. All the cases were referred after extensive cerebral ultrasound training – doctors were trained to recognize the signs pointing to possible CSVT and to ask for second opinion and MRI in these cases. There are presented: the clinical signs and ultrasound and MRI findings in the neonatal period and follow-up, the results of the aEEG monitoring, the results of the coagulation and pro-thrombotic tests, the neurologic outcome of the cases.

RESULTS: 9 out of 10 cases were symptomatic at diagnosis: seizures in 5/10 cases, apnea in 4/10 cases, respiratory distress in 1/10 cases. One case was asymptomatic in the neonatal period- diagnosed at 3 days by ultrasound, the history noted a period of decreased fetal movements one week before delivery. In all the cases, the ultrasound examination suggested the diagnosis – one case bilateral lesions of different ages, one case intraparenchymal hyperechogenicity, periventricular hemorrhagic infarctions 5 cases ; 3 cases – thalamic haemorrhages, 2 cases peri/ intraventricular hemorrhages (several cases had associations of lesions). In all the cases, the diagnosis was confirmed by MRI. Clinical seizures were present in 3/3 cases with thalamic lesions and in 4/7 case with parenchymal lesions. In 2/7 cases monitored with aEEG , electrical-only seizures were present. In 3 cases, a deficit of factor V Leyden was found both in the mother and the child. No thrombolytic therapy was used. 7 patients were discharged on anticonvulsant treatment the treatment was stopped between 3-12 months - the patients were seizure-free after stopping the medication. 8/10 cases presented with deficit of the head growth. All the patients presented with unilateral motor deficit – in two cases, the deficit was transitory. In all the other cases walking was possible, age for independent was delayed (mean - 15 months). Language deficit was present in 5/10 cases and cognitive deficit in 4/10 cases. The main determinants for unfavourable outcome were thalamic lesions or bilateral lesions.

CONCLUSIONS: Although a rare occurrence, CSVT could be diagnosed in the neonatal period. The cases are almost always symptomatic. The diagnosis is suggested by the ultrasound and confirmed by MRI. The neurological sequelae are present in all the cases consisting in motor signs, seizures - transitory - and cognitive and language deficits. A better knowledge of this entity could increase the awareness and increase the frequency of diagnosis.

Early intervention in preterm infants: Effects on neurodevelopmental outcome at preschool age

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BACKGROUND: Prematurity is associated with an increased risk of acute and chronic postnatal morbidities and long-term neurodevelopmental disabilities, even in absence of major brain injury. Early intervention strategies in preterm infants, based on parental training and multisensory stimulations, have been shown to be effective in positively modulating brain maturation and short-term neurodevelopment [1, 2]. However, little is known about long-term effects on neurodevelopment, due to significant heterogeneity among intervention protocols and target population [3].

PURPOSE: to determine, in preterm-birth children, the effects of an early intervention program on neurodevelopment at preschool age (5-6 years) and to evaluate the neurodevelopmental profile through childhood.

METHODS: this is an ancillary study, part of a larger RCT [4], that included preterm infants born between 25+0 and 29+6 weeks of gestational age

(GA) without severe neonatal comorbidities. Infants were randomized to receive early intervention (EI) or standard care (SC). SC, according to NICU protocols, included Kangaroo Mother Care and minimal handling. EI included, in addition to routine care, parental training and multisensory experiences (infant massage and visual interaction) performed by parents (Figure 1) [5]. Neurodevelopment was assessed between 5 and 6 years chronological age with the Griffiths Scales, the Child Behavior Checklist (CBCL), and the Movement ABC-2.

RESULTS: 70 preterm infants were enrolled in the RCT and 35 (EI n = 21, SC n = 14) completed the long-term follow-up, as reported in the flowchart (Figure 2). The EI group showed, at preschool age, a normal neurodevelopmental outcome with significantly higher mean General Developmental Quotient (GDQ = 90.4, p-value = 0.002), compared to SC group that exhibited a mean score below the normal range (GDQ = 81.9) (Table 1). Moreover, the mean difference in GDQ scores increased of 2.03 points for each additional year in favor of the EI group, becoming statistically significant from 3 years (p-value = 0.013) and being confirmed at 5-6 years (p-value = 0.002) (GDQ and subscale scores throughout infancy are reported in Table 1). No differences in the CBCL scores were observed between the two groups, with all the infants being within the normal range (< 60). At the Movement ABC-2 the EI group showed a higher, although not significant, total standard score compared to the SC group (mean = 8.44 versus 6.82, p-value 0.187) (Table 2), a difference that decreased when adjusting for GA and socio-economic status.

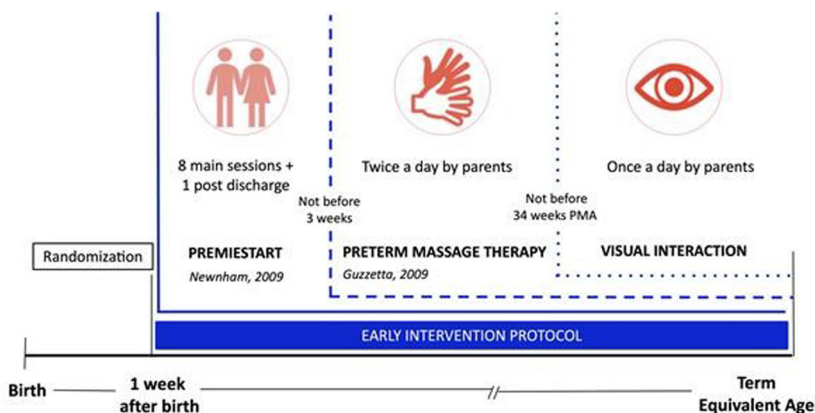


Figure 1. Early intervention protocol.

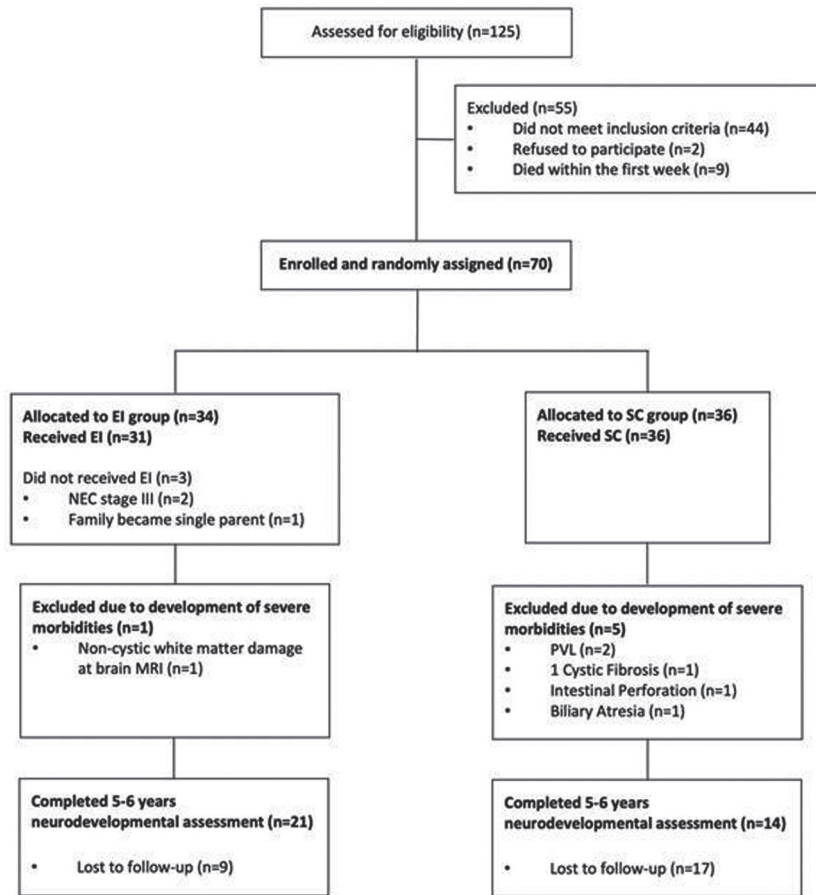


Figure 2. Study flowchart.

CONCLUSIONS: our study contributed to demonstrate the possible beneficial effects of early intervention strategies in ameliorating long-term neurodevelopment in infants born preterm, through the crucial involvement of parents. The main limitation of our study is the high dropout rate, mostly because of the COVID-19 pandemic, and possible selection bias that needs to be ruled out; therefore, further research is recommended.

REFERENCES

[1] Spittle A, Treyvaud K. The role of early developmental intervention to influence neurobehavioral outcomes of children born preterm. *Semin Perinatol.* 2016;40(8):542-548. doi:10.1053/j.semperi.2016.09.006

[2] Embarek-Hernández M, Güeita-Rodríguez J, Molina-Rueda F. Multisensory stimulation to promote feeding and psychomotor development in preterm infants: A systematic review. *Pediatrics and Neonatology.* 2022;63(5):452-461. doi:10.1016/j.pedneo.2022.07.001.

[3] Pierrat V, Marchand-Martin L, Marret S, et al. Neurodevelopmental outcomes at age 5 among children born preterm: EPIPAGE-2 cohort study. *BMJ.* Published online April 28, 2021:n741. doi:10.1136/bmj.n741

[4] Fontana C, De Carli A, Ricci D, et al. Effects of Early Intervention on Visual Function in Preterm Infants: A Randomized Controlled Trial. *Front Pediatr.* 2020;8:291. doi:10.3389/fped.2020.00291

[5] Newnham CA, Milgrom J, Skouteris H. Effectiveness of a Modified Mother–Infant Transaction Program on Outcomes for Preterm Infants from 3 to 24 months of age. *Infant Behav Dev.* 2009;32(1):17-26. doi:10.1016/j.infbeh.2008.09.004

Griffiths Scale	EI (N=21)	SC (N=14)	p-value *
<i>12 months corrected age</i>			
GDQ (General Developmental Quotient)	92.8 (4.8)	92.0 (3.1)	0.590
Foundations of learning	94.7 (5.7)	92.5 (4.1)	0.242
Language and communication	93.6 (2.8)	91.2 (3.0)	0.025
Eye and hand coordination	94.5 (4.7)	91.7 (5.8)	0.129
Personal-social-emotional	93.6 (5.4)	91.7 (5.1)	0.321
Gross motor	91.1 (12.8)	96.1 (6.4)	0.201
<i>3 years chronological age</i>			
GDQ (General Developmental Quotient)	90.4 (4.5)	84.9 (7.9)	0.013
Foundations of learning	92.7 (4.2)	89.1 (4.6)	0.024
Language and communication	91.7 (5.2)	85.7 (11.3)	0.04
Eye and hand coordination	91.9 (4.4)	87.4 (6.6)	0.024
Personal-social-emotional	89.6 (4.3)	82.9 (6.3)	0.001
Gross motor	91.9 (5.1)	89.1 (2.6)	0.077
<i>5-6 years chronological age</i>			
GDQ (General Developmental Quotient)	90.4 (6.1)	81.9 (9.4)	0.002
Foundations of learning	94.1 (5.2)	81.4 (24.8)	0.027
Language and communication	92.4 (5.5)	78.2 (24.9)	0.016
Eye and hand coordination	91.6 (7.7)	82.6 (24.4)	0.12
Personal-social-emotional	92.5 (5.3)	78.9 (23.6)	0.015
Gross motor	91.8 (10.5)	81.1 (24.2)	0.082

Values are expressed as mean (SD). * p-value from t-test

Table 1. Griffiths' general quotient and subscales scores: comparison between early intervention (EI) and standard care groups (SC) throughout infancy.

ABC standardized score	EI (N=21) ¹	SC (N=14) ¹	p-value ¹	β Coeff ²	SE ²	95% CI ²	p-value ²
Total	8.44 (3.07)	6.82 (3.25)	0.187	0.76	1.30	-1.91; 3.44	0.562
Manual dexterity	7.94 (3.28)	7.36 (3.53)	0.657	-0.47	1.38	-3.31; 2.38	0.739
Aiming and catching	8.61 (2.83)	8.09 (2.88)	0.637	-0.73	1.17	-3.14; 1.69	0.541
Balance	9.33 (2.68)	7.64 (3.35)	0.144	1.92	1.27	-0.71; 4.54	0.145

¹ EI and SC groups' mean comparison. P-value from t-test

² Parameter (β) and 95% CIs estimated using linear regression model adjusted for gestational age at birth and family socio economic status

Table 2. Early intervention (EI) effect on Movement ABC-2 scores at 5-6 years of age.

Current practices and parental attitudes of the role of neonatal therapies during therapeutic hypothermia for hypoxic ischemic encephalopathy

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BACKGROUND: Neonates with moderate to severe encephalopathy qualify for therapeutic hypothermia for a presumed diagnosis of hypoxic ischemic encephalopathy (HIE). This is an incredibly stressful time for parents and

a big source of hope is the potential for neurorehabilitation. Currently, there is no standard of care or curriculum for the involvement of neonatal therapists in cooling. A prior study surveying 58 neonatal therapists found variability of practice in the United States (US). The parent perspective of when to introduce therapies has not been evaluated. The objective of this study was to determine current practices across the US and parental perspective by surveying neonatal therapists, as well as parents of children with a history of cooling for HIE. Results of this study may serve to inform future propositions for national guidelines and educational curriculums to improve neurodevelopmental outcomes and optimize parent experience.

METHODS: This survey study included two separate anonymous surveys which were distributed online via

Table 1. HIE Parent/Caregiver Survey Responses, N = 49

	N (%)
Total No. of Survey Respondents	49 (100)
Receive Therapy	
Yes	45 (91.8)
No	4 (8.2)
Not Sure	0 (0.0)
Therapy Start Time During the Cooling Process	
While baby was cooled	3 (7.1)
While baby was rewarmed	10 (23.8)
After baby had MRI	29 (69)
Parent preference on when to meet with therapists	
While baby was cooled	15 (34.9)
While baby was rewarmed	12 (27.9)
After baby had MRI	16 (37.2)
Therapists discussed/used MRI for plan	
Yes	9 (20)
No	31 (68.9)
Not sure	5 (11.1)
Preference on educational materials	
Written only	4 (19%)
Videos only	0 (0%)
Written and videos	17 (81%)
Parents wished more time with therapists	
Yes	34 (75.6%)
No	11 (24.2)

REDCap’s survey link tool. The neonatal therapist survey included 34 questions pertaining to current practices while the parent/caregiver survey included 18 questions focused on the parental experience. Both surveys are ongoing with an offline date of November 22, 2022. Participants were and are being recruited by way professional organizations’ listservs, established parent support non-for-profit organizations, and social media sites. Participants include parents or caregivers of infants with HIE ages 6 to 12 months, as well as therapists working in a NICU that provides cooling and is in the US. IRB approval was received (MHS.2022.096).

RESULTS: At the time of data abstraction, there was a total of 49 parent respondents. Of all respondents, 91.8% (n=45) reported that their baby received therapy while admitted. Most parents reported that their baby started therapy after they had MRI (69%, n=29) and looking back, most of the parents would have preferred to meet with therapists earlier (34.9 % n=15 during cooling, 27.9% N=12 during rewarming). In general, the parents did not discuss MRI with therapists in context of therapy plan (68.9%, n=31). Most parents reported interest in educational materials in both written and video format (81%, n=25). Of a total of 16 neonatal therapy respondents, the majority report that their institution does not have a standardized protocol for assessing and treating babies with HIE (11, 68.8%).

CONCLUSION/IMPACT: Most babies with HIE receive therapy in the NICU. While most therapists meet with parents after the day of MRI, a significant proportion of parents would prefer to meet earlier in the process. Parents would be interested in further education from therapists. National guidelines, neonatal therapy education on HIE

patterns of injury for therapy plan design, as well as earlier parental education with a standardized curriculum are identified areas of improvement.

Pilot of Bilateral Infant Stimulation Study (BLISS) in the NICU

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BACKGROUND: Parents of infants admitted to the NICU often have clinically significant PTSD symptoms at time of discharge. Positive touch interventions have benefits for infants and parents, but current interventions cannot be implemented with critically ill infants. Therefore, our most at risk population is in need of interventions that use positive touch for both the parent and infant.

PURPOSE: We propose using a bilateral alternating stimulation technique as a form of positive touch for parents to engage with critically ill infants. We hypothesize

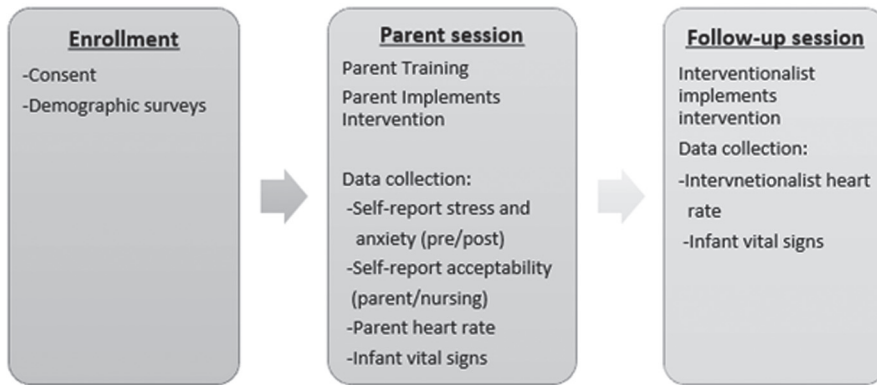


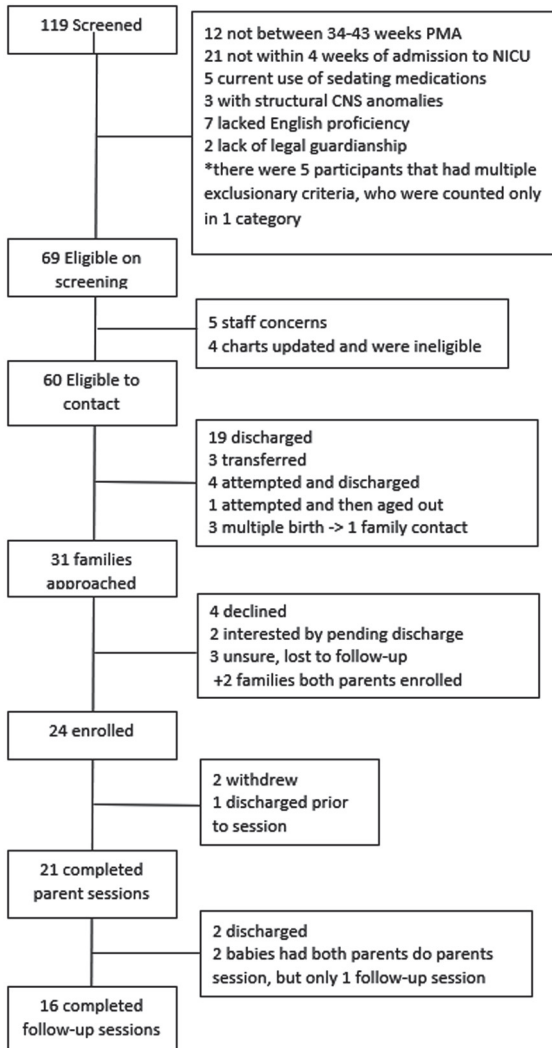
Figure 1. Flow of BLISS study events

this intervention will reduce infant autonomic arousal and reduce parental distress and anxiety. Our study aims to identify whether this intervention is feasible to complete

in a level IV pod-based NICU and acceptable to parents and NICU staff, as a first step in intervention development.

METHODOLOGY: This single arm feasibility and acceptability study was conducted in a level IV pod-based NICU. Parents were first instructed at bedside by an interventionist and then engaged their infant in the intervention. Outcomes included: parent heart rate (via wristband smartwatch); infant vital signs from bedside monitors; acceptability questionnaires; and parent self-report measures. See Figure 1.

RESULTS: We enrolled 24 parent-neonate dyads between June to September 2022. Twenty-one parents completed initial sessions (88%) and 16 infants completed follow-up sessions (76%). **Feasibility:** Feasibility benchmarks were met (set at >80%), with 100% of sessions completed without termination. Interventionists reported 89% of teaching sessions went “smoothly” and 81% of sessions overall “went well.” No sessions were rated negatively. Parents wore wristbands for 100% of sessions. Infant vital signs were collected for 76% of sessions. **Acceptability:** Parents completed the Customer Satisfaction Questionnaire (CSQ), a common measure of intervention acceptability, with scores ranging from 8-32. Mean satisfaction was 30.84 (SD 1.21), reflecting high level of acceptability. Nursing staff completed surveys for 42% of sessions; 90% of responses were positive, without any negative responses. Preliminary pre-post intervention analyses were conducted to explore outcomes; analyses were not conducted to determine effects, as this is a feasibility and acceptability study. State anxiety was measured using the Visual Analog Scale- Anxiety (VAS-A) and the State Trait Anxiety Inventory (STAI). Parents reported significantly lower anxiety post-intervention (VAS-A: M= 14.76, SD=17.04; STAI: M= 30.33, SD = 12.75) compared to pre-intervention (VAS-A: M= 23.33, SD= 27.61; STAI: M= 37.33, SD= 12.85), p = .023 and p < .001. Parental distress (Distress Thermometer) was also significantly lower post-treatment compared to pre-treatment (pre: M= 5.52, SD= 2.48; post: M= 4.29, 2.72), p = .005.



CONCLUSIONS: The BLISS study is feasible to conduct in a pod-based NICU and is acceptable to both parents and nursing staff. Preliminary data suggests the intervention is promising for further pursuit on the impact on parental anxiety and distress.

Electroencephalogram patterns on follow-up visits in extremely premature infants with periventricular leukomalacia: An observational study

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BACKGROUND AND PURPOSE: Periventricular Leukomalacia (PVL) is a common brain injury in premature newborns. Current literature provides limited guidance on the benefit of electroencephalogram (EEG) as a potential screening tool for seizure risk in this population. The purpose of this study is to describe the EEG patterns on follow-up visits in infants born premature and diagnosed with PVL.

METHODS: This is a retrospective study of premature newborns (<37 weeks gestation), who were followed in the neurodevelopmental clinic at Beaumont Children’s Hospital in Detroit MI between 2020 and 2022. Patient’s demographics, prematurity complications, head ultrasound (HUS), and EEG studies were reviewed. PVL on HUS was graded based on Agut et al 2020.

RESULTS: 155 newborns met the inclusion criteria. Within them, 27 (17%) had PVL based on HUS prior to discharge from the neonatal intensive care unit (NICU). 24 patients had grades 1-2 PVL while 3 had grade 3 based on serial HUS reviews. The mean gestational age was 26.5 ±2.3 weeks for PVL patients and 28 ±2.9 weeks for non-PVL (p=0.03). The mean birth weight for those without PVL was 1118 ±500 grams compared to 916 ±312 grams for PVL (p=0.01) (Table-1). EEG was performed on 15/27 patients with PVL at a mean age of 20 months corrected age vs. 17/128 patients without PVL at a mean age of 11.5 months corrected age. In the PVL group, EEG was normal in six patients (5/6 were grade 1), mildly slow background in two (one with grade 1 and one with grade 2). Three patients had excessive background slowing with multiple foci of excessive sharp wave discharges (three with grade 3 and two with grade 2 PVL). Patients with PVL had a trend towards worse EEG pattern (p= 0.2) when compared to no PVL. Worse PVL grade was associated with worse EEG pattern (p= 0.002).

CONCLUSION: PVL is a common brain injury in premature newborns. The relatively frequent association with an abnormal EEG, especially for high grade cystic PVL, should prompt providers to consider this test for seizure screening and early diagnosis and management.

Table 1. Demographics comparison between PVL & no-PVL (AIMS: the Alberta Infant Motor Scale)

	PVL (n=27)	No PVL (n= 128)	P-value
Gestational Age (weeks), median	26.5 (25-27)	28 (26-29)	0.03
Birth Weight (grams), median	815 (657-1089)	1007 (793-1362)	0.05
Apgar score at 5 minutes, median	6 (5-8)	8 (7-9)	0.003
Male gender (%)	57.7	55	0.8
Bronchopulmonary dysplasia (%)	69.2	48.8	0.06
IVH grade (%)			<0.0001
0	42.3	73.6	
1	3.8	20.2	
2	15.4	3.9	
3	7.7	2.3	
4	30.8	0	
Necrotizing enterocolitis (%)	3.8	8.5	0.7
Length of stay in the NICU in weeks, median	12	8	0.004
AIMS, median	33±15 (15-45)	45.5±13 (28-51)	0.02

Neonatal neuro-imaging findings and neurodevelopmental outcome at 24 months in moderate-late preterm infants: Follow-up analysis of the BIMP study

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BACKGROUND: Moderate-late preterm (MLPT) children, born between 32 and 37 weeks of gestation, account for 80% of the 15 million children born prematurely per year worldwide (1). MLPT infants have a higher risk of neurodevelopmental and behavioral problems compared to full-term infants (2-4). During the

last trimester of pregnancy, the fetal brain undergoes rapid growth and development and is therefore susceptible to injury and suboptimal development (5,6). So far, few studies assessed the relationship between neuro-imaging findings and neurodevelopment in MLPT children. These studies present conflicting results (7,8). Knowledge of this relationship may help to predict neurodevelopmental or behavioral problems and may thus enable early interventions to improve functional outcome. Our aim was to determine whether there is an association between neuro-imaging findings and neurodevelopment in MLPT infants.

METHODS: The Brain Imaging in Moderate-Late Preterm infants (BIMP) study is a prospective cohort study (9). Infants between 32+0 and 35+6 weeks' gestation were included and underwent serial cranial ultrasonography (cUS) and a single MRI examination at term equivalent age (TEA). cUS and MRI examinations were divided into normal (no lesions) and abnormal. At corrected age of 24 months, neurodevelopment was assessed using three validated parent reported questionnaires: the Ages and Stages Questionnaire (ASQ) (10), Child Behavior Checklist (CBCL) (11) and Modified Checklist for Autism in Toddlers (M-Chat)(12). Outcome was suboptimal if a score was ≥ 2 SD for the ASQ, ≥ 60 for the CBCL and ≥ 3 for the M-Chat. The results of the questionnaires were combined to a composite outcome i.e. if one of the results was suboptimal, the composite outcome was considered suboptimal. Associations between neuro-imaging findings and neurodevelopmental outcome were assessed with logistic regression analysis. We corrected for multiple comparisons using the Bonferroni correction.

RESULTS: In 141 MLPT infants follow-up was completed. Of the 141 children 40% were moderate preterm (MP) and 60% late preterm (LP). Of the 141 children 94% underwent serial cUS and 81% MRI. Abnormalities were seen on serial cUS and MRI in respectively 67% and 60% of the 141 children. For the ASQ and CBCL, respectively 23% and 13% of the children had a suboptimal score on one of the subdomains. None of the children had a suboptimal score on the M-Chat. In 31% of the children the composite outcome was suboptimal. No significant association was found between imaging findings and neurodevelopmental outcome. A significant association was found between suboptimal neurodevelopment and low educational level of mother and father respectively $p=0.022$ and $p=0.047$, however significance was revoked after multiple comparison correction.

CONCLUSION: Although follow-up analysis showed that nearly one in three MLPT children had a composite suboptimal outcome, we did not find a significant association between brain lesions on cUS and/or MRI and

neurodevelopmental outcome at 24 months corrected age as assessed by parental questionnaires.

REFERENCES

- [1] Chawanpaiboon S, Vogel J, Moller A, Lumbiganon P, Petzold M, Hogan D, et al. Global, regional, and national estimates of levels of preterm birth in 2014: a systematic review and modelling analysis. *Lancet Glob Health* 2019;7(1):e37-e46.
- [2] Voigt B, Pietz J, Pauen S, Kliegel M, Reuner G. Cognitive development in very vs. moderately to late preterm and full-term children: can effortful control account for group differences in toddlerhood? *Early Hum Dev* 2012;88(5):307-313.
- [3] Johnson S, Evans TA, Draper ES, Field DJ, Manktelow BN, Marlow N, et al. Neurodevelopmental outcomes following late and moderate prematurity: a population-based cohort study. *Arch Dis Child Fetal Neonatal Ed* 2015;100(4):F301-F308.
- [4] Hochstedler KA, Bell G, Park H, Ghassabian A, Bell EM, Sundaram R, et al. Gestational Age at Birth and Risk of Developmental Delay: The Upstate KIDS Study. *Am J Perinatol* 2020.
- [5] Kostović I, Sedmak G, Judaš M. Neural histology and neurogenesis of the human fetal and infant brain. *Neuroimage* 2019;188:743-773.
- [6] Raybaud C, Ahmad T, Rastegar N, Shroff M, Al Nassar M. The premature brain: developmental and lesional anatomy. *Neuroradiology* 2013;55(2):23-40.
- [7] Nakasone R, Fujioka K, Kyono Y, Yoshida A, Kido T, Suga S, et al. Neurodevelopmental Outcomes at 18 Months of Corrected Age for Late Preterm Infants Born at 34 and 35 Gestational Weeks. *Int J Environ Res Public Health* 2021;18(2):640.
- [8] Cheong JLY, Thompson D, Spittle A, Potter C, Walsh J, Burnett A, et al. Brain Volumes at Term-Equivalent Age Are Associated with 2-Year Neurodevelopment in Moderate and Late Preterm Children. *J Pediatr* 2016;174:91-97.e1.
- [9] Boswinkel V, Krüse-Ruijter MF, Nijboer - Oosterveld J, Nijholt IM, Edens JA, Mulder - de Tollenaer SM., et al. Incidence of brain lesions in moderate-late preterm infants assessed by cranial ultrasound and MRI: The BIMP-study. *Eur J Radiol* 2021;136:109500.
- [10]quires J, Bricker D. *Ages & Stages Questionnaires®, Third Edition (ASQ®-3): A Parent-Completed Child Monitoring System*. Baltimore: Paul H. Brookes Publishing Co., Inc; 2009.
- [11] Achenbach TM, Rescorla L. *Manual for the Child Behavior Checklist. Preschool Forms and Profiles.* : Burlington VT: University of Vermont Department of Psychiatry; 2000.
- [12] Robins DL, Fein D, Barton M. *The Modified Checklist for Autism in Toddlers, Revised with Follow-Up (M-CHAT-R/F)*. 2009.