Neurodevelopmental Outcomes of infants with Mild Neonatal Encephalopathy Treated with Therapeutic Hypothermia: A Single-Center Study

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Background

- The role of **therapeutic hypothermia (TH)** for **mild neonatal encephalopathy (NE)** remains uncertain due to variable definitions, treatment criteria, and practices[1].
- Prior studies raise concerns for **brain injury** and **possible neurodevelopmental vulnerability** among infants with mild NE.
- **Study aim** : To describe neurodevelopmental outcomes of **cooled** infants with **mild NE vs moderate-severe NE**.

Methods

- **Study Type**: Retrospective cohort of infants treated with TH in one academic Level III NICU (2019–2023).
- **TH eligibility** : Meeting physiologic criteria and Neonatal Encephalopathy Scale (NES) ≥4[2] (per unit clinical guideline)

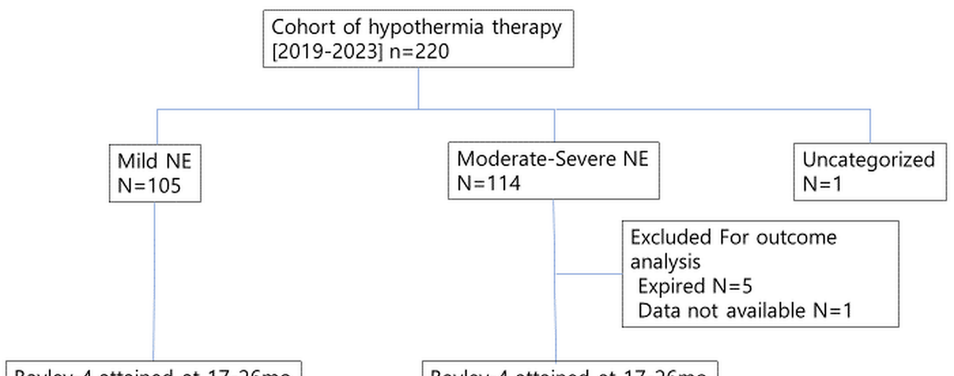
The Brigham and Women's Hospital Neonatal Encephalopathy Scale (NES)[2]

Stage	Normal (0 points each)	Mild/Stage 1 (1 points each)	Moderate/Stage 2 (2 points each)	Severe/Stage 3 (3 points each)
1. Level of Consciousness	Normal 0	Hyper-alert/Irritable 1	Lethargic/Obtuned 2	Stupor/Coma 3
2. Spontaneous Activity	Normal 0	Normal 0	Decreased 2	Absent 3
3. Muscle Tone	Normal 0	Normal 0	Mild Hypotonia 2	Flaccid 3
4. Posture	Normal 0	Mild Distal Flexion 1	Strong Distal Flexion 2	Decerebrate 3
5. Primitive Reflexes				
Suck	Normal 0	Weak 1	Weak/Absent 2	Absent 3
Moro	Normal 0	Strong/Low Threshold 1	Weak/Incomplete/High Threshold 2	Absent 3
6. Autonomic Function				
Pupils	Normal 0	Mydriasis 1	Miosis 2	Unequal/Fixed/Dilated/Poor Reflex 3
Heart Rate	Normal 0	Tachycardia 1	Bradycardia 2	Variable 3
Respiration	Normal 0	Normal 0	Periodic Breathing 2	Apnea 3
Total score				

- **NE severity classification**: NE grading was classified retrospectively using NICHD NE criteria[3] based on documented neurologic examinations. Moderate-severe NE was defined as the presence of moderate to severe findings in at least 3 of 6 categories (see table above). Infants not meeting these criteria were classified as mild NE.
- **Evaluation Tools**: TIMP (at NICU discharge and 4 months), Bayley-4 Scales (17–26 months), M-CHAT (17–26 months)

Results

- A total of **220 infants** received TH during the study period, including 105 with mild NE and 114 with moderate/severe NE, and 1 uncategorized.



- **Baseline characteristics:** moderate-severe group had a higher rate of *placental abruption, lower Apgar scores, lower postnatal (<1 h) blood pH, and higher worst NES scores before hypothermia* in the moderate/severe group, with the other parameters being similar between groups (Table 1).
- **TIMP scores** (Table 2): No differences were observed at discharge or at four months.
- **M-CHAT (Modified Checklist for Autism in Toddlers) results** were comparable (low-risk scores: 90.9% vs 82.9%, *p*=0.46).
- **Bayley-4**
  - The moderate-severe NE group had significantly lower Cognitive and Language standard scores and showed a trend toward lower Motor composite scores (Table 3).
  - **In mild NE group**, up to 21% of patients had Bayley-4 composite scores <85 (< -1SD below mean), and 37% had Gross motor scaled scores <8 (Figure 1).

Discussion and Conclusions

- Infants with **mild NE treated with TH demonstrated overall better neurodevelopment at two years** compared with those with moderate-severe NE.
- **A notable proportion of infants with mild NE had scored below the normal range across developmental domains (Figure 1)**
- The results **suggest infants with mild NE experience developmental vulnerability around age 2 years.**
- Larger studies and close post-discharge developmental follow-up are needed to better characterize outcomes in this population.

Table 1. Sample characteristics

		Mild NE (n=105)	Moderate/Severe NE (n=114)	*p*-value
		N (%) or median [IQR]	N (%) or median [IQR]	
Sex, male		62 (59.0%)	70 (61.4%)	0.783
Gestational age, weeks		39.3 [37.6–40.1]	38.5 [37.1–39.8]	0.064
Birthweight, g		3150 [2870–3660]	3190 [2502–3580]	0.350
Delivery mode, Vaginal delivery		47 (44.8%)	61 (53.5%)	0.224
Delivery Complication	Non-reassuring fetal heart tracing	87 (82.9%)	94 (82.5%)	1.000
	Shoulder dystocia/Failure to progress	12 (11.4%)	8 (7.0%)	1.000
	Tight nuchal cord	15 (14.3%)	23 (20.2%)	0.370
	Cord prolapse	4 (3.8%)	2 (1.8%)	0.430
	Placental abruption	2 (1.9%)	12 (10.5%)	**0.011**
	Uterine rupture	1 (1.0%)	2 (1.8%)	1.000
Delivery room resuscitation	Resuscitation	87 (82.9%)	95 (83.3%)	1.000
	PPV	87 (100.0%)	95 (100%)	
	Chest compression	7 (6.7%)	8 (7%)	
	Epinephrine administration	0 (0.0%)	5 (4.4%)	
Apgar Scores	At 1 min	n = 104; 2 [2–5]	n = 114; 2 [2–4]	0.278
	At 5 min	n = 104; 7 [6–8]	n = 114; 6 [4–7]	**0.002**
	At 10 min	n = 54; 8 [7–8]	n = 72; 7 [6–8]	**0.000**
Umbilical Artery blood gas	pH	n = 93; 7.08 [6.97–7.16]	n = 91; 7.07 [6.99–7.19]	0.494
	Base Deficit (mmol/L)	n = 78; 9.95 [8.03–12.67]	n = 82; 9.95 [7.72–13.30]	0.830
	Lactate (mmol/L)	n = 84; 8.70 [6.97–10.72]	n = 71; 8.20 [5.50–10.25]	0.110
Postnatal < 1hr blood gas	pH	n = 96; 7.27 [7.19–7.31]	n = 99; 7.21 [7.12–7.31]	**0.008**
	Base Deficit (mmol/L)	n = 93; 11.60 [7.50–4.30]	n = 91; 10.90 [8.15–15.20]	0.336
	Lactate (mmol/L)	n = 86; 9.50 [6.38–12.40]	n = 89; 8.50 [5.80–12.70]	0.677
Neonatal Encephalopathy Scale(NES)* score		n = 105; 4 [3.0–5.0]	n = 113; 8 [7.0–10.0]	**<0.01**
Length of Hospital Stay, days		7 [6.0–12.0]	8 [6.0–17.8]	0.137
Family Social Factors	≥2 risk factors	30 (28.6%)	33 (28.9%)	1.000
	Minor ethinicity	53 (50.5%)	55 (48.2%)	0.846
	Maternal age < 22 years	2 (1.9%)	0 (0.0%)	0.229
	Single mother	22 (21.0%)	29 (25.4%)	0.532
	Public insurance	32 (30.5%)	27 (23.7%)	0.327
	Language other than English	8 (7.6%)	7 (6.1%)	0.869

* Worst score before hypothermia therapy

Values are N (%) or median [IQR]. Group comparisons used Wilcoxon rank-sum and Fisher's exact tests, with $p < 0.05$ considered statistically significant.

Table 2. Test of Infant Motor Performance (TIMP) scores at discharge and 4 months

	Mild NE (n = 105)	Moderate/Severe NE (n = 108)	*p*-value
TIMP at discharge, median [IQR]	20 (19.0%); 59 [58–62]	21 (19.4%); 58 [55–63]	0.36
TIMP at 4 months, median [IQR]	39 (37.1%); 125 [118.5–131.5]	40 (37.0%); 123 [116.8–130.3]	0.61

Values are n (%) and median [IQR]. *p*-values from Wilcoxon rank-sum test; $p < 0.05$ considered significant.

Table 3. Bayley-4 assessment at 17-26 months

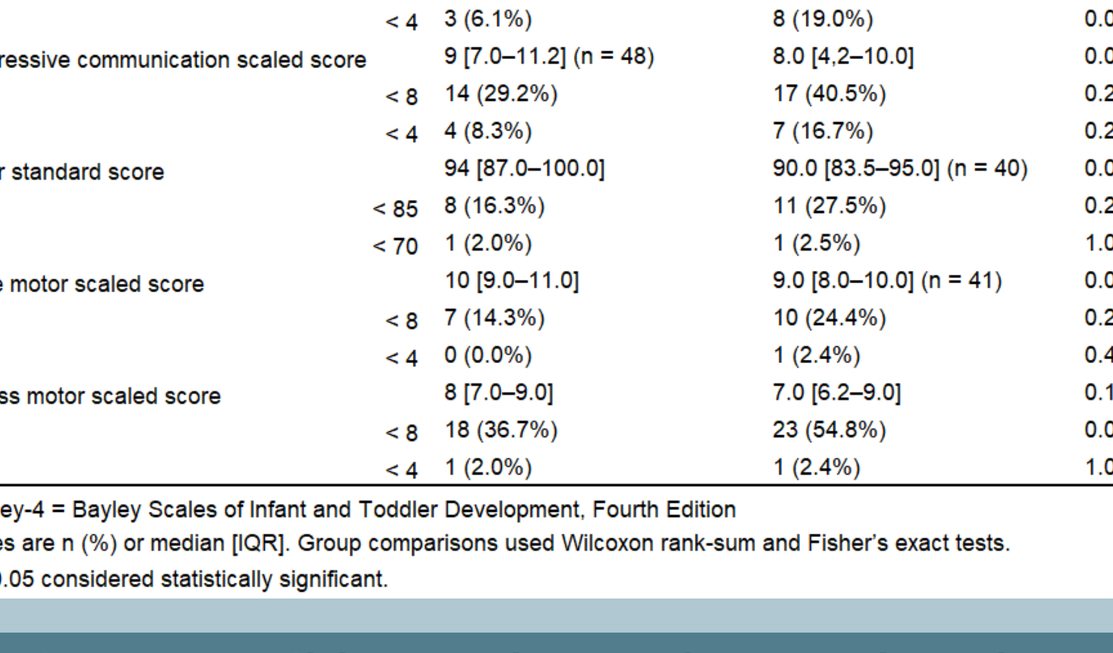
Bayley-4* (17–26 months)		Mild NE	Moderate/Severe NE	*p*-value
		n (%) or median [IQR] n = 49/105 (46.7%)	n (%) or median [IQR] n = 42/108 (38.9%)	
Age at test, months		24.1 [19.3–24.8]	23.6 [19.3–24.7]	0.433
Cognitive standard score		100 [95.0–110.0]	95 [85.0–103.8]	**0.030**
	<85	6 (12.2%)	9 (21.4%)	0.239
	<70	2 (4.1%)	5 (11.9%)	0.242
Language standard score		99 [86.0–108.8] (n = 48)	93.5 [78.0–103.0] (n = 40)	**0.049**
	<85	10 (20.8%)	12 (30.0%)	0.323
	<70	3 (6.2%)	8 (20.0%)	0.052
Receptive communication scaled score		11 [7.0–12.0]	9.5 [6.2–11.0]	0.063
	< 8	13 (26.5%)	13 (31.0%)	0.642
	< 4	3 (6.1%)	8 (19.0%)	0.059
Expressive communication scaled score		9 [7.0–11.2] (n = 48)	8.0 [4,2–10.0]	0.082
	< 8	14 (29.2%)	17 (40.5%)	0.260
	< 4	4 (8.3%)	7 (16.7%)	0.229
Motor standard score		94 [87.0–100.0]	90.0 [83.5–95.0] (n = 40)	0.063
	< 85	8 (16.3%)	11 (27.5%)	0.201
	< 70	1 (2.0%)	1 (2.5%)	1.000
Fine motor scaled score		10 [9.0–11.0]	9.0 [8.0–10.0] (n = 41)	0.059
	< 8	7 (14.3%)	10 (24.4%)	0.223
	< 4	0 (0.0%)	1 (2.4%)	0.456
Gross motor scaled score		8 [7.0–9.0]	7.0 [6.2–9.0]	0.139
	< 8	18 (36.7%)	23 (54.8%)	0.085
	< 4	1 (2.0%)	1 (2.4%)	1.000

*Bayley-4 = Bayley Scales of Infant and Toddler Development, Fourth Edition

Values are n (%) or median [IQR]. Group comparisons used Wilcoxon rank-sum and Fisher's exact tests.

$p < 0.05$ considered statistically significant.

Figure 1. Mild NE Cohort: Abnormal Bayley-4 Scores by domain (17-26 months)



Bars Show the proportion of infants with Mild NE who had scores below prespecified clinical cutoffs.
indicates mild-moderate delay (Standard score 70-84, Scaled score 4-7
indicates severe delay (Standard score <70; Scaled Score <4)

References

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2. Walsh BH et al. Differences in neonatal encephalopathy exam criteria and impact on hypothermia eligibility. Pediatr Res. 2022;92(3):791–8.
3. Seetha Shankaran et al. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. N Engl J Med 2005;353:1574-84