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

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Background

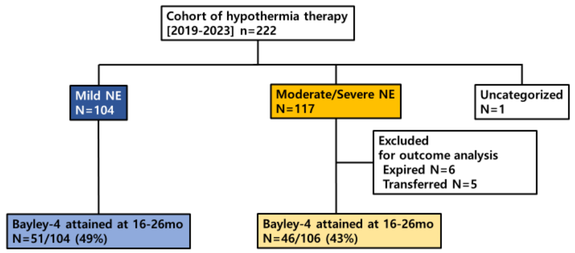
- In the cooling era, mild neonatal encephalopathy(NE) raises concerns for brain injury and neurodevelopmental vulnerability, yet the role of therapeutic hypothermia(TH) remains uncertain[1].
- In the absence of published RCTs, many centers (including ours) have extended TH eligibility to a subgroup of mild NE infants.
- Aims : Describe neurodevelopmental outcomes of **cooled mild vs moderate/severe NE infants**.

Methods

- **Study Type**: Retrospective cohort of infants treated with TH in one academic Level III NICU (Jan. 2019–Dec. 2023).
- **TH eligibility** (≥34 weeks + ≥1 of)
  - Sentinel event
  - pH ≤7.1 or BE ≤ -10 mEq/L
  - Apgar ≤5 at 10 min or Prolonged resuscitation at 10 min
  - Signs of NE or seizure

  → *TH initiated if NES[2] ≥4 or abnormal aEEG*
- **NE severity grading**: Retrospectively graded per NICHD NE criteria[3] using the worst Neonatal Encephalopathy Scale (NES)[2] assessment across serial evaluations. **Moderate/severe NE**: ≥3 moderate/severe domains, or seizures with any encephalopathy sign. **Mild NE:** not meeting above criteria.

Figure 1. Study Cohort and Follow Up



Results

- A total of **221 infants** received TH (104 mild NE, 117 moderate/severe NE; Figure 1). Moderate/severe NE group had higher rates of placental abruption, lower Apgar scores, lower postnatal pH, and higher worst NE scores (Table 1).

Table 1. Clinical Characteristics

		Mild NE (n=104)	Moderate/Severe NE (n=117)	*p*-value
		N (%) or median [IQR]	N (%) or median [IQR]	
Sex, male		60 (57.7%)	73 (62.4%)	0.494
Gestational age, weeks		39.3 [37.6–40.1]	38.5 [37.1–39.8]	0.087
Birthweight, g		3145 [2868–3645]	3200 [2500–3580]	0.385
Delivery mode, VD		47 (45.2%)	61 (52.1%)	0.346
Placental abruption		1 (1.0%)	13 (11.1%)	0.002
Delivery room resuscitation		86 (82.7%)	97 (82.9%)	1.000
Apgar Scores	At 1 min	2 [2–5]	2 [1–4]	0.149
	At 5 min	7 [6–8]	6 [4–7]	<0.001
	At 10 min	8 [7–8]	7 [6–8]	<0.001
Umbilical Artery blood gas	pH	7.1 [7.0–7.2]	7.1 [7.0–7.2]	0.429
	Base Deficit (mmol/L)	9.9 [8.1–12.7]	9.9 [7.5–13.3]	0.915
	Lactate (mmol/L)	8.7 [7.0–10.6]	8.2 [5.5–10.3]	0.139
Postnatal < 1hr blood gas	pH	7.3 [7.2–7.3]	7.2 [7.1–7.3]	0.010
	Base Deficit (mmol/L)	11.4 [7.4–14.3]	10.9 [8.1–15.3]	0.368
	Lactate (mmol/L)	9.4 [6.3–12.4]	8.5 [5.7–12.7]	0.806
NES[2] score		4.0 [3–5]	8.0 [7–10]	<0.01
Family Social Risk Factor ≥2		30 (28.8%)	34 (29.3%)	1.000

Additional variables examined included delivery complications, resuscitation types, length of hospital stay; none showed significant differences between groups unless otherwise noted. Family social factors include maternal age <21 y.o., single parents, public insurance, ethnicity and language.

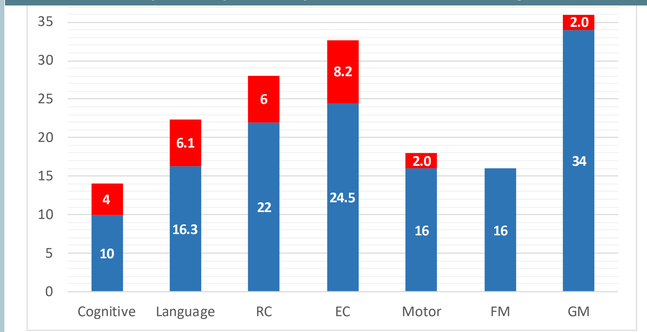
Table 2. TIMP (Test of Infant Motor Performance) Score

	Mild NE	Moderate/Severe NE	p-value
Discharge TIMP			
Raw score, median [IQR]	59.0 (58.0–62.0), n=20	58.0 (56.5–63.0), n=20	0.497
Within average, n (%)	17/20 (85.0%)	18/20 (90.0%)	1
4-month TIMP			
Raw score, median [IQR]	125.0 (118.2–131.8), n=38	123.0 (116.2–129.5), n=42	0.589
Within average, n (%)	31/38 (81.6%)	32/42 (76.2%)	0.596

Raw score: Mann-Whitney U test, Rate of Within average: Fisher's exact test

Figure 2. Mild NE Cohort at 16-26 months

: Up to 36% of Mild NE infants scored below normal range.



Bars show the proportion of infants with Mild NE who had scores below prespecified clinical cutoffs.
indicates Standard score 70-84 or Scaled score 4-7
indicates Standard score <70 or Scaled Score <4
Abbreviations: RC, Receptive Communication; EC, Expressive Communication; FM, Fine Motor; GM, Gross Motor

Table 3. Bayley-4 at 16-26 months

Bayley-4* (16-26 months)	Mild NE	Moderate/Severe NE	*p*-value
	n= 51/104 (49%)	n = 46/106 (43%)	
Age at test (months)	24 [19-24]	24 [20-25]	0.222
Cognitive Standard Score	100 [95-110]	95 [85-105]	0.076
<85	7/50 (14.0%)	11/46 (23.9%)	0.326
<70	2/50 (4.0%)	6/46 (13.0%)	0.147
Language Standard Score	98 [86-108]	94 [78-104]	0.113
<85	11/49 (22.4%)	13/44 (29.5%)	0.587
<70	3/49 (6.1%)	9/44 (20.5%)	0.061
RC Scaled Score	11 [7-12]	10 [6-11]	0.129
<8	14/50 (28.0%)	14/46 (30.4%)	0.97
<4	3/50 (6.0%)	8/46 (17.4%)	0.111
EC Scaled Score	9 [7-11]	8 [4-10]	0.128
<8	16/49 (32.7%)	19/46 (41.3%)	0.509
<4	4/49 (8.2%)	8/46 (17.4%)	0.224
Motor Standard Score	94 [87-100]	90 [81-95]	0.073
<85	9/50 (18.0%)	13/44 (29.5%)	0.282
<70	1/50 (2.0%)	2/44 (4.5%)	0.598
FM Scaled Score	10 [8-11]	9 [7-10]	0.042
<8	8/50 (16.0%)	12/45 (26.7%)	0.307
<4	0/50 (0%)	1/45 (2.2%)	0.474
GM Scaled Score	8 [7-9]	7 [6-9]	0.112
<8	18/50 (36.0%)	25/46 (54.3%)	0.109
<4	1/50 (2.0%)	2/46 (4.3%)	0.606

- **Bayley-4 (Bayley Scales of Infant and Toddler Development, 4th)**
  - Although mild NE showed a trend toward better outcomes, no statistically significant differences were found between groups except for fine motor scaled score (Table 3).
  - **In the mild NE group**, 31.4% *had Standard scores <85 across domains, and 36% had Gross motor scaled scores <8* (Figure 2).
- **M-CHAT (Modified Checklist for Autism in Toddlers) :** Low-risk scores comparable between groups at 16-26 months (90.9% vs 81.2%, *p*=0.306).

Discussion and Conclusions

1. Mild NE treated with TH showed comparable neurodevelopment to moderate/severe NE at two years, except in fine motor.
2. Notably, a substantial proportion of infants with **mild NE scored below the normal range** across developmental domains (Figure 2).
3. Larger studies and close post-discharge developmental follow-up are needed to better characterize developmental vulnerability in this population.

References

1. El-Dib M et al. Should therapeutic hypothermia be offered to babies with mild neonatal encephalopathy? Pediatr Res. 2019;85(4):442–8. **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