Status of Child and Adolescent Outcome following Mild HIE

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Frequency of Encephalopathy and Acidosis

Swedish Pregnancy Registry

- 166,558 births from June 2018-May 2020

Acidosis pH <7.0 was 1331 infants (1.19%)

Mild encephalopathy was 177 infants (0.11%)

Moderate/severe encephalopathy: 134 (<1%)

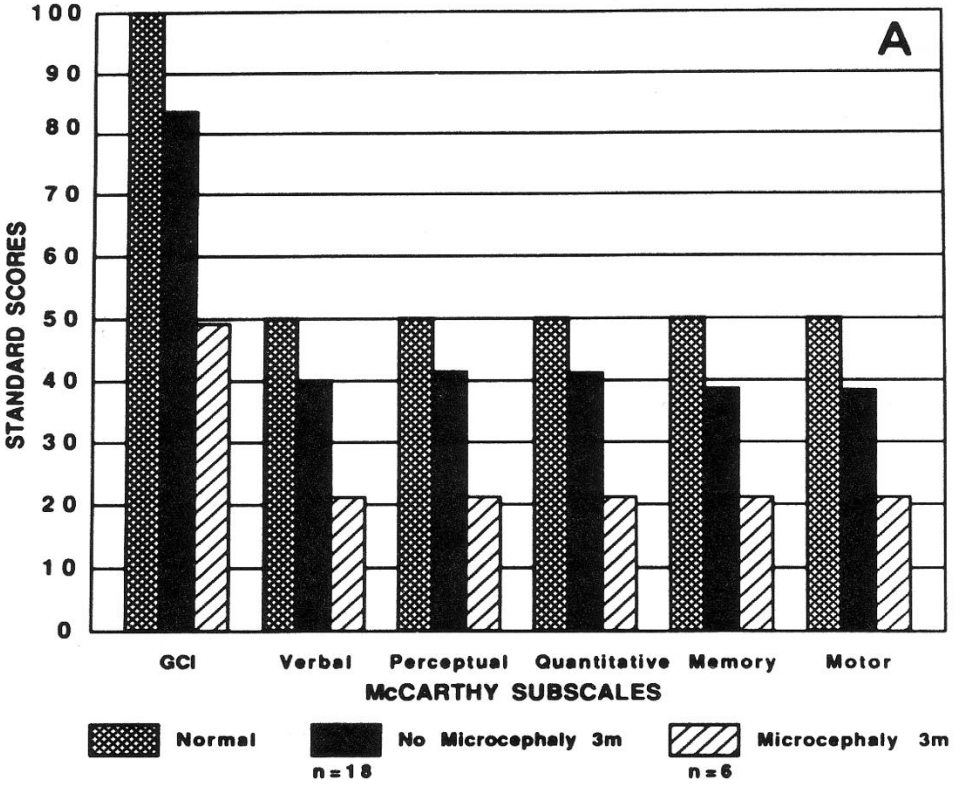
Johnsson 2021

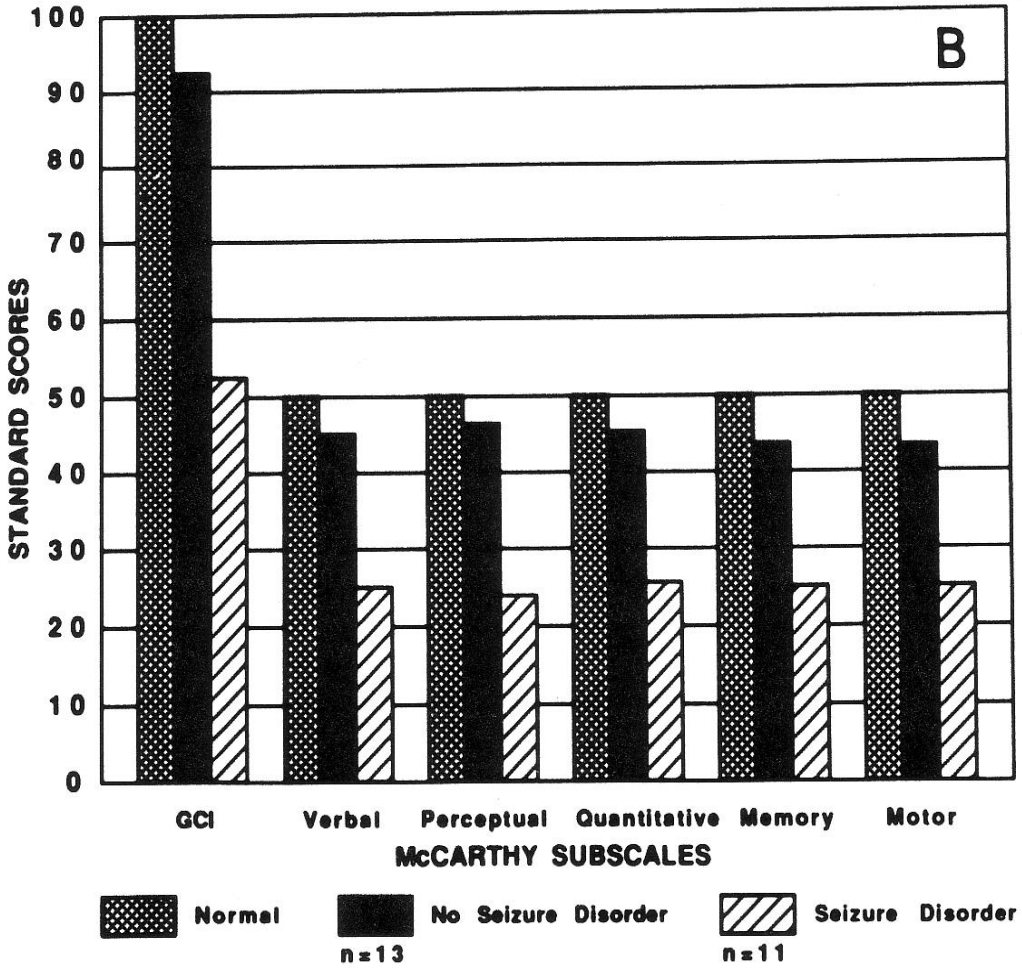
- Observational Data on FU after **Moderate or Severe HIE** among Term Infants

Outcomes of Children with Birth Depression/Encephalopathy before Hypothermia Therapy: Challenges

- Cohort studies
- Each had unique inclusion criteria
- Different evaluation methods
- Varied durations of follow-up
  - Disability rate with moderate encephalopathy 6-21%
  - Disability rate with severe encephalopathy 42-100%

Shankaran 1991, Robertson 2003,
Marlow 2005, Gonzales 2006,
de Vries 2010


A
100
90
80
70
60
50
40
30
20
10
0
STANDARD SCORES
GCI
Verbal
Perceptual
Quantitative
Memory
Motor
McCARTHY SUBSCALES
Normal
No Microcephaly 3m
n=18
Microcephaly 3m
n=6


B
100
90
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STANDARD SCORES
GCI
Verbal
Perceptual
Quantitative
Memory
Motor
McCARTHY SUBSCALES
Normal
No Seizure Disorder
n=13
Seizure Disorder
n=11

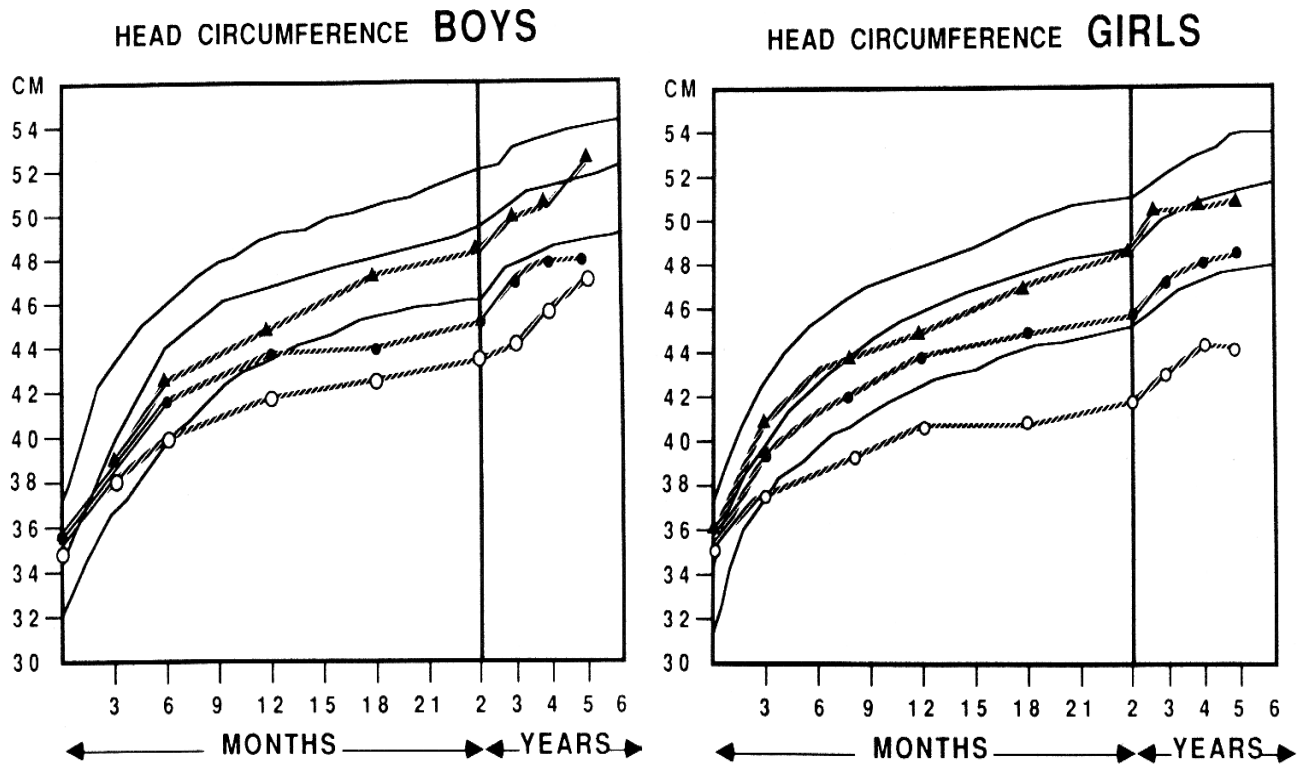


Fig. 1. (Shaded areas indicate normal ranges. Nellhaus, G., Composite International and Interracial Graphs. *Pediatrics,* 41 (1968) 106. (A) Head growth of all boys ●——●; boys with no motor deficits ▲----▲ (n = 7), and boys with motor deficits ○----○ ⟨n = 6). (B) Head growth of all girls ●----●; girls with no motor deficits ▲----▲ (n = 7) and girls with motor deficits ○----○ (n = 4).

Non-disabled Survivors with Asphyxia

Compared to healthy children, IQ was 8-10 points lower along with lower achievement of

- Everyday motor
  - walking , running, climbing stairs
- Complex motor
  - Straight-line or tandem walking, hopping, balance, Romberg
- Fine motor
  - Finger-nose, alternate fingers

Robertson: Fetal and Neonatal Brain Injury, 2003

Nondisabled Children with HIE

- Assessed by psychometric and behavioral testing
  - Lower executive function
  - Delays in school readiness
  - Delay in reading, spelling, and arithmetic
  - Lower language and memory scores
  - Decreased sensory motor perception

Robertson 2003, Marlow 2005, Odd 2011

Children with Birth Depression/Encephalopathy

- Possibility of an increase in symptoms related to:
  - Attention deficit hyperactivity disorder
  - Anxiety, depression, attention regulation
  - Time perception, thought problems
  - Autism

Lindstrom 2006, Badawi 2006, Odd 2011, Van Handel 2013

- RCT Data on FU after Moderate or Severe HIE in Term Infants

Does neuro-protection seen in the HIC trials at 18 months persist to childhood?

1) 6 to 7-year outcome of CoolCap trial

- 62 of 135 (46%) surviving children were assessed by WeeFIM parental questionnaire
- Disability status at 18m was strongly associated with WeeFIM ratings

Guillet et al, Pediatr Research 2012

2) NICHD 6 to7-year outcomes, Shankaran 2014
Primary Outcome: Death or IQ <70

Hypothermia N=97	Control N=93	Unadjusted RR (95% CI)	Adjusted RR (95% CI)
46 (47%)	58 (62%)	0.76 (0.58,0.99)	0.78 (0.61,1.01)

NICHD NRN Secondary Outcomes

Outcomes at 6-7 years	Hypothermia N=97	Control N=93	Adjusted RR (95% CI)
Death	27 (28%)	41 (44%)	0.66 (0.45,0.97)
Death or CP	41 (43%)	56 (60%)	0.75 (0.57,0.99)

3) TOBY: Primary Outcome IQ ≥85

Azzopardi 2014

Hypo N=163	Control N=162	RR (95% CI)	P value
75 of 145 (52%)	52 of 132 (39%)	1.31 (1.01-1.71)	0.04

TOBY Trial: Secondary Outcomes

Outcomes	Hypo N=163	Control N= 162	RR (95% CI)
Death	29%	30%	0.95 (0.68,1.33)
CP (no data for 18 Hypo 27 control)	21%	36%	0.59 (0.37,0.95)

NICHD Hypothermia RCT: CP and Growth at 6-7 years: Vohr et al 2013

Characteristics at 6-7 year	Mod/Severe CP N=23	No CP N=92
Gastrostomy feeds	52%	0%
Physical therapy	87%	7%
Occupational therapy	83%	9%
Re-Hospitalization	78%	25%
Full Scale IQ < 70	96%	10%
Full Scale IQ < 55	87%	2%
		All $P < 0.05$

NICHD Hypothermia RCT:CP & Growth 6-7y

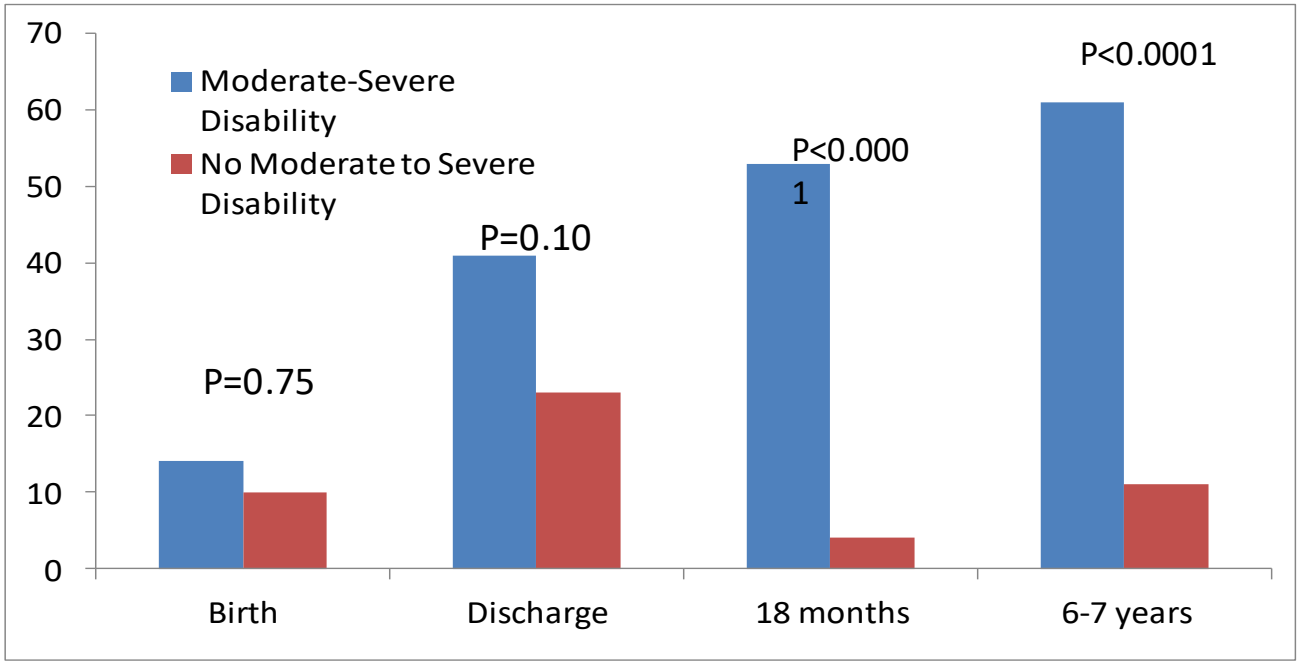
Re-hospitalization at 18-22 months for CP group:

- 23% for intractable seizures
- 54% gastrostomy or fundal plication

Re-hospitalization at 6-7 years for CP

- 61% pneumonia
- 56% surgery / tendon releases
- 44% reflux / dehydration
- 56% seizures
- 22% failure to thrive

Head Circumference <10 percentile as a Predictor of Childhood Outcome



Cognitive Outcome after Neonatal HIE: NICHD

- Almost all children with CP had IQ<70 (96%)
- 9% of children without CP had IQ <70 and 31% had scores 70-84
- Children with IQ <70: 23% had normal gait, 6-16% had ability to perform complex motor function and 10% intact fine motor coordination

Pappas 2018

Rates of Special Education Services

	18-22 Months	6-7 Years
Hypothermia Group	**N=63**	**N=63**
Early Intervention/ Special education	30%	32%
Speech therapy	17%	30%
Behavior problems	21%	7%
Questionable	15%	N/A

Neonatal, 18m Functional Status and 6-7y Disability

Variable	No/Mild Disability N=74	Mod/Severe Disability N=37
Birth		
Severe HIE	15%	32%
18 Month		
Public Insurance	47%	78%
Functional Status mean (SD), higher score better status		
Independence	98 (8)	54 (35)
General Health	98 (6)	87 (14)

All $P < 0.05$

Neonatal,18m Family Resource Scale and 6-7y Disability

Variable	No/Mild Disability N=74	Mod/Severe Disability N=37
18m Family Resource Scale, mean (SD), higher score have more resources		
Total	134(16)	127(19)
Money	23(5)	20(7)

P < 0.05; Basic needs, Time for self, Time for family: NS

18-month Impact on Family Scale and 6-7year Disability

Variable	No/Mild Disability N=74	Mod/Severe Disability N=37
18m Impact on Family Scale, mean (SD); higher score greater impact		
Total	26(8)	33(9)
Financial Impact	4(2)	5(2)
Duration of planning	9(3)	12(3)
Caretaker Burden	6(2)	8(3)
Family Burden	7(2)	9(3)
All $P < 0.05$, Coping was not different		

TOBY: HRQOL

- The health-related quality of life assessed among 75 in hypothermia and 70 in the control group noted more children in the cooled group had normal neurological function and IQ scores ≥85.

- Children in the hypothermia group performed better in speech and dexterity, while emotional functioning was similar in the two groups

Campbell 2018

Observational Data after Moderate/severe HIE: FU in Childhood

- 51 children who were cooled for moderate or severe HIE and who did not have CP
- 45% of cognitive scores decreased from infancy to childhood
- cognitive outcome was influenced by socioeconomic status

Rupac 2025

Observational Data: Moderate/severe HIE: FU in Early Adolescence

- Term, born 2007-2009, treated with hypothermia at Karolinska University Hospital n=66
- Movement ABC-2 and WISC IV/V and Parent Questionaire at 10-12y
- Mortality 12%, 15% CP. In absence of major neuromotor impairment IQ was normal. Emerging deficits in 26% among prior favorable (including executive difficulties in 19%)
- Subtle difficulties may be undetected at early school age

Grossman 2023

Observational Data: Mild and Moderate HIE: FU in Early Adolescence

- 23 adolescents assessed at 14.5 years, 11 mild, 12 moderate compared to siblings/healthy peers
- Neuropsychological and behavioral outcomes similar
- Lower scores in attention/executive function, verbal reasoning and sensory motor ability compared to healthy peers.
- More peer problems and need for remedial provisions in the HIE group

Halpin *2022*

Observational Data: Mild and Moderate HIE: Sleep as outcome

- 4-6 years after neonatal encephalopathy (n=30 moderate, n=15 mild) compared to 55 age-matched controls

- Higher pathological sleep scores along with lower quality of life scores were noted in the HIE group

Zareen 2012

Hypothermia for Mild HIE

- Recent survey of global opinion: 35 countries, majority would consider cooling, LMIC more likely to cool
- Registry data: VON, TOBY, US CHNC etc: >2000 mild HIE infants have been cooled
- No Follow-up data has been presented from majority of these reports

Murray 2016, Murthy 2014, Chevallier 2013, Pfister 2012, Mehta 2017, Oliviera 2018, Conway 2018, Gagne-Loranger 2016, Massaro 2015, Kracer 2014, Kariholu 2018, Walsh 2017, Goswami 2019, Shipley 2021, Yieh 2021, Singla 2022

FU after Mild HIE based on Observational studies

Outcomes in Infancy, Childhood, Adolescence

Prospective Research on Infants with Mild Encephalopathy (PRIME)

- Infants with birth acidosis/need for resuscitation with ≥ 1 abnormality on Sarnat score at <6 hrs. of age
- Primary Outcome: Seizures or any abnormality on aEEG, MRI, discharge neuro exam. Available on 54 of 63 (86%)
- Abnormalities seen on 28/54 (52%); abnormal EEG (4), MRI (9), discharge neuro exam (22)

Prempunpong 2017

PRIME Follow-Up

- At 18-22 mos. Outcome *mild:* cognitive score 70-84 or >85 *and* GMFCS 1-2, seizures or hearing deficit, *moderate* if cognitive score is 70-84 *and* GMFCS 2, seizures or hearing deficit or *severe* if cognitive <70 or GMFCS 3-5.
- Outcome available for 51/63 (81%) with 43 completing Bayley assessments
- 7/43 (16%) had disability and Bayley <85 occurred in cognitive score in 16%, language 32% and motor in 14%

Chalak 2018

Follow up of mild HIE: Finder 2020

Follow-up of 4 cohorts (Ireland, Sweden) of HIE assessed at 2 years

690 with neonatal data, 219 (31%) lost. 152 controls, 185 children with PA without HIE, and 134 children with HIE, of whom 14 had died

Infants with mild HIE (n = 55, *8 treated hypothermia*) had lower cognitive composite scores compared with controls, 97.6 (11.9) vs 103.6 (14.6)

There was no significant difference in the mean cognitive composite scores between untreated children (n = 47) with mild HIE and surviving children with moderate HIE (n = 53) with TH.

Neurodevelopmental outcomes after mild HIE at 2 years n=55, 8 treated with hypothermia

Table 2. Bayley Scales of Infant and Toddler Development, Third Edition Composite Scores in Surviving Children With Perinatal Asphyxia (PA) or Hypoxic Ischemic Encephalopathy (HIE)[a]

	Control (n = 152)		PA Without HIE (n = 185)		Mild HIE (n = 55)		Moderate HIE (n = 53)	
Variable	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)
Cognitive composite score	152	103.6 (14.6)	185	102.6 (15.7)	55	97.6 (11.9)[b]	53	98.4 (18.1)
Language composite score	133	101.8 (16.8)	148	101.1 (16.9)	47	99.1 (17.6)	51	97.5 (20.1)
Motor composite score	147	100.8 (10.8)	170	100.5 (11.8)	46	99.5 (16.3)	48	99.2 (17.3)

	Difference in Composite Scores (95% CI)[a]	
Variable	Mean Difference	Adjusted[b]
Cognitive composite score	−6.0 (−9.9 to −2.1)	−4.9 (−8.7 to −1.2)
Language composite score[d]	−2.7 (−8.5 to 3.1)	−4.7 (−10.7 to 1.3)
Motor composite score[e]	−1.4 (−6.4 to 3.7)	−2.1 (−7.4 to 3.1)

Childhood Outcome in Mild HIE: Population based Cohort study

Torn 2023

- Swedish National Health Registry, births 2009-2015
- 414 infants with mild HIE (33 received hypothermia) were compared to 504,661 with no HIE followed up to 6y, average 3.3y
- Outcome was composite of CP, epilepsy, and mental retardation
- 17 children had CP
- A 4-fold increased likelihood for composite of CP, epilepsy and mental retardation were noted among children with mild HIE

Outcome Childhood after Mild HIE: Murray 2016

- 5-year outcome of 22 children with mild HIE, none of whom received cooling, 19 moderate and 5 severe HIE
- 30 children who were controls
- Mild HIE infants had significantly lower full-scale IQ, performance and verbal IQ compared to controls
- No difference in cognitive outcome between mild and moderate HIE infants

School Outcomes after HIE: Reese 2025

- Regional cohort (Western Australia) with follow up to adolescence, assessment of school performance
- 550 children with HIE, 558,355 population controls
- BUT……Assessment among 58 and 61% in the 2 cohorts
- Children with *moderate or severe encephalopathy* perform at level lower than their peers (8 to 13 years) in reading and writing
  Most (62.4%) pass their grade level
- Children with mild encephalopathy performed similar to controls

Observational Data: Mild and Moderate HIE: FU in Early Adolescence

- 23 adolescents assessed at 14.5 years, 11 mild, 12 moderate HIE compared to siblings/healthy peers
- Neuropsychological and behavioral outcomes similar
- Lower scores in attention/executive function, verbal reasoning and sensory motor ability compared to healthy peers.
- More peer problems and need for remedial provisions in the HIE group

Halpin *2022*

Ongoing CE Study on Infants with Mild HIE

Comparative Effectiveness for Cooling Prospectively among Infants with Mild HIE: COOL PRIME

- Multicenter Longitudinal Observational study
- Receipt of cooling or no cooling based on center practice
- 460 participants
- Start date Dec 1, 2022
- Primary outcome: Comparison of Bayley IV domains between TH and normothermia infants
- PI: Lina Chalak UT Southwestern

Only RCT on Infants with Mild HIE

RCT of hypothermia for Mild HIE: COMET

- Multicenter RCT
- Randomized to either hypothermia or targeted Normothermia
- 426 participants
- Start date December 2024
- Primary outcome: Bayley IV cognitive scores between hypothermia and normothermia infants
- PIs: Sudhin Thayil Imperial College, Seetha Shankaran UT Austin

Challenges regarding these data

- Inconsistent definition of mild HIE
- Retrospective nature of reports
- Inclusion of infants not limited to HIE
- Diagnosis of mild encephalopathy over hours to days
- Varying rates of follow-up
- Varied psychometric measures used
- Lack of “controls” in hypothermia era reports

Conclusions Regarding Child and Adolescent Outcome following Mild HIE

- Unclear rate of disability, probably around 20%
- Need for special education services in school
- At risk for CP
- Cognitive scores are lower than healthy children
- Unclear if children with mild HIE are similar to cooled infants with moderate HIE
- Need for evidenced based data from an RCT

Questions?

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