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Title Page

School-age outcomes of children without cerebral palsy cooled for neonatal hypoxic-ischaemic encephalopathy in 2008-2010.

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Abbreviations:

aEEG Amplitude integrated electroencephalogram

CP Cerebral palsy

FSIQ Full-scale Intelligence Quotient

IQR Interquartile range

MABC-2 Movement Assessment Battery for Children - Second edition

n Number of participants

HIE Hypoxic-ischaemic encephalopathy

NICHD NRN trial National Institute of Child Health and Human Development Neonatal Research Network randomized control trial of whole-body hypothermia.

NICU Neonatal intensive care unit

TH Therapeutic hypothermia

TOBY The Total Body Hypothermia for Neonatal Encephalopathy trial.

WISC-IV Wechsler Intelligence Scale for Children ® - Fourth UK Edition (WISC-IV UK)

Abstract

Objective Since therapeutic hypothermia (TH) became standard care for neonatal hypoxic-ischaemic encephalopathy (HIE), even fewer infants die or have disability at 18-month assessment than in the clinical trials. However longer-term follow-up of apparently unimpaired children is lacking. We investigated the cognitive, motor and behavioural performances of survivors without cerebral palsy (CP) cooled for HIE, in comparison to matched non-HIE control children at 6-8 years.

Design Case-control study

Participants 29 case children without CP, cooled in 2008-2010 and 20 age, sex and social-class matched term-born controls

Measures Wechsler Intelligence Scales for Children, Fourth UK Edition, Movement Assessment Battery for Children, Second Edition (MABC-2), Strengths and Difficulties Questionnaire.

Results Cases compared to controls had significantly lower mean (SD) Full-Scale IQ (91 (10.37) vs 105 (13.41); mean difference (MD): -13.62, 95% CI -20.53, -6.71) and total MABC-2 scores (7.9 (3.26) vs 10.2 (2.86); MD: -2.12, 95% CI -3.93, -0.3). Mean differences were significant between cases and controls for verbal comprehension (-8.8, 95%CI-14.25,-3.34), perceptual reasoning (-13.9, 95%CI-20.78,-7.09), working memory (-8.2, 95%CI-16.29,-0.17), processing speed (-11.6, 95% CI-20.69,-2.47), aiming and catching (-1.6, 95%CI-3.26,-0.10) and manual dexterity (-2.8, 95%CI-4.64,-0.85). The case group reported significantly higher median (IQR) total (12(6.5-13.5) vs 6(2.25-10), P=.005) and emotional behavioural difficulties (2(1-4.5) vs 0.5(0-2.75), P=.03) and more case children needed extra support in school (34% vs 5%, P=.02) than the control group.

Conclusions School-age children without CP cooled for HIE still have reduced cognitive and motor performance and more emotional difficulties than their peers, strongly supporting the need for school-age assessments.

Keywords Hypoxic-ischaemic encephalopathy, therapeutic hypothermia, cognitive, motor, behavioural outcomes, school-age

INTRODUCTION

Therapeutic hypothermia (TH) is the standard neuroprotective intervention for neonatal hypoxic-ischaemic encephalopathy (HIE).[1] In the pre-hypothermia era, children who had HIE were reported to have impaired cognitive[2] and motor[3] abilities and school readiness scores and delayed expressive language[4] even in the absence of cerebral palsy (CP). Two trials of TH that had similar definitions of HIE have reported markedly differing results for cognitive scores at 6-7 years, with mean IQ scores of cooled children (including those with CP) nearly 4 points higher[5] or 19 points lower[6] than the test mean score of 100. The studies do not report cognitive abilities of children without CP separately. This discrepancy in IQ indicates the need for a matched control comparison group to determine how children cooled for NE perform compared to peers who did not have HIE. Whilst the clinical trials reported motor outcomes pertaining to functioning of children with CP[5] and simple neurological examination[6], motor performance in children without CP is unknown,

Furthermore, contemporary cohorts of infants cooled for HIE differ from infants cooled in the clinical trials: they are cooled earlier (0.75[7] to 3.9[8] hours vs 4.7[9] to 4.9[10] hours), cooling is administered using servo-controlled mechanism of core temperature regulation[11] rather than manual technique,[9] health care providers are likely to be more experienced with TH and contemporary cohorts have reported a lower incidence of death or disability (26.3[12] to 33.0%[7 8 13] vs 44.0 to 53.1%)[1] and reduction in the incidence and severity of CP[14] than the clinical trials. Therefore, re-analysis of TH trials data to identify the cognitive abilities of cooled children without CP may not be generalisable to contemporary cohort of infants cooled for HIE.

In this study, we aimed to determine the cognitive, motor and behavioural outcomes and educational provision amongst children aged 6-8 years who were cooled for HIE and did not develop CP by comparing them with age, sex and socio-economic class matched control children.

METHODS

Study design and participants

We conducted a prospective case-control study at the University of Bristol, UK between October 2016 and October 2017. The Health Research Authority approved the study (REC-ID:15.SW.0148). We investigated a cohort of children who underwent TH for HIE using a standard protocol, at St Michael's Hospital, Bristol.[15] TH, using servo-controlled whole-body cooling, was commenced in infants born at ≥36 weeks gestation with evidence of perinatal asphyxia and subsequent moderate to severe HIE assessed by clinical and amplitude integrated EEG assessment scored based on voltage pattern.[9]

Case definition

Children from this cohort who were aged 6-8 years (born between April 2008 and February 2010) and did not have a diagnosis of CP comprised the cases. We excluded children who 1] were cooled outside the standard criteria; 2] had an additional diagnosis e.g. a metabolic disorder; 3] did not have English as their primary spoken language.

Control definition

We recruited controls from schools around Bristol. We included children who were born at ≥36 weeks gestation, had not had HIE and had English as their primary spoken language and

were best matched to the case by age, sex and social class. It was emphasised to parents that they would not be given the results of individual assessments to minimise the chance of recruiting children about whom parents had concerns. Social class was defined as A, B, C1, C2, D, E groups based on the national readership survey.[16]

Developmental and Educational History

We obtained a detailed educational, developmental, medical, and social history. We measured height, weight, head circumference and performed a physical examination to rule out CP; no children were excluded. We collected data on the age when the child started walking (defined as the age at which the child was able to take five steps independently)[17], the provision of additional support in the classroom (defined as having a 1:1 classroom assistant for a portion of the school day, receiving additional classes, or being part of a catch-up group) and the need for statements of special educational needs/educational health plan.

Psychometric and motor assessments

A psychologist (JT), blinded to case-control status, assessed the cognitive abilities of the children using the Wechsler Intelligence Scale for Children – Fourth UK Edition (WISC-IV)[18] including subscales of working memory, processing speed, verbal comprehension, perceptual reasoning from which full-scale IQ (FSIQ) is derived. A researcher (RLK) assessed their motor abilities using the Movement Assessment Battery for Children – Second edition (MABC-2),[19] which was videotaped, and double scored by a separate assessor (SJ). Scoring differences in three children were agreed by consensus. The MABC-2 gives three subscales (Manual Dexterity, Aiming and Catching, and Balance) standard scores with a mean (SD) of 10(3). The sum of the subscales scores provides a total score, which when ≤56 or ≤67 places a child at ≤5th or ≤15th centile (high-risk for or at risk of motor impairment).[19]

Behavioural assessments

Parental perception of behavioural difficulties was recorded using the Strengths and Difficulties Questionnaire (SDQ).[20] The SDQ comprises 5 scales (Emotional, Conduct, Hyperactivity, Peer Problems and Prosocial) of 5 items each with a maximum score of 2 per item. The total difficulties score ranges from 0-40 and is the sum of the scales excluding the Prosocial scale. A higher score indicates increasing difficulties, aside from the Prosocial subscale where a higher score indicates better behaviour. Parents also completed the impact supplement which evaluates the effect of the child's difficulties on the family resulting in an "impact score" with a range of 0-10.

Outcomes

We defined the primary outcome as the mean (SD) FSIQ and the total MABC-2 standard scores. Secondary outcomes included: subscale scores from the WISC-IV and MABC-2, percentage of case children with IQ<1 or 2SD below the test mean and the control group mean compared to controls, total MABC-2 scores ≤15th or ≤5th centile[19], and SDQ scores.

Statistical analysis

Normality was tested with Q-Q plot and Shapiro-Wilk's test. Normally distributed variables are summarised as mean (SD) and variables with skewed distribution are summarised as median (IQR). We compared proportions including the aEEG pattern before TH, abnormal neonatal MRI defined as moderate or severe lesions in the basal ganglia and thalami or abnormal posterior limb of the internal capsule or severe white matter lesions,[21] social class, need for educational support, children with a FSIQ <1 or <2 SD and MABC-2 total score

≤15th and 5th centiles between the case and control children using Chi squared/Fisher's exact test. We used the independent samples t-test to compare the normally distributed variables including the WISC-IV FSIQ and total MABC-2 scores, subscales of WISC-IV and MABC-2 between case/control groups and to compare FSIQ scores between children who received additional support at school and those who did not. Mann-Whitney U test was used to compare the variables with skewed distribution including height, age of independent walking and SDQ scores. A probability of <0.05 (two-sided testing) was considered significant. We performed the analysis using IBM SPSS version 24 (IBM Corp., Armonk, NY, USA).

RESULTS

Recruitment of study cohort

We had 40 eligible children. Eleven families did not participate (7 were not-contactable and 4 refused) (Figure 1). The neonatal background characteristics, including aEEG background activity and evidence of neonatal MRI brain injury[21] and 18-month developmental status were similar between the case children who did and did not participate in the study (supplemental Table 1). Among cases 26/29 had a moderately abnormal aEEG (Sarnat grade II encephalopathy) and 3/29 had a severely abnormal aEEG (Sarnat grade III). No case children had a known diagnosis of visual, hearing or speech impairment nor were such problems apparent during testing.

We contacted 133 schools to recruit the controls. Among the 40 families that responded, 20 children who were best comparable to the cases in terms of age, sex and social class comprised the control group (Figure 1, Table 1).

Table 1 Case-control comparison of demographics, early development and educational needs

Characteristic	Cases (n=29)	Controls (n=20)	P Value
Age at testing in years, mean (SD)	7.0 (0.5)	7.0 (0.6)	0.71
Male sex n (%)	20(69%)	12 (60%)	0.56
NRS[16] Social Grade n (%)			
A (Upper middle class)	4 (14%)	3 (15%)	
B (Middle class)	8 (28%)	6 (30%)	
C1 (Lower middle class)	6 (21%)	4 (20%)	
C2 (Skilled working class)	7 (24%)	5 (25%)	
D (Working class)	3 (10%)	2 (10%)	
E (Casual worker or unemployed)	1 (3%)	0 (0%)	0.98
Gestational age in weeks, median (IQR)	40.1 (39.3-40.7)	39.9 (38–41)	0.59
Birth weight in g, median (IQR)	3200 (3012-3680)	3544 (3118-3997)	0.10
Age starting playgroup in months, median (IQR)	24 (13-36)	24 (12-36)	0.67
Age of independent walking in months, median (IQR)	13 (12-15)	12 (11-14)	0.02
Statement of special educational needs, n (%)	1 (3%)	0 (0%)	1.0
Extra classroom support, n (%)	10 (34%)	1 (5%)	0.02
Weight in kg, median (IQR)	23.7 (21.4-27.25)	24.6 (22.9-26.7)	0.65

Weight centile, median (IQR)	48.0 (31.9-84.3)	61.05 (47.33-80.83)	0.64
Height in cm, median (IQR)	121 (117-126)	125 (124-130)	0.03
Height centile, median (IQR)	43.8 (17.5-75)	71.1 (50.5-87.2)	0.02
Body mass index (BMI), median (IQR)	15.9 (14.9-17.9)	15.5 (14.9-16.1)	0.21
Head circumference in cm, median (IQR)	52.4 (51.5-53.7)	52.6 (51.8-53.1)	0.73

Case-control comparison

A higher proportion of case children were receiving additional support in the classroom than control children (10/29 (34%) versus 1/20 (5%), P= .02); odds ratio: 10.0, 95% CI 1.16 to 86.0, and one case child had a statement of special educational needs (none in the control group) (Table 1).

The case and control groups were of comparable gestational age, birth weight, weight and head circumference at 6-8 years (Table 1). Whilst median (IQR) height centile[22] at 6-8 years was significantly lower in the case group than the control group 43.8 (17.5-75) vs 71.1 (50.5-87.2), P= .02, weight centile and BMI were comparable. There was a weak positive correlation between birth weight and height at 6-8 years (r=0.28) in case children but not in control children (r=0.03).

Median age at commencement of playgroup was similar between cases and control but the median (IQR) age of independent walking was 1 month later in the cases compared to controls (13 months (12-15) versus 12 months (11-14), P= .02).

Primary outcomes

All 20 control children completed the motor and cognitive assessments. One case child refused to complete the WISC-IV processing speed subscale, preventing the calculation of processing speed and therefore FSIQ score. Case children compared to controls had a significantly lower mean (SD) FSIQ (91 (10.37) versus 105 (13.41); mean difference (MD) -13.62, 95% CI -20.5 to -6.71) and total MABC-2 score (8 (3.26) versus 10 (2.86), MD -2.12, 95% CI -3.93 to -0.30) (Table 2). The test scores of children with severely abnormal aEEG before cooling (n=3) were within the distribution of scores of children with moderately abnormal aEEG although in the lower half of the distribution (supplemental figure 1).

Secondary outcomes

The case group had significantly lower mean standardized scores in all 4 subscales of the WISC-IV and the Manual Dexterity and the Aiming and Catching subscales, but not the Balance subscale of the MABC-2 than controls (Table 2, Figure 2). A significantly higher proportion of case children had FSIQ <1 SD below the control mean (<92) than controls and MABC-2 total score ≤15th centile but not at ≤5th (Table 2).

Children who received additional help at school had significantly lower mean (SD) FSIQ (87.5 (13.8)) than those who did not (99.6 (12.31), MD: -12.1, 95%CI -21.15 to -3.11). Case children who did not receive extra help at school still had statistically lower mean (SD) scores than controls in verbal comprehension (96.2 (7.54) vs 102.8(10.36), MD:-6.7, 95%CI -12.65 to -0.72), perceptual reasoning (90.7 (10.77) vs 103.6(12.55), MD:-12.9, 95%CI -20.59 to -5.20) and FSIQ (94.1 (7.56) vs 105.2 (13.78), MD: -11.1, 95%CI -18.44, -3.67). The case group scored significantly higher in the Total difficulties and Emotional behavioural

difficulties scales of the SDQ compared to control children. Scores for Hyperactivity and Conduct problems were also higher for cases than controls, the difference approaching statistical significance (Table 2).

Table 2 Primary and secondary outcomes at 6-8 years of age

	Case group (n=29)	Control group (n=20)	Difference (95%CI) Cases versus controls	P value
Primary Outcome				
FSIQ, Mean (SD)	91 (10.37) *	105 (13.41)	-13.62 (-20.53 to -6.71)	<0.001
MABC-2 Total score, Mean (SD)	7.9 (3.26)	10.2 (2.86)	-2.12 (-3.93 to -0.30)	0.02
Secondary outcomes				
WISC-IV subscales				
Verbal comprehension, Mean (SD)	94 (8.79)	103 (10.09)	-8.8 (-14.25 to -3.34)	0.002
Perceptual reasoning, Mean (SD)	89 (11.15)	103 (12.49)	-13.9 (-20.78 to -7.09)	<0.001
Working memory, Mean (SD)	94 (13.76)	102 (13.82)	-8.2 (-16.29 to -0.17)	0.04
Processing speed Mean (SD)	96 (13.76) *	107 (17.59)	-11.6 (-20.69 to -2.47)	0.01
FSIQ <2 SD below test mean, n (%)	1 (3.5%) *	0 (0%)		1.0
FSIQ <1 SD below test mean, n (%)	6 (21%) *	1 (5%)		0.21
FSIQ <2 SD below control mean, n (%)	2 (7.1%)*	1 (5%)		1.0

FSIQ <1 SD below control mean, n (%)	14 (50%)*	3 (15%)		0.02
MABC-2 subscales				
Aiming and catching, Mean (SD)	8.5 (2.72)	10.2 (2.85)	-1.6 (-3.26 to -0.10)	0.05
Aiming and catching score ≤5th centile, n (%)	5 (17.2%)	1 (5.0%)		0.38
Balance, Mean (SD)	8.8 (3.33)	10.1 (2.94)	-1.3 (-3.13 to 0.55)	0.16
Balance score ≤5th centile, n (%)	6 (20.7%)	0 (0%)		0.07
Manual Dexterity, Mean (SD)	7.7 (3.53)	10.4 (2.76)	-2.8 (-4.64 to -0.85)	0.005
Manual Dexterity score ≤5th centile, n (%)	9 (31.0%)	1 (5.0%)		0.034
MABC-2 total score ≤15th centile, n (%)	11 (38%)	1 (5%)		0.008
MABC-2 total score ≤5th centile, n (%)	7 (24%)	1 (5%)		0.08
SDQ Subscales scores				
Total difficulties, Median (IQR)	12 (6.5-13.5)	6 (2.25-10)		0.005
Emotional problems Median (IQR)	2 (1-4.5)	0.5 (0-2.75)		0.03
Hyperactivity, Median (IQR)	2 (1-3)	1 (0-2)		0.06
Conduct problems	4 (2.5-6.5)	3 (1-5)		0.06

Median (IQR)			
Peer problems, Median (IQR)	0 (0-2.5)	0 (0-1)	3.56
Prosocial, Median (IQR)	9 (7.5-10)	9 (8.25-10)	0.13
Impact score, Median (IQR)	0(0-2.5)	0 (0-2.0)	0.31

* Missing data from 1 child (n=28)

DISCUSSION

Our study found that school-age children cooled for HIE even in the absence of CP have significantly lower cognitive and motor scores with an IQ, on average, 14 points lower than their peers. Consistent with these findings, a third of the case children were receiving additional classroom support and parents of case children reported significantly higher Total and especially Emotional difficulties than parents of control children.

Cognitive abilities were particularly affected in the perceptual reasoning and processing speed domain with scores on average 14 points and 12 points lower than their peers. However, in NICHD NRN trial of TH, verbal IQ was more affected than performance IQ and processing speed in cooled children with and without CP.[6] In our cohort, a higher proportion of case children had subnormal IQ scores (<1 SD below the mean) when compared to the control mean rather than the test mean. This highlights the importance of comparing cognitive abilities to a contemporary matched control group rather than test standardisation norms. Comparing our case children to cooled children without CP from the NICHD NRN trial,[6] we

observed a lower proportion with FSIQ <1SD (21% vs 32%) and <2SD (3.5% vs 11%) below the test mean indicating that the outcomes in the post-hypothermia trial era might be better than that reported in this clinical trial. The mean IQ of our case children was 91; unfortunately, the corresponding data from the clinical trials is unavailable. The lower cognitive abilities reported in this study are in line with prior studies reporting lower cognitive abilities in non-cooled children with HIE without severe disability[2 4 23 24] indicating that this effect is still present, despite the use of TH.

Motor assessment in the clinical trials has been limited to functional ability within CP i.e. Gross Motor Function Classification System [5] or a general neurological examination,[6] and lacked an assessment of coordination difficulties using a validated scale. With such a scale, the MABC-2, we observed that 38% of case children were at a higher risk of motor impairment and had lower total scores and lower scores in two of the subscales than controls. In addition, we also found that parents reported case children to walk independently 1 month later than parents of the peer group. In non-cooled children aged 5-6 years who had grade 2 NE and did not develop CP, 12% had MABC-1 scores ≤15th centile.[3] We included infants with grade 3 NE and used the MABC-2 rather than MABC-1,[3] which makes a direct comparison with the above study difficult.

Higher rates of hyperactivity,[2 4] anxiety and depression[25] have been reported in non-cooled children with moderate NE based on parent and/or teacher questionnaires. Vision, hearing, speech, emotion and pain at 6-7 years measured using parental questionnaire was comparable between the cooled and the non-cooled groups in the TOBY trial.[26] However, when compared to peers, we found that cooled children without CP have increased difficulties with emotional problems and overall difficulties with behaviour.

A third of the case children were already receiving additional educational support in school, indicating that their reduced performances in the psychometric and motor assessments are related to real world educational difficulties. However, this group did not explain the overall lower scores in case children, as those not receiving extra help at school still had lower cognitive scores than the control children.

Case children were significantly shorter than their peers, with no difference in weight or BMI. This new observation requires further research to ascertain the effect of HIE on growth.

Limitations include a small sample size that come from a higher socio-economic group than the rest of the country, a higher proportion (70%) of males with a follow-up rate of 73% although similar to TOBY trial childhood follow-up undertaken in the UK (males in cooled group: 70% vs 63%; study follow-up rate: 73% vs 79%)[5] may influence generalizability. . However, our study excluded non-hypoxic-ischaemic neonatal encephalopathy and represents a well-defined cohort of children who underwent TH for neonatal HIE since TH became standard practice.

In conclusion, this study shows that despite the protective effect of TH, cooled children who do not develop CP have reduced behavioural, cognitive, and motor performance at 6-8 years compared to peers; with a third of the case children already receiving additional support in the classroom. These concerning findings adds weight to the argument that follow-up for children who had HIE without major problems in infancy should extend beyond 18-24 months.

Contributors Statement:

Richard Lee-Kelland: Dr Lee-Kelland contributed to the study design, recruited participants, conducted the study, collected and analyzed the data, wrote the first draft of the manuscript and approved the final version as submitted.

Sally Jary: Dr Jary contributed to the study design, assisted with data collection, contributed to the revisions of the paper and approved the final manuscript as submitted

James Tonks: Dr Tonks contributed to the study design, performed psychometric assessments, collected data, contributed to revisions of the paper and approved the final manuscript as submitted.

Frances Cowan: Professor Cowan contributed to the study design, revised the paper and approved the final manuscript as submitted.

Marianne Thoresen: Professor Thoresen formed the newborn cohort, headed the steering group, obtained funding for major part of the staff salaries, contributed to study design, revised the paper and approved the final manuscript as submitted.

Ela Chakkarapani: Dr Chakkarapani conceptualized and designed the study, obtained funding for the study and part of the staff salary, supervised analysis, drafted the second version of the manuscript, completed revisions of the paper and approved the final manuscript as submitted.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Ethical approval: The study has favourable ethical opinion from the NRES Committee South

West-Frenchay and the Health Research Authority (15/SW/0148).

The work has been presented in the Pediatric Academic Societies conference in San Francisco (2017) and the Neonatal Spring Meeting in London (2017).

What's already known on this topic?

- Prior to the routine use of therapeutic hypothermia for neonatal hypoxic-ischaemic encephalopathy, school-age children had cognitive and motor difficulties even in the absence of cerebral palsy.
- Therapeutic hypothermia trials report variable Intelligence Quotient scores above or below the test mean at 6-7 years in cooled children with and without cerebral palsy.
- Contemporary cohorts of infants cooled for neonatal hypoxic-ischaemic encephalopathy report reduced death and disability at 18 months compared to the clinical trials.

What this study adds?

- School-age children who underwent therapeutic hypothermia for neonatal hypoxic-ischaemic encephalopathy since it became standard practice have significantly lower cognitive scores and on average 14 IQ points lower than matched peers even in the absence of cerebral palsy.
- Motor scores were lower than their peers particularly affecting manual dexterity skills.
- Cooled children without cerebral palsy have behavioural scores lower than those of their peers and a 10 fold increased odds of requiring additional support at school.

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Figure captions:

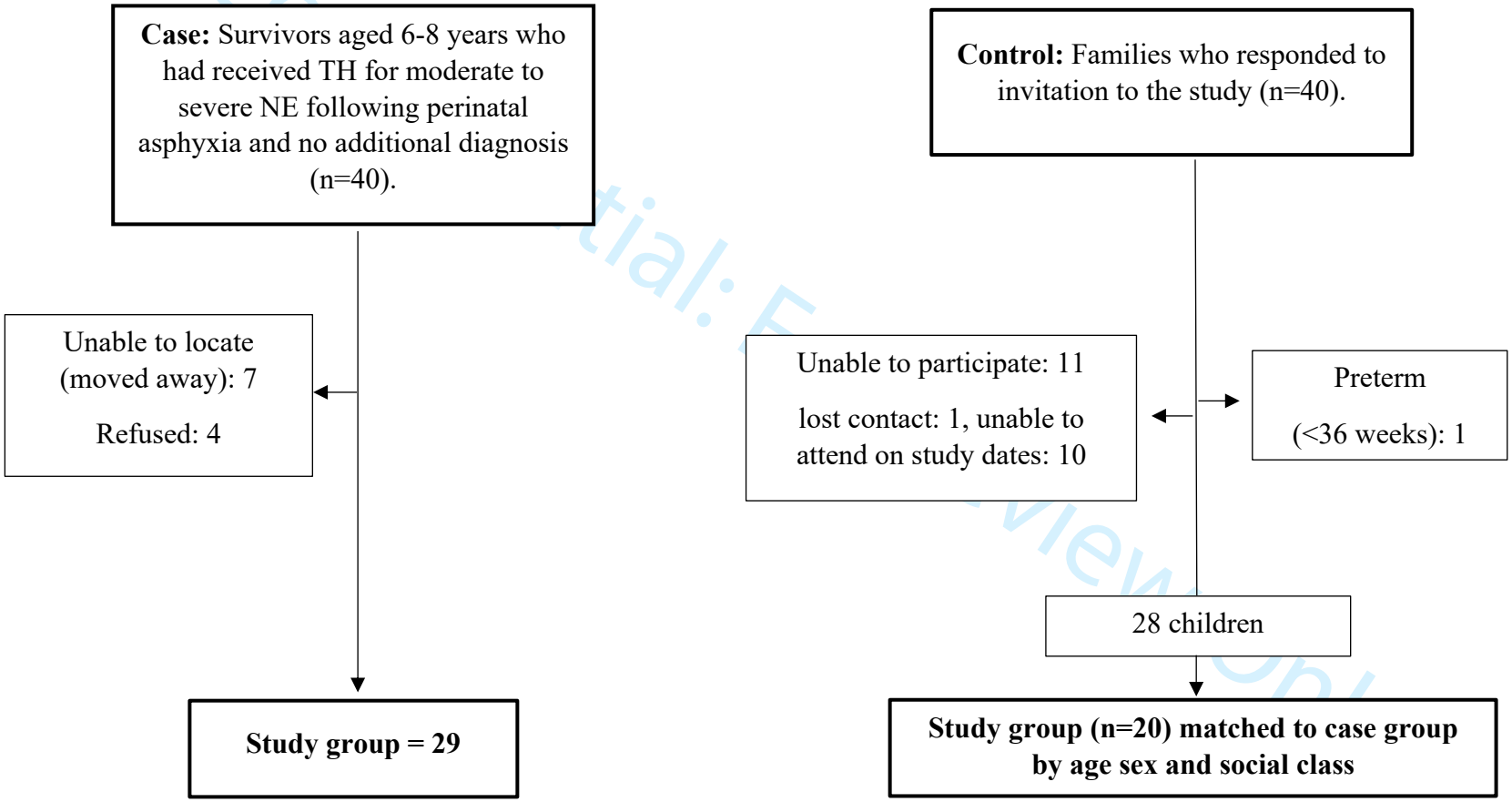
Figure 1: Flow chart showing recruitment of cases and control children.

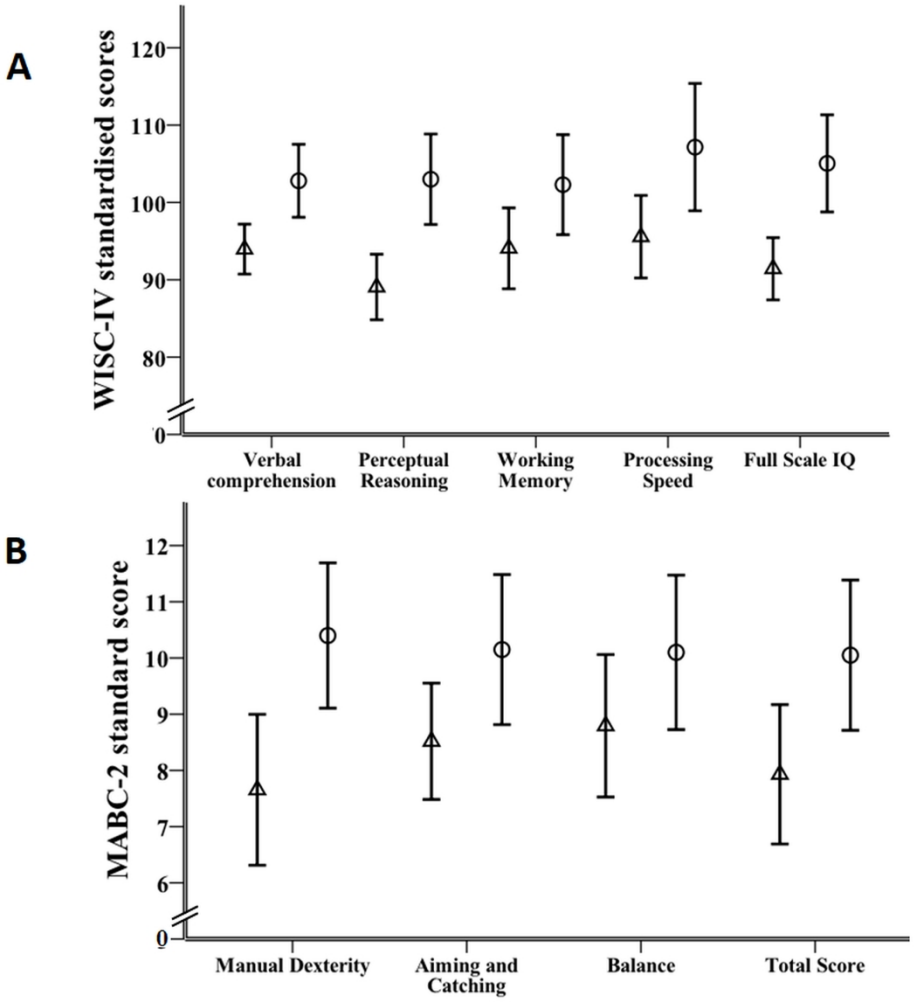
Figure 2: Comparison of WISC-IV standardized scores and MABC-2 total and subscale standard scores between case and control children. For full-scale IQ and the different WISC domains (cases n=28 (processing speed, full scale IQ) and n=29 (verbal comprehension, perceptual reasoning, working memory), controls n=20.) Data represents the mean scores with 95% confidence intervals. The triangles denote the case children scores and the circles denote the control children scores.

Supplemental Table 1: Comparison of characteristics between children included and excluded in the case group

Supplemental Figure 1: Distribution of WISC-IV standardized scores and MABC-2 total and subscale standard scores in the case group. The grey circles represent children who had a moderately abnormal aEEG (n=26) and the black squares represent children who had a severely abnormal aEEG (n=3) before cooling. The dotted line represents the population mean for the scores.

Flow chart showing recruitment of cases and controls





Comparison of WISC-IV standardized scores and MABC-2 total and subscale standard scores between case and control children. For full-scale IQ and the different WISC domains (cases n=28 (processing speed, full scale IQ) and n=29 (verbal comprehension, perceptual reasoning, working memory), controls n=20.) Data represents the mean scores with 95% confidence intervals. The triangles denote the case children scores and the circles denote the control children scores.

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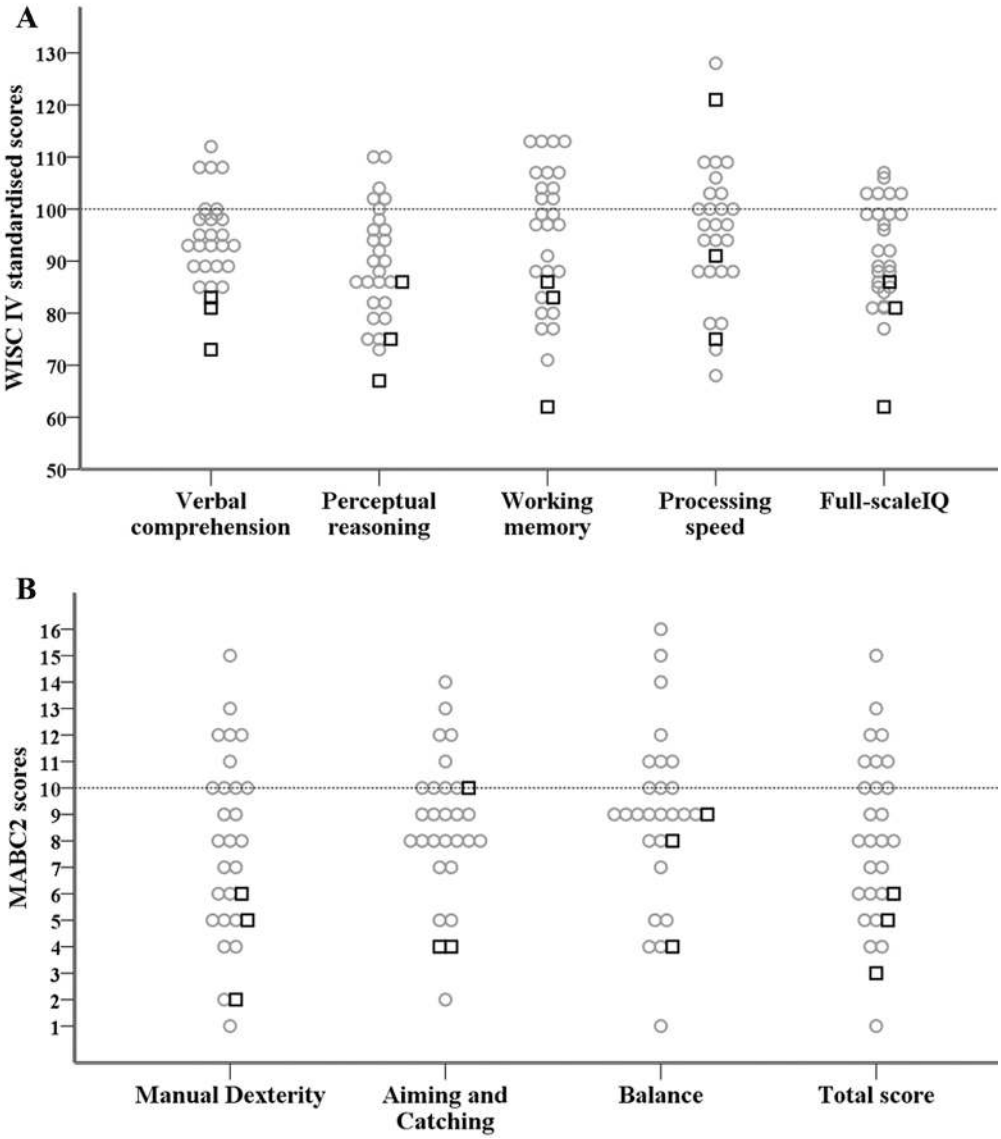
Supplemental Table 1 Comparison of characteristics between children included and excluded in the case group

Variable	Included in case group N=29	Excluded from case group N=11	P value
Gestation weeks, Median (IQR)	40.0 (39.0-40.7)	40.2 (40.0-41.7)	0.30
Males, n (%)	20 (69%)	5 (45.5%)	0.27
Birth weight Kg, Median (IQR)	3.2 (3.01-3.68)	3.4 (2.78-4.20)	0.43
Birth Head circumference cm, Median (IQR)	35.3 (34.0-36.0)	34.2 (33.5-35.0)	0.28
Worst pH within 1 hr of birth, Median (IQR)	6.9 (6.81-7.04)	7.0 (6.90-7.20)	0.20
Worst base excess within 1 hr of birth Median (IQR)	-16.0 (-24.7—10.95)	-13.5 (-16.7—9.0)	0.16
Apgar score at 10 min, Median (IQR)	6 (5-8)	6(4-8) *	0.68
Encephalopathy grade before TH, Median (IQR)	2 (2-3)	2 (2-3)	0.84
Intrapartum complications			
Fetal heart rate decelerations, n (%)	15 (51.7%)	3 (27.3%)	
Thick meconium stained liquor, n (%)	4 (13.8%)	2 (18.2%)	
Shoulder dystocia, n (%)	2 (6.9%)	2 (18.2%)	

Vaginal breech delivery, n (%)	2 (6.9%)	1 (9.1%)	
Cord around the neck, n (%)	2 (6.9%)	0 (0.0%)	
Antepartum haemorrhage, n (%)	1 (3.4%)	1 (9.1%)	
Reduced fetal movements, n (%)	1 (3.4%)	0 (0.0%)	
Cord prolapse, n (%)	1 (3.4%)	1 (9.1%)	
Unexpectedly flat at birth, n (%)	1 (3.4%)	0 (0.0%)	
Placental abruption, n (%)	0 (0.0%)	1 (9.1%)	0.51
aEEG pattern before TH			
Moderately abnormal n (%)	27/29 (93%)	11/11 (100%)	
Severely abnormal n (%)	2/29 (7%)	0/11 (0%)	1.0
Abnormal neonatal MRI predictive of neurodevelopmental impairment n (%)	4 (13.8%)	1 (10.0%)	1.0

* Data missing for one child



Distribution of WISC-IV standardized scores and MABC-2 total and subscale standard scores in the case group. The grey circles represent children who had a moderately abnormal aEEG (n=26) and the black squares represent children who had a severely abnormal aEEG (n=3) before cooling. The dotted line represents the population mean for the scores.

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