BMJ Open

Long-term consequences of neonatal encephalopathy in the hypothermia era: protocol for a follow-up cohort study at 9 years of age

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ABSTRACT

Introduction Therapeutic hypothermia (TH) became the standard of care treatment for neonates with moderate and severe neonatal encephalopathy (NE) in most industrialized countries about 10 years ago. Although TH is effective in reducing mortality and the incidence of severe developmental disabilities, the recent literature converges in reporting frequent cognitive and behavioural difficulties at school entry in children with NE-TH. Although these challenges are deemed minor compared with cerebral palsy and intellectual disability, their impacts on a child's self-determination and family's well-being are quite significant. Therefore, the nature and extent of these difficulties need to be comprehensively described so that appropriate care can be offered.

Methods and analysis The current study will be the largest follow-up study of neonates with NE treated with TH to characterize their developmental outcomes and associated brain structural profiles at 9 years of age. Specifically, we will compare executive function, attention, social cognition, behaviour, anxiety, self-esteem, peer problems, brain volume, cortical features, white matter microstructure and myelination between children with NE-TH and matched peers without NE. Associations of perinatal risk factors and structural brain integrity with cognitive, behavioural and psycho-emotional deficits will be evaluated to inform about the potential aggravating and protective factors associated with function.

Ethics and dissemination This study is supported by the Canadian Institute of Health Research (202203PJT-480065-CHI-CFAC-168509), and received approval from the Pediatric Ethical Review Board of the McGill University Health Center (MP-37-2023-9320). The study findings will be disseminated in scientific journals and conferences and presented to parental associations and healthcare providers to inform best practices.

Trial registration number NCT05756296.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study where children who had neonatal encephalopathy treated with therapeutic hypothermia will undergo long-term comprehensive neurodevelopmental and neuroimaging assessment at 9 years of age.

⇒ Typically, developing peers, matched for age and sex, will be enrolled and evaluated for comparison.

⇒ Perinatal history and neonatal brain MRI are available for the cohort of children with neonatal encephalopathy and will be put in relation with the 9-year outcomes to improve prognosis discussion in the perinatal period.

⇒ We anticipate a number of losses at follow-up, which may limit the generalization of our findings to the general population.

INTRODUCTION

The incidence of birth asphyxia in Canada is approximately 2.4 cases per 1000 live births.[1] Neonatal encephalopathy (NE) secondary to birth asphyxia often results in brain injuries contingent on changes in cerebral haemodynamics, with an initial decrease of blood flow to the brain (primary lesions), followed by a return of blood flow in an injured brain and the initiation of a cascade of pathologic pathways (secondary lesions or 'reperfusion injury').[2–4] This cascade includes an accumulation of extracellular glutamate with excessive activation of glutamate receptors, calcium influx and generation of reactive oxygen and nitrogen species, leading to cell death and definitive brain injury with long-term functional impairments.[2 3] Therapeutic hypothermia (TH) (ie, cooling to an oesophageal temperature of 33.5°C initiated within the first 6 hours of life and continued for 72 hours) is currently the only clinically proven neuroprotective treatment to minimize brain injury in near-term/term neonates with moderate or severe NE.[5–7] TH is thought to be protective mainly by reducing brain perfusion and metabolism, as well as mitigating reperfusion injury, reducing excessive free radical production and depressing the immune response and various potentially

harmful pro-inflammatory reactions.[8] The first TH trials showing benefits for NE were published in the 2000s, and TH was subsequently adopted in high-income countries, including Canada, as a standard of care treatment for neonates with moderate to severe NE in the early 2010s.[9–11] However, despite TH, many children with NE still develop brain injury and long-lasting neurodevelopmental deficits.[6 9 12–14]

The most frequent brain injury patterns observed on routine MRI following NE (treated or not with TH) include the basal ganglia, watershed or total cortical patterns of injury.[12 13 15 16] These patterns of neonatal brain injury correlate strongly with adverse outcomes such as cerebral palsy (CP) and global developmental delay in children with NE-TH followed-up at 2–3 years of age.[12 17 18] However, whether perinatal MRI findings are also associated with later school-age outcomes remains to be evaluated. Moreover, beyond the typical brain injuries detected on conventional MRI, cumulating evidence suggested that neonates with NE-TH also present with altered brain microstructure,[19 20] disrupted cerebral perfusion,[21–24] aberrant metabolic profile[25] and cerebellar injuries,[26] as well as disrupted postnatal brain maturation processes, such as altered brain growth[27 28] and myelination.[29] Yet, prospective longitudinal follow-up imaging studies evaluating the brain's structural integrity beyond the first month of life are non-existent in this population and strongly limit our understanding of the possible brain plasticity processes following NE and TH. Whether these early-life alterations persist over time and produce long-term functional deficits remains to be determined. Going in this direction, a recent exploratory cross-sectional study of 33 children aged 6–8 years with NE-TH without neonatal brain injury described widespread microstructural alterations of the cerebral white matter when compared with typically developing controls, suggesting that some of the previously identified early brain alterations persist at school-age and possibly beyond.[30] Still, the extent to which long-lasting altered brain development may impede long-term functioning in children with NE-TH remains unclear.

Studies from the pre-TH era reported frequent cognitive deficits and poorer academic performance in school-aged survivors of NE without severe disability.[31–33] Specifically, lower IQ, poorer working memory and attention regulation, decreased long-term memory and more problematic behaviour, including increased socialization difficulties, anxiety and depressive symptoms, have been documented, indicating a greater need for specialized educational and health services than their peers without NE.[34–36] However, whether these difficulties are still present in cohorts of children with NE-TH remains to be confirmed. Three of the initial TH trials (which compared children with NE who received TH to children with NE who had not) performed follow-up at the age of school entry (ie, 5–7 years)[14 37 38] and reported rates of 17%–21% for CP and 23%–27% for borderline or impaired intellectual abilities in children with NE-TH.[14 38] However, by

focusing only on the severe disabilities, our understanding of the many complex cognitive and psycho-affective abilities highly associated with school and life success as well as with family well-being remains limited.[39–44]

The pressing need to create updated knowledge about school-age outcomes in these new cohorts of children with NE-TH has resulted in emerging literature over the past 5 years. A number of recent small cross-sectional studies in early school-aged children with NE-TH without CP or neonatal brain injury have reported lower intellectual quotient, attentional, reasoning, memory, language and fine motor skills as well as more hyperactivity, oppositional behaviour and emotional distress when compared with typically developing peers without NE.[45–50] However, many critical psycho-affective and socio-cognitive skills remain to be comprehensively described in this high-risk group of children so that their psycho-educational needs can be anticipated. Moreover, it is important to note that by excluding children with CP and with brain injury, previous reports have overlooked an important subset of NE-TH survivors who are also at greater risk for behavioural problems. Indeed, we previously reported that about 40% of school-aged Canadian children and adolescents with CP also present with behavioural and psycho-affective difficulties predominantly related to peer problems and emotional symptoms.[51 52] There is a range of motor and cognitive profiles in children with NE-TH and brain injury (ie, not all children with CP will present with intellectual disability), and their outcomes need to be comprehensively described as well.[53 54]

Aim and hypotheses
The overarching goal of this study is to characterise the cognitive, behavioural and psycho-emotional profile and related brain profiles of children with NE-TH at 9 years of age. Specifically, we aim:

1. To compare cognitive, behavioural and psycho-emotional abilities using comprehensive standardised assessments of outcomes between 9-year-old children with NE-TH and age-matched and sex-matched peers without NE.

Hypothesis 1: Children with NE-TH will display lower IQ, executive functioning, attention, social cognition and self-esteem, but more anxiety and behavioural and peer problems than age-matched and sex-matched peers without NE-TH.

2. To compare structural brain integrity using quantitative MRI between 9-year-old children with NE-TH and age-matched and sex-matched peers without NE.

Hypothesis 2: Children with NE-TH will present with smaller total and regional (eg, basal ganglia, hippocampus, cerebellum) brain volumes, atypical cortical and subcortical morphometry, and widespread white matter microstructural alterations and hypomyelination when compared with age-matched and sex-matched peers without NE-TH.

3. To evaluate the relationships between cognitive, psycho-emotional and motor skills at 9 years and (1)

individual and perinatal risk factors and (2) structural brain integrity at 9 years.

Hypothesis 3: A combination of individual (eg, socio-economic), perinatal factors (eg, neonatal brain injury) and markers of aberrant brain integrity (eg, volume, microstructure) will be associated with domain-specific deficits at 9 years in children with NE-TH.

METHODS AND ANALYSIS
Design
This study is a prospective multicenter follow-up study of an existing clinical cohort of children who received TH for NE at the two largest level 3 paediatric institutions and neonatal follow-up programmes in Quebec (Canada), the Montreal Children's Hospital (MCH) of the McGill University Health Centre and the Centre Hospitalier Universitaire Ste-Justine (CHUSJ). Recruitment and data collection is expected to start in August 2023 and end by 31 March 2027.

Study population
Children born between 2014 and 2018, who received whole-body cooling to an oesophageal temperature of 33.5°C initiated within the first 6 hours of life, continued for 72 hours, and then slowly rewarmed for moderate or severe NE at one of our two centres will be approached. Eligibility for TH at our institutions followed established guidelines in previous TH trials.[5] Participants with a history of (1) congenital infections, (2) genetic or metabolic disorders or (3) major brain malformations (eg, lissencephaly), as well as (4) any contraindication for MRI (eg, metal implant, claustrophobia) will be excluded.

For each of two same-sex and same-age NE-TH participants, a matched control for age (±6 months of mean age) and sex will be recruited. Participants born at term (gestational age ≥37 weeks and weight appropriate for gestational age) without neonatal complication will be considered as eligible controls. Children with a previous history of neurodevelopmental delay or disorder, or a traumatic brain injury will be ineligible.

Assessment procedure
For this study, enrollees will complete one study visit to perform the standardised evaluations and a brain MRI. Children will have the opportunity to familiarise themselves with the MRI environment on a mock scanner before the scan and to watch a movie or listen to the music of their choice during the scan (or examination). Parents will be invited to complete a series of questionnaires during their child's testing or at a moment of their choice via a provided secure link. The visit will start with the outcome evaluations that are the most cognitively demanding and breaks will be provided as necessary. Outcome evaluations will be conducted by trained research staff or trainees blinded to the details of the child's neonatal and developmental history, and group allocation (ie, NE-TH vs controls) to the extent possible.

The choice of outcome measures has been made based on their clinical significance, psychometric properties and availability in both French and English, considering the bilingual context of Quebec.

Children's ability profile
Cognitive abilities
Estimated IQ will be assessed using the Wechsler Abbreviated Scale of Intelligence 2nd ed (WASI-2). Executive functions refer to a group of cognitive processes typically mediated by the frontal lobe and encompass a range of skills such as inhibitory control, cognitive flexibility, working memory and problem-solving.[55] We will assess inhibition and cognitive flexibility (Stroop test),[56] planning (Tower—Delis-Kaplan Executive Function System (D-KEFS) and the copy of the Rey-Osterrieth Complex Figure),[57 58] impulsivity (Conner Continuous Performance Test—3rd Ed (CPT-3)),[59] working memory (Digit Span) and word retrieval (verbal fluency—D-KEFS). The specific attentional skills that will be evaluated include immediate (Digit Span, forward) and visual selective and sustained attention (CPT-3). Visual memory will also be assessed using the Rey-Osterrieth Complex Figure (immediate and delayed recalls, and recognition). Social cognition refers to cognitive skills involved with the processing and handling of social information, which underlies how people perceive and react during social interaction.[60] Two subtests of the Developmental NEuroPSYchological assessment 2nd ed (NEPSY-II) will be used, namely the Affect Recognition and Theory of Mind and Affect Recognition subtests, to characterise ability to recognise affects, as well as the ability to understand that others have thoughts, ideas and feelings, and how emotion relates to social context.[61] We anticipate a subset of children with NE-TH to present with severe intellectual limitations and who will not be able to complete most of these relatively complex cognitive measures. With these children, the Leiter Intelligence Test, a non-verbal measure, will be performed to extract an estimated IQ.[62]

Psycho-emotional abilities
To complete children's neuropsychological profiles, we will evaluate the presence of behaviour and psycho-affective difficulties. Behaviour and emotional problems will be assessed with the Behaviour Assessment System for Children 3rd Ed (BASC-3), while social competencies and peer problems will be evaluated with the Pediatric Evaluation of Emotions, Relationships, and Socialization (PEERS-Q).[63] Self-esteem will be evaluated using the Self-Concept Inventory from the Beck Youth Inventories-II[64] to collect children's perception of their competence and positive self-worth. Children's anxiety and emotional regulation will be assessed using the Spence Children's Anxiety Scale,[65] the Multidimensional Anxiety Scale for Children[66] and the Difficulties in Emotion Regulation Scales.[67] Predominance of profiles (eg, predominantly affective, cognitive or generalised) will be examined

following an in-depth interpretation of the cognitive and psycho-emotional outcomes.

Motor abilities

To explore relationships between motor and cognitive abilities, motor skills will be evaluated using the Movement Assessment Battery for Children-2nd Ed[68] in children without CP. In children with CP, motor skills will be evaluated with the Gross Motor Function Measure[69] and subsequently be classified using the Gross Motor Function Classification System and the Manual Ability Classification System.[70 71] Visual-motor integration will be assessed with the Berry-Buktenica Developmental Test of Visual-Motor Integration.[72]

Functional profiles

Lastly, to characterise the functional impact of the deficits identified, we will assess children's adaptative behaviour using the Adaptive Behaviour Assessment Systems 3rd Ed.[73] Table 1 summarises the outcome evaluations and primary evaluated constructs.

Table 1	List of outcome measures			
Construct	**Measure: subtests**	**Outcome of interest**	**Administration**	**Respondent**
Cognitive abilities	Wechsler Abbreviated Scale of Intelligence 2nd Ed	Estimated IQ, verbal comprehension index, perceptual reasoning index	Evaluation	Child
	Leither Intelligence Test	Estimated IQ (children with severe verbal limitaions)	Evaluation	Child
	Digit span	Immediate attention and working memory	Evaluation	Child
	Stroop	Inhibition and cognitive flexibility	Evaluation	Child
	Delis-Kaplan Executive Function System—Tower	Planning, impulstivity	Evaluation	Child
	Conner Continuous Performance Test—3rd Ed	Visual selective and sustained attention, impulsivity, processing speed	Evaluation	Child
	Rey–Osterrieth Complex Figure	Visuo-constructive skills, visuospatial memory, planning	Evaluation	Child
	Delis-Kaplan Executive Function System: Verbal fluency	Word retrieval, lexical and semantic access	Evaluation	Child
	NEPSY-II: Theory of Mind	Social cognition: ability to understand that others have their own thoughts, and how emotion relates to social context.	Evaluation	Child
	NEPSY-II: Affect Recognition	Social cognition: affect recognition	Evaluation	Child
Psycho-emotional abilities	Behavior Assessment System for Children 3rd Ed	Behavioural symptoms, internalising and externalising problems, self-esteem	Questionnaire	Child and parent
	Paediatric Evaluation of Emotions, Relationships, and Socialization	Social competences	Questionnaire	Parents
	Beck Youth Inventories-II: Self-Concept Inventory	Self-esteem	Questionnaire	Child
	Spence Children's Anxiety Scale Multidimensional Anxiety Scale for Children Difficulties in Emotion Regulation Scales	Child's anxiety Child's anxiety Emotional regulation	Questionnaire	Child and parent
Motor skills	Movement Assessment Battery for Children-2nd Ed	Motor abilities (children without CP)	Evaluation	Child
	Berry-Buktenica Developmental Test of Visual-Motor Integration	Perceptual and visual motor abilities	Evaluation	Child
	Gross Motor Function Measure-2nd Ed	Motor abilities (children with CP)	Evaluation	Child
Functional profile	Adaptive Behavior Assessment System	Functional skills necessary for daily living	Questionnaire	Parent

CP, cerebral palsy.

Table 2	MRI sequences
1	Three-dimensional T1-weighted (T1w) turbo field echo using an inversion-recovery and compressed sensing-acceleration (IV: 0.8 mm, TE/TR/TI: 2.24/2400/1060 ms, TA: 2:30).
2	Three-dimensional T2-weighted turbo spin-echo using compressed sensing-acceleration (IV: 0.8 mm, TE/TR=293/2500 ms, TA: 3:35).
3	Two-dimensional multishell pulse gradient spin-echo echoplanar diffusion-weighted images (IV: 2 mm, TE/TR=89/4800 ms; b0 s/mm^2,7 interleaved measurements, b=300 s/mm^2, 8 directions, b=1000 s/mm^2, 32 directions, b2000 s/mm^2, 60 directions, total number of diffusion directions: 100, TA: 9:13). A b=0 image with reverse phase encode direction (posterior-anterior) will also be acquired.
4	Three-dimensional multi-parametric mapping (MPM) protocol using compressed sensing-acceleration for proton density (PD), T1 relaxation time and magnetisation transfer saturation (MTsat) mapping that includes three gradient echo sequences with T1w (IV: 1.0 mm, TE/TR: 3.5/11 ms, flip angle: 15°, TA: 1:58, PDw (TE/TR: 3.5/28 ms, flip angle: 5°, TA: 5:00) and MTw (TE/TR: 3.5/28 ms, 12 ms single-lobe Sinc-Gauss MT pulse at 2.2 kHz off-resonance with flip angle 540 deg, TA:5:00).
5	Three-dimensional multi-echo gradient echo quantitative susceptibility mapping (QSM) using compressed sensing-acceleration (IV: 1 mm, TE_1: 4.9 ms, delta_TE: 5.6 ms, 5 echoes, TR: 31 ms, TA: 3:53).

IV, isotropic voxel; TA, time acquisition; TE, echo time; TR, time repetition.

Brain MRI

A multimodal brain MRI will be completed on a 3 Tesla Philips scanner (Ingenia Elition X, Best, The Netherlands, software release R5.7+) using a 32-channel receive head coil. The acquisition parameters are listed in table 2. Total and regional brain tissue and structure volume and morphometry will be quantified using a validated automatic pipeline: the Multiple Automatically Generated Templates segmentation algorithm (MAGeT-Brain).[74 75] Tissue volume and cortical features such as cortical thickness, folding and sulci depth will be extracted using CIVET.[76] We anticipate that these automatic pipelines will fail in a subset of children who will present with substantial structural distortions secondary to neonatal injury. In these participants, we will perform manual segmentation of the brain tissue, structures and remaining lesions.

A neonatal brain MRI that included a high-resolution T1w image was acquired on a 3 Tesla MRI for all NE-TH newborns in this cohort in the perinatal period after TH completion as part of the standard of care.[12 19] Structural MRI data will be harmonised using combat to control for discrepancies in image acquisition between different scanners.[77 78] Growth will be defined as the volumetric differences and morphometrical changes between the neonatal period and 9 years for each structure of interest (eg, hippocampus, cerebellum).

Microstructural features will be quantified using the traditional diffusion tensor indices (eg, fractional anisotropy (FA) and mean diffusivity (MD)), as well as the neurite orientation density and dispersion imaging microstructure model[79] which outputs the neurite density index (NDI) and orientation dispersion index (ODI). To investigate the myelin content of brain tissue, MTsat maps will be calculated from the MPM data and B1 map,[80 81] as well as quantitative susceptibility maps (QSM) and R2* maps from the 3D multi-echo gradient-echo data. Each subject's MTsat, QSM and R2* maps will be linearly registered to their diffusion-weighted image or anatomical T1w. All the microstructural features will be extracted along major white matter tracts using the TractoFlow pipeline.[82 83] Structural connectome analyses will also be explored using Micapipe and the Brain Connectivity Toolbox.[84 85]

Other variables

Considering the known associations between cognitive and brain development, sex and socio-economic status (SES),[86–88] and that the expression of the behavioural outcomes can be modulated by gender,[89] these variables will also be collected. Sex will be determined by the physical appearance of genitalia recorded at birth and gender will be self-reported by the child. Although we will use maternal education as the primary measure of SES considering that maternal education has been shown to be the most informative indicator of SES in other Canadian NICU survivors,[90] we will also collect other indicators, such as employment, income and ethnicity, to comprehensively describe the sample and explore other associations.[91]

For the NE-TH group, detailed medical history including prenatal, perinatal and postnatal factors, such as the modified Sarnat scores for NE and the severity of neonatal brain injury will be extracted from existing clinical and research databases. For the controls, perinatal and developmental history will be collected through parental questionnaires.

Statistical analysis

Descriptive statistics will first be used to characterise the study sample. Individuals and perinatal variables will be compared between children with NE-TH and controls and those differing significantly between groups will be considered as potential confounders in subsequent analyses as needed.

Aim 1

Outcomes at 9 years of age will be compared between children with NE-TH and controls using a generalised linear model (GLM) with group, sex or gender, SES and neonatal brain injury as fixed effects. Based on the same

model, adjusted mean estimates (least-squares means) for each categorical variable will be produced to evaluate heterogeneity in outcomes by these factors.

Aim 2

Volumetric and morphometric differences between children with NE-TH and controls will be compared using GLM with group, sex and total brain volume as fixed effects. The magnitude of the group differences for each of the volumetric measurements will be quantified using effect size mapping. Comparisons of tract-average FA, MD, NDI, ODI, MTsat, QSM and R2* metrics between the two groups will be performed using two-sample permutation t-tests with N=10 000 permutations.[83] Due to the comparison of multiple neuropsychological and brain outcomes, false discovery rate (FDR) correction following the Benjamini-Hochberg method will be used.[92]

Aim 3

To evaluate determinants of cognitive, psycho-emotional and motor skills, a separate multiple logistic regression model will be created for each outcome identified as statistically different between the cases and controls. Participants will be classified as having normal or abnormal function using 1.5 SD below the scale's normative mean as the cut-off. The classification category will serve as the dependent variable, while pre-selected brain metrics (from Aim 2) and important demographic and perinatal risk factors (eg, age, sex, SES, neonatal brain injury) will be included as independent variables. FDR correction will be applied using a corrected level of q<0.05 as the threshold for statistical significance.

Sample size and power calculation

To detect a between-group significant difference of moderate effect size on the outcome evaluations such as of IQ, using a power of 80%, an alpha level of 5%, three covariates with a combined R-squared of 0.2 (conservative), and a 2:1 group ratio, 22 children with NE-TH and 11 matched controls (total=33) would be sufficient. Considering our plan to include key stratification factors (ie, sex or gender, SES, neonatal brain injury) in our analyses, the minimal sample size was estimated at 198 children (n_{NE-TH}=132 and $n_{Controls}$=66) to provide sufficient power to detect a group difference of the magnitude mentioned above within each of the strata.

Patient and public involvement

The scope of the research questions addressed in this proposal was first formalised in close collaboration with two parent partners (ie, parents of children with NE-TH) and several knowledge-user collaborators (ie, clinicians involved with the follow-up of children with NE-TH and an elementary school teacher). The parent partners have participated in the development of the study aims, methods, procedures and prioritisation of outcomes. They also confirmed that the study visit's length and scope are reasonable and feasible. They will continue to advise on the recruitment and coordination mechanisms to maximise enrolment and participants' experience and remain involved with each step of the project. Parent partners and knowledge users will be involved in disseminating the findings to their respective group of stakeholders.

Data management

Individual, clinical and outcome data will be entered into a REDCap database, a secure web-based electronic data capture tool for research studies and accessible by assigned research staff only. Data will be saved locally, backed up on our institution-protected server and disposed 7 years after the completion of the study. At time of recruitment, participants will provide written consent if they agree to have their anonymised data stored in the Brain and Child Development (BCD) database owned by the principal investigator (MB-R) to foster future projects and collaborations. The management of the BCD database complies with our institutional standard and its management framework has been approved by the local Research Ethic Boards. This framework also sets out the data access, collaboration policy, and the terms and conditions on which de-identified data will be made accessible to the research community following reasonable request at the end of the data collection.

Ethics and dissemination

The protocol was approved by the institution's Research Ethic Boards (MP-37-2023-9320) where the study will be conducted. Written informed parental consent and children's assent will be obtained for all participants. In collaboration with the parent partners and knowledge-user on this application, an audience-specific summary of findings will be broadly disseminated through parental organisations and healthcare stakeholders. For widespread dissemination, the results of this study will be presented at national and international conferences and published in peer-review journals.

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