Cerebral Palsy after Neonatal Encephalopathy: How Much Is Preventable?

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Objectives To determine the expected proportion of term cerebral palsy (CP) after neonatal encephalopathy (NE) that could theoretically be prevented by hypothermia and elucidate the perinatal factors associated with CP after NE in those who do not meet currently used clinical criteria required to qualify for hypothermia ("cooling criteria").

Study design Using the Canadian CP Registry, we categorized children born at ≥36 weeks with birth weight ≥1800 g with CP after moderate or severe NE according to the presence or absence of cooling criteria. Maternal, perinatal, postnatal, and placental factors were compared between the 2 groups. A number needed to treat of 8 (95% CI 6-17) to prevent one case of CP was used for calculations.

Results Among the 543 term-born children with CP, 155 (29%) had moderate or severe NE. Sixty-four of 155 (41%) met cooling criteria and 91 of 155 (59%) did not. Shoulder dystocia was more common in those who did not meet cooling criteria (OR 8.8; 95% CI 1.1-71.4). Low birth weights (20% of all singletons), small placentas (42%), and chorioamnionitis (13%) were common in both groups.

Conclusions The majority of children with CP after NE did not meet cooling criteria. An estimated 5.1% (95% CI 2.4%-6.9%) of term CP after NE may be theoretically prevented with hypothermia. Considering shoulder dystocia as an additional criterion may help recognize more neonates who could potentially benefit from cooling. In all cases, a better understanding of the antenatal processes underlying NE is essential in reducing the burden of CP. *(J Pediatr 2015;167:58-63)*.

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Therapeutic hypothermia has proven to be an effective neuroprotective intervention and has been applied increasingly to neonates with specific clinical criteria and moderate or severe neonatal encephalopathy (NE) within the first 6 hours of life.[1-3] The number of such neonates needed to treat (number needed to treat; NNT) to prevent 1 subsequent case of cerebral palsy (CP) is 8 (95% CI 6-17) according to recent meta-analyses.[2,3] Some pediatric neurologists are hoping that hypothermia will reduce the frequency of CP in term-born neonates with NE, but the overall proportion of term CP that could be prevented by hypothermia in this population has not yet been established.[4]

Furthermore, there is no neuroprotective strategy for term neonates with NE who do not meet current clinical criteria for hypothermia.[5] More specific information concerning the pathways to CP in this population is needed before potentially effective therapies can be developed and applied.[6,7] Using the Canadian Cerebral Palsy Registry (CCPR), we aimed to investigate term-born children with later CP after moderate or severe NE. The objectives were: (1) to determine the expected proportion of term CP after NE that could theoretically be prevented by hypothermia; and (2) to elucidate the perinatal factors associated with CP after NE in those who do not meet the clinical criteria required to qualify for hypothermia.

Methods

The study was conducted using data extracted from the CCPR, which builds on the development and implementation of the Cerebral Palsy Register of Québec. The CCPR captures cases of CP identified through both pediatric rehabilitation centers and university hospitals at which provincial pediatric neurology and developmental pediatric services are located, from the birth year of 1999 until 2011. The registry covers most of Quebec, the greater Toronto area of Ontario, and the entire provinces of British Columbia, Alberta, Nova Scotia, and

CCPR	Canadian Cerebral Palsy Registry
CP	Cerebral palsy
HIE	Hypoxic-ischemic encephalopathy
NE	Neonatal encephalopathy
NNT	Number needed to treat

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Newfoundland, and includes more than one-half (approximately 18 million individuals) of the Canadian population. Once cases are identified, parental consent is obtained, and the maternal and child's records are reviewed. These data are supplemented by a standardized parental interview and physical examination of the child by a pediatric neurologist, developmental pediatrician, or child physiatrist. Local ethics board approval was obtained from each participating institution. The Montreal Children's Hospital-McGill University Health Center research ethics board provided central approval for data storage, analysis, and overall operations.

To be enrolled in the CCPR, a child must be at least 2 years of age and meet current diagnostic consensus criteria for CP, which include a clinical diagnosis of a nonprogressive motor impairment resulting from a presumably early insult to the developing brain.[8] The diagnosis is confirmed whenever possible at 5 years of age, and the children without CP were removed from the registry.[9] Patients within the CCPR included for analysis in this study: (1) were born at ≥ 36 weeks; (2) had a birth weight of ≥1800 g; and (3) fulfilled criteria for moderate or severe NE during the first week of life. We then categorized the neonates according to the presence or absence of currently used clinical criteria required to qualify for hypothermia ("cooling criteria").

Criteria for NE were derived from the Sarnat score.[10] Neonates with moderate NE were either lethargic, hypotonic, manifested seizures, or had decreased reflexes. Those with severe NE manifested either flaccid coma, brainstem findings, or difficult-to-control seizures. Clinical cooling criteria were derived from the National Institute of Child Health and Human Development randomized controlled trial of therapeutic hypothermia and the Position Statement of the Canadian Paediatric Society.[11,12] Neonates were required to have evidence of both "fetal" and "neonatal" distress. "Fetal distress" was evident by at least one of the following: (1) sentinel event (abruptio placenta, cord accident, uterine rupture, or shoulder dystocia); (2) pH ≤ 7.0 or base deficit ≥16 mEq/L from the umbilical cord or blood collected within the first hour of life; or (3) severe fetal heart rate abnormalities. "Neonatal distress" was evident by at least one of the following: (1) Apgar score ≤ 5 at 10 minutes; or (2) delivery room resuscitation (intubation, cardiac massage, or administration of epinephrine or normal saline bolus). For the purposes of cooling group assignment, when the 10-minute Apgar score or pH was not documented in the records, they were assumed to have been normal, and when sentinel events, severe fetal heart rate abnormalities, and delivery room resuscitation were not documented in the records, they were assumed to have been absent.

Maternal, paternal, perinatal, postnatal, and placental factors were compared in an attempt to identify variables that potentially distinguish those who met cooling criteria from those who did not.

Birth weight, placental weight, and placental-to-birth weight percentiles of singletons were based on sex and gestation by the use of contemporary Canadian percentile curves.[13,14]

Seven randomized controlled trials have evaluated hypothermia and each assessed the incidence of CP. Two subsequent meta-analyses established that the NNT to prevent one case of CP was 8 (95% CI 6-17 and 6-16).[2,3] This NNT is applicable to our cohort of children with CP who: (1) had moderate or severe NE; and (2) met clinical cooling criteria.

Statistical analysis was performed with SPSS 20.0 (SPSS Inc, Chicago, Illinois). For comparisons between the two groups, the χ^2 test or 2-sided Fisher exact test were used for univariate analysis of categorical variables as appropriate and the Student *t* test for continuous variables. ORs and their 95% CIs were calculated where appropriate. A P of <.05 was a priori considered significant. We applied unconditional logistic regression analysis selectively when 2 variables that act along the same causal pathway were significant.

Results

Between 1999 and June 2011, a total of 1001 patients were enrolled into the CCPR. Of these, 543 were ≥36 weeks' gestation and had a birth weight ≥1800 g. Of them, 155 of 543 (29%) had a history of moderate or severe NE (it is this group that comprises the study cohort) and 388 of 543 (71%) did not (361 did not have moderate or severe NE and 27 did not have documentation of a neurologic examination during the neonatal period). Among those with NE, 64 of 155 (41%) met currently used cooling criteria, but 91 of 155 (59%) did not. Cord or first hour of life blood pH was available in 62 of 64 and 65 of 91 neonates, and 10-minute Apgar score was available in 55 of 64 and 53 of 91 neonates in either group (**Table I**). In 41 of 47 cases (87%) in which the 10-minute Apgar score was unavailable, the 5-minute Apgar score was >5. Eleven neonates with NE who met cooling criteria (17%) and 2 who did not meet them (2%) were actually cooled, all of whom were born in 2009 or later. Among those without moderate or severe NE, 9 of 388 (2%) otherwise met cooling criteria (2 with mild NE and 7 without NE), and 379 of 388 (98%) did not meet cooling criteria (5 with mild NE and 374 without NE) (**Figure**; available at www.jpeds.com).

The features and degree of NE in the 155 children with moderate or severe NE are summarized in **Table II**. Hypotonia as a feature of NE was significantly more common in those who met cooling criteria (P = .020). The clinical characteristics of children with CP after NE are listed in **Table I**. There were no significant differences between the 2 groups with respect to antenatal maternal and paternal variables. Thirty of 151 (20%) singletons were <10th percentile for weight (similar in both groups).

Signs of perinatal distress, such as low pH, cesarean delivery, low Apgar scores, and resuscitation at birth requiring intubation, cardiac massage, or epinephrine, were significantly more common in those who met cooling criteria (P < .0001), as expected. Overall, 22 of 64 (34%) of those who met cooling criteria vs 8 of 91 (9%) of those who did not had an abruptio placenta, uterine rupture, or cord