OBSTETRICS

A case-control study of hypoxic-ischemic encephalopathy in newborn infants at >36 weeks gestation

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OBJECTIVE: The purpose of this study was to determine risk factors that are associated with hypoxic ischemic encephalopathy (HIE).

STUDY DESIGN: This was a case-control study that included newborn infants with HIE who were admitted to the hospital between January 2001 and December 2008. Two control newborn infants were chosen for each case. Logistic regression and classification and regression tree (CART) analysis that compared control infants and cases with grade 1 HIE and control infants and cases with grades 2 and 3 HIE was performed.

RESULTS: Two hundred thirty-seven cases (newborn infants with grade 1 encephalopathy, 155; newborn infants with grade 2 encephalopathy, 61; newborn infants with grade 3 encephalopathy, 21) and 489 control infants were included. Variables that were associated independently with HIE included higher grade meconium, growth restriction, large head circumference, oligohydramnios, male sex, fetal bradycardia, maternal pyrexia and increased uterine contractility. CART analysis ranked high-grade meconium, oligohydramnios, and the presence of obstetric complications as the most discriminating variables and defined distinct risk groups with HIE rates that ranged from 0—86%.

CONCLUSION: CART analysis provides information to help identify the time at which intervention in labor may be of benefit.

Key words: CART, hypoxic ischemic encephalopathy, meconium, oligohydramnios, uterine contraction

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Intrapartum asphyxia in mature newborn infants causes 10-15% of cases of cerebral palsy, and its prevention is a major justification for the hospitalization of low-risk mothers who give birth in developed countries.[1-4] Despite advances in obstetric and neonatal care over the last 4 decades, the rate of cerebral palsy in normally formed newborn infants with a birthweight of >2.5 kg has not declined.[5] In addition, the seizure rate and the neonatal encephalopathy rate in newborn infants with a birthweight of >2.5 kg (which is often a marker of acute intrapartum neonatal brain injury) show no decline.[6]

★ EDITORS' CHOICE ★

The objective of this study was to determine risk factors that are associated with the development of hypoxic ischemic encephalopathy (HIE).

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Materials and Methods

Patient selection

Inclusion criteria were newborn infants who were born at the Rotunda Maternity Hospital in Dublin from January 2001 to December 2008 at ≥36 weeks 0 days' gestation and who required admission to the neonatal intensive care unit at ≤24 hours after delivery with evidence of encephalopathy. Newborn infants who were born between January 2001 and July 2005 were identified retrospectively. Newborn infants who were born between July 2005 and December 2008 were identified prospectively.

Grade of encephalopathy was assigned as the highest stage of encephalopathy (Sarnat and Sarnat[7] grading) that had been documented in the clinical notes and/or as noted on serial examination by a member of the research team (B.C.H., M.D.K., or S.M.). Two control newborn infants (the infants who were born before and after each case) were chosen for each case. Exclusion criteria for cases were out-born infants, <36 weeks' gestation, the presence of a major congenital anomaly, or any primary cause for encephalopathy other than

TABLE 1
Obstetrics definitions used in data acquisition

Variable	Definition
Antenatal trauma	Significant fall, accident, or abdominal injury in the antenatal period
Late booking	Initiation of antenatal care at >24 weeks' gestation
Pregnancy-induced hypertension	Maternal blood pressure ≥140/90 mm Hg on 2 separate occasions >4 hours apart
Preeclampsia	New onset hypertension and proteinuria at >20 weeks' gestation
Proteinuria	>0.3 g protein/d in a 24-hour urine collection or, in the absence of a 24-hour urine collection, the presence of 2+ protein on dipstick
Gestational diabetes mellitus	Glucose intolerance with onset or first recognition during pregnancy and a normal glucose tolerance test by 6 weeks after delivery
Substantial antepartum hemorrhage	Vaginal blood loss equal to or greater than a menstrual period
Nonsubstantial antepartum hemorrhage	Vaginal blood loss less than a menstrual period
Fetal bradycardia	Decrease in the baseline fetal heart rate <100 beats/min
Late decelerations	Transient decrease in fetal heart rate that occurs at or after the peak of a uterine contraction
Fetal tachycardia	Increase in baseline fetal heart rate to ≥160 beats/min
Early decelerations	Transient decrease in fetal heart rate that coincides with the onset of a uterine contraction
Fetal heart rate variability	The beat-to-beat changes in fetal heart rate
Unsatisfactory cardiotocogram	The presence of a fetal bradycardia and/or late decelerations and/or fetal tachycardia and/or early decelerations (transient decrease in fetal heart rate that coincides with the onset of a uterine contraction) and/or fetal heart rate variability <5 beats/min
Satisfactory cardiotocogram	Baseline rate: 110-160 beats/min; moderate variability; absence of any late or variable decelerations; accelerations that may or may not be present
High-grade meconium	Grade 3 (thick or pea soup consistency) meconium or meconium that requires tracheal suction
Maternal pyrexia	Temperature ≥38°C measured with a tympanic thermometer
Duration of first stage of labor	The time from when the cervix was fully effaced and at least 1-cm dilated (in the presence of regular contractions) up to the time of full dilation
Shoulder dystocia	Difficult delivery of the shoulders that required additional obstetric maneuvers to release the shoulders after gentle downward traction failed
Uterine rupture	A defect that involves the entire uterine wall that was symptomatic and required surgical intervention
Placental abruption	Presence of retroplacental hematoma and clinical symptoms (as assessed by the clinical team at the time of delivery)

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hypoxia-ischemia. Exclusion criteria for control infants were out-born infants, <36 weeks' gestation, the presence of a major congenital anomaly, or any signs of encephalopathy in the neonatal period. If an infant was excluded as a control, then the infant who was delivered either before or after this infant was chosen.

The obstetrics definitions that were used in data acquisition are outlined in Table 1.

Further details on data acquisition are available in the Appendix.

The data were analyzed by logistic regression analysis to identify the variables that were associated independently with HIE and with a classification and regression trees (CART) analysis to help define the distinct clinical groups at higher risk of HIE. CART analysis examines a dataset to find the best variables and associated cutoff points to group the data into those with and without the outcome in question. Splitting stops when the statistical process determines no further discriminating advantage with any of the remaining factors.[8] Two analyses were carried out: 1 analysis compared control infants and cases with grade 1 HIE; 1 analysis compared control infants and cases with grades 2 and 3 HIE. Criteria for inclusion included reaching statistical significance ($P < .25$) in the univariate analysis (Tables 2-4) and clinical importance. Factors of clinical importance were defined as factors that have been associated with asphyxia and/or neonatal encephalopathy from previous published studies or deemed important from clinical practice. Logistic regression analysis was used to produce estimates of the odds ratios.

Ethical approval was obtained from the research ethics committee at The Rotunda Hospital.