Antepartum and Intrapartum Factors Preceding Neonatal Hypoxic-Ischemic Encephalopathy

WHAT’S KNOWN ON THIS SUBJECT: Etiology and timing of onset of neonatal hypoxic-ischemic encephalopathy continue to be controversial. Previous studies suggest antepartum events are the main contributing factors, but have used a broad definition of encephalopathy and included infants with genetic, congenital, and developmental abnormalities.

WHAT THIS STUDY ADDS: Our study suggests that when strict criteria defining hypoxic-ischemic encephalopathy are applied with supporting neuroimaging evidence of an acute hypoxic-ischemic insult, intrapartum events are the final and necessary pathway leading to this condition.

abstract

OBJECTIVE: To determine whether antepartum factors alone, intrapartum factors alone, or both in combination, are associated with term neonatal hypoxic-ischemic encephalopathy (HIE).

METHODS: A total of 405 infants ≥35 weeks’ gestation with early encephalopathy, born between 1992 and 2007, were compared with 239 neurologically normal infants born between 1996 and 1997. All cases met criteria for perinatal asphyxia, had neuroimaging findings consistent with acute hypoxia-ischemia, and had no evidence for a non-hypoxic-ischemic cause of their encephalopathy.

RESULTS: Both antepartum and intrapartum factors were associated with the development of HIE on univariate analysis. Case infants were more often delivered by emergency cesarean delivery (CD; 50% vs 11%, P < .001) and none was delivered by elective CD (vs 10% of controls). On logistic regression analysis only 1 antepartum factor (gestation ≥35 weeks) and 7 intrapartum factors (prolonged membrane rupture, abnormal cardiotocography, thick meconium, sentinel event, shoulder dystocia, tight nuchal cord, failed vacuum) remained independently associated with HIE (area under the curve 0.88; confidence interval 0.85–0.91; P < .001). Overall, 6.7% of cases and 43.5% of controls had only antepartum factors; 20% of cases and 5.8% of controls had only intrapartum factors; 69.5% of cases and 31% of controls had antepartum and intrapartum factors; and 3.7% of cases and 19.7% of controls had no identifiable risk factors (P < .001).

CONCLUSIONS: Our results do not support the hypothesis that HIE is attributable to antepartum factors alone, but they strongly point to the intrapartum period as the necessary factor in the development of this condition. Pediatrics 2013;132:e952–e959

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KEY WORDS: perinatal asphyxia, neonatal encephalopathy, hypoxic-ischemic encephalopathy, perinatal risk factors, intrapartum risk factors

ABBREVIATIONS: BW—birth weight; CD—cesarean delivery; CI—confidence interval; CTG—cardiotocography; GA—gestational age; HIE—hypoxic-ischemic encephalopathy; NE—neonatal encephalopathy; OR—odds ratio; PROM—prolonged rupture of membranes; TOBY—Total Body Hypothermia for Neonatal Encephalopathy

Dr Martinez-Biarge conceived and planned the study, reviewed and collated the data, and drafted the first version of the manuscript; Dr Diez-Sebastian did the statistical analysis and critically reviewed the manuscript; Dr Wusthoff conceived and planned the study and discussed the analysis; Dr Mercuri conceived and planned the study, collected data, and discussed the analysis; Dr Cowan conceived and planned the study, collected data, discussed the analysis, and contributed to the final manuscript as submitted; and all authors approved the final manuscript as submitted.

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The etiology of neonatal encephalopathy (NE) continues to generate debate.1–3 It is a syndrome with a wide variety of clinical features; when the infant presents with specific neurologic abnormalities during the first 24 hours after delivery following an acute event likely to lead to hypoxia-ischemia, the condition is referred to as neonatal hypoxic-ischemic encephalopathy (HIE).4 Often infants who have NE have perinatal antecedents, onset of symptoms, and a clinical course that are consistent with and typical of HIE. However, in some cases investigations are necessary to look for non–hypoxic-ischemic causes of NE such as infection, trauma, inborn errors of metabolism, and other genetic disorders.4,5 After excluding infants who have such alternative diagnoses, neuroimaging data consistently show evidence of an acute hypoxic-ischemic insult in the vast majority of encephalopathic newborns. Even in the absence of an obvious inciting intrapartum event, seldom is evidence for longstanding antenatal injury or additional developmental disorders found.6–8 Several epidemiologic studies have identified adverse sociodemographic factors, maternal conditions, and antenatal complications in association with NE, and these data have focused attention on the antenatal period as the origin of HIE.9–12 However, these studies have used inclusion criteria and definitions of encephalopathy that do not limit the study cohorts to infants likely to have HIE, and the role of many antepartum and intrapartum factors in the causal pathway of neonatal HIE remains unclear.

The aim of this study was to investigate antepartum and intrapartum factors associated with NE in term or near-term infants who had evidence of an acute hypoxic-ischemic insult and who did not have another identified cause for their encephalopathy.

**METHODS**

**Study Population**

This is a retrospective case-control study of infants >35 weeks’ gestation with HIE (as described below) born at or referred to the Hammersmith/Queen Charlotte’s Hospitals between 1992 and 2007.

**Cases**

Inclusion criteria were (1) poor condition at birth (5-minute Apgar score <5 and/or arterial cord blood pH <7.1 and/or need for major resuscitation), and (2) NE. NE was defined as a clinical syndrome present from birth and characterized by difficulty initiating and/or maintaining respiration, altered consciousness, and abnormal tone and reflexes, with or without seizures.4,13 Infants were excluded if, either in the neonatal period or at follow-up, an identifiable metabolic disorder, severe congenital malformation, or infection or genetic abnormality was diagnosed.

**Controls**

As part of a project investigating perinatal findings and neurodevelopmental outcomes in a normal population,14–16 250 infants were recruited from the postnatal wards at Queen Charlotte’s Hospital between 1996 and 1997. The only inclusion criteria were that the infants were regarded as normal at birth and were sent to the postnatal ward. Parity, maternal age, and mode of delivery in these infants were similar to those of the global population born in the same hospital in the 6 months preceding the recruitment.15 All these infants underwent a detailed neurologic examination; 177 also had a cranial ultrasound scan after their examination, and 103 infants were assessed at 12 to 18 months of age; none showed signs of cerebral palsy or developmental delay.16 For the purposes of this study we excluded 6 infants who were <35 weeks’ gestational age (GA) at birth or in whom GA was uncertain, 3 in whom the neurologic examination was not optimal, 1 who developed clinical hypoglycemia, and 1 in whom the ultrasound scan showed grade 2 intraventricular hemorrhage and periventricular densities.

The project involving controls was approved by the Research Ethical Committee of the Royal Postgraduate Medical School. Maternal consent was requested individually.15 Ethical permission for scanning the HIE infants was obtained from the Hammersmith Hospital research ethics committee and individually from the parents.

**Data and Definitions**

Antenatal and perinatal data were documented from the medical notes and from parental reports using the same standardized proforma for both groups. This was done at the time of referral (cases) or recruitment (controls). Demographic data included maternal age and race, and family history of seizures and/or neurologic disorders. By using information from the National Statistics Postcode Directory (http://census.ac.uk) we obtained deprivation scores for every infant. The Index of Multiple Deprivation is a measure of multiple deprivation in a small area based on 7 dimensions: income, employment, health and disability, education, skills and training, barriers to housing and services, living environment, and crime. Higher scores reflect more disadvantaged areas.17

Maternal conditions included chronic hypertension, thyroid disease, depression, and thrombotic or autoimmune disease. Obstetric history included parity, previous history of miscarriages, and infertility treatment (any treatment to achieve the index pregnancy). Complications during gestation included gestational hypertension, respiratory or urinary tract infection, significant antepartum bleeding, cholestasis, and an episode of reduced fetal movements as reported by the mother before labor.
Intrapartum factors recorded were: onset of labor, intrapartum complications, mode of delivery, Apgar scores, cord pH, and resuscitation measures. Prolonged rupture of membranes (PROM) was defined as an interval of >24 hours between the rupture of the membranes and the delivery. Prolonged second stage was defined as a second stage of labor >2 hours. Abnormal cardiotocography (CTG) included persistent late or variable decelerations, fetal bradycardia, and/or reduced fetal heart variability. Sentinel events included uterine rupture, placental abruption, cord prolapse, acute reduced fetal heart variability. Sentinel decelerations, fetal bradycardia, and/or normal cardiotocography (CTG) in a second stage of labor had failed. Failed instrumental shoulders after gentle downward traction obstetric maneuvers to release the shoulders after gentle downward traction had failed. Failed instrumental delivery (vacuum or forceps) was defined as the delivery of the infant by emergency cesarean delivery (CD) after an attempted instrumental delivery had been unsuccessful. Elective CD was defined as a CD undertaken before the onset of labor in which there was no current fetal concern.

Infant characteristics included GA, gender, birth weight (BW), head circumference, and multiplicity. Growth centiles were calculated by using the British growth reference charts. Resuscitation was considered major if the infant required intubation for ventilation with or without cardiac compressions and epi-nephrine. Details of the clinical course, seizures, stage of HIE, and age at death were also collected.

**Statistical Analyses**

Data were analyzed by using SPSS version 11.5 (SPSS Inc, Chicago, IL). Categorical variables were compared in univariate analysis by using χ² or Fisher exact test and continuous variables by using ANOVA test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression. A multiple correspondence analysis was done to identify potential groupings of risk factors. Forward stepwise binary regression analysis was performed to determine independent variables associated with HIE. Variables associated with a univariate P value < .10 were included in the multivariate analysis. To test the hypothesis that HIE has its origin in the antenatal period, the multivariate analysis was done in 2 steps. The first step included only antepartum factors; in the second step intrapartum factors were added to the analysis. We calculated the predictive ability of each model by using receiver operating characteristic (ROC) curves. Factors that were not considered part of the causal pathway, but the direct consequence of the hypoxic-ischemic event, such as emergency CD, low Apgar scores, low cord pH, and need for major resuscitation, were not included in the multivariate analysis. P values < .05 were considered significant for all comparisons.

**RESULTS**

Of the 555 infants in our database, 405 fulfilled the entry criteria. Of the 150 infants not included were 58 who did not meet all the criteria for perinatal asphyxia but who had some early signs of encephalopathy, including 16 who were born in good condition but suffered an acute postnatal collapse, and 71 who had other diagnoses (congenital malformations/infections, or metabolic/genetic abnormalities). Of the included 405 infants, 393 (97%) had a brain MRI scan; 352 infants (87%) were scanned within the first 6 postnatal weeks and 41 (10%) were scanned later, at a median age of 3 months (mean 4.25 months, SD 3.3, range 2–19). A total of 54 infants were included in the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial; these infants were scanned, with few exceptions, within the first 4 weeks (71% in the first 2 weeks); 77% of the infants not included in the TOBY trial were scanned within the first 3 weeks. Twelve infants were not scanned because they died before the scan could be done (7), because parents refused (2), or because the encephalopathy was mild and the ultrasound scans consistently showed no abnormalities (3).

HIE was mild in 61 infants (15%) and moderate or severe in 314 (77.5%). In 30 infants (7.5%) the severity could not be established or this information was not available. A total of 47 infants (12%) received hypothermia treatment; 54 (13%) were treated with antibiotics for >48 hours for clinically suspected and/or culture-proven sepsis.

**Univariate Analysis**

Case mothers were more likely to be younger, primiparous, and of non-Caucasian origin (Table 1). There were no differences in socioeconomic factors. Other family and maternal characteristics were similar between cases and controls. Infertility treatment was more frequent among cases. Complications during pregnancy did not differ between cases and controls, except for the incidence of vaginal bleeding that was more frequently reported in controls. The rate of induced labor was similar between cases and controls, although control infants more often experienced artificial rupture of membranes. The following intrapartum complications were significantly more prevalent in cases than in controls: PROM, thick meconium, sentinel events, shoulder dystocia, tight nuchal cord, abnormal CTG, and failed vacuum delivery (Table 1). Case infants were more often delivered by emergency CD; no case infant was delivered by elective CD (compared with 10% of controls). Cases were significantly
TABLE 1 Univariate Risk Factors for Neonatal HIE

<table>
<thead>
<tr>
<th>Demographic data and family history</th>
<th>Cases (n = 405)</th>
<th>Controls (n = 239)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of seizures</td>
<td>19/278 (7)</td>
<td>8/235 (5)</td>
<td>2.08 (0.89–4.84)</td>
</tr>
<tr>
<td>Family history of neurologic diseases</td>
<td>13/276 (5)</td>
<td>6/235 (5)</td>
<td>1.9 (0.70–5.04)</td>
</tr>
<tr>
<td>Maternal age &lt;20 y</td>
<td>19/387 (6)</td>
<td>3/226 (1)</td>
<td>4.6 (1.3–15.6)</td>
</tr>
<tr>
<td>Maternal age ≥35 y</td>
<td>67/357 (20)</td>
<td>60/236 (25)</td>
<td>0.73 (0.49–1.08)</td>
</tr>
<tr>
<td>Maternal race non-Caucasian</td>
<td>126/336 (37)</td>
<td>52/232 (22)</td>
<td>2.07 (1.42–3.03)</td>
</tr>
<tr>
<td>Multiple Deprivation Index (mean ± SD)</td>
<td>20.5 ± 13.8</td>
<td>21.2 ± 10.9</td>
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</table>

<table>
<thead>
<tr>
<th>Maternal conditions and obstetric history</th>
<th>Cases (n = 405)</th>
<th>Controls (n = 239)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregestational hypertension</td>
<td>6/322 (2)</td>
<td>8/238 (3)</td>
<td>1.0 (0.74–1.36)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>6/321 (2)</td>
<td>7/238 (3)</td>
<td>1.0 (0.51–2.04)</td>
</tr>
<tr>
<td>Depression</td>
<td>8/322 (2)</td>
<td>5/238 (2)</td>
<td>1.0 (0.51–2.04)</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>7/333 (2)</td>
<td>1/238 (0.4)</td>
<td>5.17 (0.3–17.3)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17/331 (5)</td>
<td>11/238 (5)</td>
<td>1.1 (0.5–2.2)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>29/306 (9)</td>
<td>10/238 (4)</td>
<td>1.8 (0.5–6.7)</td>
</tr>
<tr>
<td>Prolonged second stage (&gt;2 h)</td>
<td>39/237 (26)</td>
<td>22/238 (9)</td>
<td>1.0 (0.3–3.2)</td>
</tr>
<tr>
<td>Tight nuchal cord</td>
<td>45/398 (11)</td>
<td>15/237 (6)</td>
<td>1.8 (1.0–3.5)</td>
</tr>
<tr>
<td>Abnormal CTG</td>
<td>210/366 (57)</td>
<td>23/238 (10)</td>
<td>2.0 (0.5–7.6)</td>
</tr>
</tbody>
</table>

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<tr>
<th>Intrapartum complications</th>
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</thead>
<tbody>
<tr>
<td>Induced labor</td>
<td>83/300 (28)</td>
<td>55/214 (27)</td>
<td>1.0 (0.71–1.5)</td>
</tr>
<tr>
<td>Artificial rupture of membranes</td>
<td>83/270 (31)</td>
<td>77/181 (43)</td>
<td>0.6 (0.4–0.88)</td>
</tr>
<tr>
<td>PROM (&gt;24 h)</td>
<td>28/283 (10)</td>
<td>5/224 (2)</td>
<td>4.81 (1.8–12.7)</td>
</tr>
<tr>
<td>Maternal pyrexia</td>
<td>13/305 (4)</td>
<td>7/226 (3)</td>
<td>1.47 (0.57–3.7)</td>
</tr>
<tr>
<td>Thick meconium</td>
<td>97/334 (29)</td>
<td>1/226 (3)</td>
<td>5.5 (3.1–8.6)</td>
</tr>
<tr>
<td>Sentinel event</td>
<td>19/229 (8)</td>
<td>2 (1)</td>
<td>33.4 (8.1–136.9)</td>
</tr>
<tr>
<td>Shoulder dystocia</td>
<td>29/396 (7)</td>
<td>1 (0.4)</td>
<td>18.8 (5.3–15.9)</td>
</tr>
<tr>
<td>Prolonged second stage (&gt;2 h)</td>
<td>39/237 (16)</td>
<td>22/238 (9)</td>
<td>1.35 (0.8–2.2)</td>
</tr>
<tr>
<td>Tight nuchal cord</td>
<td>45/368 (11)</td>
<td>15/237 (6)</td>
<td>1.89 (1.03–3.5)</td>
</tr>
<tr>
<td>Abnormal CTG</td>
<td>270/356 (77)</td>
<td>44/238 (21)</td>
<td>12.6 (8.3–19.1)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Delivery and resuscitation</th>
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<tbody>
<tr>
<td>Spontaneous vaginal delivery</td>
<td>132/305 (53)</td>
<td>137/238 (58)</td>
<td>0.37 (0.26–0.5)</td>
</tr>
<tr>
<td>Vacuum-assisted delivery</td>
<td>28/305 (9)</td>
<td>31/238 (13)</td>
<td>0.5 (0.3–0.87)</td>
</tr>
<tr>
<td>Failed vacuum</td>
<td>31/305 (8)</td>
<td>4/238 (2)</td>
<td>4.99 (1.7–14.3)</td>
</tr>
<tr>
<td>Forceps-assisted delivery</td>
<td>38/305 (10)</td>
<td>18/238 (8)</td>
<td>1.22 (0.7–2.2)</td>
</tr>
<tr>
<td>Failed forceps</td>
<td>6/305 (2)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Elective CD</td>
<td>0</td>
<td>24/238 (10)</td>
<td>—</td>
</tr>
<tr>
<td>Emergency CD</td>
<td>196/356 (50)</td>
<td>27/238 (11)</td>
<td>7.7 (4.9–12)</td>
</tr>
<tr>
<td>Apgar 1 min &lt;3</td>
<td>248/350 (65)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Apgar 5 min &lt;5</td>
<td>202/371 (54)</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Arterial cord pH &lt;7.00</td>
<td>209/313 (67)</td>
<td>0/180</td>
<td>—</td>
</tr>
<tr>
<td>Arterial cord pH &lt;7.10</td>
<td>249/313 (80)</td>
<td>1/180 (0.5)</td>
<td>—</td>
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<table>
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<tr>
<th>Infant characteristics</th>
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<tbody>
<tr>
<td>GA, mean ± SD</td>
<td>39.8 ± 1.3</td>
<td>39.6 ± 1.2</td>
<td>—</td>
</tr>
<tr>
<td>GA &lt;37 wk</td>
<td>30/398 (8)</td>
<td>8/234 (4)</td>
<td>2.1 (0.88–4.5)</td>
</tr>
<tr>
<td>GA &gt;41 wk</td>
<td>94/386 (24)</td>
<td>29/244 (12)</td>
<td>2.2 (1.4–3.5)</td>
</tr>
<tr>
<td>Male</td>
<td>229/405 (56)</td>
<td>121/238 (51)</td>
<td>1.25 (0.91–1.7)</td>
</tr>
<tr>
<td>BW (kg), mean ± SD</td>
<td>3.3 ± 0.6</td>
<td>3.3 ± 0.8</td>
<td>—</td>
</tr>
<tr>
<td>BW &lt;10th centile</td>
<td>61/560 (17)</td>
<td>25/238 (11)</td>
<td>1.7 (1.02–2.7)</td>
</tr>
<tr>
<td>BW &lt;3rd centile</td>
<td>21/560 (6)</td>
<td>4/238 (2)</td>
<td>3.5 (1.2–10.4)</td>
</tr>
<tr>
<td>Twin</td>
<td>15/359 (4)</td>
<td>2/238 (1)</td>
<td>4.7 (1.07–20.9)</td>
</tr>
<tr>
<td>Second twin</td>
<td>13/390 (3)</td>
<td>1/238 (0.5)</td>
<td>8.2 (1.07–63.14)</td>
</tr>
</tbody>
</table>

* Including other conditions not listed above (asthma, diabetes, cardiac, renal, or gastrointestinal problems).

More likely to be <37 weeks’ or >41 weeks’ GA and to have a BW <10th and <3rd centile. Twins were at higher risk for developing HIE (Table 1).

Case and control infants were divided in 4 categories according to whether they had been exposed to antepartum factors, intrapartum factors, neither, or both (Table 2). Only in 4% of cases was there no risk factor found. The presence of at least 1 antepartum factor was common and its frequency was almost identical in cases and controls. Intrapartum factors, alone or in combination with antepartum factors, were found in 90% of infants who had HIE, compared with 37% of controls.

Multiple correspondence analysis did not reveal any specific patterns of risk factors in our case infants.

Multivariate Analysis

The following antepartum variables were included in the first logistic regression analysis: maternal age <20 years, infertility treatment, primiparity, GA <37 and >41 weeks, low BW, twin, male, and postgestational and gestational hypertension. Six factors were found to be independently associated with HIE (Table 3): GA <37 and >41 weeks, maternal age <20 years, primiparity, postgestational hypertension, and multiplicity (twins). The predictive value of this model was moderate, with an area under the curve of 0.66 (CI: 0.61–0.71; P < .001; Fig 1).

The following intrapartum variables were added to the multivariate analysis: induced labor, PROM, thick meconium, prolonged second stage, sentinel events, shoulder dystocia, tight nuchal cord, failed vacuum delivery, and abnormal CTG. One antepartum factor (GA >41 weeks) and 7 intrapartum factors (PROM, thick meconium, sentinel events, shoulder dystocia, nuchal cord, failed vacuum, and abnormal CTG) remained significantly and independently associated with HIE (Table 3).
The other 5 antepartum variables included in the first regression analysis were dropped from the model. The predictive value of this second model was significantly higher, with an area under the curve of 0.88 (0.85–0.91; P<.001) (Fig 1).

**DISCUSSION**

In this case-control study we found that only 1 antepartum factor but multiple intrapartum factors were independently associated with the development of neonatal HIE. Although some antepartum factors appeared to be related in the univariate and first multivariate analyses, they did not remain as independent factors when intrapartum variables were considered. This suggests that antepartum factors may predispose some women to experience adverse intrapartum episodes but that their presence alone is not sufficient to cause HIE in their infants. It is also possible that some antepartum factors may increase fetal susceptibility to perinatal hypoxia-ischemia. The relation between maternal age, parity, previous obstetric history, fetal growth, and other maternal conditions with intrapartum complications such as sentinel events or abnormal CTG has previously been explored.26–29

In 1998 Badawi et al in a large case-control study of NE in Western Australia concluded that there was no evidence of intrapartum hypoxia in over 70% of cases; intrapartum factors alone occurred in only 5% of cases. Their definition of encephalopathy included infants who presented with seizures alone or with a combination of neurologic signs (not necessarily an abnormal level of consciousness) at any time during the first postnatal week. No criteria for perinatal asphyxia were required; and only in a minority of cases was cord pH available. Infants who had Down syndrome and open neural tube defects were excluded, but not infants who had other birth defects, which accounted for 23.2% of cases compared with 2.3% of controls.10,11 It is likely that the different inclusion criteria accounts for the difference in our findings and that the contribution of antepartum factors is different when infants who have genetic disorders are included in such a study. Locatelli et al used inclusion and exclusion criteria similar to ours in a hospital-based study of 27 cases and 100 term controls. Intrapartum factors alone were found in 22% of cases and a combination of antepartum and intrapartum factors was identified in an additional 44%.12 Apart from the small number of cases, in this study no multivariate analysis was done and thus it is not possible to know the real contribution of each factor to the outcome.
Both studies reported a high frequency of antepartum factors in infants who had NE. Based on this, it was concluded that the cause of NE is more likely to start antenatally, although the equivalent distribution of antepartum and intrapartum factors in the control group was not provided. We found that antepartum factors were common in both cases and controls (Table 2) but the frequency of exposure to intrapartum factors was different and significantly higher in HIE infants compared with controls.

Two more studies have reported that intrapartum risk factors are present only in a minority of NE cases; both used a broad definition of encephalopathy and also included infants who had genetic, congenital, and developmental abnormalities. Other studies, using a stricter definition of encephalopathy that automatically excludes most conditions with an antenatal or genetic origin, have found that intrapartum events are the main or a contributing factor in the causal pathway of HIE. None of the previous studies has used a precise definition of encephalopathy that did not change through the period of recruitment time, cases were referred from different hospitals and areas in and around London. Despite this potential selection bias we did not find differences in socioeconomic background between cases and controls, except that more case mothers were of non-Caucasian origin. Cultural differences and language difficulties may be a barrier for effective communication during labor and may delay the recognition of an emergency situation. Lastly, we cannot exclude that other factors not considered in our study may play a role in the causal pathway of HIE. Even with our relatively large study population we were unable to identify potential temporal sequences of risk factors; missing data for some variables and the retrospective nature of this analysis might have been another limitation in our study.

The strengths of this study are the large number of cases and controls that allowed us to find strong associations between risk factors and outcome. We used a precise definition of encephalopathy that did not change through the
study period. Unlike other epidemiologic studies almost all our cases had brain MRI scans that were consistent with a diagnosis of HIE and excluded other causes of encephalopathy. The majority of infants were scanned in the first 3 weeks, the optimal period for lesion detection on conventional MRI. Although some infants were scanned later, none had findings inconsistent with the perinatal onset of hypoxic-ischemia. Infants who had congenital malformations/infections or who had other diagnoses were excluded from this study. In addition, most cases were followed by us or in the TOBY trial, and hence we know that later problems followed by us or in the TOBY trial, and this study. In addition, most cases were examined and a detailed antenatal and perinatal history was taken; a significant proportion of them were also followed by our experienced team for at least 12 to 18 months by using standardized examinations.

**CONCLUSIONS**

Our results do not support the hypothesis that neonatal HIE starts antenatally, but point to the intrapartum period as the necessary factor for its development. To elucidate etiologies, future studies should examine closely the timing of intrapartum events involved in HIE and should evaluate the role of genetic, thrombophilic, infectious, and placental factors in the causal pathway of this condition. This will help us to understand better the pathogenesis of HIE and to design effective strategies to reduce its incidence and consequences.

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