Risk Factors for Neonatal Arterial Ischemic Stroke: The Importance of the Intrapartum Period

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Objective To investigate risk factors for neonatal arterial ischemic stroke (NAIS), and compare them with those present in term controls and infants with hypoxic-ischemic encephalopathy (HIE).

Study design Antepartum and intrapartum data were collected at presentation from 79 infants with NAIS and compared with 239 controls and 405 infants with HIE. The relationships between risk factors and NAIS were explored using univariable and multivariable regression.

Results Compared with controls, infants with NAIS more frequently had a family history of seizures/neurologic diseases, primiparous mothers, and male sex. Mothers of infants with NAIS experienced more intrapartum complications: prolonged rupture of membranes (21% vs 2%), fever (14% vs 3%), thick meconium (25% vs 7%), prolonged second stage (31% vs 13%), tight nuchal cord (15% vs 6%), and abnorm8al cardiotocography (67% vs 21%). Male sex (OR 2.8), family history of seizures (OR 6.5) or neurologic diseases (OR 4.9), and ≥1 (OR 5.8) and ≥2 (OR 21.8) intrapartum complications were independently associated with NAIS. Infants with NAIS and HIE experienced similar rates though different patterns of intrapartum complications. Maternal fever, prolonged rupture of membranes, prolonged second stage, tight nuchal cord, and failed ventouse delivery were more common in NAIS; thick meconium, sentinel events, and shoulder dystocia were more frequent in HIE. Abnormal cardiotocography occurred in 67% of NAIS and 77.5% of infants with HIE. One infant with NAIS and no infant with HIE was delivered by elective cesarean (10% of controls).

Conclusions NAIS is multifactorial in origin and shares risk factors in common with HIE. Intrapartum events may play a more significant role in the pathogenesis of NAIS than previously recognized. *(J Pediatr 2016;173:62-8)*.

The etiology of neonatal arterial ischemic stroke (NAIS) remains unclear in the majority of symptomatic term infants.[1] The association between NAIS, coagulation abnormalities, and specific genetic mutations/polymorphisms has been extensively studied,[2-6] but their role in the pathogenesis of NAIS remains controversial and frequently no specific thrombophilic factors are identified in affected infants.[7] Several epidemiologic studies have identified both antepartum and intrapartum conditions,[8-13] as well as neonatal sepsis/meningitis, hypoglycemia, and congenital heart disease as risk factors for NAIS.[14-16] It is likely that the etiology of NAIS is multifactorial and that the risk increases when multiple risk factors are present.[8,11]

Although it is accepted that perinatal asphyxia is a risk factor for NAIS, and both neonatal hypoxic-ischemic encephalopathy (HIE) and NAIS involve hypoxia-ischemia, HIE and NAIS are generally considered to be 2 different entities. Perhaps because previous studies have included infants with presumed perinatal stroke,[5,8,12] with other underlying conditions[9] or have combined term and preterm infants[5,8,9,12]; the potential role of perinatal hypoxia-ischemia in the pathogenesis of NAIS in otherwise healthy term-born infants has not received much attention. However, the co-occurrence of neonatal HIE and NAIS has been described.[11,16-18]

We hypothesize that NAIS in the acutely symptomatic term-born infant shares with HIE risk factors along their causal pathways. In order to investigate this we compared: (1) antepartum and intrapartum data from infants with NAIS with data from a large control group of asymptomatic term infants who had a detailed normal neonatal neurologic examination and were normal on neurodevelopmental follow-up; and (2) antepartum and intrapartum data of infants with NAIS with a group of term infants with neonatal HIE.

CTG	Cardiotocography
GA	Gestational age
HIE	Hypoxic-ischemic encephalopathy
MRI	Magnetic resonance imaging
NAIS	Neonatal arterial ischemic stroke
PROM	Prolonged rupture of membranes

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Methods

Between 1992 and 2012, all infants referred for neurologic investigation to the Hammersmith and Queen Charlotte's Hospitals were included in a longitudinal prospective cohort. All infants in this cohort routinely had a neonatal magnetic resonance imaging (MRI). From this cohort, we retrospectively identified all infants ≥35 weeks gestational age (GA) with MRI evidence of NAIS. NAIS was defined as a focal parenchymal brain lesion occurring as a result of the occlusion of a specific cerebral artery.[19] Infants with lesions in a parasagittal distribution were not included. The timing of the infarction was considered to be perinatal, based on their appearances on conventional and diffusion-weighted imaging. Since 1994, all neonates had diffusion-weighted imaging as part of the routine sequence protocol.[20,21]

Between 1996 and 1997, 250 infants were sequentially recruited from the postnatal wards at Queen Charlotte's Hospital. All these infants were considered normal at birth and on routine postnatal check. All underwent a detailed neurologic examination, 177 also had a cranial ultrasound scan, and 103 were assessed at 12-18 months of age; none showed signs of cerebral palsy or developmental delay.[22] Of the 250 original infants, 6 were excluded because they were <35 weeks GA or because their GA was uncertain; 3 because 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 echo densities.

In order to investigate any commonality of risk factors with HIE, a second case group of 405 term infants with HIE was used for comparison. This group was recruited between 1992 and 2007 from the same longitudinal prospective cohort as the group of infants with NAIS. All infants with HIE presented with poor condition at birth (5-minute Apgar score <5 and/or arterial cord blood pH <7.1 and/or need for major resuscitation) and developed clinical encephalopathy immediately after birth (difficulty initiating and/or maintaining respiration, altered consciousness, and abnormal tone and reflexes, with or without seizures). None of these infants received therapeutic hypothermia. Infants were excluded from this group if, either in the neonatal period or at follow-up, an identifiable metabolic disorder, severe congenital malformation, or infection or genetic abnormality was diagnosed. The majority of infants with HIE (393, 97%) had a brain MRI scan. The images in all these infants were either normal, or showed lesions consistent with an acute global hypoxic-ischemic insult.[17] None had findings suggestive of an antenatal insult or congenital developmental abnormality.[17] The characteristics of this group of infants have been previously described.[23]

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

A detailed antenatal and perinatal history was obtained at the time of the referral (cases) or recruitment (controls) from obstetric and neonatal notes and from parental interviews using the same standardized protocol. Data collected can be seen in **Table I** (available at www.jpeds.com).

Statistical Analyses

Data were analyzed using SPSS v 11.5 and v 19 (IBM SPSS Statistics, Armonk, New York). Categorical variables were compared by using χ^2, Mantel-Haenszel test, and Fisher exact test, and continuous variables by using ANOVA test. ORs and 95% CIs were calculated using logistic regression. Forward stepwise binary regression analysis was performed to determine independent variables associated with NAIS. Variables associated with a univariable P value of <.10 were included in the multivariable analysis.

Results

Seventy-nine newborn infants were identified by MRI as having an arterial ischemic infarction; the territory of the middle cerebral artery was involved in all cases except one. The infarction affected the left side in 53 infants (67%), the right side in 21 (26%), and was bilateral in 6 (7%). Most infants (75/79; 95%) had neonatal seizures; the median postnatal age when seizures were first seen was 19 hours (range 1-96 hours); 36% were within the first 12 hours, 62% within the first 24 hours, and 81% within the first 36 hours. Eight infants showed mild (6) or moderate (2) signs of encephalopathy; 6 infants were diagnosed with hypoglycemia, and 3 were treated with antibiotics for suspected or proven infection. Two infants presented with meconium aspiration syndrome. No infant was identified as having a congenital abnormality, cardiac or metabolic disorder; none had surgery or culture-proven meningitis. Two infants showed mild dysmorphisms that could not be ascribed to a known syndrome despite extensive investigation. Only 1 infant died in the neonatal period; she had infarcted both cerebral hemispheres.

Neurodevelopmental outcome was available for 64 infants (81%) at a median age of 26 months (range 12-48 months); 20 (31%) had developed a hemiplegia, as expected from the site of the lesion on neonatal MRI[24] and another 13 (20%) had minor motor signs or mild asymmetries, but did not meet criteria for cerebral palsy. None had developed unexpected symptoms suggestive of another or additional diagnosis than NAIS.

Antepartum and Intrapartum Risk Factors in Infants with NAIS Compared with Controls

Family history of seizures and other neurologic diseases were significantly more frequent in infants with NAIS compared with controls. Case mothers were more likely to be primiparous and to report autoimmune diseases and gynecologic problems. There were no other maternal differences between

the 2 groups. Complications during pregnancy did not differ between infants with NAIS and controls, except for the incidence of viral infections and significant abdominal pain without specific diagnosis, which were more often reported by mothers of infants with NAIS. Of infants with NAIS, 70% were male (vs 50% of controls). There were more infants with NAIS born postterm (>42 weeks) and with a birthweight <third percentile (Table II).

Infants with NAIS experienced significantly more intrapartum complications: prolonged rupture of membranes (PROM), maternal fever, thick meconium, abnormal cardiotocography (CTG) tracing, prolonged second stage, failed instrumental delivery, and tight nuchal cord at delivery. The presence of multiple intrapartum risk factors was more frequent in cases than controls: 32%, 26%, 17%, and 9% of cases had 1, 2, 3, or 4 of these intrapartum factors, compared with 24%, 9%, 2.5%, and 0.5% of controls (χ^2 for trend = 59.55; $P < .001$). Two-thirds of control infants (64%) did not experience any complications during labor, compared with 15% of infants with NAIS. The presence of 1 intrapartum factor was associated with increased risk of NAIS (OR 5.63; CI 2.1-14.6; $P < .001$) and when 2 or more intrapartum factors were present the risk was much higher (OR 19.14; CI 7.4-49.03; $P < .001$). Being born by spontaneous vaginal or elective cesarean delivery were both protective factors, whereas emergency cesarean delivery (because of abnormal CTG or obstructed labor) and failed instrumental delivery were associated with an increased risk. Infants with NAIS were born in poorer condition, although fewer than 10% had Apgar scores <3 at 1 minute or <5 at 5 minutes; and only 14% needed major resuscitation (vs 1% controls). Cord pH values were significantly lower in cases than controls but only in 2 cases were they <7.0 (Table II).

In the multivariable analysis, male sex, family history of seizures, family history of neurologic diseases, and the presence of 1 or more intrapartum factors were all independently associated with NAIS (Table III). The area under the receiver operator curve of this model was 0.845 (0.783-0.908; $P < .001$).

Antenatal and Perinatal Factors in Infants with NAIS and HIE and Controls

Antepartum and intrapartum factors were compared between the 3 groups: infants with NAIS, infants with HIE, and controls, using the Mantel-Haenszel χ^2 test to evaluate the presence of a linear trend in proportions across the 3 groups (Table IV).

The 3 groups differed significantly regarding the presence of 5 antepartum factors (Table IV), which were all more frequent in infants with NAIS compared with infants with HIE and control. There were also significant differences between the 3 groups regarding intrapartum factors, which were always more prevalent in infants with NAIS and HIE than in controls. Some factors were more common in infants with NAIS, and others were more common in infants with HIE; in all cases there was an increase in risk from controls to one or the other case group, as shown by the significant linear trend (Table IV). Infants with NAIS showed the highest prevalence of maternal fever, PROM, prolonged second stage, tight nuchal cord, and failed vacuum delivery. Infants with HIE most frequently experienced thick meconium, sentinel events (uterine rupture, placental abruption, cord prolapse, maternal collapse), shoulder dystocia, and abnormal CTG. The rate of abnormal intrapartum CTG was very high in infants with NAIS and HIE (67% and 77.5%, respectively).

Discussion

This study compared detailed antepartum and intrapartum data from a large number of term infants with stroke of confirmed perinatal onset to a well-documented, individually examined group of controls. We found a significant association between NAIS with few antepartum and several intrapartum risk factors. When we also compared the infants with NAIS with those with HIE, we found that all the intrapartum factors but not the antepartum factors associated with NAIS were also highly prevalent in infants with HIE.

Previous studies have found an increased risk of NAIS associated with different intrapartum complications.[8,11,18] However, despite these findings, the potential role of the intrapartum period in the causal pathway of NAIS has not been specifically investigated. We compared our infants with NAIS not only with a control group, but also with a well characterized group of infants with HIE with evidence of an acute hypoxic-ischemic insult, in whom we had previously shown that intrapartum events were a necessary factor in the development of this condition.[17,23] Our hypothesis was that if intrapartum events play a role in the pathogenesis of NAIS, this condition should share similar risk factors with HIE.

Only a minority of infants with NAIS showed the typical signs of perinatal asphyxia (low Apgar scores, low pH values, major resuscitation at birth), and only 10% of the total cohort developed clinical encephalopathy in agreement with previous reports.[9,10,14-16] Despite this, NAIS was preceded by the same intrapartum antecedents as HIE, and the presence of these factors was independently associated with both NAIS and HIE.[21] Compared with HIE, infants with NAIS tended to experience longer labors, whereas more acute and severe intrapartum complications, such as sentinel events, shoulder dystocia, or thick meconium, were more prevalent in infants with HIE. Some intrapartum factors may play a role in the pathogenesis of NAIS in a similar way as in HIE. It is possible that, depending on previous predisposing factors, including genetic factors, and/or the severity of the hypoxic-ischemic insult, some infants will develop HIE, whereas others will have a focal lesion. A milder insult, not enough to cause HIE, might be the final trigger for an ischemic stroke in a predisposed infant.

The preponderance of male infants in NAIS has been reported in most epidemiologic studies,[11,12,19,25] and our data

Table II. Univariable risk factors for NAIS

	NAIS (n = 79)	Controls (n = 239)	OR (95% CI)	*P* value
Demographic data and family history				
Family history of seizures	12/75 (16)	8/235 (3)	5.5 (2.1-14.02)	<.001
Family history of neurologic diseases	11/75 (15)	6/235 (3)	6.6 (2.4-18.7)	<.001
Maternal age (y), mean ± SD	31.15 ± 4.8	30.7 ± 5.11	-	.53
Non-Caucasian ethnicity	18/76 (24)	52/232 (22)	1.07 (0.6-1.98)	.87
Maternal conditions and obstetric				
Pregestational hypertension	1 (1.3)	0	-	.25
Thyroid disease	5 (6)	5/234 (2)	3.1 (0.87-11)	.42
Depression	2 (2.5)	7/234 (3)	0.84 (0.17-4.14)	1.00
Thrombotic disease	2 (2.5)	2/234 (1)	6 (0.54-67)	.16
Autoimmune disease	5 (6)	1/234 (0.4)	15.7 (1.8-137)	.004
Gynecological problems	7 (9)	4/222 (1.8)	5.3 (1.5-18.6)	.009
Previous miscarriage	15/63 (24)	38/221 (17)	1.5 (0.76-2.9)	.27
Infertility treatment	4/78 (5)	3/230 (1.3)	4 (0.9-18.7)	.07
Primiparity	60 (77)	122/236 (52)	3.06 (1.7-5.5)	<.001
Complications during gestation				
Hypertension	7 (9)	15/234 (6)	1.4 (0.55-3.6)	.45
Cholestasis	0	1/236 (0.4)	-	1.00
Respiratory infection	1 (1.3)	4/236 (2)	-	1.00
Urinary tract infection	5 (6)	11/236 (5)	1.3 (0.46-4.1)	.55
Viral infection	9 (11)	9/235 (4)	3.2 (1.2-8.4)	.02
Abdominal pain	9 (11)	0/222	60 (3.4-1044)	<.001
Reduced fetal movements	9/64 (14)	20/173 (12)	1.2 (0.53-2.9)	.65
Intrapartum complications				
Induced labor	25/77 (32.5)	55/204 (27)	0.76 (0.43-1.35)	.37
Artificial rupture of membranes	18/40 (45)	77/181 (43)	0.9 (0.45-1.8)	.86
PROM	15/72 (21)	5/224 (2)	11.5 (4.02-33.05)	<.001
Maternal fever >38°C	11 (14)	7/238 (3)	5.3 (2-14.3)	.0009
Thick meconium	20 (25)	16/231 (7)	4.55 (2.22-9.34)	<.001
Sentinel event	3 (4)	2 (1)	4.6 (0.77-28.5)	.10
Shoulder dystocia	3 (4)	1 (0.4)	9.4 (0.96-91.7)	.048
Prolonged second stage (>2 h)	18/51 (31)	29/225 (13)	3.7 (1.8-7.3)	.0003
Tight nuchal cord	12 (15)	15/237 (6)	2.6 (1.2-5.9)	.02
Abnormal CTG tracing	40/60 (67)	44/205 (21)	7.3 (3.9-13.7)	<.001
Delivery and resuscitation				
Unassisted vaginal	15 (19)	137/238 (58)	0.17 (0.1-0.3)	<.001
Assisted vaginal	26 (33)	50 (21)	1.84 (1.05-3.2)	.047
Vacuum assisted	14 (18)	31/238 (13)	1.4 (0.72-2.8)	.35
Forceps assisted	12 (15)	19/238 (8)	2.06 (0.95-4.4)	.07
Failed instrumental	14 (18)	4/238 (2)	12.6 (4-39.6)	<.001
Failed vacuum	11 (14)	4/238 (2)	9.4 (2.9-30.6)	<.001
Failed forceps	3 (4)	0	21.8 (1.1-427.5)	.015
Elective prelabor cesarean	1 (1.3)	24/238 (10)	0.11 (0.01-0.85)	.008
Emergency cesarean	37 (47)	27/238 (11)	6.8 (3.8-12.5)	<.001
Epidural analgesia	51/67 (76)	156/222 (70)	1.35 (0.7-2.5)	.44
Apgar 1 min <3	7/78 (9)	0	49.8 (2.8-883.7)	<.001
Apgar 5 min <5	5/78 (6.5)	0	35.7 (1.95-653.6)	<.001
Arterial cord pH, mean ± SD	7.18 ± 0.10	7.27 ± 0.07	-	<.001
Arterial cord pH <7.10	11/58 (19)	1/180 (0.5)	41.9 (5.2-333)	<.001
Major resuscitation	11 (14)	2/231 (1)	18.5 (4-85.6)	<.001
Infant characteristics				
GA (wk), mean ± SD	40.1 ± 1.37	39.7 ± 1.21	-	.018
GA >42 wk	3/79 (3.8)	0/234	21.5 (1.1-420)	.015
Male	55/79 (70)	121/239 (51)	2.21 (1.3-3.8)	.004
Birthweight (kg), mean ± SD	3.36 ± 0.5	3.37 ± 0.5	-	.92
Birthweight <10th centile	15/77 (19)	25/231 (11)	2 (0.99-4)	.076
Birthweight <third centile	5/77 (6.5)	4/231 (2)	3.9 (1.03-15.07)	.046

Data presented as n (%) unless specified.

support this with the regression analysis showing that being male is an independent risk factor for NAIS. HIE is also more frequent in male infants, although not to the same extent as NAIS.[26] Female fetuses seem to be more resistant to hypoxia; they have been found to have higher intrapartum heart rates and fewer periods of bradycardia.[27] Term male infants experience more intrapartum complications and have worse pregnancy and neonatal outcomes.[28,29]

The other antepartum factor independently associated with NAIS was a family history of seizures or other neurologic diseases, occurring in 15% of cases of NAIS. These were a mixture of neurologic problems; no family had a history of stroke, and only 1 child had both a family member with a neurologic disease and another with epilepsy. The possible importance of this positive family history is difficult to interpret, but it was also noted in our

Table III. Multivariable risk factors analysis of NAIS, compared with controls

Factors	OR (95% CI)	*P* value
Male sex	2.8 (1.17-6.99)	.021
Family history of seizures	6.56 (1.68-25.62)	.007
Family history of neurologic diseases	4.9 (0.97-24.67)	.054
1 intrapartum factor (vs no factors)	5.85 (1.9-17.99)	.002
2 or more intrapartum factors (vs no factors)	21.8 (7.1-66.7)	<.001

previous study,[17] and in a large Western Australian study on neonatal encephalopathy (where some of the included infants likely had a stroke; and some may have had other genetic disorders)[30] and does suggest that genetic factors may increase susceptibility to perinatal focal lesions.

We found a highly significant difference in primiparity rate with 77% of cases of NAIS and only 51% of controls having their first child, as was also found by others.[8,10] However, despite this significant difference, primiparity did not remain an independent risk factor for NAIS in the multivariable analysis, as we also found in our HIE cohort.[23] Primiparity may predispose some women to experience more intrapartum complications.[31]

Infants with NAIS had a significantly high prevalence of PROM. Lee et al[8] and Harteman et al[10] also found that PROM was more common in infants with stroke, although the first study included preterm infants and term infants without neonatal symptoms. This may support a role for inflammation in the causal pathway for NAIS in a manner similar to its implication in the pathway for preterm brain injury.[32] It has been also suggested that infants born to mothers exhibiting pyrexia during labor are at increased risk of perinatal brain injury.[10,33,34] Maternal fever was more common in our cases with NAIS and may be another factor supporting the possibility of inflammation in the causal pathway.

Although the association between epidural analgesia and maternal fever is well established,[35] the rate of epidural analgesia in infants with NAIS and controls was very similar, therefore, epidurals are not likely to be the only explanation for the increased rate of fever in mothers of infants with NAIS. Established infection like meningitis has been associated with procoagulant states and cerebral infarction,[10,11,15] but overt or proven infection was found in only 3 case infants in our cohort. None was found to have meningitis, and there was no significant increase in detected maternal sepsis. Unfortunately, the paucity of placental data did not allow us to examine this issue in detail.

There are several strengths to this study. Apart from including for the first time a group of infants with HIE for comparison, both case groups are large and homogeneous in terms of all infants being born at term, having early symptomatology suggestive of a recent cerebral insult and not being complicated by other neonatal problems (eg, congenital cardiac diseases, meningitis). Brain MRI scans consistently indicated that these lesions were of perinatal onset.[21] Infants with symptoms presenting in the late neonatal period were not included, and there were no cases of presumed perinatal infarction. Rather than relying on retrospective data collection or data from registries, the perinatal data for the 3 groups in this study were collected at presentation and not only from obstetric and neonatal notes, but also by direct history taking from the parents. The number of control infants is large and the cohort is well characterized.

There are also some limitations. The study is not population-based, as our hospital is a tertiary center, and many cases of NAIS and HIE were referred around birth for assessment. The incidence of NAIS is such that in order to gather a large number of cases, all of whom were

Table IV. Antenatal and perinatal factors in infants with NAIS and HIE and controls

Antepartum factors	Controls N = 239	OR	HIE N = 405	OR (95% CI)	NAIS N = 79	OR (95% CI)	*P* (χ^2)	*P* (linear-by-linear)
Male sex	50.8%	1	56.5%	1.26 (0.9-1.7)	70%	2.21 (1.3-3.8)	.014	.005
Family history of seizures	3.4%	1	6.8%	2 (0.9-4.8)	16.2%	5.5 (2.1-14)	.001	<.001
Family history of neurological diseases	2.6%	1	4.7%	1.9 (0.7-5.5)	15%	6.6 (2.4-18.7)	<.001	<.001
Birthweight <third percentile	1.7%	1	5.8%	3.51 (1.2-10.3)	6.6%	4 (1.05-15.3)	.041	.020
Primiparity	51.7%	1	60.4%	1.42 (1.03-1.9)	76.6%	3.06 (1.7-5.5)	<.001	<.001
Intrapartum factors*	**Controls N = 239**	**OR**	**HIE N = 405**	**OR (95% CI)**	**NAIS N = 79**	**OR (95% CI)**	***P* (χ^2)**	***P* (linear-by-linear)**
Maternal pyrexia	3%	1	4.3%	1.47 (0.5-3.7)	14%	5.4 (2-14.5)	<.001	.001
PROM	2.2%	1	10%	4.8 (1.8-12.6)	20.8%	11.5 (4-33)	<.001	<.001
Prolonged second stage	13%	1	16.5%	1.33 (0.8-2.2)	32%	3.18 (1.5-6.4)	.004	.004
Tight nuchal cord	6.3%	1	11.4%	1.9 (1.03-3.5)	15.2%	2.6 (1.18-5.9)	.036	.010
Failed vacuum delivery	1.7%	1	8%	5 (1.7-14.3)	14%	9.4 (2.9-30.6)	<.001	<.001
Intrapartum factors†	**Controls N = 239**	**OR**	**NAIS N = 79**	**OR (95% CI)**	**HIE N = 405**	**OR (95% CI)**	***P* (χ^2)**	***P* (linear-by-linear)**
Thick meconium	7%	1	24.4%	4.3 (2.09-8.9)	29%	5.5 (3.1-9.6)	<.0001	<.0001
Sentinel event	0.8%	1	3.8%	4.6 (0.7-28.5)	22%	33.3 (8.1-137)	<.0001	<.0001
Shoulder dystocia	0.4%	1	3.8%	9.4 (0.9-91.6)	7.3%	18.8 (2.5-139)	<.0001	<.0001
Abnormal CTG	21.5%	1	66%	7.13 (3.7-13.4)	77.5%	12.6 (8.3-19.1)	<.001	<.0001

A complete list of risk factors for the HIE subgroup has been previously reported.[23]
*Intrapartum factors more prevalent in infants with NAIS.
†Intrapartum more prevalent in infants with HIE.

investigated neonatally, referral is necessary to a tertiary center. Although it is possible that cases of NAIS and HIE not born at our institution may have been exposed to different obstetric protocols and levels of antenatal care, nearly all were born in hospitals in and around London and within the National Health System service, which provides a fairly uniform standard of care. The period of recruitment of controls was significantly narrower but was entirely within the period when cases were enrolled. It is possible that, over the wider period of time when infants with NAIS and HIE were recruited, the prevalence of some demographic factors has changed. However, this should have affected the rate of NAIS or HIE instead of the strength of the association between risk factors and neonatal outcome.

Another limitation is that although coagulation and prothrombotic data were acquired for most cases as part of their clinical investigations, equivalent data are not available for our controls. Only 14% of infants with NAIS had an abnormality identified (data not presented here), though testing for the methylene tetrahydrafolate-reductase gene was not done in all and testing for abnormalities of lipoproteins and homocysteine was only done in more recent years. Only 2 of our families were aware of a thrombotic or bleeding tendency, and those children's screens were normal. None of the mothers had a stroke in relation to delivery, none of our cases has to date gone on to have another stroke, and, to our knowledge, none of their siblings has been similarly affected. It is well known that the recurrence rate of neonatal stroke is very low.[36] Thus, even though prothrombotic tendencies are relevant to the etiology of NAIS, they are not identifiable at present in many infants.

Overall, our results suggest that both antepartum and intrapartum factors are involved in the pathogenesis of symptomatic term NAIS. Infants with NAIS and HIE experience similar rates, though different patterns, of intrapartum complications. Although we still do not know the etiology of NAIS, the significant number of commonalities shared with HIE makes it biologically plausible to think that the pathogenesis of these 2 conditions is related. Our data support the view that the intrapartum period is highly relevant to the genesis of NAIS, which has important implications as some adverse events in labor have the potential to be avoided. Future studies should take intrapartum events into account when evaluating the role of inflammatory and thrombophilic processes, genetic variations and placental pathology in the etiology of NAIS. ■

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References

1. Raju TN, Nelson KB, Ferriero D, Lynch JK , NICHD-NINDS Perinatal Stroke Workshop Participants. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. Pediatrics 2007;120:609-16.
2. Günther G, Junker R, Strater R, Schobess R, Kurnik K, Heller C , et al. Childhood Stroke Study Group. Symptomatic ischemic stroke in full-term neonates: role of acquired and genetic prothrombotic risk factors. Stroke 2000;31:2437-41.
3. Mercuri E, Cowan F, Gupte G, Manning R, Laffan M, Rutherford M, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 2001;107:1400-4.
4. Kurnik K, Kosch A, Strater R, Schobess R, Heller C, Nowak-Göttl U, Childhood Stroke Study Group. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. Stroke 2003;34:2887-92.
5. Curry CJ, Bhullar S, Holmes J, Delozier CD, Roeder ER, Hutchison HT. Risk factors for perinatal arterial stroke: a study of 60 mother-child pairs. Pediatr Neurol 2007;37:99-107.
6. Simchen MJ, Goldstein G, Lubetsky A, Strauss T, Schiff E, Kenet G. Factor V Leiden and antiphospholipid antibodies in either mothers or infants increase the risk for perinatal arterial ischemic stroke. Stroke 2009;40:65-70.
7. Kenet G, Lütkhoff LK, Albisetti M, Bernard T, Bonduel M, Brandao L, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation 2010;121:1838-47.
8. Lee J, Croen LA, Backstrand KH, Yoshida CK, Henning LH, Lindan C, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA 2005;293:723-9.
9. Kirton A, Armstrong-Wells J, Chang T, Deveber G, Rivkin MJ, Hernandez M, et al. Symptomatic neonatal arterial ischemic stroke: the International Pediatric Stroke Study. Pediatrics 2011;128:e1402-10.
10. Harteman JC, Groenendaal F, Kwee A, Welsing PM, Benders MJ, de Vries LS. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. Arch Dis Child Fetal Neonatal Ed 2012;97:F411-6.
11. Grunt S, Mazenauer L, Buerki SE, Boltshauser E, Mori AC, Datta AN, et al. Incidence and outcomes of symptomatic neonatal arterial ischemic stroke. Pediatrics 2015;135:e1220-8.
12. Darmency-Stamboul V, Chantegret C, Ferdynus C, Mejean N, Durand C, Sagot P, et al. Antenatal factors associated with perinatal arterial ischemic stroke. Stroke 2012;43:2307-12.
13. Luo L, Chen D, Qu Y, Wu J, Li X, Mu D. Association between hypoxia and perinatal arterial ischemic stroke: a meta-analysis. PLoS One 2014;9:e90106.
14. Fitzgerald KC, Golomb MR. Neonatal arterial ischemic stroke and sinovenous thrombosis associated with meningitis. J Child Neurol 2007;22:818-22.
15. McQuillen PS, Barkovich AJ, Hamrick SEG, Perez M, Ward P, Glidden DV, et al. Temporal and anatomic risk profile of brain injury with neonatal repair of congenital heart defects. Stroke 2007;38:736-41.
16. van der Aa NE, Dudink J, Benders MJ, Govaert P, van Straaten HL, Porro GL, et al. Neonatal posterior cerebral artery stroke: clinical presentation, MRI findings, and outcome. Dev Med Child Neurol 2013;55:283-90.
17. Cowan F, Rutherford M, Groenendaal F, Eken P, Mercuri E, Bydder GM, et al. Origin and timing of brain lesions in term infants with neonatal encephalopathy. Lancet 2003;361:736-42.
18. Ramaswamy V, Miller SP, Barkovich AJ, Partridge JC, Ferriero DM. Perinatal stroke in term infants with neonatal encephalopathy. Neurology 2004;62:2088-91.

19. Govaert P, Ramenghi L, Taal R, de Vries L, Deveber G. Diagnosis of perinatal stroke I: definitions, differential diagnosis and registration. Acta Paediatr 2009;98:1556-67.
20. Cowan FM, Pennock JM, Hanrahan JD, Manji KP, Edwards AD. Early detection of cerebral infarction and hypoxic-ischemic encephalopathy in neonates using diffusion-weighted magnetic resonance imaging. Neuropediatrics 1994;25:172-5.
21. Dudink J, Mercuri E, Al-Nakib L, Govaert P, Counsell SJ, Rutherford MA, et al. Evolution of unilateral perinatal arterial ischemic stroke on conventional and diffusion-weighted MR imaging. AJNR Am J Neuroradiol 2009;30:998-1004.
22. Haataja L, Mercuri E, Cowan FM, Dubowitz L. Cranial ultrasound abnormalities in full term infants in a postnatal ward: outcome at 12 and 18 months. Arch Dis Child Fetal Neonatal Ed 2000;82:F128-33.
23. Martinez-Biarge M, Diez-Sebastian J, Wusthoff CJ, Mercuri E, Cowan FM. Antepartum and intrapartum factors preceding neonatal hypoxic-ischemic encephalopathy. Pediatrics 2013;132:e952-9.
24. Mercuri E, Rutherford M, Cowan F, Pennock J, Counsell S, Papadimitriou M, et al. Early prognostic indicators of outcome in infants with neonatal cerebral infarction: a clinical, electroencephalogram, and magnetic resonance imaging study. Pediatrics 1999;103:39-46.
25. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G. International Pediatric Stroke Study Group. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke 2009;40:52-7.
26. Lee AC, Kozuki N, Blencowe H, Vos T, Bahalim A, Darmstadt GL, et al. Intrapartum-related neonatal encephalopathy incidence and impairment at regional and global levels for 2010 with trends from 1990. Pediatr Res 2013;74(Suppl 1):50-72.
27. Dawes NW, Dawes GS, Moulden M, Redman CW. Fetal heart rate patterns in term labor vary with sex, gestational age, epidural analgesia, and fetal weight. Am J Obstet Gynecol 1999;180:181-7.
28. Sheiner E, Levy A, Katz M, Hershkovitz R, Leron E, Mazor M. Gender does matter in perinatal medicine. Fetal Diagn Ther 2004;19:366-9.
29. Dunn L, Prior T, Greer R, Kumar S. Gender specific intrapartum and neonatal outcomes for term babies. Eur J Obstet Gynecol Reprod Biol 2015;185:19-22.
30. Badawi N, Kurinczuk JJ, Keogh JM, Alessandri LM, O'Sullivan F, Burton PR, et al. Antepartum risk factors for newborn encephalopathy: the Western Australian case-control study. BMJ 1998;317:1549-53.
31. Chauhan SP, Magann EF, Scott JR, Scardo JA, Hendrix NW, Martin JN Jr. Cesarean delivery for fetal distress: rate and risk factors. Obstet Gynecol Surv 2003;58:337-50.
32. Dammann O, Kuban KC, Leviton A. Perinatal infection, fetal inflammatory response, white matter damage, and cognitive limitations in children born preterm. Ment Retard Dev Disabil Res Rev 2002;8:46-50.
33. Grether JK, Nelson KB. Maternal infection and cerebral palsy in infants of normal birthweight. JAMA 1997;278:207-11.
34. Peebles DM, Wyatt JS. Synergy between antenatal exposure to infection and intrapartum events in causation of perinatal brain injury at term. BJOG 2002;109:737-9.
35. Arendt KW, Segal BS. The association between epidural labor analgesia and maternal fever. Clin Perinatol 2013;40:385-98.
36. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics 2007;119:495-501.

Table I. Antepartum and intrapartum data

Demographic data and family history
- Maternal age
- Maternal race: Caucasian, African descent, Asian, middle Eastern
- Family history of seizures.
- Family history of other neurologic disorders (not included in the previous category).

Maternal conditions and obstetric history
- Chronic hypertension (hypertension diagnosed before the beginning of the index pregnancy)
- Thyroid disease
- Depression
- Thrombotic conditions (ileofemoral thrombosis, deep vein thrombosis)
- Autoimmune diseases (ulcerative colitis, antilupus antibodies, diabetes)
- Gynecological problems (endometriosis, polycystic ovaries, others)
- Parity (parity before delivery of the infant)
- Previous history of miscarriages
- Infertility treatment (in vitro fertilization or any other treatment to achieve the index pregnancy).

Complications during gestation
- Gestational hypertension (not present before the beginning of the index pregnancy)
- Respiratory illness (infection, asthma)
- Urinary tract infection
- Significant antepartum bleeding
- Cholestasis
- Significant abdominal pain
- Episode of reduced fetal movements, as reported by the mother before labor.

Labor and delivery
- Onset of labor (spontaneous, induced)
- Artificial rupture of membranes
- PROM (defined as an interval of more than 24 h between the rupture of the membranes and the delivery)
- Maternal fever (intrapartum fever of more than 38°C)
- Presence of meconium
- Abnormal CTG, including persistent late or variable decelerations, fetal bradycardia, and/or reduced fetal heart variability.
- Prolonged second stage (defined as a second stage of labor longer than 2 h).
- Sentinel events (included uterine rupture, placental abruption, cord prolapse, acute fetal exsanguination, and maternal collapse).
- Shoulder dystocia (defined as a delivery that required additional obstetric maneuvers to release the shoulders after gentle downward traction had failed).
- Tight nuchal cord
- Mode of delivery:
  - spontaneous or unassisted vaginal,
  - instrumental vaginal (vacuum or forceps)
  - elective prelabor cesarean (undertaken prior to the onset of labor where there was no current fetal concern).
  - emergency cesarean during labor, usually due to abnormal CTG or obstructed labor
  - failed instrumental (vacuum or forceps), defined as the delivery of the infant by emergency cesarean after an attempted instrumental delivery had been unsuccessful.
- Apgar scores at 1 and 5 min
- Cord pH values
- Resuscitation measures. Major resuscitation included intubation for ventilation with or without cardiac compressions and epinephrine.

Infant characteristics
- GA
- Sex
- Birthweight and head circumference at birth. Growth centiles were calculated using the British growth reference charts
- Multiplicity

Neonatal clinical course
- Presence and stage of encephalopathy, defined as a clinical syndrome characterized by difficulty initiating and/or maintaining respiration, altered consciousness, and abnormal tone and reflexes, with or without seizures.
- Presence, onset, and duration of clinical seizures. Pharmacologic treatment.
- Neonatal infection (considered when the infant was treated with antibiotics for at least 48 h for clinically suspected and/or culture-proven sepsis).
- Neonatal hypoglycemia: blood glucose <45 mg/dL (2.6 mmol/L) within the first 2 d after birth.
- Other neonatal complications: meconium aspiration syndrome, other respiratory problems, multisystem dysfunction, need for inotropes.
- Infarct: arterial territory, side affected; other imaging findings

Neurodevelopmental outcome
- Age at the most recent assessment
- Presence, type and severity of cerebral palsy. Cerebral palsy was classified using the Surveillance of Cerebral Palsy in Europe definition and classification criteria.
- Results of the Griffiths Mental Developmental and/or the Bayley scales
- Results from the standardized neurologic examination, including head circumference measurement
- Presence and severity of other developmental and health problems: vision and hearing impairment, behavioral problems, feeding and communication impairment, presence and severity of seizures.