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

Miriam Martinez-Biarge, PhD[1,*], Jeanie L. Y. Cheong, MD[1,2,*], Jesus Diez-Sebastian, PhD[3], Eugenio Mercuri, PhD[1,4], Lilly M. S. Dubowitz, MD[1], and Frances M. Cowan, PhD[1]

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

From the [1]Department of Pediatrics, Imperial College London, London, United Kingdom; [2]Departments of Newborn Research and Neonatal Services, Royal Women's Hospital, Melbourne, Australia; [3]Biostatistics Department, La Paz University Hospital, Madrid, Spain; and [4]Pediatric Neurology Unit, Catholic University, Rome, Italy

*Contributed equally.

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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