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Risk Factors for Perinatal Arterial Ischemic Stroke: A Case–Control Study

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Abstract

Introduction: Arterial ischemic stroke in newborns is an important cause of neonatal morbidity and mortality. Its pathophysiology and associated risk factors are not yet clearly understood and defined. **Objective:** The aim of this retrospective study was to investigate possible risk factors in diagnosed cases of PAIS (perinatal arterial ischemic stroke). **Materials and methods:** Case–control study. Clinical data of patients with PAIS diagnosis were analyzed. Two healthy controls were selected for each PAIS case, matched for gestational age. Risk factors were explored using univariable and multivariable analysis. **Outcome:** 40 patients were included in the study, 24 males and 16 females; 52.5% of cases were diagnosed within the first month of birth, and 47.5% were retrospectively diagnosed. The results showed a male predominance (66.7%). The distribution of cerebral ischemic injury was predominantly medial cerebral artery (87.5%) and occurred more commonly in the left cerebral hemisphere (62.5%). Significant risk factors in the univariate analysis ($P < 0.05$) were primiparity, stillbirth, neonatal sepsis, asphyxia, twin pregnancy, placenta abruption, emergency cesarean section, Apgar score $\leq$7 after 5 min, breech presentation, and hyperbilirubinemia. In the multivariate analysis, primiparity (OR 11.74; CI 3.28–42.02), emergency cesarean section (OR 13.79; CI 3.51–54.13), birth asphyxia (OR 40.55; CI 3.08–532.94) and Apgar score $\leq$7 after 5 min (OR 13.75; CI 1.03–364.03) were significantly associated factors with PAIS. Only five (16.6%) patients had an abnormal thrombophilia study. **Conclusion:** Risk factors of primiparity, emergency cesarean section, birth asphyxia, and Apgar score $\leq$7 after 5 min were significantly associated with perinatal stroke. More studies with a larger number of patients and with prolonged follow up are required to establish more clearly the associated risk factors involved in this pathology.

Keywords

perinatal stroke, arterial ischemic stroke

Introduction

Stroke is the third most common cause of death in adults in the world, and an important cause of mortality and chronic neurological morbidity in children. Arterial ischemic stroke has emerged as an important cause of neurological disability in children. The reported annual incidence ranges from 1.2 to 8 per 100,000 children[1] and 1 per 2500–4000 live births for neonates[2].

The risk of maternal stroke also increases in the perinatal period and it is 34 times more frequent between two days before and one day postpartum than during previous stages in pregnancy or in non-pregnant women[3]. This increased vulnerability in mother and child to present a brain ischemic event is probably related to the activation of clotting mechanisms induced by childbirth, presumably an evolutionary adaptation to decrease the risk of hemorrhage at this crucial moment[4].

Due to the different nominations for this pathology, the National Institute of Child Health and Human Development and the National Institute of Neurologic Disorders and Stroke decided to define the terms[5,6]. Perinatal arterial ischemic stroke (PAIS) was defined as a focal disruption of cerebral blood flow occurring between 20 weeks of gestation and postnatal day 28. Because the exact timing of the stroke usually is not clear, ischemic perinatal stroke is

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defined according to gestational age or postnatal age at diagnosis. Three subcategories were defined: fetal ischemic stroke, neonatal arterial ischemic stroke (NAIS), and presumed perinatal ischemic stroke (PPIS). Fetal ischemic stroke is diagnosed before birth by use of fetal imaging methods or, in stillbirths, by neuropathologic examination. NAIS is diagnosed after birth and on or before postnatal day 28 (including in preterm infants) and PPIS is diagnosed in infants after 28 days of age in whom it is presumed (but not certain) that the ischemic event occurred some time from week 20 of gestation through postnatal day 28.

Some perinatal ischemic strokes will be symptomatic during the neonatal period, while others may not be recognized for months or years, or never be diagnosed if they do not develop enough symptoms to suspect a stroke[7]. The development of new and better techniques of neuroimaging and its greater availability has increased the diagnosis of perinatal ischemic stroke.

Multiple risk factors have been implicated, including maternal, obstetric, anatomic, and genetic considerations, but their precise roles in the pathogenesis of stroke are not accurately known. In addition, there are no clearly identified predictors on which to base treatment and prevention strategies[8].

This study aimed to identify risk factors in patients diagnosed with perinatal arterial ischemic stroke.

Patients and Methods

This is a case–control study. Patients with the diagnosis of PAIS were collected from the Neonatology Service, from Pediatric Emergency Room, and Pediatrics Neurology Outpatient Clinic of the San Borja Arriarán's Hospital, Santiago, Chile between the years 1993 and 2016. Chile has a dual health care system under which its citizens can voluntarily opt for coverage by either the public National Health Insurance Fund (FONASA, in Spanish) or any of the country's private health insurance companies. Currently, 68% of the population is covered by the public fund and 18% by private companies. San Borja Arriarán Hospital is part of the public health system and oversees the specific area of Santiago, Chile. However, its pediatric neurology department acts as a national referral center for complex neurology patients from all over the country. The inclusion criteria for this study were patients with the diagnosis of neonatal arterial stroke or presumed perinatal stroke, term birth ($\geq$37 weeks gestational age), neurological impairment suggesting stroke, and neuroimaging (CT or MRI) compatible with arterial ischemic cerebral injury. For every case, two healthy controls were randomly selected from the Puerperal Room of San Borja Arriarán's Hospital. The controls were matched for gestational age.

Full clinical data were collected from cases and control patients, including age of presentation, gender, neuroimaging, and thrombophilia study. A detailed antenatal and perinatal history was obtained at the time of the referral (cases) or recruitment (controls) from obstetric and neonatal notes. Potential risk factors were classified in three groups: antenatal, perinatal, and neonatal. The antenatal group risk factors included: maternal age, history of polycystic ovarian syndrome, maternal high body mass index (>30), primiparity, history of stillbirth, twin pregnancy, placenta abruption, preeclampsia, vaginal blood loss, maternal infection, preterm labor symptoms (women delivering at term who had preterm labor earlier in the pregnancy), oligohydramnios, intrauterine growth restriction, and gestational diabetes. The perinatal group risk factors included: prolonged rupture of membranes (>24 hours), maternal fever (>38°C), meconium-stained amniotic fluid, fetal heart abnormalities (repetitive or prolonged late decelerations, fetal bradycardia, nonreassuring fetal heart tracing, or fetal distress), elective cesarean section, emergency cesarean section, breech presentation, and use of forceps. The neonatal group risk factors included: gestational age >42 weeks, small for gestational age (SGA; birth weight <P3), large for gestational age (LGA; birth weight >P97), Apgar $\leq$3 at 1 min, Apgar $\leq$7 at 5 min, hypoglycemia (blood glucose <45 mg/dl or 2.6 mmol/L), early-onset sepsis, hyperbilirubinemia, birth asphyxia, use of catheterism, polycythemia, and congenital heart disease.

Because infants with PAIS were matched for several factors to controls, conditional logistic regression was used. In the univariable analysis, the association between the individual possible risk factors and PAIS was studied. To determine whether risk factors were independently associated with PAIS, a multivariable conditional logistic regression analysis was performed. Interactions were systematically tested and removed from the final model if they did not reach statistical significance. P values < 0.05 were considered statistically significant. Analysis was performed using STATA®V.12.

Results

Patient Population

Forty patients were included in the study, 24 (60%) males and 16 (40%) females. Mean gestational age was 39 weeks and mean gestational weight was 3.301 g. Twenty-one (52.5%) patients were diagnosed before postnatal day 28 and 19 (47.5%) patients were diagnosed after 28 days (PPIS).

Clinical Presentation

Eighteen (45%) patients diagnosed with NAIS presented with clinical symptoms in the first three days of life (range: <1–14 days). The most frequent reported symptoms in the NAIS patients were seizures (86%), impairment of consciousness (19%), feeding difficulties (14%), hypotonia (9.5%), and apneas (9.5%). In the PPIS group, the age of symptoms presentation was very wide (range: 12 days to 2 years), and the most frequent symptom was focal neurological impairment (94.7%). (Table 1)

Table 1. Clinical Presentation NAIS and PPIS Groups.

Clinical presentation	NAIS ($n = 21$)	PPIS ($n = 19$)
Seizures	18 (86%)	1 (5.2%)
Impairment of consciousness	4 (19%)	1 (5.2%)
Feeding difficulties	3 (14%)	1 (5.2%)
Hypotonia	2 (9.5%)	0 (0%)
Apneas	2 (9.5%)	0 (0%)
Focal neurological impairment	0 (0%)	18 (94.7%)

n: number of patients; NAIS: neonatal arterial ischemic stroke; PPIS: presumed perinatal ischemic stroke.

Table 2. Stroke Distribution.

PAIS	Total
Vascular distribution	
MCA	35 (87.5%)
ACA	1 (2.5%)
PCA	4 (10%)
Unilateral	41 (95.3%)
Left	25 (62.5%)
Right	13 (32.5%)
Bilateral	2 (5%)

ACA: anterior cerebral artery; MCA: middle cerebral artery; *n*: number of patients; PAIS: perinatal arterial ischemic stroke; PCA: posterior cerebral artery.

Neuroimaging Study

Thirty-eight (95%) patients were studied with a brain CT and 25 (62.5%) patients with a brain MRI; only two patients were studied exclusively with MRI. In four cases, cranial ultrasound suggested neonatal arterial territory cerebral infarction.

The distribution of cerebral ischemic injury was predominantly medial cerebral artery (87.5%); the second most frequent stroke localization was in the posterior cerebral artery (PCA) (10%). In 38 (95%) patients the vascular compromise was unilateral, and two (5%) patients had a bilateral compromise (both patients had a PCA lesion). The left lobar lesion was the most frequent one (62.5%) (Table 2).

Thrombophilia Study

Thirty-one (77.5%) patients had a thrombophilia study done (including prothrombin, APTT, protein C, S, antithrombin III, lipoprotein (a), factor V Leiden, prothrombin G20210A, lupus anticoagulant, and antiphospholipid antibodies). Only 5 (16.6%) patients had an abnormal result: Protein C deficiency in two cases, factor V Leiden heterozygous mutation in one case, positive lupus anticoagulant in one case, and high antiphospholipid IgM antibodies in one case (Table 3).

Risk Factors Associated with PAIS

In the univariate analysis, comparing the 40 cases and their 80 control subjects, the antenatal risk factors associated with PAIS included primiparity, twin pregnancy, placenta abruption, and history of stillbirth. Perinatal complications associated with PAIS included emergency cesarean section and breech presentation. After delivery, infants with PAIS were significantly more likely to be given an Apgar score ≤ 7 after 5 min, or to have neonatal sepsis, asphyxia, and hyperbilirubinemia (Table 4). These 10 risk factors were studied in a multivariable analysis. Four risk factors were independently associated with the risk of PAIS: primiparity (OR 11.74; CI 3.28–42.02), emergency cesarean section (OR 13.79; CI 3.51–54.13), birth asphyxia (OR 40.55; CI 3.08–532.94), and Apgar score ≤ 7 after 5 min (OR 13.75; CI 1.03–364.03) (Table 5).

Table 3. Thrombophilia Study Results.

Thrombophilia study	31
Normal	26
Abnormal	5
Protein C deficiency	2
Factor V Leiden (heterozygous mutation)	1
Lupus anticoagulant	1
Antiphospholipid IgM antibodies	1

Discussion

The objective of this study was to identify risk factors in patients with diagnosis of NAIS.

We found a male predominance in our studied patients. The reasons behind the predominance of boys diagnosed with NAIS are not clear[9,10], but recent works suggest that gender differences in the occurrence of pediatric arterial ischemic stroke are associated with elevated endogenous testosterone concentrations and that risk of cerebral thromboembolism increases in a concentration-dependent fashion with testosterone levels among males[11]. In addition, cell death pathways in response to ischemia are also influenced by gender; a male predominance in the mechanisms of caspase-dependent and -independent apoptotic death has been shown after neonatal hypoxic-ischemic lesions[12,13] and focal ischemia[14]. A possible role of gender in stem cell treatment for neonatal hypoxic-ischemic encephalopathy (HIE) and stroke is being investigated[15].

The majority of patients in our study had unilateral lesions in the middle cerebral artery (88.4%), particularly on the left side (65%), consistent with populations in previous studies[16]. The International Pediatric Stroke Study has shown that perinatal stroke occurs in the anterior circulation 70% of the time, and in 73% of newborns the left hemisphere was affected[17]. Variable vulnerability to ischemic lesions and anatomic settings might explain why the left side is more commonly involved[18–20]. It has been suggested that the origin of the left carotid artery from the aorta allows a more direct vascular route to the brain for cardiac emboli[21–23].

Table 4. Univariate Analysis of Risk Factors for PAIS.

	(%)			
	Cases	Controls		
No.	40	80	OR (95% IC)	P value
Male	24 (60%)	48 (60%)	1.0 (0.46–0.87)	1.000
Antenatal risk factors				
Maternal age (years) (mean)	24	24	0.97 (0.92–1.03)	0.737
High body mass index (>30)	1 (2.5%)	8 (10%)	0.23 (0.03–1.91)	0.269
Polycystic ovarian syndrome	0 (0%)	4 (5%)	N/C	0.300
Primiparity	27 (33.75%)	26 (65%)	3.65 (1.64–8.10)	0.002*
History of stillbirth	1 (2.5%)	15 (18.75%)	0.11 (0.01–0.87)	0.020*
Twin pregnancy	3 (7.5%)	0 (0%)	N/C	0.035*
Placenta abruption	4 (10%)	0 (0%)	N/C	0.011*
Pre-eclampsia	6 (15%)	8 (10%)	1.59 (0.51–4.94)	0.547
Vaginal blood loss	1 (2.5%)	0 (0%)	N/C	0.333
Maternal infection	5 (12.5%)	9 (11.25%)	1.13 (0.35–3.62)	1.000
Preterm labor	5 (12.5%)	3 (3.75%)	3.66 (0.83–16.21)	0.115
Oligohydramnios	1 (2.5%)	1 (1.25%)	2.03 (0.12–33.25)	1.000
Intrauterine growth restriction	0 (0%)	5 (6.25%)	N/C	0.168
Gestational diabetes	0 (0%)	5 (6.25%)	N/C	0.168
Perinatal risk factors				
Prolonged rupture of membranes (>24 h)	1 (2.5%)	9 (11.25%)	0.20 (0.02–1.66)	0.162
Maternal fever (>38°C)	1 (2.5%)	1 (1.25%)	2.03 (0.12–33.25)	1.000
Meconium-stained amniotic fluid	3 (7.5%)	5 (6.25%)	1.22 (0.28–5.37)	1.000
Fetal heart rate abnormalities	9 (22.5%)	8 (10%)	2.61 (0.35–2.14)	0.054
Elective cesarean section	9 (22.5%)	20 (25%)	0.87 (0.35–2.14)	0.824
Emergency cesarean section	14 (35%)	11 (13.75%)	3.38 (1.36–8.39)	0.009*
Breech presentation	3 (2.5%)	0 (0%)	N/C	0.035*
Use of forceps	2 (5%)	0 (0%)	N/C	0.111
Neonatal risk factors				
Post-term newborn	2 (5%)	0 (0%)	N/C	0.109
Apgar $\leq$ 3 at 1 min	3 (7.5%)	1 (1.25%)	6.41 (0.64–63.67)	0.107
Apgar $\leq$7 at 5 min	4 (10%)	1 (1.25%)	8.78 (0.94–81.34)	0.042*
SMA (birth weight <P3)	3 (7.5%)	11 (13.75%)	0.51 (0.13–1.94)	0.361
LGA (birth weight >P97)	1 (2.5%)	8 (10%)	0.23 (0.03–1.91)	0.265
Hypoglycemia	2 (5%)	2 (2.5%)	2.05 (1.33–22.36)	0.600
Early-onset sepsis	7 (17.5%)	2 (3.75%)	5.44 (1.33–22.36)	0.015*
Hyperbilirubinemia	5 (12.5%)	2 (2.5%)	5.57 (1.03–30.12)	0.040*
Birth asphyxia	6 (15%)	1 (1.25%)	13.94 (1.62–120.26)	0.005*
Use of catheterism	2 (5%)	0 (0%)	N/C	0.109
Polycythemia	0 (0%)	0 (0%)	N/C	N/C
Congenital heart disease	0 (0%)	0 (0%)	N/C	N/C

*Statistically significant; N/C: not calculable

Table 5. Multivariate Analysis of Risk factors for PAIS.

	OR	95% IC
Primiparity	11.74	3.28–42.02*
Emergency cesarean section	13.79	3.51–54.13*
Birth asphyxia	40.55	3.08–532.94*
APGAR $\leq$7 at 5 min	13.75	1.03–364.03*

*Statistically significant

There are not many case–control studies for risk factors in patients diagnosed with neonatal arterial stroke. In our group, primiparous mother, emergency cesarean section, asphyxia, and Apgar score $\leq$7 after 5 min were significantly associated with neonatal arterial stroke.

Primiparous pregnancies have also recently been identified as a risk factor for neonatal stroke[24,25]. Lee et al.[24], in a case–control study, found that primiparity was one of the factors more common in the neonate cases with stroke than in the control group (73% vs. 44%, P = 0.002). Its pathophysiology is not clear. Primiparity may predispose some women to present more intrapartum complications.

Emergency cesarean section, birth asphyxia, and Apgar score $\leq$7 after 5 min are often associated with fetal distress, and suggest an important role for hypoxia-ischemia as one of the possible causes of neonatal stroke[26–28].

HIE is a known cause of diffuse brain damage in neonates, but has not been associated with focal vascular lesions. In previous studies, Ramaswamy et al.[7] observed that only 6/127 patients with perinatal stroke had a diagnosis of associated HIE, and Harbert et al.[29] reported only 15/315 patients with this association. However, in more recent studies, asphyxia has been proposed as a factor involved in the development of stroke in neonates. Michoulas et al.[30] analyzed neuroimaging of 62 newborns with perinatal stroke; in 26/62 (47%) they showed focal ischemic lesions in conjunction with diffuse lesions secondary to ischemic hypoxic damage. Hypoxia and ischemia may play a role in the activation of thrombogenesis since it has been observed that levels of physiological inhibitors of coagulation, including antithrombin III, protein C and S, are reduced, causing hypercoagubility[31]. Emerging data from experimental models, especially in mice, of cerebral ischemia in neonatal rodents have shown that hypoxia is a rapid and potent stimulus of spontaneous coagulation in mice[32].

In this study there was no association of other risk factors such as pre-eclampsia, neonatal infection, hypoglycemia, etc. In addition, although a thrombophilia study was not performed in all patients, this association was uncommon (16.5%). The incomplete collection of the thrombophilia study is a major limitation, owing primarily to the retrospective nature of the study and subject collection for many years, during which testing options changed regularly. Previous evaluations of prothrombotic abnormalities in perinatal stroke populations are limited[33], suffering from similar limitations and population heterogeneity[34].

Although there has been much interest in the role of thrombophilic factors in the pathogenesis of neonatal stroke, the absence of comprehensive data from cohorts makes it difficult to ascertain the relative importance of these factors. Similarly, placental pathology is very limited to date.

It would be ideal if large prospective cohort studies with detailed advanced neuroimaging, comprehensive prothrombotic screening, and placental histology could be performed. This would, of course, be logistically difficult, but the information provided would be invaluable in the understanding of the multifactorial pathway of neonatal stroke. A better understanding of the risk factors and interactions with the process of labor and delivery may lead to interventions that could potentially reduce the incidence of a condition that is associated with significant neurological morbidity.

Our study was subject to a number of limitations. The period over which controls were enrolled was significantly limited compared with the enrollment of cases, but was within the period when cases were recruited. The incomplete and variable collection of thrombophilia studies is another limitation, owing to the retrospective nature of the study and subject collection for many years, during which testing options have changed. Also, equivalent information of thrombophilia studies is not available for the controls. Since the study recruited infants over 10 years, obstetric policies, imaging protocols, and neonatal procedures may have changed.

Conclusion

The physiology of PAIS is not known with certainty. The following risk factors are significantly associated with neonatal arterial stroke: primiparous mother, emergency cesarean section, asphyxia, and Apgar score ≤ 7 after 5 min. More studies with a larger number of patients and with prolonged follow up are required to establish more clearly the associated risk factors involved in this pathology.

Ethical Approval

This study was approved by our institutional review board.

Statement of Human and Animal Rights

This article does not contain any studies with human or animal subjects.

Statement of Informed Consent

Statement of Informed Consent was obtained written from legally authorized representatives.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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