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Ischemic and Hemorrhagic Perinatal Stroke in a Neonatal Intensive Care Unit: A 10-Years Survey

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Abstract

Background: *Perinatal stroke has been associated with a multifactorial etiology and it is an important cause of long term neurologic impairment.*

Methods: *This is a retrospective study on risk factors, clinical manifestations and follow-up of newborns admitted in a level three Neonatal Intensive Care Unit between January 2006 and December 2015 with the final diagnosis of perinatal stroke. The selected perinatal stroke cases were those with magnetic resonance imaging confirmation and the selected risk factors were chosen based on recent review studies or meta-analyzes.*

Results: *Seventeen cases were identified (13 ischemic and four hemorrhagic) and the most common clinical presentation was seizure, 20 to 48 hours after delivery, occurring in 88% of newborns. All ischemic stroke cases had at least one specific risk factor, and 60% had more than three. Only one hemorrhagic stroke case had a specific risk factor. Four placentas had histological abnormalities. A prothrombin gene mutation was detected in one ischemic stroke case. There was no stroke recurrence or death, with a mean follow-up of 43 months. 62% of the infants had neurologic sequelae (motor impairment and epilepsy). All ischemic stroke cases with more than two risk factors had neurologic sequelae.*

Conclusions: *Ischemic stroke cases usually presented specific risk factors. An association between risk factors´ number and a worse neurologic outcome was also observed in ischemic stroke cases.*

Keywords: Perinatal stroke, neonatal seizures, newborn, risk factors

Introduction

Perinatal stroke (PS) is currently defined as an acute neurologic syndrome with chronic sequelae due to cerebral injury of vascular origin, occurring between 20 weeks of gestation and 28 days of postnatal life.[1] Perinatal arterial ischemic stroke (AIS) has an estimated incidence of one in 2300 to one in 5000 newborns (NB) which exceeds 10 times the childhood stroke.[1,2] Its incidence ranks only second to stroke in the general population (adult and pediatric stroke).[1] The major subtypes comprise AIS, cerebral venous thrombosis and hemorrhagic stroke (HS) which account respectively for 70, 20, and 10 percent (%) of acute symptomatic PS.[2] Temporal classification based on neuroimaging and clinical features comprises fetal, neonatal and perinatal presumed stroke.[2-4] A multifactorial etiology based on prenatal, perinatal and neonatal risk factors is presumed.[4]

Identification of a causative factor for PS remains difficult to achieve in most cases with no current means of prevention.[5]

Pathophysiology of AIS includes thromboembolism, vasculopathy of cerebral arteries and hemostatic disturbances, but globally is poorly understood with most cases remaining idiopathic. The HS can result from two main mechanisms: a primary hemorrhage resulting from vascular anomalies or bleeding diatheses; a secondary conversion of arterial or venous ischemic infarction.[6]

Prothrombotic disorders have been associated with AIS but substantial levels of evidence are limited.[7-10] Current studies argue that rates of thrombophilia in children with PS are similar to those in the normal population and routine testing for thrombophilia should not be done.[7,10] Current guidelines recommend anticoagulation treatment only for NB with proven cardioembolic stroke.[11changed]

Perinatal stroke is an important cause of chronic neurologic disability in children and some authors state that perinatal AIS is the most common identifiable cause of cerebral palsy.[6] In a previous study, Béjot et al. described that after PS, 39% infants will develop epilepsy, 58% motor deficits, 25% language delay acquisition and 25% behavior problems.[7] Even in infants with an early reassuring development, long term neurodevelopmental follow-up should be accomplished.[12]

The aim of this study was a comparison between AIS and HS in a PS case series, characterizing clinical data as well as laboratory and imaging features; identifying already recognized risk factors for each subtype and evaluating neurologic outcome. Comparing neurologic outcome based on the number of risk factors was also targeted.

Material and Methods

Participant Selection

Subjects were identified from a Neonatal Intensive Care Unit integrated in a perinatal center with inborn babies of an Oporto single tertiary stand-alone children's hospital. Registries were recorded from the electronic medical database of all babies born from 2006 and 2015 with final diagnosis of stroke, confirmed by magnetic resonance imaging (MRI).

Exclusion criteria were outborn NB, preterm intraperiventricular hemorrhage associated with venous infarcts, periventricular leukomalacia, hypoxic-ischemic encephalopathy and traumatic lesions. Neuroimaging studies of all neonates were reviewed by experienced pediatric neurologists and neuroradiologists.

Data Acquisition

Clinical data were obtained by medical records. They included mode of delivery, Apgar scores, need for resuscitation, gestational age, birth weight, sex, age at presentation, clinical manifestation, age of diagnosis by MRI and hospitalization length. Laboratory and neurophysiological data were also collected. Cerebral ultrasound (US) and MRI studies were performed to determine the stroke characteristics, affected vessels, and location of the lesions.

The risk factors considered in this study for both AIS and HS were based on a recent meta-analysis on AIS risk factors´ and recent publications related to HS, respectively.[4,9,12,13] The risk factors for AIS considered in this study included: oligohydramnios, pre-eclampsia, intrapartum fever >38ºC, abnormal cardiotocography (CTG), meconium-stained amniotic fluid, cord abnormalities, instrument-assisted (forceps or vacuum) delivery, emergency cesarean section (CS), umbilical arterial pH <7.10, male gender, small for gestational age (SGA), need for resuscitation at birth, Apgar score of less than seven at five minutes and hypoglycemia (blood glucose 2.6 mmol/L) within the first two days after birth. The risk factors for HS considered were: fetal distress, placental abruption, complex congenital heart disease, neonatal sepsis, hemostatic abnormalities (low platelet count, prolonged prothrombin time, partial thromboplastin time and activated clotting time, low fibrinogen, congenital bleeding disorder and heparin exposure) and postmaturity (babies born after 42 weeks).[14]

Abnormal CTG included persistent late or variable decelerations, fetal bradycardia and/or reduced fetal heart variability.[4] Fetal distress corresponded only to a non-reassuring fetal heart tracing and/or decreased fetal movement prior to delivery.[12] Considered cord abnormalities were cord entanglements, hypercoiling, true knots, strictures and short cords.[4] Resuscitation at birth included the need of intubation for ventilation with or without cardiac compressions and/or epinephrine.

Other unclear or less described risk factors for PS as abnormal prothrombotic studies and placenta abnormalities were separately recorded.[3,6]

Outcome data were obtained from medical records of follow-up medical appointments and included death, stroke recurrence, post-stroke anti-epileptic drug treatment (at sixth and eighteenth month), neurologic sequelae and neurodevelopmental outcome (with in a minimum age of 18 months). Abnormal neurologic outcome was defined by the presence of hemiparesis and/or epilepsy. Speech problems were searched in children from the age 24 months. Neurodevelopmental global assessment was obtained by Griffiths Mental

Development Scale or clinical evaluation by a developmental pediatrician.

Data Analysis

Data were analyzed using SPSS statistical software, version 22.0 (SPSS Inc., Chicago, IL, USA). Categorical variables were summarized using frequencies (n) and percentages (%). For continuous variables, data were summarized by the median with interquartile range (IQR).

Results

Subjects And Clinical Manifestations

Out of 31826 live births between January 2006 and December 2015, there were 17 (0.0005%) PS cases identified, 13 AIS and 4 HS. Male represented 76% and 24% were preterm NB. Detailed demographic and clinical data for each stroke subtype are listed in Table 1.

Table 1. *Demographic, clinical and neuroimaging/neurophysiologic data.*

Data/ Stroke subtype	Ischemic (n=13) n (%) or median (IQR)	Hemorrhagic (n=4) n (%) or median (IQR)	Total (n=17) n (%) or median (IQR)
Demographic and clinical data			
Male gender	9 (69)	4 (100)	13 (76)
GA (weeks)	38 (36-39)	39 (36-39)	39 (36-39)
GA vs. BW (g)	3135 (2700-3530)	2970 (2745-3515)	2970 (2745-3515)
AGA	12 (92)	4 (100)	16 (94)
LGA	1(8)	-	1(6)
SGA	-	-	-
Newborn twins	2 (15)	-	2(12)
Eutocic delivery	4 (31)	3 (75)	7 (41)
Vacuum delivery	2 (15)	1 (25)	3 (18)
Forceps delivery	1 (8)	-	1 (6)
Cesarean section	6 (46)	-	6 (35)
1-min Apgar score	8 (5-9)	8 (5-9)	8 (5-9)
5-min Apgar score	10 (8-10)	10 (8.5-10)	10 (8.5-10)
Hospitalization (days)	14 (7-15)	13 (7-15)	13 (7-15)
Clinical manifestations			
Seizure	11 (85)	4 (100)	15 (88)
Time of presentation (h)	24 (20-48)	37 (24-48)	24 (24-48)
Hemisphere localizing clinical seizures	8 (62)	3 (75)	11 (65)
Feeding problems	5 (38)	1 (25)	6 (35)
Apnoeia	2 (15)	-	2 (12)
Cyanosis	2 (15)	-	2 (12)
Altered limb tone	1 (8)	-	1 (6)
Neuroimaging and neurophysiologic studies			
Cranial US:			
Normal	3 (23)	2 (50)	5 (29)

Abnormal	10 (77)	2 (50)	12 (70)
Diagnosis by MRI (day)	8 (6-12)	8 (6-12.5)	8 (6-12.5)
Brain affected territory (MRI)			
Left MCA	10 (77)	n.a.	10 (59)
Right MCA	1 (8)	n.a.	1 (6)
Watershed	2 (15)	n.a.	2 (12)
EEG†			
Normal	1 (8)	2 (50)	3 (18)
Abnormal	11 (92)	2 (50)	13 (76)

AGA = Adequate for gestational age, BW = Birth weight, EEG = Electroencephalography, GA = Gestational age, h = hours, LGA = Large for gestational age, min = minute, n.a. = not applicable, SGA = Small for gestational age, † One asymptomatic case did not receive EEG evaluation

In this cohort, all symptomatic cases included NB which developed seizures, being a total of 15 NB (88% of all PS cases). The median onset time of symptoms was 24 hours for AIS and 37 hours for HS and hemisphere localizing clinical seizures were found in 65% of cases. The two asymptomatic cases (AIS cases) were born at 36 weeks of gestation: one case had a history of fetal distress and emergent cesarean; the other case had a history of placental abruption and a vacuum delivery. Both stroke cases were suspected by neonatal cerebral US.

Imaging And Neurophysiological Studies

Cerebral US was performed in all NB included in this study (70% abnormal). Median age for diagnosis confirmation by MRI was the eighth day for both stroke groups. The two cases without clinical seizures were diagnosed later at ninth and thirteenth day by MRI, after a suspicious neonatal cranial US. Most frequently affected cerebral territory in MRI was that of left middle cerebral artery (MCA) (59%). Amplitude-integrated electroencephalography (aEEG) was performed in five neonates and was abnormal in the three AIS cases and normal in 2 the HS cases. Electroencephalography (EEG) was done in 16 cases (81% abnormal) – main results and distribution patterns are summarized in Table 1. Illustrative case images of AIS subtype can be seen on Figure 1 and Figure 2.

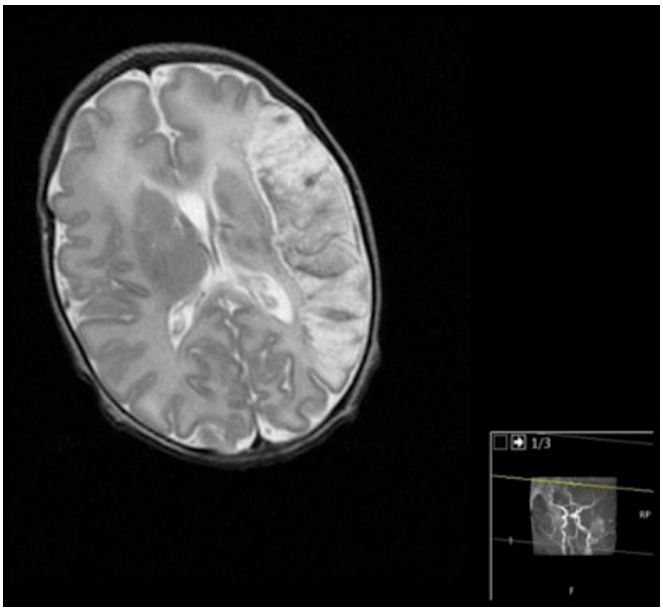

Fig 1. *Ischemic Stroke (MCA territory) at day twelve of life- MRI T2 with an extensive lesion on left frontotemporoparietal lobes and basal ganglia.*

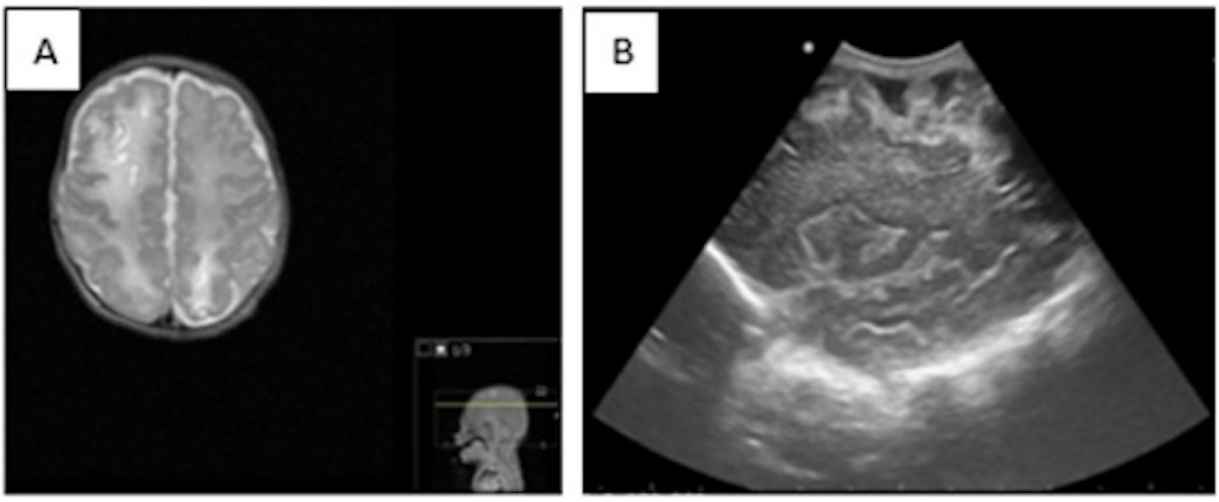

Fig. 2. *Ischemic Stroke (Watershed) at day 10 of life.* ***(A)*** *MRI T2 Ischemic lesions involving vascular border zones (right frontal and left parietal subcortical areas supplied by distal vessels of major arteries).* ***(B)*** *Cranial US: right parasagittal scan with hyperechogenicity of the right parietal convexity with cortex damage.*

Risk Factors

Most of the identified risk factors occurred in AIS group. The recognized risk factors identified in AIS group and HS group are listed in Table 2.

Table 2. *Ischemic and hemorrhagic risk factors´ data.* [4,9,12,13]

Risk Factors/ Stroke subtype	Ischemic (n=13) n (%)	Hemorrhagic (n=4) n (%)	Total (n=17) n (%)
Prenatal			
Intrapartum fever >38°C *	2 (15)	2 (50)	4 (24)
Oligohydramnios *	1 (8)	1 (25)	2 (12)
Pre-eclampsia *	1 (8)	-	1 (6)
Primiparity *	8 (62)	3 (75)	11 (65)
Perinatal			
Forceps or vacuum delivery *	3 (23)	1 (25)	4 (24)
Abnormal CTG*/Fetal distress†	3 (23)/-	-/-	3 (18)
Placental abruption †	1 (8)	-	1 (6)
Cord abnormalities *	1 (8)	-	1 (6)
Emergency CS *	3 (23)	-	3 (18)
Meconium-stained AF *	2 (25)	-	2 (12)
Neonatal			
Male *	9 (69)	4 (100)	13 (76)
Sepsis †	2 (15)	1 (25)	3 (18)
Resuscitation at birth *	2 (15)	-	2 (12)
5-min Apgar score <7 *	1 (8)	-	1 (6)
Hypoglycemia *	3 (23)	-	3 (18)
Hemostatic abnormalities †	1 (8)	-	1 (6)

All AIS cases had at least one specific AIS risk factor and just one case of all HS cases (25%) had a specific HS risk factor (neonatal sepsis).

Prothrombotic study was performed in three cases (18%): two AIS and one HS, one of which had an abnormal result - an AIS case with a heterozygous mutation G20210A on prothrombotic gene – a term neonate born by an emergent CS (fetal distress) whose father had the same mutation.

Placental histologic evaluation was performed in nine cases (eight for AIS and one for HS cases). Four placentas (50% of AIS cases) had abnormalities: chorioamnionitis/funisitis (two cases), thrombus (one case) and unspecific lesions (one case). Chorioamnionitis and funisitis occurred in a case of maternal fever; thrombus occurred in a fetal hydrops' case; unspecific lesions were found in a case of placental abruption.

Treatment And Outcome

During hospitalization 13 cases (76%) needed at least one anti-epileptic and four (31%) needed an association of two anti-epileptic (75% of AIS; 25% of HS). No cases received anticoagulation therapy. At the sixth month after event, the frequency of anti-epileptic therapy was higher in HS group; on the contrary, at the eighteenth month it was higher in AIS group (Table 3).

Table 3. *Follow-up and outcome in post-stroke infants.*

Follow-up and outcome / Stroke subtype	Ischemic (n=12*) n (%)	Hemorrhagic (n=4) n (%)	Total (n=16) n (%)
AE therapy	7 (58)	3 (75)	10 (62)
At 6th month	7 (58)	3 (75)	10 (62)
At 18th month	5 (42)	1 (25)	6 (38)
Neurologic sequelae	7 (58)	3 (75)	10 (62)
Epilepsy only	1 (8)	2 (50)	3 (19)
Hemiparesis only	4 (33)	-	4 (25)
Speech problems only	-	-	-
Epilepsy + Hemiparesis	1 (8)	-	1(6)
Speech problems + Hemiparesis	-	1 (25)	1 (6)
Epilepsy + Speech problems	1 (8)	-	1 (6)
ND evaluation	11† (92)	4 (100)	15† (94)
Normal	4 (36)	3 (75)	7 (44)
Abnormal	7 (64)	1 (25)	8 (50)

AE = Anti-epileptic drugs, ND = Neurodevelopmental

* One stroke case was lost to follow-up at four months of age. Anti-epileptic drugs and neurologic sequelae results included the lost case.

† One case had not available neurodevelopmental evaluation. Neurodevelopmental total results only include the children evaluated.

There was no recurrence of PS or death during this period.

The mean and median follow-up period were, respectively, 43 and 39 months (ranging from 18 to 80 months) for AIS and HS. One case was lost to follow-up at four months of age.

Neurological sequelae were present in 62% (58% AIS e 75% HS) of the 16 NB evaluated and are summarized in Table 3. Most common problems were hemiparesis (25%) and epilepsy (19%). One HS case developed refractory epilepsy and performed hemisferectomy at two years of age. Post stroke epilepsy incidence was similar at six and 18 months in both groups among patients who remained on anti-epileptic treatment. Speech problems were found in three cases: one AIS of the left MCA territory and two HS, at the ages of 63, 45 and 49 months respectively.

All AIS cases with more than two AIS risk factors had an abnormal neurologic outcome (Figure 3).

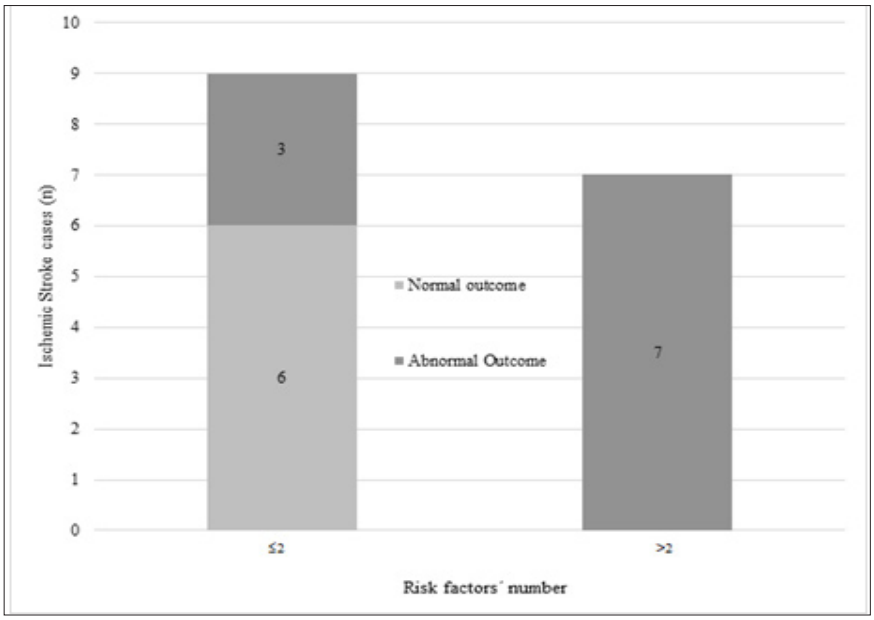

Fig 3. *Graphical representation of neurologic outcome based on AIS risk factors number in AIS group.*

The only HS case with a specific HS risk factor had an abnormal neurologic outcome (Figure 4).

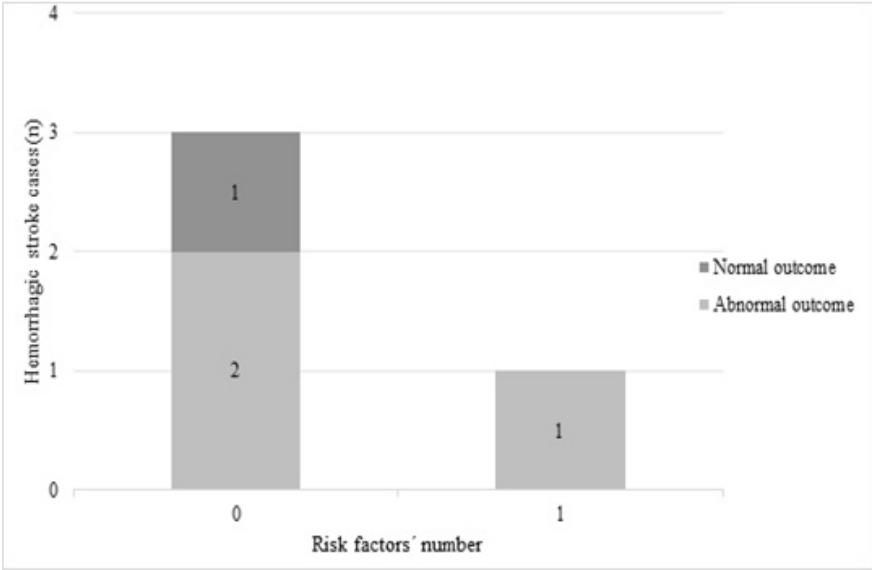

Fig 4. *Graphical representation of neurologic outcome based on HS risk factors number in HS group.*

From the 16 PS cases´ which had follow-up medical appointments, only in one case the neurodevelopmental evaluation was not available. Out of the 15 cases evaluated, 8 (53%) showed an abnormal neurodevelopmental evaluation (Table 3).

Discussion

Perinatal stroke incidence (one in 1872 live births) in this case series was higher than the incidence already described.[2] In agreement with previous studies, IS was the most common subtype of PS.[12]

As Lee et al. described in a 2017 published study, we confirm the predominance of male sex and full-term neonates in this PS case series.[6]

Seizures were the most common manifestation and presented in both AIS and HS groups, being consistent with previous studies which cite an incidence up to 92%.[6] Therefore, a differentiation of the two PS subtypes seems to be difficult based exclusively on clinical features. On the other hand, one should keep high level of suspicion if infants develop unexplained

seizures. The time between symptoms and confirmed diagnosis had an average of seven and six days for AIS and HS, respectively. The later diagnosis which occurred in two asymptomatic cases was insufficiently to consider this fact responsible for a poorer neurologic outcome, not confirming that previously described in literature.[3]

Besides having a significant impact in understanding PS pathogenesis, extensive prothrombotic screening and placental studies were only performed in specified cases, reflecting the already controversy published statements on this subject.[13]

Pathologic examination of the placenta was performed in a limited number of patients. It possibly indicates the different professionals´ attitude on the placentae selection, given the unspecificity of PS risk factors. On the other hand, as clinical manifestations of PS did not occur immediately after birth, many placentas can be unconsciously rejected. As prothrombotic and placental studies can have a significant impact in understanding PS pathogenesis, the need of a protocol in these two aspects seems to be of crucial importance.

The lack of studies on risk factors for HS as well as the limited case number collected in the present are important limitations. They might be partly responsible for having failed to detect specific risk factors for HS.

The presence of the same risk factors in HS and AIS cases´ could suggest common pathological pathways.

Mortality rate compared to that reported by Lee et al. (around 5%) may be justified by the lower number of stroke cases included in this single tertiary hospital-based study.[6] On the other hand, morbidity rate was significant – 62% of infants developed neurological sequelae. Nevertheless, the rate of motor dysfunction, speech problems and post-stroke epilepsy was lower to data previously reported.[6,7,15] The possible occurrence of serious long-term sequelae in PS, as reported by Amlie-Lefond and Ojemann, occurred in one case with intractable epilepsy requiring neurosurgery.[12]

Speech problems were only detected in patients after 45 months, and the number of affected children can be underestimated by the wide range of ages of follow-up assessments.

The association between risk factors´ number and a worse neurologic outcome in AIS was observed. As PS seems to be a multifactorial etiologic condition, the presence of multiple risk factors could reflect the presence of different etiologic factors, contributing to cumulative risk and increased neurologic impairment.

The main limitations of this study were the retrospective design and the limited number of patients (especially in the hemorrhagic group), based on a single tertiary hospital.

Conclusions

The present study reinforces the importance of a closer follow-up of post-stroke NB (regarding epilepsy and physical and neurocognitive acquisitions), suggesting a special attention in those cases with a combination of risk factors. An earlier supportive and rehabilitation intervention strategy in these high-risk NB could improve neurological outcome and provide a better life quality for children and their families. Important advances in the field of neonatal neurology were supported by the number of recognized risk factors for PS identified in this work, but in cases of HS we were still unable to demonstrate at least one risk factor. Much less is known about HS risk factors comparing to AIS risk factors, supporting the need of more research in this area. Also with few available data in literature, hemodynamic changes of neonatal period (transition from fetal to neonatal circulation), namely prothrombotic vascular changes of placenta (bi-directional shunt with movement of possible thrombus from the cord to left MCA of the NB), should deserve special attention.

Further prospective, human and animal studies are warranted to improve our knowledge about the mechanisms and timing of neurologic lesions establishment, verify possible common pathological pathways of specific risk factors, and confirm the potential contribution of risk factors´ combination to a poorer neurologic outcome.

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