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ORIGINAL PAPER

Arterial ischemic stroke (AIS) in childhood: clinical report from a single control center

Anna Portale[1] · Agata Fiumara[1] · Luisa Scalora[1] · Filippo Greco[1] · Pierluigi Smilari[1] · Valeria Venti[1] · Elena Pustorino[1] · Piero Pavone[1]

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Abstract

Introduction Stroke is the clinical designation for a rapidly developing loss of brain function due to an interruption in the blood supply to all or part of the brain. It is the third cause of death in adults and one of the top 10 causes in pediatric age.

The perinatal period of onset is the second only to adult age group in the incidence of stroke. Arterial ischemic stroke during childhood occurs most frequently in the perinatal period with an incidence of 1 out 2300–5000 live infant births.

Materials and methods This is a retrospective study that includes 28 patients affected by perinatal arterial ischemic stroke. Family and gestational history, risk factors of perinatal stroke, gender and clinical data of affected children and outcome are reported.

Results A stroke family history was registered in three unrelated families. Gestational history disclosed cases of threats of abortion, preterm delivery, hyperthermia, gestosis, and placental disorders. In the children, onset of seizures were reported within 3 days of life and diagnosis of stroke was confirmed by brain MRI which disclosed involvement of the middle cerebral artery in all the cases. Hemilateral cerebral palsy, epileptic seizures, and intellectual disability from mild to severe were the most frequent complications.

Conclusion Stroke is still a common and dreadful events in perinatal period as this disorder is often unpredictable and cause of severe neurological impairment.

Keywords Stroke · Seizures · Neurological impairment · Cerebral palsy

Introduction

The National Institute of Health Workshop on Perinatal Stroke has been defined perinatal arterial ischemic stroke (AIS) as a condition with acute encephalopathy, seizures, or neurologic deficits presenting in term or preterm infant before the 29th postnatal day, with brain imaging confirming a parenchymal infarct in the appropriate arterial territory [1].

Arterial ischemic stroke during childhood occurs most frequently in the perinatal period with an incidence of 1 out 2300–5000 live infant births [1–3]. The incidence is similar to that of adulthood and about 17 times greater than the first and second infancy [2]. AIS occurs even more frequently among preterm newborns. AIS refers to a distinct pattern of ischemic brain injury in arterial distribution that occurs during the prenatal, intrapartum, or neonatal period (Table 1) [1–3]. It can be subclassified according to different stages in fetal AIS; diagnosed before birth through the use of neuropathological examination that reveal a pattern of ischemic brain injury in an arterial distribution; neonatal with acute presentation of encephalopathy manifesting as seizure, altered mental status or neurological deficit between birth and the 29th postnatal day for which a pattern of ischemic brain injury in an arterial distribution is evident by clinical neuroimaging; and, presumed perinatal AIS which is diagnosed in individuals > 28 days of age with focal neurological deficits and a corresponding chronic infarct in arterial distribution in whom it is presumed (but not proven) that the ischemic injury occurred between the 20 week of fetal life through the 28 postnatal day but was not detected during that period [4, 5].

On the basis of the clinical features of AIS and neonatal age, two groups are distinguished: AIS in newborns, which

✉ Piero Pavone
ppavone@unict.it

[1] Department of Pediatrics, AOU Policlinico-Vittorio Emanuele, University of Catania, via S. Sofia 78, 95123 Catania, Italy

Table 1 Classification of prenatal, neonatal, or presumed perinatal AIS (1–3)

- Fetal: diagnosed before birth through the use of neuropathological examination that reveals a pattern of ischemic brain injury in an arterial distribution;
- Neonatal: acute presentation of encephalopathy manifesting as seizure, altered mental status or neurological deficit between birth and the 29th postnatal day for which a pattern of ischemic brain injury in an arterial distribution is evident by clinical neuroimaging;
- Presumed perinatal: it is diagnosed in individuals > 28 days of age with focal neurological deficits and a corresponding chronic infarct in arterial distribution in whom it is presumed (but not proven) that the ischemic injury occurred from 20 weeks of fetal life through 28 postnatal days but was not detected during that period.

occurs with neonatal seizures in 69–90% of full-term newborn babies with the first crisis usually occurring within the first 12 h and no later than the first 3 days of life and often associated with other symptoms as apnea, change in the level of consciousness, abnormal tone, feeding difficulties; and, in preterm infants in whom AIS may occur asymptomatic and be diagnosed by neuroradiologic examinations [6–8].

Although cerebral ultrasound is the most widely used method, it is not very sensitive in the diagnosis of ischemic lesions. Even CT cannot lead to the recognition of ischemic lesions, especially if the lesion is small and if the exam is performed in the first 24 h after the event. Moreover, CT scan should be avoided since expose the patient to significant amounts of radiation. MRI with T1-, T2-weighted, and DWI sequences is the gold standard for the diagnosis of AIS [9, 10].

Here, we report on 28 patients diagnosed and followed up at the Pediatric Clinic of the University of Catania, Italy, who presented in perinatal period ischemic stroke, at the aim to analyze risk factors, clinical data, and neurologic sequelae linked to this disorder.

Materials and methods

This retrospective study includes 28 patients followed up for neurological diseases at the Pediatric Clinic of the University of Catania, Italy, in the period between January 1996 and February 2015. The selected patients presented these inclusion criteria: presumptive diagnosis of perinatal stroke and early presentation of clinical symptoms (seizures), or late complications (such as hemiparesis and/or other neurologic impairments); neuroradiological investigations (CT scan or MRI scan), which highlighted the presence of vaso-occlusive pathology in the middle cerebral artery. Patients in whom there was evidence of hemorrhagic stroke, venous sinus thrombosis, cerebral malformations, meningoencephalitis, tumors, trauma, hematological diseases, metabolic diseases, and genetic syndromes were excluded from the study.

Of the 28 patients, the following parameters were evaluated: family and gestational history, gender, and type of clinical presentation, neurologic investigations, congenital, and acquired risk factors and outcome. Neuroradiological investigations include cerebral ultrasound, TC, MRI, and blood tests with metabolic screening, infectious and autoimmune diseases, coagulation, dosage of homocysteine, folate and vitamin B_{12}, and the genetic study for thrombophilia (Leiden's factor, G20210A mutation of factor II, polymorphisms of MTHFR gene and PAI1 gene).

Results

Among the 28 children, 14 (50%) were males and 14 (50%) were females. The average age at diagnosis were 20 months and 12 days (range 1 day–14 years), the average actual age was 9 years and 7 months (range 9 months–19 years). Family history displayed genetic mutations for thrombophilia in four patients (14%), in three stroke (10%), and in two cerebral aneurism (7%). Gestational history showed in six cases (21%) threats of abortion and in five (17%) pregnant hypertension or gestosis. In Table 2, the main clinical data of the patients are summarized. Twenty-one patients (75%) were born at term of pregnancy, 7 (25%) were born between 35 and 36 weeks. The average gestational age was 38 weeks. Twenty-four newborns weighed more than 2500 g (85%) and for less than 2500 g (15%). Seven preterm and four newborns presented with asphyxia at term. The clinical data showed in three newborns (10%), the onset of seizures appearing during the first 36 h. The crises were partial in one case and generalized in the other two. Eight children (28%) had seizures between 1 and 6 months of age, six (21%) between 6 and 12 months, and 11 beyond the first year of life. Seizures were partial in five children (17%), tonic clonic generalized in three (10%), in three cases (10%) West syndrome was diagnosed, and in two cases convulsions of complex febrile types. All 28 patients performed EEG every 6 months/1 year and typical EEG anomalies were reported in 11 patients (39%).

Regarding neuroradiological data, all 28 patients performed MRI, and in 12 patients angiographic study was conducted. In all the cases, the involvement of the middle cerebral artery emerged. The left branch was involved in 19 patients (68% of total cases). Among these 19 patients, 12 had occlusion of the main branch of the middle cerebral artery, while in 4 patients the terminal branches were occluded. The right middle cerebral artery was involved in 9 patients (32% of cases), almost always in the main branch (in a single case terminal branches were involved).

Overall assessment of the risk factors show that all 28 patients had at least one risk factor in their history. Table 3 resumes the presence of various risk factors which are

Table 2 Clinical data of the patients

ID	Sex	Gestational age	Asphyxia at birth	Weight at birth	Familial history	Gestational history	Diagnostic method	Age at diagnosis	Signs and symptoms at diagnosis	Current age (years)	Motor and cognitive state	Convulsive crisis	Onset of seizures
1	F	40	Yes	4000	–	Diabetes, threats of abortion	CT, MRI, angioM-RI	1 day	Neonatal convulsions	16	Right hemiplegia mental retardation	-Neonatal convulsions -West syndrome	6 months
2	F	40	Yes	3400	–	Gestational hypertension	MRI	5 months	Hemiplegia West syndrome	17	Right hemiplegia mental retardation	-Neonatal convulsions -West syndrome	5 months
3	F	39	No	3400	–	Infections	MRI, angio MRI	10 months	Hemiplegia	14	Right hemiplegia	Complex febrile convulsions	3 years
4	M	38	No	3400	–	Threats of abortion	MRI	6 months	Hemiplegia	11	Right hemiplegia	No	–
5	M	36	Yes	3500	Stroke	Gestosis	MRI, angio MRI	3 days	Generalized convulsive crisis	15	Right hemiplegia Mental retardation	No	–
6	M	40	No	3750	Cerebral aneurysm	Threats of abortion	MRI	3 years	Hemiplegia	14	Right hemiplegia	No	–
7	M	40	Yes	3100	–	–	MRI, angio MRI	6 months	Hemiplegia	19	Right hemiplegia mental retardation behavioral disorder	Partial epilepsy	8 years
8	F	40	No	2900	Multiple sclerosis	–	MRI	9 months	Hemiplegia	18	Left hemiplegia Mild mental retardation	Partial epilepsy	3 years
9	F	36	No	2020	Genetic thrombophilia	oligohydramnios	MRI	6 months	West syndome	15	Right hemiplegia	West syndrome	6 months
10	F	40	Yes	3550	Stroke	–	MRI, angioM-RI	4 years	Hemiplegia	12	Mild hemiplegia	No	–
11	F	40	No	2300	–	IUGR	MRI	1 months	Coagulopathy	10	Right hemiplegia	No	–
12	F	40	No	3010	–	–	MRI, angioM-RI	12 months	Hemiplegia	8	Left hemiplegia	No	–
13	F	40	No	3180	Not available	Not available	MRI, angioM-RI	16 months	Hemiplegia	8	Right hemiplegia attention deficit	Partial epilepsy	4 years
14	F	35	Yes	3360	Genetic thrombophilia	Threats of abortion	MRI	3 days	Generalized convulsive crisis	7	Right hemiplegia Behavioral disorder	Generalized epilepsy	5 months
15	M	36	Yes	2510	–	Gestosis, diabetes	MRI	5 months	Hemiplegia	6	Right hemiplegia, mild mental retardation	Partial epilepsy	2 years
16	M	38	No	3220	–	–	MRI	16 months	Hemiplegia	7	Left hemiplegia	No	–
17	F	38	No	3180	Cerebral aneurysm	Threats of abortion	MRI, angioM-RI	7 months	Hemiplegia generalized convulsive crisis	8	Left hemiplegia mental retardation	Generalized epilepsy	7 months
18	M	40	No	3600	–	–	MRI	3 years	Hemiplegia	6	Right hemiplegia	No	–

Table 2 (continued)

ID	Sex	Gestational age	Asphyxia at birth	Weight at birth	Familial history	Gestational history	Diagnostic method	Age at diagnosis	Signs and symptoms at diagnosis	Current age (years)	Motor and cognitive state	Convulsive crisis	Onset of seizures
19	M	36	Yes	2650	Hypertension	Threats of preterm delivery	MRI	14 years	Hemiplegia	17	Right hemiplegia	No	–
20	M	40	No	3450	–	–	MRI	6 years	Hemiplegia partial epilepsy	10	Right hemiplegia	Partial epilepsy	7 years
21	M	40	No	3300	–	–	MRI	2 years	Hemiplegia	6	Left hemiplegia hyperactivity	No	–
22	M	36	No	1950	–	Gestosis	MRI, angioMRI	9 months	Hemiplegia	3	Left hemiplegia	No	–
23	M	38	Yes	2800	Stroke	–	MRI, angioMRI	2 years	Hemiplegia	10	Right hemiplegia	No	–
24	F	36	Yes	2660	Genetic thrombophilia	Twin pregnancy, Intrauterine death according to foetus	MRI	5 months	Hemiplegia	4	Left hemiplegia	No	–
25	M	40	No	3375	Genetic thrombophilia febrile convulsions	–	MRI, angioMRI	13 months	Hemiplegia	3	Right hemiplegia mental retardation	No	–
26	F	38	No	2480	–	IUGR	MRI, angioMRI	9 months	Hemiplegia	2	Right hemiplegia	No	–
27	M	40	No	3000	Mental retardation epilepsy, febrile convulsions	–	MRI	2 years	Hemiplegia	4	Left hemiplegia	Febrile convulsions	6 months
28	F	37	Yes	2770	–	Gestosis, gestational diabetes	MRI	3 months	Occasional diagnosis With cerebral ultrasonography	0.75	Left hemiplegia	No	–

Table 3 Congenital and acquired risk factors

ID	sex	Familial history	Gestational history	Placental pathologies	Intrapartum factors	Antiphospholipid antibodies	Anticoagulant proteins	G1691A proteins	G20210A Leiden	PAI-1 4G	MTHFR mutations	Homocysteine folate vitamin B12	No factors
1	F	–	Diabetes, threats of abortion	–	Asphyxia at birth	Negative	Normal	Negative	Negative	Homozygous 4G / 4G	Heterozygous A1298C	Normal	5
2	F	–	Gestational hypertension	–	Asphyxia at birth	Negative	Partial protein C deficiency	Negative	Negative	Heterozygous 4G / 5G	Homozygous C677T	Normal	5
3	F	–	Infections	–	–	Negative	Normal	Negative	Negative	Negative	Homozygous C677T	Normal	2
4	M	–	Threats of abortion	–	–	Negative	Normal	Negative	Negative	Homozygous 4G / 4G	Heterozygous A1298C	Normal	3
5	M	Stroke	Gestosis	–	Asphyxia at birth	Negative	Normal	Negative	Negative	Homozygous 4G / 4G	Heterozygous C677T	Normal	5
6	M	Cerebral Aneurysm	Threats of abortion	–	–	Negative	Normal	Negative	Negative	Negative	Homozygous C677T	Normal	3
7	M	–	–	–	Asphyxia at birth	Negative	Normal	Negative	Negative	Negative	Heterozygous A1298C	Normal	2
8	F	Multiple sclerosis	–	–	–	Negative	Normal	Negative	Negative	Negative	Homozygous C677T	Normal	2
9	F	Genetic thrombop-hilia	Oligohydramnios	–	–	Negative	Normal	Negative	Negative	Homozygous 4G / 4G	Heterozygous A1298C/ C677t	Normal	4
10	F	Stroke	–	–	Asphyxia at birth	Negative	Normal	Negative	Heterozygous G20210A	Homozygous 4G / 4G	Homozygous C677T	Normal	5
11	F	–	IUGR	–	–	Negative	Partial protein C deficiency	Negative	Negative	Heterozygous 4G / 5G	Negative	Normal	3
12	F	–	–	–	–	Negative	Normal	Negative	Negative	Heterozygous 4G / 5G	Homozygous C677T	Normal	2
13	F	Not available	Not available	–	–	Negative	Normal	Negative	Negative	Negative	Heterozygous C677T	Normal	1
14	F	Genetic thrombop-hilia	Threats of abortion	–	Asphyxia at birth	Negative	Partial protein C deficiency	Negative	Negative	Negative	Homozygous C677T- Heterozygous A1298C/- WT	Normal	5
15	M	–	Gestosis, diabetes	–	Asphyxia at birth	Negative	Partial protein C deficiency	Negative	Negative	Negative	Heterozygous C677T	Normal	5
16	M	–	–	Placental insuffi-ciency	–	Negative	Not available	Not available	Not available	Not available	Not available	Not available	1
17	F	Cerebral aneurysm	Threats of abortion	–	–	Negative	Normal	Negative	Negative	Negative	Negative	Normal	2
18	M	–	–	–	–	Negative	Normal	Negative	Negative	Negative		Normal	1

Table 3 (continued)

ID	sex	Familial history	Gestational history	Placental pathologies	Intrapartum factors	Antiphospholipid antibodies	Anticoagulant proteins	G1691A proteins	G20210A Leiden	PAI-1 4G	MTHFR mutations	Homocysteine folate vitamin B12	No factors
											Homozygous C677T		
19	M	Hypertension	Threats of preterm delivery	Placental pathology	asphyxia at birth	Negative	Normal	Negative	Negative	Heterozygous 4G / 5G	Heterozygous C677T	Normal	6
20	M	–	–	–	–	Negative	Partial protein C deficiency	Not available	Not available	Not available	Not available	Not available	1
21	M	–	–	Partial posting of placenta	–	Negative	Normal	Negative	Negative	Heterozygous 4G / 5G	Homozygous C677T	Normal	3
22	M	–	Gestosis	–	–	Negative	Normal	Negative	Negative	Negative	Heterozygous C677T	Normal	2
23	M	Stroke	–	–	Asphyxia at birth	Negative	Partial protein S deficiency	Negative	Negative	Negative	Heterozygous A1298C	Normal	4
24	F	Genetic thrombop-hilia	Twin pregnancy, intrauterine death according to fetus	–	Asphyxia at birth, meconi-um aspiration	Negative	Normal	Not available	Not available	Not available	Not available	Not available	4
25	M	Genetic thrombop-hilia febrile convul-sions	–	Partial posting of placenta	–	Negative	Normal	Negative	Negative	Heterozygous 4G / 5G	Heterozygous A1298C/ C677T	Normal	5
26	F	–	IUGR	Partial posting of placenta	–	Negative	Normal	Heterozygous H1299R	heterozygous G20210A	Homozygous 4G / 4G	Homozygous C677T	Normal	6
27	M	Mental retardation epilepsy, febrile convul-sions	–	–	–	Not executable	Normal	Heterozygous H1299R	Negative	Heterozygous 4G / 5G	Heterozygous C677T	Not executable	6
28	F	–	Gestosis, gestational diabetes	–	Asphyxia at birth	Anti beta2 glycoprotein positive	Partial protein C deficiency	Negative	Negative	Homozygous 4G / 4G	Heterozygous C677T	Normal	7

distinguished into congenital and acquired. From the complete coagulation evaluation (PT, aPTT, fibrinogen, antitrombine III, S protein, C protein), it was found that 5 patients had a partial C protein deficit, with values around 35–50% (normal values70–140%), and only one had a partial protein S deficiency with values around 47% (normal values 54.7–123.7%). The antiphospholipid antibodies dosing was not very significant, as it was found in all patients within normal limits, with the exception of one patient whose dose was positive for antibodies to anti β2-glicoprotein I IgG. In two patients (a 4-year-old male and a 2-year-old female), the status of heterozygosis for the HR2 haplotype of the V factor was found (H1299R, A→G al nucleotide 4070),considered a cause of thrombosis, especially if associated with double heterozygosis to the V factor mutation Leiden (G1691A), not found in our patients. As regards the prothrombin gene, it was positive for the mutation G20210A in heterozygosis in two patients. The gene most affected by polymorphisms is that of the enzyme MTHFR, involved in 23 patients (82%). Two mutations have been studied: C677T and A1298C. Eight subjects were identified who presented the C677T mutation in homozygosis (29% of cases), and 7 in heterozygosis (25%). The A1298C mutation was found in a rarer percentage of cases; 4 patients presented it in heterozygosis and only one in homozygosis. Three patients were compound heterozygous (C677T/A1298C).

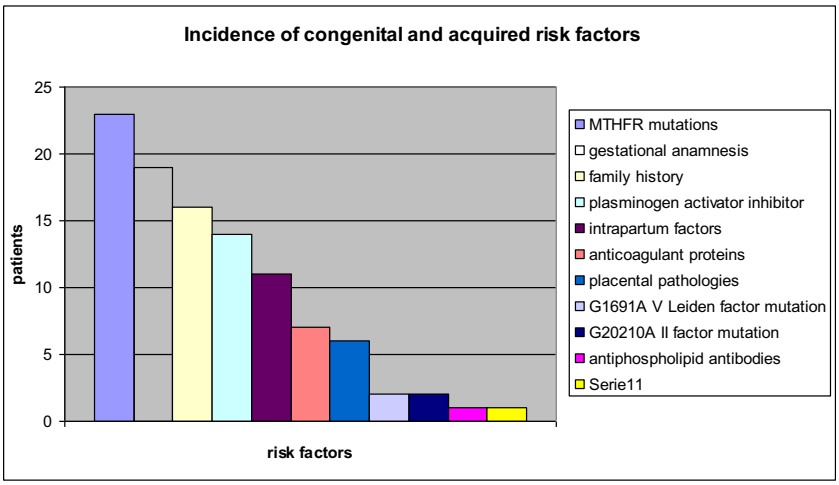
Also, mutations of the type 1 plasminogen activator inhibitor gene have been found in a relevant percentage of cases (50%, 14 patients). Seven patients presented homozygosis 4G/4G (25%), the other seven were heterozygous 4G/5G (25%).

The dosage of homocysteinemia by HPLC did not show values higher than normal (normal values < 14–15 μmol/l), and folates and vitamin B_{12} dosage, also result within the normal range. The most represented factor is the mutations of the MTHFR (23 patients) (graph 1), followed by pregnancy anomalies (19 patients), positive family history (16 patients), PAI-1 mutations (14 patients), and intrapartum factors (11 patients). The other data were present in fewer cases. Moreover, more than half of our patients had a positive history for more than three risk factors (18 patients, 64% of cases). Finally, in two cases, the diagnosis was occasional by coagulation anomalies and abnormality at fontanellar ultrasound.

Complications of AIS in the group of patients were very high. The evaluation of long-term psychomotor and cognitive development showed the presence in all patients of hemiplegia. In 5 patients (18%), motor defect was mild and involved upper or lower limb. In some cases, the motor deficits were associated with mild or moderate developmental delay or intellectual disability, (8 patients, 29% of the total). In 4 children (14%), behavioral disorders (DOC or ADHD) were also observed.

Discussion

The growing attention of the scientific community towards the perinatal arterial ischemic stroke and closely linked to a greater understanding of the importance of this pathology as a cause of cerebral palsy, disability and permanent morbidity. Data from the main epidemiological studies of recent years agree to identify the stroke as the most frequent cause of hemiplegia [11]. With regard to epidemiological data, 28 patients with a precise numerical equality were selected in our case by female and male subjects. We cannot therefore report a prevalence of sex, contrarily to what is reported in many scientific studies that document a greater frequency of the event in male subjects [12–14]. In the study of Golomb et al. [11], conducted on a cohort of 1187 patients, affected by both arterial and venous stroke at different ages (0–19 years), the study has shown a prevalence in male sex (60%), also in relation to stratification by age (61% of 341 subjects with perinatal ischemic stroke), and subtypes (58% of arterial ischemic stroke,



Graph 1 Incidence of congenital and acquired risk factors

65% of the thrombosis of the venous sinuses). The highest percentage of males was seen among children with arterial ischemic stroke history and trauma [11].

Family history may be suggestive for the diagnosis of stroke as we found parental cases of stroke in three, cerebral aneurism in two and genetic thrombophilia in four patients. Regarding maternal risk factors, in 68% of cases of our study, the pregnancy had a non-physiological course (threats of abortion or preterm birth, gestosis, gestational diabetes, placental diseases and IUGR). A study of Wu et al. [15], on a series of 38 patients with perinatal arterial ischemic stroke with motor defects, concluded that preeclampsia and IUGR can increase the risk of stroke in term or "near-term." Golomb et al. showed that in their case series, most patients had a positive maternal and gestational anamnesis for preeclampsia, infections, gestational diabetes, or threats of abortion [13].

From a clinical point of view, several scientific studies divide patients with perinatal arterial ischemic stroke into two groups: in a smaller group, the diagnosis is placed early because of the onset of acute signs and symptoms in the first days after birth (neonatal arterial ischemic stroke). In the other larger group, the diagnosis is made retrospectively for the onset of symptoms after the first month of post-natal life (presumed perinatal arterial ischemic stroke). Our case studies, in agreement with international studies, have supported the thesis that most cases have a late presentation. In only 3 cases, the stroke were diagnosed within the 28th day of life, with partial or generalized seizures. In the remaining 25 (89%), eight children (28%) had seizures between 1 and 6 months of age, six (21%) between 6 and 12 months, and 11 beyond the first year of life. The clinical presentation started mainly with variable strength deficits (contralateral hemiparesis to the encephalic lesion in the 76% of cases) and/or epileptic episodes (12%). In one patient, the diagnosis was made following the onset at the age of the 6 months of life of convulsions with a diagnosis of infantile spasms associated with an hypsarrhythmic EEG recording in the absence of recognizable motor deficit. Finally, in two children, the diagnosis was occasional, at 1 and 3 months of life, following the finding of coagulation abnormalities and cerebral ultrasound abnormalities, respectively. The causes of diagnostic delay are related to the absence of relevant symptoms up to a certain period of life. The reason why some children are symptomatic at birth, while others do not is still unknown. According to some authors, the hypothesis would be that in these last subjects the cerebrovascular event could have occurred before delivery, in uterus, and that, therefore, in these children could be established unknown mechanisms of vascular compensation [16]. Finally, about the relationship with epilepsy, out of the 13 affected children (43%), six presented with drug-resistant epilepsy and two with West syndrome. According to literature, the data of study state that perinatal arterial ischemic stroke is a phenomenon that occurs more frequently in term or "late preterm" newborns. In fact, in our series, 75% of the subjects were born at term of pregnancy, 25% were born between 35 and 36 weeks of gestation, with an average age of 38 weeks. In the same way, studies carried out on international or European series affirm that the average gestational age is between 39 and 40 weeks of gestation (range 36–42 weeks) [6, 14]. Birth weight is adequate for the gestational age in most of the cases, as was reported in our cohort (84% vs 14%).

All of the patients in our study performed brain-MRI, including MRI angiography in 12 of them (Fig. 1). Neuroimaging examinations showed the exclusive involvement of the middle cerebral artery in all 28 patients in its main branch or in its terminal branches. The left hemisphere was the most affected, with radiological findings of thrombosis or its outcomes in the territories vascularized by the left middle cerebral artery (68% of cases vs 32%). These data are in agreement with those obtained from other studies, which agree that, in all subclasses of perinatal arterial ischemic stroke, in most cases, the vascular damage is unilateral and involves the left hemisphere in the territory of average cerebral artery [16–18]. In a case series, Lee et al. [2]. found that in 87% of cases, the event is unilateral; in 53%, it involves the left middle cerebral artery; while in 35%, the right one [7]. About the affected hemisphere, there was a predominance of 70% for the left, with involvement of the average cerebral artery in 90% of cases [13, 15]. This predominance could be explained in part by the presence of the Botallo duct, responsible for the passage of the thrombus in the left vascular circle with consequent achievement of the cerebrovascular district and a vascular asymmetry linked to the anatomical position of the left common carotid or a different degree of maturation and vulnerability of the left hemisphere with respect to the right one [19, 20].

The pathogenetic mechanism of perinatal AIS is vasal occlusion, due to a thrombus or an embolus from the intra or extracranial vessels, from the heart or from the placenta. Most of the authors observe the presence of congenital risk factors in more than half of the studied population with an incidence of 42 to 72%. Gunther et al. [21] showed that the percentage of thrombotic risk factors in patients with arterial ischemic stroke was higher compared to a homogeneous control group for age and sex without thrombotic events (68% vs 24%). Mercuri et al. [22] and Suppiey et al. [23] have shown association to congenital risk factors and neurological outcome. In this study, in 25 patients (89%), the presence of at least one risk factor was observed: the polymorphisms of the enzyme MTHFR gene were the most frequent (82%), in accordance with many other works in the literature [24–27]. The second congenital prothrombotic factor in our population was the mutation of the (PAI-1) gene. The role of this mutation in determining the stroke is still little known. Lynch et al. [26] suggest that the presence of the 4G allele of the PAI-1 may be associated with increased ischemic risk. This risk factor would

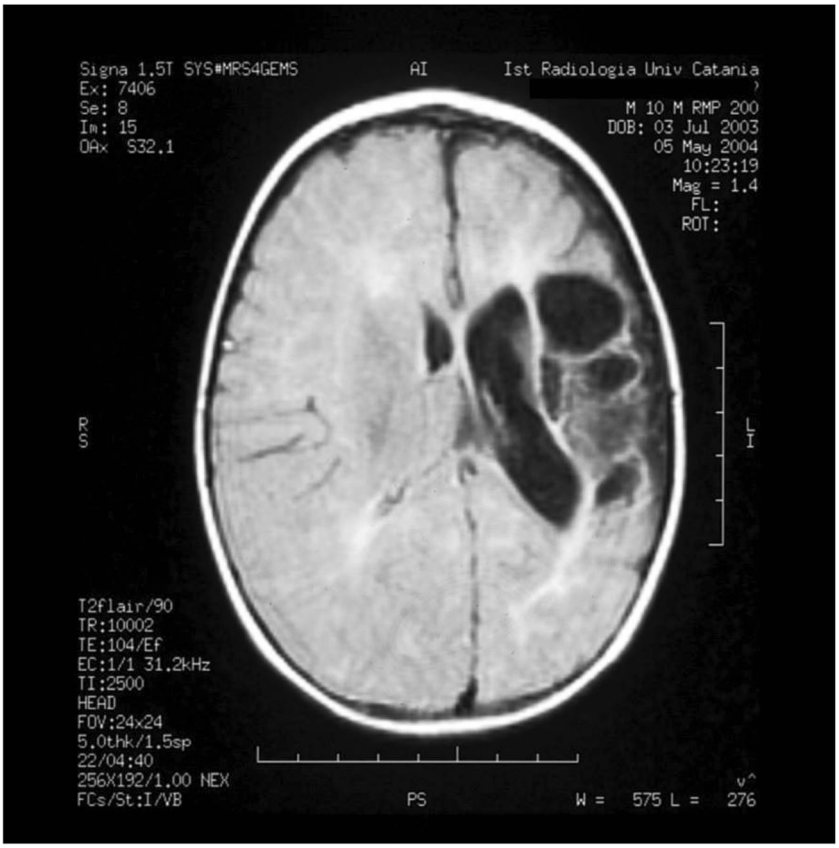


Fig. 1 MRI, porencephalic cyst of the left cerebral hemisphere

act by increasing the activity of plasminogen which is however influenced by many other factors. In 2008, first guidelines (followed by latest updates) for management and treatment of perinatal stroke were published [28, 29]. As regards the prothrombotic risk factors, in the newborns, a physiological hypercoagulability status is observed (low levels of antithrombin, protein C, protein S, tissue plasminogen factor inhibitor, with high values of hemoglobin, fetal proteins) [30] and in this state of hypercoagulability, other risk factors can be act in association. This supports the hypothesis that perinatal arterial ischemic stroke is associated with a combination of different predisposing conditions, both congenital and acquired.

The guidelines for the American Heart Association's ischemic stroke [31] show that, in the acute phase, support measures such as hydration, anticonvulsants, and antibiotics may be important, while thrombolysis is not recommended because neither its efficacy nor his safety has been demonstrated. In cases of venous sinus thrombosis (SVT), heparin treatment is recommended only in neonates with severe thrombophilic disorders that might cause multiple systemic or cerebral emboli despite supportive therapy. After the acute phase, anticoagulant or antiplatelet therapies are not recommended, given the low rate of recurrence of the disease; use is suggested only if a second thromboembolic event occurs. Lehman et al. [32] identified all pediatric strokes for residents of the GCNK region that occurred in July 1, 1993–June 30, 1994, and calendar years 1999, 2005, and 2010. Stroke cases were ascertained by screening discharge ICD-9 codes, and verified by a physician. Pediatric stroke was defined as stroke in those < 20 years of age. Stroke rates by study period, overall, by age and by race, were calculated. Eleven children died within 30 days, yielding an all-cause case fatality rate of 15.7% (95% confidence interval 1.1%, 26.4%) with 3 (27.3%) ischemic, 6 (54.5%) hemorrhagic, and 2 (18.2%) unknown stroke type. The pediatric stroke rate of 4.4 per 100,000 in the GCNK study region has not changed over 17 years [32].

In accordance with the guidelines, the patients of the present study were not treated and are not currently being treated with anticoagulants or antiplatelet agents.

Complications were common in our group of patients. Twenty-eight showed hemilateral cerebral palsy involving 18 in the right side and 9 in the left. In seven developmental delay and intellectual disability ranging from mild to severe, two and six cases, respectively. Twelve patients suffered by epileptic seizures with EEG abnormalities consisting of slow waves or focal-wave complexes of focal types in 17 patients. Death after neonatal AIS is uncommon. The mortality rate after neonatal AIS is 0.16 per 100.000 live births, [2, 21]. Long-term sequelae from neonatal AIS can include motor, cognitive, or behavioral difficulties, as well as epilepsy. AIS is the most identified cause of congenital hemiplegia. More

than 80% of infants with AIS have hemiparesis and/or language, vision, cognition, and behavior deficits that occur in 20 to 60% of AIS survivors. The most common long-term neurological sequelae is represented by hemiplegia, which is present in 50–75% of cases [1]. Between 38 and 46% of neonates with AIS will develop epilepsy and in 15% of cases develops drug-resistant epilepsy [3–17]. Treatment of perinatal AIS in the acute setting has been largely supportive and symptomatic. Data are lacking to support prophylactic treatment with an antithrombotic after stroke in neonates [1–3].

Conclusions

In relation to our retrospective study and literature review, we can state that perinatal arterial ischemic stroke is an entity, still in many ways unknown and controversial, which is of considerable importance as a cause of permanent disability and morbidity. Thrombophilic screening is essential to identify thromboembolic risk groups and to define appropriate prevention and treatment strategies.

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Compliance with ethical standards

Conflicts of interest There are no conflicts of interest.

References

1. Lehman LL, Rivkin MJ (2014) Perinatal arterial ischemic stroke: presentation, risk factors, evaluation and outcome. Pediatr Neurol 51(6):760–768
2. Lee J, Croen LA, Backstrand KH et al (2005) Maternal and infant characteristics associated with perinatal arterial stroke in the infant. JAMA 293:723–729
3. Raju TNK, Nelson KB, Ferriero D, Lynch JK (2007) 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 120:609–616
4. Lynch JK, Hirtz DG, deVeber G, Nelson KB (2002) Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. Pediatrics 109:116–123
5. Grinnon ST, Miler K, Marler JR et al (2012) National Institute of neurological disorders and stroke common data element project-approach and methods. Clin Trials 9:322–329
6. Nelson KB, Lynch JK (2004) Stroke in newborn infants. Lancet Neurol 3:150–158
7. Wu YW, Linda CE, Henning LH et al (2006) Neuroimmaging abnormalities in infants with congenital hemiparesis. Pediatr Neurol 35:191–196
8. Osler W (1987) The cerebral palsies of children. Mac Keith Press. Blackwell Scientific Publications, Oxford
9. Freud S (1968) Infantile cerebral paralysis. University of Miami Press, Coral Gables
10. Bremme KA (2003) Haemostatic changes in pregnancy. Best Pract Res Clin Haematol 16:153–168
11. Golomb MR, Fullerton H, Nowak-Gottl U, deVeber G (2009) International pediatric stroke study group. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke 40:52–57
12. Silvey M, Carpenter SL (2013) Inherited thrombophilia in children. Curr Probl Pediatr Adolesc Health Care 43:163–168
13. Golomb MR, Dick PT, MacGregor DL, Curtis R et al (2004) Neonatal arterial ischemic stroke and cerebral sinovenous thrombosis are more commonly diagnosed in boys. J Child Neurol 19:493–497
14. Darmercy-Stamboul V, Chantegret C, Ferdynus C et al (2012) Antenatal factors associated with perinatal arterial ischemic stroke. Stroke 43:2307–2312
15. Wu YW, March WM, Croen LA, Grether JK (2004) Perinatal stroke in children with motor impairment: a population-based study. Pediatrics 114:612–619
16. Golomb MR, MacGregor DL, Domi T et al (2001) Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcome. Ann Neurol 50(2):163–168
17. Benders MJ, Groenendaal F, Uiterwaal CS et al (2007) Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. Stroke 38:1759–1765
18. Harteman JC, Groenendal F, Kwee A et al (2012) Risk factors for perinatal arterial ischemic stroke in full-term infants: a case-control study. Arch Dis Child Fetal Neonatal Ed 97:411–416
19. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, Ferriero D, Jones BV, Kirkham FJ, Scott RM, Smith ER, American Heart Association Stroke Council, Council on Cardiovascular Disease in the Young (2008) Management of stroke in infants and children: a scientific statement from a special writing group of the American Hearth Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke 39:2644–2691
20. Jaigobin C, Silver FL (2000) Stroke and pregnancy. Stroke 31: 2948–2951
21. Gunther G, Junker R, Strater R et al (2000) Symptomatic ischemic stroke in full-term neonates: role of acquired and genetic prothrombotic risk factors. Stroke 31:2437–2441
22. Mercuri E, Cowan F, Gupte G, Manning R, Laffan M, Rutherford M, Edwards AD, Dubowitz L, Roberts I (2001) Prothrombotic disorders and abormal neurodevelopmental outcome in infants with neonatal cerebral infarction. Pediatrics 107:1400–1404
23. Suppiej A, Franzoi M, Gentilomo C et al (2008) High prevalence of inherited thrombophilia in 'presumed peri-neonatal' ischemic stroke. Eur J Haematol 80:71–75
24. Kocaman C, Yilmaz Y (2012) Etiological analysis of presumed perinatal stroke. Brain Dev 34:133–139
25. Del Balzo F, Spalice A, Ruggieri M, Greco F et al (2009) Stroke in children: inherited and acquired factors and age-related variations in the presentation of 48 paediatric patients. Acta Paediatr 98:1130–1136
26. Lynch JK, Han CJ, Nee LE, Nelson KB (2005) Prothrombotic factors in children with stroke or porencephaly. Pediatrics 116:447–453

27. Rook JL, Nugent DJ, Young G (2005) Pediatric stroke and methylenetetrahydrofolate reductase polymorphisms: an examination of C677T and A1298C mutations. J Pediatr Hematol Oncol 27:590–593
28. De Moerloose P, Boehlen F (2007) Inherited thrombophilia in arterial disease: a selective revue. Semin Hematol 44:106–113
29. Monagle P, Chalmers E, Chan A et al (2008) Antithrombotic therapy in neonates and children: American College of Chest Physicians Evidence-based Clinical Practice Guideline (8th edition). Chest 133:887S–968S
30. Saxonhouse MA, Manco-Jhonson MJ (2009) The evaluation and management of neonatal coagulation disorders. Semin Perinatol 33:52–65
31. Callaghan WM, MacDorman MF, Shapiro-Mendoza CK, Barfield WD (2017) Explaining the recent decrease in US infant mortality rate, 2007–2013. Am J Obstet Gynecol 216(1):73.e1–73.e8. https://doi.org/10.1016/j.ajog.2016.09.097
32. Lehman LL, Khoury JC, Taylor JM, Yeramaneni S, Sucharew H, Alwell K, Moomaw CJ, Pearlso K, Flaherty M, Khatri P, Broderick JP, Kissela BM, Kleindorfer DO (2018) Pediatric stroke rates over 17 years: report from a population-based study. J Child Neurol 33(7):463–467