Original article

Perinatal stroke: a six-year experience in a level-III maternity

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Abstract

Aims: To study the incidence of perinatal stroke in a level-III maternity as well as potential risk factors, clinical presentation, neuroimaging, classification and clinical outcome of children with a minimum follow-up of 24 months.

Methods: Historical prospective follow-up of all term and late preterm newborns diagnosed with perinatal stroke from January 2008 to December 2013.

Results: Fifteen perinatal strokes were diagnosed in a total of 17,056 newborns (incidence 0.9/1,000). Thirteen had potential risk factors and fourteen were symptomatic. Median age at diagnosis was two days. Seizures were the most frequent symptom (14/15), being three focal-clonic, one multifocal-clonic, two generalized-tonic, three focal-tonic and five subtle. Cerebral ultrasound was performed in eleven newborns at an early stage, suggesting the diagnosis in six. Cerebral magnetic resonance imaging (MRI) confirmed the diagnosis in fifteen. Six had an arterial ischemic stroke, eight a cerebral venous thrombosis and one a hemorrhagic stroke. An electroencephalogram was obtained in all newborns with seizures revealing epileptic activity in eight. Search for prothrombotic disorders (in newborn and both parents) showed four newborns heterozygous methylene tetrahydrofolate reductase mutation and two neonatal alloimmune thrombocytopenia. No recurrence of stroke was reported. Formal development evaluation was performed in thirteen and was normal in eleven, while in two revealed delayed psychomotor development, both of which with epilepsy. On the neonatology outpatient clinic follow-up, the current median age is 3 years and 11 months.

Conclusions: This study reinforces the need to maintain high level of suspicion for perinatal stroke and the importance of MRI in the classification and etiological study. Our follow-up supported a good outcome of perinatal stroke.

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Introduction

Perinatal stroke can be defined as an acute neurologic syndrome due to cerebral injury of vascular origin occurring between 20th week of gestation and day 28th of postnatal life [1, 2]. Three subcategories were defined, incorporating the timing of the condition. "Fetal ischemic stroke" is diagnosed before birth using fetal imaging methods. "Neonatal stroke" is diagnosed after birth and before day 28th postnatal. "Presumed perinatal stroke" is diagnosed in infants with more than 28 days of life in whom it is presumed, but not certain, that the stroke occurred sometime from 20th week of gestation through day 28th postnatal [3-5]. Also, there are three major clinical-anatomic subtypes: arterial ischemic stroke, hemorrhagic stroke, and cerebral venous thrombosis [3-5].

Perinatal stroke is not rare. In fact, stroke is 17 times more common in the perinatal period than later in childhood or beyond [6]. The usual distribution of the different types of stroke are: 70% arterial ischemic, 20% hemorrhagic and 10% cerebral venous thrombosis [4, 5]. Despite the results published concerning incidence, it is likely to be underestimated as it is largely based on retrospective cohort studies.

The etiology is complex and multifactorial with many potential risk factors being described. Maternal, placentar, fetal/neonatal and delivery risk factors are present in up to 75% of cases [4]. Age of diagnosis depends on stroke location. The most common presenting clinical signs are seizures, altered mental status and abnormal tone. Others may present hemiparesis or even respiratory and feeding difficulties [7].

In relation to diagnosis, magnetic resonance imaging (MRI) is the most sensitive imaging modality for detection of stroke and is therefore the goal standard [8]. As recurrence rates are low, treatment of perinatal stroke has been largely supportive. Few data exist about the use of anticoagulation therapy after stroke [9, 10].

Outcomes of perinatal stroke are generally poor, being the most common cause of hemiparetic cerebral palsy and other additional sequelae, including intellectual disabilities, developmental and behavioral disorders, and epilepsy. Children with perinatal stroke are considered to grow into their deficits when specific developmental stages are reached [11].

Aims

The purpose of this study was to determine the incidence of perinatal stroke in a level-III maternity as well as potential risk factors, clinical presentation, neuroimaging, lesion classification and clinical outcome of children with a minimum follow-up of 24 months.

Patients and methods

For the current historical prospective study, full-term and late pre-term newborns (≥ 34 gestational week) admitted to the neonatal unit of Hospital de Braga with a stroke diagnosed during the first 28 days of life and confirmed by neuroimaging between January 2008 and December 2013 were included. Follow-up consisted of a structured neurologic and developmental assessment (Schedule of Growing Skills II, Wechsler Intelligence Scale for Children or Griffiths Mental Development Scales). Exclusion criteria were hypoxic-ischemic encephalopathy with criteria for therapeutic hypothermia and/or posterior diagnosis of an inborn error of metabolism. The incidence of stroke diagnosis was calculated based on the Hospital de Braga statistical office (number of perinatal stroke in relation to births during the study period). Results are presented with descriptive statistics.

Results

Fifteen perinatal strokes were diagnosed during this period (incidence of 0.9/1,000). The sex ratio was 8:7 (F:M) and mean duration of hospitalization was 16.4 days (minimum of 7 days, maximum of 51 days).

Potential risk factors were present in thirteen newborns. Maternal and placentar risk factors included one case of infertility, nine primipara women, four with advanced maternal age (≥ 35 years), five maternal thrombocytopenia and two gestational diabetes. Fetal and perinatal risk factors were one intrauterine growth restriction, presence of meconium in the amniotic fluid in two, need of early neonatal resuscitation in one and two newborns with patent foramen ovale. In this series, there were seven dystocic deliveries. The median gestational age was 38 weeks and there were two cases of premature delivery at week 34 and 35 of gestation. Risk factors are summarized on **Tab. 1**. Of the fifteen newborns, fourteen were symptomatic presenting seizures. Only one had an incidental diagnosis which occurred during the study of a suspected cranial fracture (patient 9, **Tab. 2**). Seizures were classified as subtle in five, focal clonic in one, subtle and focal clonic in two, subtle and generalized tonic in one, multifocal clonic in one, generalized tonic in one and focal tonic in three newborns. Nine were hypotonic. Other presenting symptoms were irritability in two, feeding difficulties in two and hemiparesis in one newborn. The mean age of diagnosis was 3.1 days (standard deviation of 3.9 days).

Cranial ultrasound was performed at an early stage in eleven of the fourteen newborns with seizures, being unremarkable in five and altered in six. Cranial ultrasound revealed abnormal features in one hemorrhagic stroke (right temporo-occipital parenchymal hematoma), one ischemic stroke (left supratentorial hypoxic-ischemic lesion) and in four cerebral venous thrombosis (subependymal hemorrhage, left thalamic hematoma, right fronto-parietal hypoxic-ischemic lesion, intraventricular hemorrhage). The remaining four patients performed an MRI as first workup exam. Overall, MRI was performed in all cases (T1, T2 and diffusion-weighted imaging), complemented with gadolinium venography when cerebral venous thrombosis was suspected. It was successfully performed using chloral hydrate and allowed to diagnose six arterial ischemic strokes (two with hemorrhagic transformation and three showing evidence of wallerian degeneration), one hemorrhagic stroke and eight cerebral venous thromboses (seven with hemorrhagic transformation) (**Figures 1-4**). Regarding the arterial ischemic strokes, the middle cerebral artery was affected in four and the posterior cerebral artery in two, being all strokes cortico-subcortical. The newborn with hemorrhagic stroke

Table 1. Risk factors.

|	Sex	GA	Potential risk factor						
			MA	Primiparity	Placenta/AF	Delivery	Resuscitation	Apgar score	Other
1	F	37	36	N	-	Eutocic	-	9/10	+AP Mab; MT
2	M	34	33	Y	Meconium	Cesarian	-	9/10	Gestational diabetes
3	F	38	32	Y	-	Eutocic	-	9/10	Patent FO; MT
4	M	41	34	Y	-	Ventouse	-	8/10	MT
5	M	38	25	N	-	Eutocic	-	9/10	N
6	F	37	33	Y	-	Eutocic	-	9/10	IUGR
7	F	38	42	N	-	Cesarian	-	10/10	+AP Mab; MT
8	F	35	39	Y	-	Eutocic	-	9/10	H – MTHFR
9	F	38	32	Y	-	Cesarian	-	8/9	Infertility
10	M	40	34	N	-	Forceps	-	9/10	H – MTHFR; patent FO
11	F	41	34	Y	-	Cesarian	-	10/10	N
12	F	39	42	N	-	Eutocic	-	10/10	Gestational diabetes; MT
13	M	41	24	Y	-	Eutocic	+	6/10	H – MTHFR
14	M	38	19	Y	Meconium	Cesarian	-	8/10	N
15	M	39	17	N	-	Eutocic	-	8/10	H – MTHFR

F: female; M: male; GA: gestational age; MA: maternal age; N: no; Y: yes; AF: amniotic fluid; +AP Mab: positive anti-platelet maternal antibody; MT: maternal thrombocytopenia; FO: foramen ovale; IUGR: intra-uterin growth restriction; H – MTHFR: heterozygotic MTHFR. Patients identification number corresponds to the number in **Tab. 2** and in **Figures 2-5**.

Table 2. Description of patients.

Patient	Type of stroke	Seizure	Clinical presentation			Neuroimaging	
			Bradycardia	Tone	Other	Transfontanellar US	Vascular territory
1	I → H	Subtle	Y	Hypotonic	-	Normal	MCA – L
2	T → H	Subtle + Focal clonic	N	Hypertonic	Irritability + Diabetes insipidus	Subependymal hemorrhage	Superior longitudinal and left transverse VST
3	T → H	Subtle + Generalized tonic	Y	Hypertonic	-	Left thalamic hematoma	Left thalamic vein
4	I [WD]	Focal clonic	N	Hypotonic	-	Normal	MCA – L
5	T → H	Focal tonic	Y	Hypotonic	Feeding difficulties	Normal	Superior longitudinal and right lateral VST
6	T → H	Focal tonic	Y	Hypotonic	-	Right fronto-parietal hypoxic-ischemic lesion	Superior longitudinal and right transverse and sigmoid VST
7	H	Subtle	Y	Hypotonic	-	Right temporo-occipital parenchymal hematoma	Multiple supratentorial hematomas
8	T	Subtle	N	Hypotonic	-	Normal	Superior longitudinal and left transverse VST
9	T → H	-	N	Normal	Suspected cranial fracture line	-	Superior longitudinal VST
10	I [WD]	Generalized clonic	N	Hypotonic	-	Normal	MCA – R
11	I	Subtle	N	Hypertonic	-	-	PCA – L
12	T → H	Generalized tonic	N	Hypertonic	-	-	Deep cerebral and left transmedullary veins
13	I → H	Focal tonic	N	Hypotonic	Hemiparesis	-	MCA – L
14	I [WD]	Subtle + Focal clonic	Y	Hypotonic	Irritability + Feeding difficulties	Left supratentorial hypoxic-ischemic lesion	PCA/MCA - L
15	T → H	Sublte	N	Hypertonic	Irritability	Intraventricular hemorrhage	Deep cerebral veins

I: ischemic; H: haemorrhagic; T: thrombosis; WD: wallerian degeneration; Y: Yes; N: No; MCA: middle cerebral artery; L: left; VST: venous sinus thrombosis; R: right; PCA: posterior cerebral artery.
Patients identification number corresponds to the number in **Tab. 1** and in **Figures 2-5**.
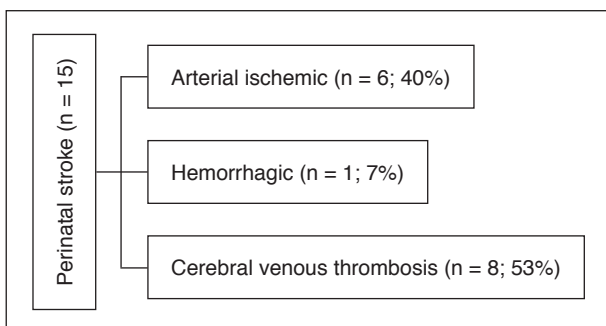

Figure 1. Flow-chart: types of stroke in our cohort.

had multiple supratentorial hematomas. Cerebral venous thrombosis occurred in the superior longitudinal sinus in five, thalamic vein in one and deep cerebral and transmedular veins in two patients. In total, nine strokes were left, four right and two bilateral. An electroencephalogram (EEG) was obtained in all newborns with seizures revealing epileptic activity in eight.

The search for prothrombotic disorders were performed in all cases (newborn and both parents), and showed four newborns heterozygous methylene tetrahydrofolate reductase mutation and two neonatal alloimune thrombocytopenia (patient 1 and 2). Cardiac evaluation was performed in all newborns and revealed two patent foramen ovale. No clinical recurrence of stroke was reported.

Management of perinatal stroke was supportive. Adequate oxygenation and ventilation was ensured.
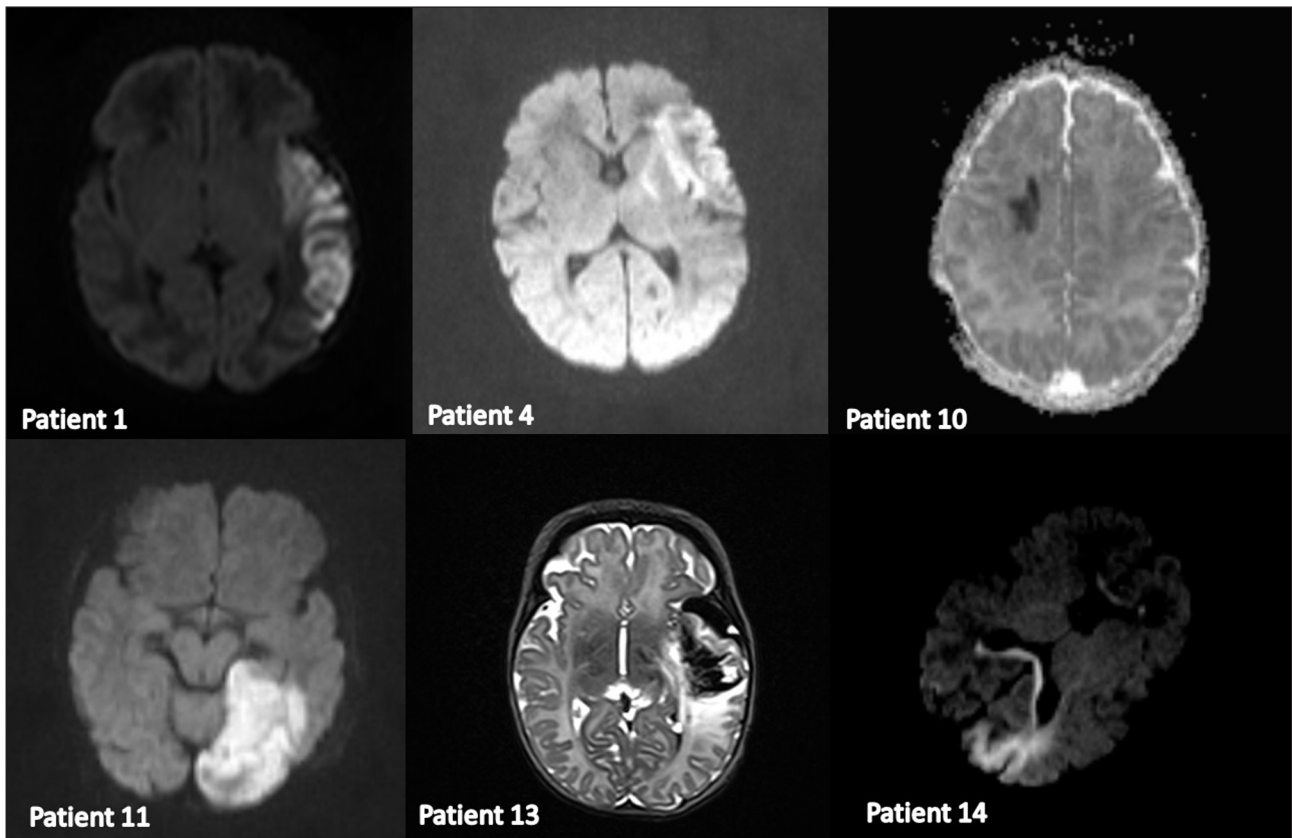
Figure 2. Six cases of arterial ischemic strokes. Patient 1: axial diffusion-weighted image (DWI) reveals left middle cerebral artery (MCA) ischemic stroke; patient 4: axial DWI reveals left MCA ischemic stroke; patient 10: axial DWI reveals right MCA ischemic stroke; patient 11: axial DWI reveals left posterior cerebral artery (PCA) ischemic stroke; patient 13: axial T2-weighted image reveals left MCA ischemic stroke; patient 14: axial DWI reveals left MCA and PCA ischemic stroke.
Patients identification number corresponds to the number in **Tables 1** and **2**.
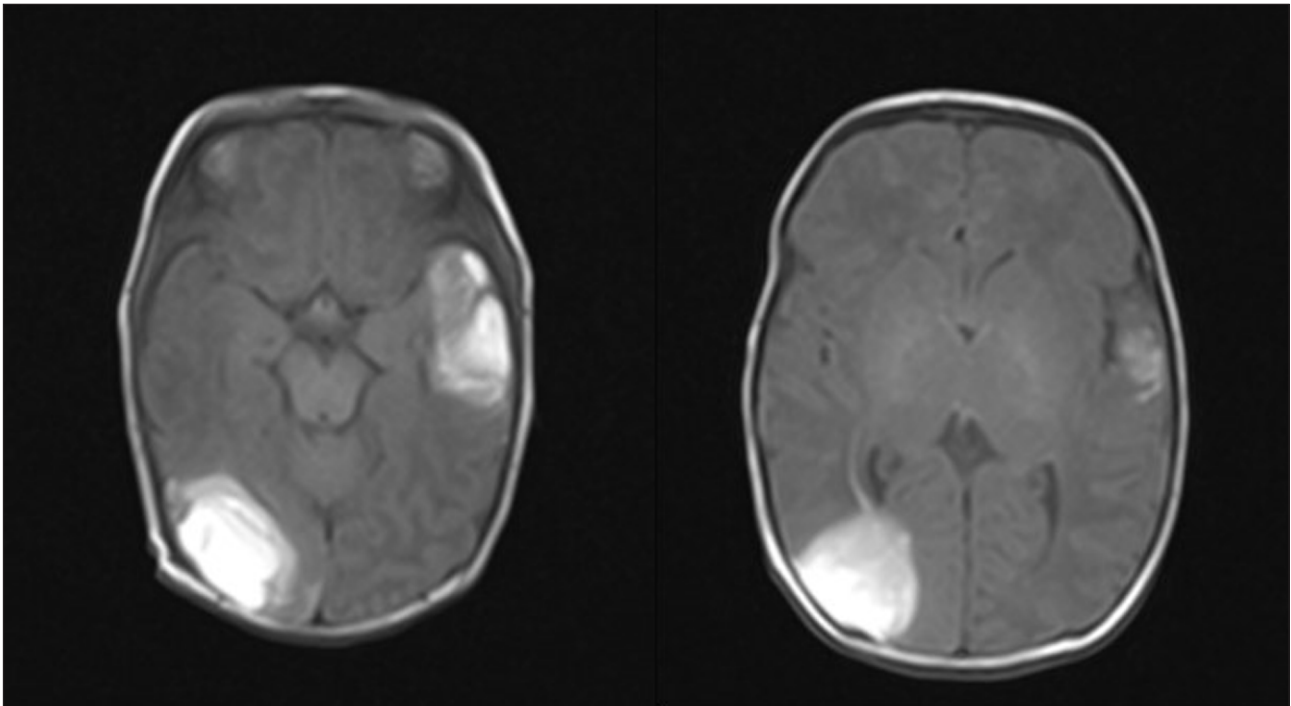
Figure 3. One case of hemorrhagic stroke. Axial T1-weighted image reveals a right parietal-occipital and left temporal hemorrhagic stroke (both images correspond to patient 7).
Patient identification number corresponds to the number in **Tables 1** and **2**.
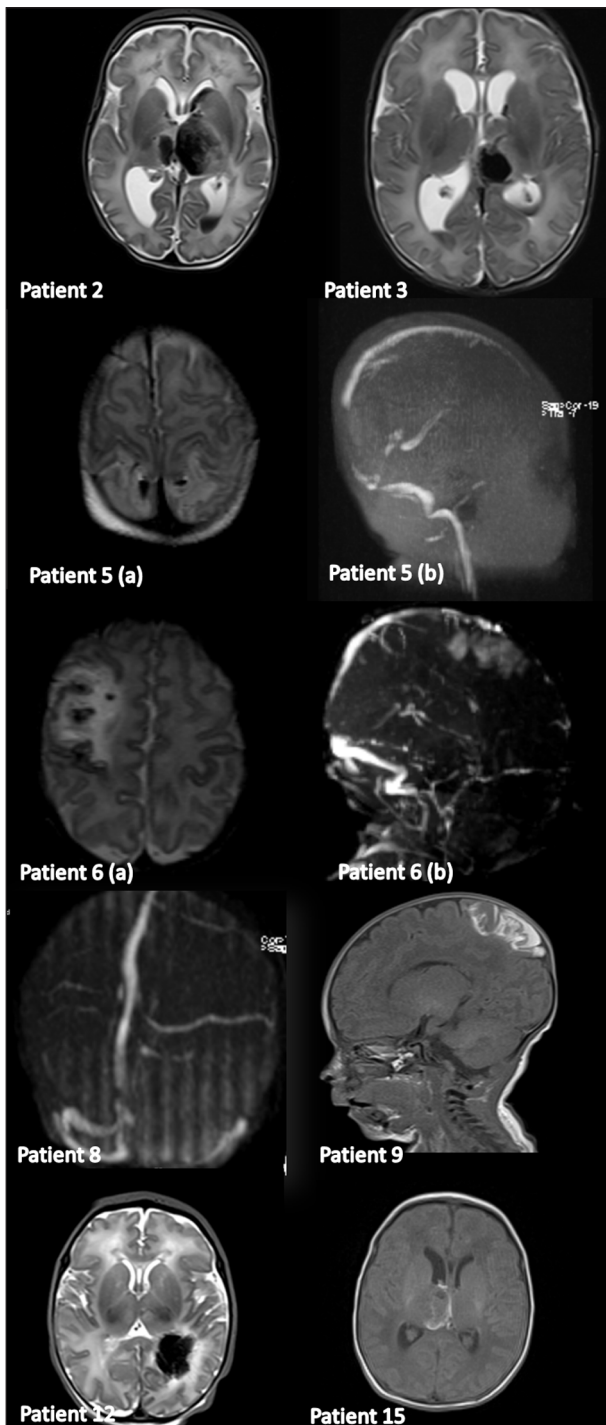
Figure 4. Eight cases of cerebral venous thromboses. Patient 2: axial T2-weighted image reveals a bilateral thalamic hemorrhagic stroke; patient 3: axial T2 reveals a left thalamic hemorrhagic stroke; patient 5 (a): axial T1 reveals a bilateral parietal hemorrhagic stroke; patient 5(b): magnetic particle imaging (MIP) reveals a superior longitudinal and lateral venous sinus thrombosis (VST); patient 6 (a): axial T2 reveals a frontal hemorrhagic stroke; patient 6 (b): MPI image reveals a superior longitudinal and right transverse and sigmoid VST; patient 8: MPI image reveals a superior longitudinal and left transverse VST; patient 9: sagittal T1 reveals a parietal hemorrhagic stroke; patient 12: axial T2 reveals an occipital hemorrhagic stroke; patient 15: axial T1 reveals an intraventricular hemorrhage.

Patients id number corresponds to the number in **Tables 1** and **2**.

Seizures were treated with phenobarbital in ten and a combination of phenobarbital and phenytoin was needed in four to achieve seizures remission. On average, anticonvulsants were stopped by the age of 5 months (minimum of 1 month; maximum of 10 months).

None was treated with anticoagulants. There were no deaths registered among newborns with perinatal stroke.

All patients were sent to the neonatology outpatient clinic, notwithstanding a formal development evaluation was not performed in two (patients 8 and 15), one of which abandoned follow-up at 12 months of age. Imaging follow-up was performed in five patients with MRI and in four patients with transfontanelar US. Physical medicine and rehabilitation evaluated the entire cohort: physiotherapy was prescribed in seven newborns (patients 1-3, 5-7, 12; average therapy duration was fourteen months) and speech therapy in four (patients 1, 2, 5 and 15). Development evaluation was performed in thirteen, using Schedule of Growing Skills II, Wechsler Intelligence Scale for Children (WISC-III) or Griffiths Mental Development Scales. The average age at this evaluation was 3 years and 8 months (minimum 23 months, maximum of 6 years). It was normal in eleven (patients 1, 3, 4, 6, 7, 9-14), while in two revealed delayed psychomotor development (patients 2 and 6). The last two presented cerebral venous thrombosis with hemorrhagic transformation and symptomatic epilepsy, one of which also had a mild brachial predominance right hemiparesis (patient 2).

The patients average current age is 3 years and 11 months (minimum 24 months, maximum 7 years). Schematic follow-up of patients is presented in **Fig. 5**.

Discussion

This study describes the clinical presentation and follow-up of a group of newborns with perinatal stroke who were born in our center. In none of these newborns was possible to distinguish between fetal or neonatal stroke. Fetal stroke, or that which occurs between 14 weeks of gestation and the onset of labor, can be diagnosed when a stroke is detected prenatally by ultrasonography and should always be confirmed by prenatal MRI. We found a higher incidence of neonatal stroke compared to the reported literature [11], particularly related to cerebral venous thrombosis etiology [3, 6, 12], which we relate to our accessibility to MRI. Although
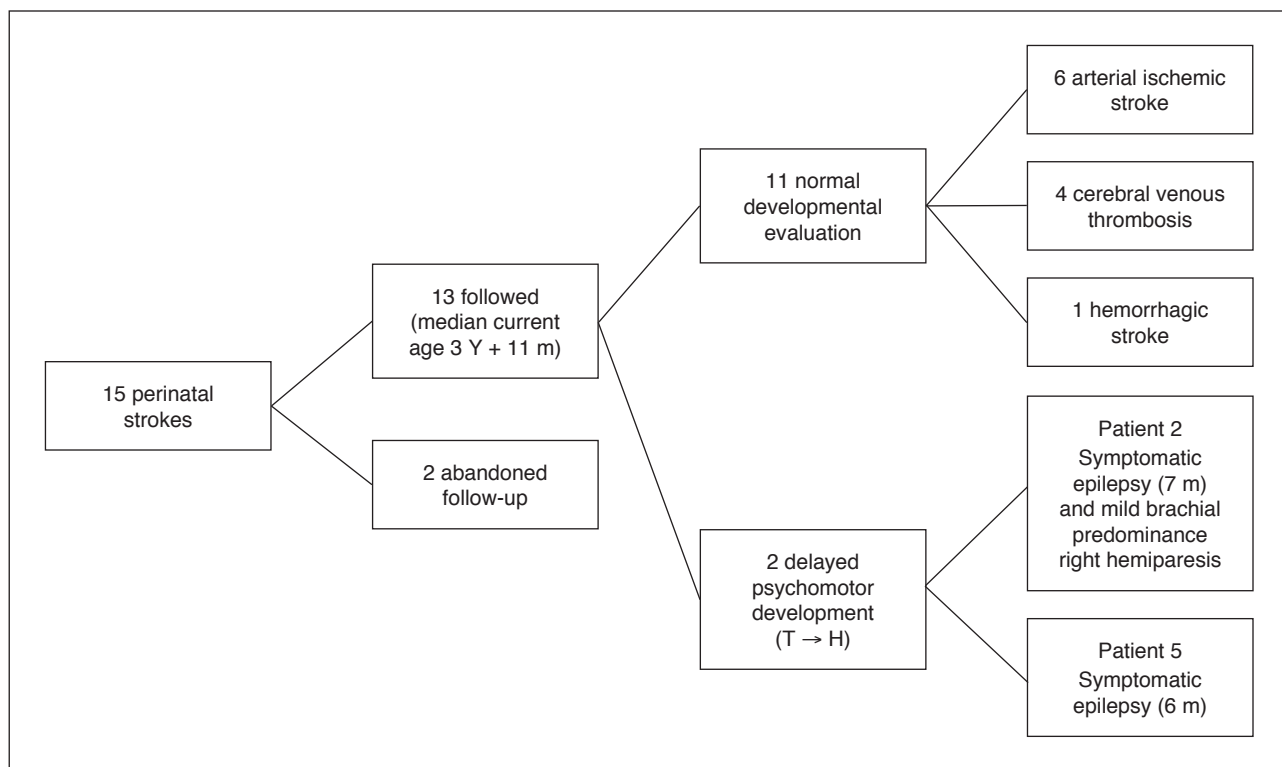
Figure 5. Flow-chart: schematic follow-up of patients.

T: trombosis; H: haemorrhagic; Y: years; m: months.

Patients identification number corresponds to the number in **Tables 1** and **2**.

several potential risk factors have been associated with perinatal stroke, little is known about the exact pathophysiological mechanisms responsible for most cases and most potential risk factors have been identified in small retrospective case series which do not necessarily reflect a causal relation [13-15]. In our study we found these potential risk factors in thirteen patients. There was a significant percentage of dystocic delivery (7 patients) which is known to be a major risk for stroke. Nevertheless, two patients had more than one risk factor, which supports the hypothesis that this is a multifactorial condition [14, 16, 17]. The clinical presentation of perinatal stroke varies from nonspecific to obvious neurological symptoms, which may make the diagnosis difficult [16-19]. In our series, seizures were the most common clinical manifestation, which is consistent with the published data [6, 19-21]. As described in literature, seizures are common in association with ischemia in children, especially newborns, and are generally the most common clinical finding that leads investigations in neonates. In one patient, the event was clinically silent [7]. The majority were symptomatic within the first 48 hours of life, which should be the period of greatest suspicion of stroke.

Neonatal neuroimaging plays an important role in both diagnosis and prognosis. Modern neuroimaging has greatly improved the detection and understanding of perinatal stroke. The most accurate method for detecting stroke is MRI and thus it is the exam of choice [6, 17, 22]. In our study, assessment by neuroimaging methods was based on the cranial ultrasound and MRI. MRI was performed very early due to its good accessibility and the low sensitivity of cranial ultrasound for stroke at an early stage. Vascular lesions were often distributed on the left side (9 patients), which is consistent with the literature data that refers a predominance of the left side lesions due to differences in vulnerability and maturation, or the presence of vascular asymmetry [18, 19]. It is also thought that left hemisphere may be more vulnerable to embolic lesions [18, 19].

Standard EEG should be done in case of suspicion of epileptiform activity, as it is usually the first diagnostic tool available for assessment of brain function [16, 19, 21]. Continuous EEG was not available in our unit during the study period.

Management of perinatal stroke is not yet established and there is still ongoing discussion on whether anticoagulants should or should not be used [5]. The American College of Chest Physicians recommends anticoagulation therapy in newborns with a first ischemic stroke if evidence of an ongoing cardioembolic source is documented,

and in the case of cerebral venous thrombosis in the absence of relevant intracranial hemorrhage [2, 9, 10]. More recently, published guidelines support anticoagulation for neonatal cerebral venous thrombosis without hemorrhage, and for newborns with hemorrhage, either initial anticoagulation or clinical observation with early repeat imaging. At present, anticoagulation practice in cerebral venous thrombosis varies between countries [26]. Anticoagulation was not used in our series. In our series, all newborns had a normal cardiac evaluation. We had no significant number of patients with prothrombotic disorders, although screening has been made in all.

Because most of the infants presented with seizures, the frequent use of anticonvulsants is expected [8]. In our study it was used in all that presented seizures (n = 14). Nowadays phenytoin is generally not used in neonates. There is a lack of guidelines regarding the optimal duration of anticonvulsant treatment. In our hospital, it was continued until no epileptiform activity was detected on EEG although debatable [18].

Beyond the neonatal period, therapy aims to prevent and treat sequelae and requires a multidisciplinary approach. Therapy should be started as soon as any neurologic sign or symptom is recognized. Epilepsy is another sequela described and requires adequate pharmacological approach.

In relation to neurodevelopmental outcome, both short-term and long-term outcome mainly depends on the stroke extent and location [1]. Mortality rate tends to be low and recurrence is rare. No consensus exists on cognitive outcome, which may depend on the follow-up duration [3, 27]. In this series, most patients showed no neurological sequelae, being our follow-up a satisfactory indicator of the presence of some cognitive impairment. The relatively long follow-up of most patients is an asset of our study, confirming the overall good prognosis of perinatal stroke. Despite the recent progress, the pathogenesis remains unknown and therapies are lacking, mainly due to its low incidence. Further research studies and case-control studies should be performed to improve management and new therapies.

Declaration of interest

The Authors declare that there is no conflict of interest. The Authors declare that they do not have financial interests or affiliations with institutions, organizations, or companies that are mentioned in the manuscript or whose products or services are discussed.

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