

## Presumed perinatal ischemic stroke. A review

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### ABSTRACT

The risk of stroke is actually highest during the perinatal period. However, some newborn infants may have no signs indicative of the need of brain imaging, or brain images taken may not be sensitive enough to diagnose ischemic injuries; so, the diagnosis of stroke may be delayed several months or years.

The neurological picture in patients with perinatal stroke detected through neuroimaging months or years after the neonatal period is called presumed perinatal ischemic stroke.

Although a presumed perinatal ischemic stroke is just a confirmation of the existence of an important level of underdiagnosis in relation to perinatal stroke, establishing the extent of this condition has allowed to improve knowledge on perinatal ischemic vascular disease.

**Key words:** stroke, perinatology, cerebral palsy, neurology.

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### INTRODUCTION

Ischemic cerebrovascular disease used to be considered a problem that affected almost exclusively adults, but it is now increasingly recognized in the pediatric population.

At present, its incidence is assumed to be 13/100 000 children per year (similar to the incidence of central nervous system tumors), and half of these are ischemic strokes.<sup>1</sup>

Approximately 25-30% of these occur in the perinatal period, either prenatally or in the early postnatal days, resulting in a fetal stroke, in the first case, or in a neonatal stroke, in the latter. Both types are considered perinatal strokes because it is difficult to establish whether stroke occurred before, during or after childbirth.<sup>2</sup>

Recognizing perinatal stroke poses a challenge. Sometimes, its diagnosis is delayed for months and years after the initial event and is made based on sequelae seen in the infant instead of on the acute symptoms of stroke. A new term has been proposed for newborn infants with a perinatal

stroke diagnosed beyond the neonatal period: presumed perinatal ischemic stroke (PPIS).

Although, in the past years, PPIS has been included as a different type of perinatal stroke in addition to fetal stroke and neonatal stroke, it is just a confirmation of a delayed diagnosis of any of these two types of stroke.

Underdiagnosis is different in terms of hemorrhagic stroke. The fact that neurological and systemic symptoms are more evident and, above all, the higher sensitivity to visualize blood in a cranial transfontanellar ultrasound make it less likely to miss the diagnosis of hemorrhagic stroke in a newborn infant.

For this reason, in this review we will focus exclusively on ischemic strokes. Diagnosis of perinatal stroke will be assessed to establish a theoretical framework to afterwards review clinical and imaging characteristics of PPIS.

### Clinical manifestations and diagnosis of perinatal stroke

Perinatal stroke is defined as an ischemic or hemorrhagic event resulting from the interruption of blood flow to the brain which occurs from 20 weeks of gestation through 28 days of life.<sup>3</sup>

The incidence of perinatal stroke has been estimated at 1 every 1600-4000 live newborn infants; 80% are of ischemic nature and, even though it is difficult to know the actual incidence of ischemic cases, it is probably higher than 1 every 1500 live newborn infants, making the perinatal period one of the moments in life with the highest risk for stroke.<sup>1,4-6</sup>

Such high incidence of perinatal stroke is because both the mother and the fetus have transient risk factors,

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which are typical of late stages of pregnancy, childbirth and the first postnatal weeks, when the newborn infant is prone to a prothrombotic state (Table 1). Due to this transient predisposition, the risk of recurrence is very low, between 2% and 3%.<sup>4,7</sup>

A stroke in utero will hardly cause acute symptoms that may guide diagnosis, but in severe cases, it may be suspected during routine ultrasonographic control and confirmed by means of antenatal magnetic resonance imaging (MRI). However, many cases of stroke in utero are not identified during antenatal control but recover before birth and will have a normal or minimally complicated birth with no signs during the neonatal period suggestive of the need to have additional tests done.

Neonatal stroke may cause no symptoms or subtle or nonspecific symptoms; therefore, a high level of suspicion and an adequate selection of additional tests are necessary for a correct diagnosis. The most common clinical manifestation of neonatal stroke is the presence of focal seizures. Most of the times, infants do not look severely ill during an acute event;

therefore, in order to prevent underdiagnosis, the possibility of a stroke should be suspected in all newborn infants with focal seizures or any other signs of acute involvement of the brain with no clear cause, even in spite of their good general condition.

Given the nonspecific clinical presentation of perinatal stroke, its diagnosis is mainly done based on brain imaging. However, not all imaging methods are sensitive enough to ischemic injuries. Choosing an inadequate neuroimaging method for a newborn infant suspected of stroke leads to mistakenly ruling it out based on a false negative result and therefore, to underdiagnosis. This is especially common when using transfontanelar ultrasound: most hemorrhagic strokes will be diagnosed, but ischemic injuries will hardly be visualized.

Undoubtedly, an MRI is the method of choice to diagnose perinatal stroke. Therefore, if a vascular event is suspected in a newborn infant, once hemorrhagic stroke has been ruled out by ultrasonography, an MRI should be requested to look for ischemic injuries.<sup>8,9</sup>

TABLE 1. Risk factors for perinatal ischemic stroke. Modified from Cheong, J., et al.<sup>7</sup>  
Examples included between brackets

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**Maternal factors**

Primiparity  
Prothrombotic state (factor V Leiden, lipoprotein(a), MTHFR mutation)  
Autoimmune disorders (antiphospholipid antibodies, systemic lupus)  
Substance abuse (cocaine)

**Pregnancy-related factors**

Physiological prothrombotic state  
Preeclampsia  
Oligohydramnios  
Twin to twin transfusion syndrome  
Fetal-maternal hemorrhage  
Congenital infections (TORCH, varicella)

**Childbirth-related factors**

Inflammatory factors (chorioamnionitis, prolonged rupture of membranes, maternal fever with gastroenteritis)  
Prolonged labor  
Fetal distress  
Umbilical cord anomalies  
Interventions during childbirth (forceps, emergency C-section)

**Placental disorders**

**Factors related to the newborn infant**

Physiological prothrombotic tendency  
Normally increased hematocrit and blood viscosity  
Transient right-to-left shunt  
Hypoglycemia  
Congenital heart disease/vascular surgery  
Infections (meningitis, sepsis)

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MTHR: methylene tetrahydrofolate reductase.

TORCH: toxoplasmosis, other, rubella, cytomegalovirus, herpes simplex and HIV.

In order to achieve an optimal sensitivity during visualization of ischemic injuries, diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) sequences are required, because traditional T1- and T2-weighted sequences may not show ischemic injuries in the first 48-72 hours following stroke initiation (*Figure 1*).<sup>9,10</sup>

In the diffusion image, the infarcted region will appear hyperintense (bright signal). The correlation between a (positive) hyperintense diffusion image and hypointense ADC (dark) confirms the presence of cytotoxic edema and, therefore, the ischemic nature of an acute injury. Pseudonormalization of these images in newborn infants usually occurs between 7 and 10 days after infarction.<sup>11</sup>

After the first 24-48 hours of the event, the presence of cytotoxic edema and vasogenic edema will lead to a positive T2 image, which will show hyperintensity in the infarcted region.<sup>8</sup> Blurring of the cortex-white matter junction due to hyperintensity of cortical ischemia is an early sign of stroke observed in T2, the so-called "missing cortex sign".<sup>12</sup>

The combination of T1, T2, DWI and ADC images allows a high level of sensitivity to diagnose perinatal ischemic stroke, regardless of the time when the injury occurred. In spite of the advances in imaging techniques, many fetal strokes and some neonatal strokes will not be diagnosed in their acute phase and will present some time later as PPIS.

### Presumed perinatal ischemic stroke

In 2007, an expert panel organized by the National Institute of Neurological Disorders and Stroke defined PPIS in term newborn infants and older than 28 days of life with a normal neonatal neurological history who subsequently had neurological deficit or seizures secondary to a chronic focal infarction observed in neuroimaging.<sup>3</sup>

This definition establishes that infarction is caused by either an arterial or a venous ischemic stroke, and includes multiple or bilateral infarctions, but excludes global injuries, such as hypoxic-ischemic encephalopathy, watershed hypoxic injuries and periventricular leukomalacia. The chronic nature of the injury is indicated by neuroimaging based on the absence of restriction in the diffusion image and the presence of encephalomalacia, gliosis, atrophy or Wallerian degeneration (*Table 2 and Figure 2*).

Among all characteristics described in *Table 2*,

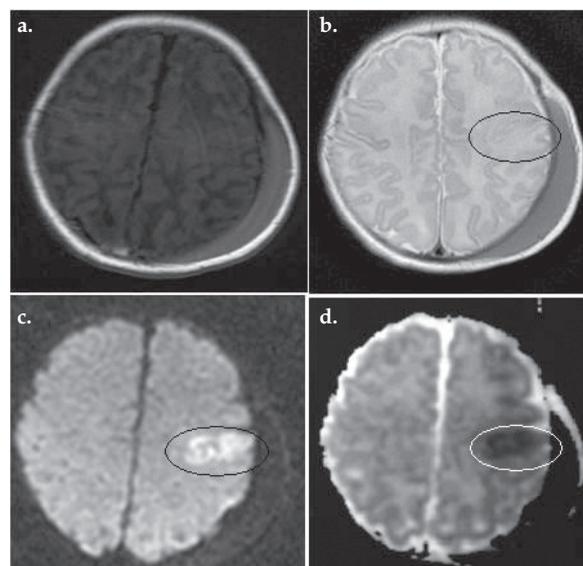
the absence of an acute presentation is suggestive of the fact that the stroke occurred in the perinatal period because, as explained above, a perinatal stroke may be asymptomatic or cause subtle and nonspecific symptoms that do not guide treating physicians to request imaging tests. However, some locations may give rise to doubt regarding the possibility of a PPIS actually occurring in the first months of life but after the neonatal period, for example, a stroke that causes small injuries in the occipital lobe due to a cerebral artery branch occlusion may present only with visual defects, which in the case of an infant, may go unnoticed (*Figure 3*).

### Age at diagnosis and clinical manifestations of presumed perinatal ischemic stroke

In general, PPIS is recognized before one year of life. Most patients present due to hemiparesis, global developmental delay (GDD) or seizures.

Patients taken to the doctor's office due to hemiparesis, the main complaint, are usually between four and eight months old and have

FIGURE 1. Arterial ischemic stroke in a newborn infant



T1 (a), T2 (b), diffusion (c) and apparent diffusion coefficient (d). MRI was done on the third day of life, 48 hours following initiation of focal clonic seizures in the right arm. An ischemic stroke in the middle cerebral artery territory is easily visible in the diffusion and apparent diffusion coefficient images (circled); however, infarction is not seen in T1. T2 shows blurring of the cortex in the infarcted area (circled), which may not be noticed if not specifically looked for based on diagnostic suspicion.

motor injuries that become apparent when infants start using their arms to grab objects. A lesser use of the affected arm will manifest as an early handedness. These infants usually rotate their trunk in order to grab an object that is on the affected side opposite to their healthy arm; and this should be a reason to consult a specialized physician.

Children with seizures or GDD are usually diagnosed at different ages, either before or after the usual age of infants with hemiparesis. Less often, PPIS may present years after the neonatal period due to learning disabilities, cognitive or visual deficit or any other symptoms related to the injury location.<sup>13</sup>

Similarly to other etiologies resulting in cerebral palsy, the concept of “outgrowing a deficit” is applicable to infants with perinatal stroke and, therefore, to infants with PPIS. Perinatal stroke sequelae are observed months or years after the acute event, as the child develops skills related to control by the affected area and new symptoms may appear during their long-term follow-up.

### Diagnostic approach

Evidence of its chronic nature suggests that symptoms observed at present are a late manifestation of the sequelae caused by the original event, even in cases of children with acute symptoms, such as seizures.

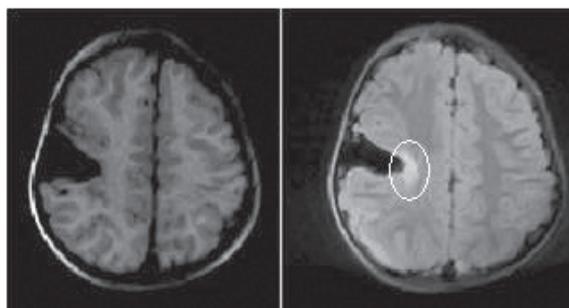
PPIS may be caused by arterial or venous infarctions. A differentiation between both types is based on the vascular areas involved.<sup>14,15</sup>

Venous infarctions are especially frequent in neonatal neurology due to germinal matrix hemorrhage, which occurs in preterm infants and may result in compression of the terminal vein and infarction of tributary veins. Such venous ischemic infarctions usually become hemorrhagic,

so they have traditionally been called Grade IV intraventricular hemorrhage.<sup>15-18</sup>

These injuries affect periventricular white matter, resulting in cystic encephalomalacia,

FIGURE 2. Head MRI, T1 axial and FLAIR in a 2-year-old child presenting with gait alterations



No perinatal or postnatal pathological history observed. At the time of the examination, left brachiofacial hemiparesis was observed. During guided case history, right-handedness is referred in the first months of life, but it was not considered pathological.

MRI showed a cavitated injury in the right middle cerebral artery territory. The FLAIR sequence shows gliosis around the injury site (circled).

FIGURE 3. MRI requested to an 18-month-old apparently healthy girl due to focal seizure. T1 image shows an area with encephalomalacia in the left posterior cerebral artery territory. This is an old injury, but due to the absence of pathological history, it is not possible to determine the exact time when it occurred

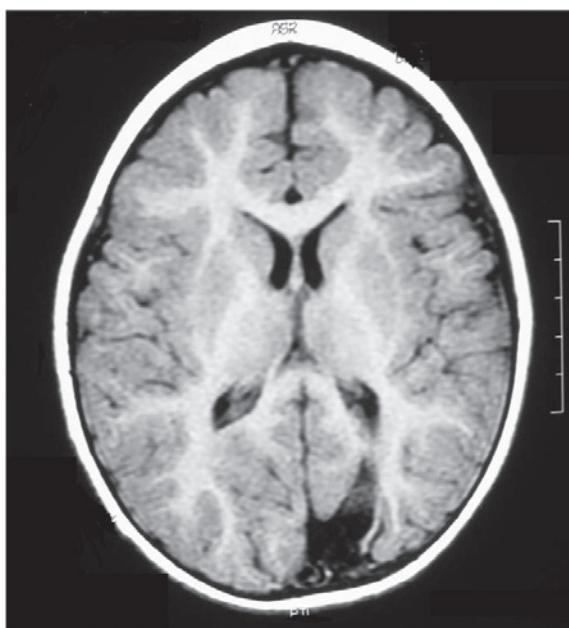


TABLE 2. Characteristics that define a presumed perinatal ischemic stroke

1. Clinical signs observed in the first year of life or later, but always within the neonatal period.
2. Ischemic vascular injuries observed through neuroimaging which are anatomically consistent with the patient's course.
3. Presence of signs showing that injuries observed in such images are chronic (old injuries).
4. Absence of an acute episode in the infant's history that may correspond to the time when the stroke occurred.

which involves the ventricle wall and produces localized dilation with visible signs of gliosis (Figure 4).

Periventricular venous infarctions usually affect the posterior limb of the internal capsule, which appears hyperintense in T2. Small areas of the caudate nucleus and posterior putamen may also be affected because they are drained by the medullary venous system but, unlike arterial infarctions, such nucleus will be less affected than periventricular white matter and the cerebral cortex is preserved, therefore facilitating its differentiation from arterial injuries.

Arterial injuries involve the arterial vascular territory, so they are easily recognized (Figure 2). Injuries in lenticulostriate arteries, which are branches of the middle cerebral artery, cause subcortical injuries involving the basal ganglia, but they are easily differentiated from periventricular venous infarctions because they mainly affect the putamen and the basal ganglia injury is larger than that of affected white matter.

In an article published by Kirton, et al., 78% of PPIS cases corresponded to arterial injuries, and the middle cerebral artery was the most commonly affected one. Periventricular venous infarction was the second most common cause of PPIS, and accounted for 22% of all cases, and for 75% when considering subcortical injuries only.<sup>19</sup>

Given that PPIS is a perinatal stroke diagnosed at a later stage, the risk of recurrence is similar to that of perinatal stroke (less than 3%). Nevertheless, diagnostic approach should be supplemented with tests aimed at recognizing risk factors.

Although there are no evidence-based recommendations for the prevention and management of risk factors for perinatal stroke, which hinders the selection of tests aimed at their assessment, it is always recommended to rule out congenital heart diseases given that cardiac embolism is one of the primary known causes of perinatal stroke, second to idiopathic cases.<sup>4</sup> Prothrombotic and vascular causes should also be ruled out, although the age at which PPIS is diagnosed may help to disregard some of these diagnoses.<sup>13</sup>

## PROGNOSIS

As a clinical condition, a distinctive feature of PPIS is that it presents with the sequelae of the original event; therefore, its clinical manifestation somehow accounts for the prognosis of the acute event. Between 50% and 75% of infants with

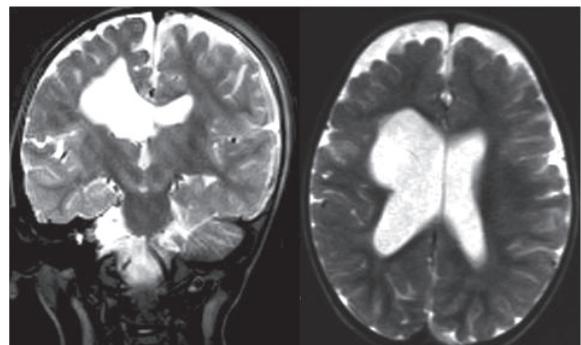
perinatal stroke diagnosed in the perinatal period will have long-term sequelae.<sup>20,21</sup> Such percentage may even be higher with a longer follow-up of patients, who may have cognitive, behavioral or motor symptoms that are not evident in the first years of life.

In addition, all patients diagnosed with PPIS have some sequelae that initially led to requesting tests that eventually allowed to make the diagnosis. However, given that PPIS is usually diagnosed in the first year of life, when brain functions are not completely developed in infants, new deficits may appear during long-term follow-up.<sup>22</sup>

Some motor sequelae, for example, delayed-onset dystonia, and most cognitive or language sequelae may be observed years after diagnosis. This situation calls for a close monitoring of neurological development in infants diagnosed with PPIS in order to approach each stage of development in an early and adequate manner.

It is worth noting that PPIS has been an interesting model to evaluate the prognosis of perinatal ischemic injuries. In the study by Kirton, et al. mentioned above, the prognosis of different types of PPIS was reviewed. Findings included major cognitive, language, and behavioral compromise and epilepsy in patients with arterial infarctions involving the cortex, while venous infarctions were mainly associated with motor disorders, which were also observed as part of the sequelae of arterial events.<sup>19</sup>

FIGURE 4. MRI of an 18-month-old girl diagnosed with presumed perinatal ischemic stroke based on the presence of mild left hemiparesis. Coronal and axial T2 images show a right periventricular cystic focal injury compatible with periventricular venous infarction



## CONCLUSIONS

PPIS is the current confirmation of an underdiagnosed perinatal stroke, turning it into an important warning sign in relation to recognizing strokes during the first month of life. Such underdiagnosis prevents the infant with a perinatal stroke from receiving specialized follow-up and an early diagnosis and management of possible neurological development disorders that may develop as the child grows.

The accurate recognition and description of this condition have allowed, and enable to go on looking into the mechanisms of injury related to prenatal and neonatal strokes, their sequelae and risk factors.<sup>13,19,23,24</sup> ■

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