Perinatal stroke: mechanisms, management, and outcomes of early cerebrovascular brain injury

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Perinatal stroke encompasses a heterogeneous group of focal neurological injuries early in brain development that probably affects more than 5 million people worldwide. Many such injuries are symptomatic in the first days of life, including neonatal arterial ischaemic stroke, cerebral sinovenous thrombosis, and neonatal haemorrhagic stroke. The remaining focal neurological injuries usually present later in the first year with motor asymmetry, such as arterial presumed perinatal ischaemic stroke, periventricular venous infarction, and presumed perinatal haemorrhagic stroke. The numerous sequelae of these injuries include hemiparesis (cerebral palsy), epilepsy, and cognitive, language, and behavioural challenges. In this Review we summarise each perinatal stroke disease, examining the epidemiology, pathophysiology, acute management, and outcomes, including the effect on parents and families, and emerging therapies to mitigate these lifelong morbidities.

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Introduction

Perinatal stroke comprises a diverse but specific group of cerebrovascular diseases that occur between 20 weeks of fetal life and 28 days postnatal life.[1] The estimated incidence of perinatal stroke is between one in 1600 and one in 3000 livebirths,[2–4] although rigorous, population-based estimates for all types do not yet exist. This incidence suggests that the perinatal timeframe is the most focused lifetime period of risk for stroke.[5] Outcomes are often poor and most survivors have lifelong disability. Perinatal stroke accounts for most hemiparetic cerebral palsy and many individuals also have cognitive consequences and epilepsy.[5] These outcomes result in major morbidity for the entire family[6] (eg, caregiver depression, family functioning) and substantial economic costs for society.[7] Despite the effect of perinatal stroke, little high-quality evidence exists regarding pathophysiology, resulting in few options for treatment and prevention.

Advances in neuroimaging have helped to define specific perinatal stroke disease states, facilitating both clinical care and research progress. Roughly half of all perinatal strokes present in the first days of life, typically with seizures, and are termed acute symptomatic perinatal stroke.[8] The remainder typically present in infancy as hemiparetic cerebral palsy, with imaging confirmation of remote stroke, and are termed presumed perinatal stroke. Both acute and presumed perinatal stroke can be arterial or venous and ischaemic or haemorrhagic (figure 1), resulting in six clinical and radiographic disease states (figure 2). Using this framework, we review the pathophysiology, presentation, diagnosis, and management of each type of perinatal stroke. We conclude by summarising the adverse outcomes they share and the strategies to mitigate them towards improved outcomes for children and families.

Acute symptomatic perinatal strokes

Neonatal arterial ischaemic stroke

Neonatal arterial ischaemic stroke is the most common type of acute neonatal stroke, comprising about 90% of published cases.[9] Most stroke events occur near term, but some cases have been seen in preterm infants.[10] It presents in the first 28 days of life and appears on neuroimaging as a focal area of ischaemic infarction corresponding to one or more arterial territories. The most common presentation is seizure (either focal or generalised), which occurs in 70–90% of infants.[11] Typical timing is 12–72 h following delivery, and onset outside the first hours of life can help to clinically distinguish neonatal arterial ischaemic stroke from other causes of neonatal seizure.[12] Other presentations include encephalopathy, irritability, lethargy, increased or decreased muscle tone, or feeding difficulties. Diffusion MRI is the gold standard for diagnosis of acute stroke in the neonate,[1] ideally with vascular imaging.[13] Arterial changes might be observed in many cases, including occlusion and flow defects, but true arteriopathy is rarely described.[14] The distribution of neonatal arterial ischaemic stroke is typically the middle cerebral artery and the left side predominates (figures 1, 2A).[15] Involvement of the cerebral cortex probably increases the risk of seizures,[16] while diaschisis of the motor pathways can help predict motor disability.[17]

The pathophysiology of neonatal arterial ischaemic stroke remains incompletely understood in most cases. Substantial evidence arises from case-control studies[8,18–22] examining potential clinical risk factors (table). Given the

Key messages

- There are six specific perinatal stroke diseases definable by clinical presentation and neuroimaging.
- Periventricular venous infarction is an in-utero stroke that predominantly causes motor disability (hemiparetic cerebral palsy).
- Arterial ischaemic strokes typically cause large lesions near term with both motor and non-motor morbidities.
- Causative mechanisms are poorly understood. Suggestions of causation based on weak evidence or theory should be avoided.
- Guilt and anxiety of the mother and family about the cause of perinatal stroke is common and should be addressed early and repeatedly.

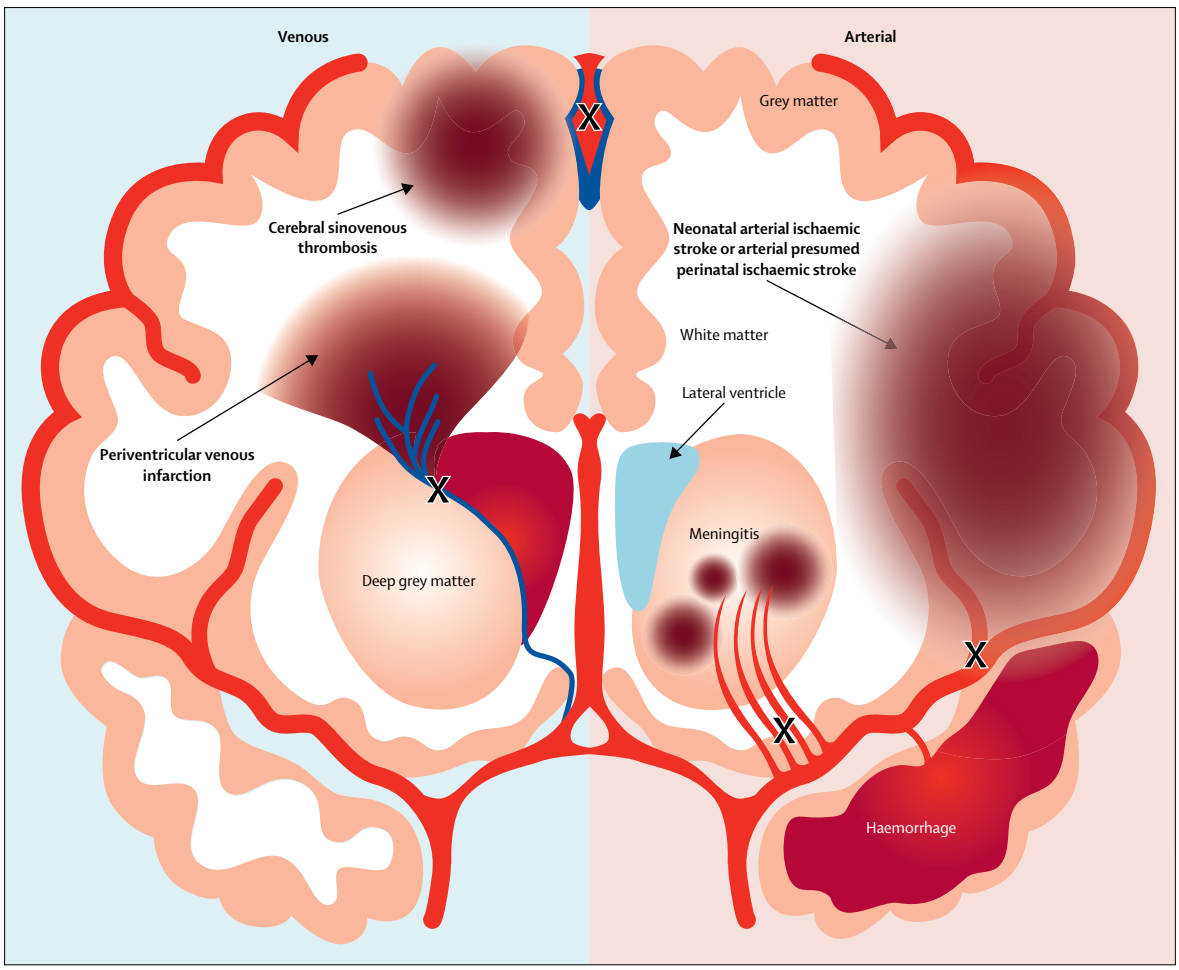

Figure 1: **Schematic of perinatal stroke types**
Cerebral sinovenous thrombosis is shown as occlusion of the superior sagittal sinus with adjacent venous infarction, and periventricular venous infarction is shown with intraventricular haemorrhage and compression of the medullary vein with subsequent venous infarction of the periventricular white matter. X demonstrates area of vessel occlusion for adjacent stroke.

relative homogeneity of the variables explored, the associations suggested are notably inconsistent. A consistent maternal factor is nulliparity, which was a significant risk factor in four studies, with odds ratios (ORs) ranging from 2·0 to 3·4.[8,19–22] Some studies suggest that pre-eclampsia or gestational diabetes are associated with neonatal arterial ischaemic stroke, but this link was modest and inconsistent across studies. The most consistently associated factors are the non-specific intrapartum markers of difficulty with transition that are highly associated with each other. These include emergency caesarean section (OR 3·8–18·0),[8,19–22] need for resuscitation (4·5–18·5),[8,18,20,21] fetal heart rate abnormality (4·5–8·2),[8,19,21,22] meconium staining (4·5–4·9),[8,18,19,21,22] prolonged second stage of labour (1·5–8·9),[8,19,21,22] and 5 min Apgar score less than 7 (4·0–35·7).[8,19–21] Intrauterine growth restriction and small for gestational age have been consistently associated with neonatal arterial ischaemic stroke (2·4–3·9),[19,21,22] suggesting there could be more chronic stressors on the infant. Male sex appears to be a consistent risk factor across studies (1·0–2·2),[18,20,21] which has been noted for some time, although explanations remain elusive.[23] These are non-specific findings encountered in many cases of neonatal encephalopathy and other non-neurological conditions, and even in healthy children. As a group, these risk factors do not satisfy established criteria for causation. Given the common co-occurrence of neonatal arterial ischaemic stroke with other forms of hypoxic-ischaemic encephalopathy,[24] these associations might just be indicative of a fetus at risk of difficult transition, such as one connected to an abnormal placenta.

The potential role of the placenta in neonatal arterial ischaemic stroke merits consideration. Strong indirect evidence supports placental thromboembolism as a leading cause of neonatal arterial ischaemic stroke, including common bilateral or multiple vascular territory lesions suggestive of proximal embolic source (but with normal cardiac evaluations) and an extremely low frequency of recurrence of less than 1–2%.[25] More direct

evidence comes from a case-control study that reported perinatal stroke to be associated with any category of placental pathology (OR 5·1, 95% CI 1·9–14·0) as well as amniotic fluid inflammation (OR 2·6, 95% CI 1·1–6·1).[26] Other small studies have further supported an association between placental disease and neonatal arterial ischaemic stroke.[27,28] Preclinical perinatal stroke models further suggest direct roles for disordered inflammation in its pathogenesis.[29,30] Difficulty in obtaining placental tissue hours or days after birth, when neonatal arterial ischaemic stroke is diagnosed, is a substantial barrier to the investigation of this issue.

No substantial evidence exists for trauma as a cause of neonatal arterial ischaemic stroke. One interpretation of the possible association of neonatal arterial ischaemic stroke with operative delivery[20,31] is a role for direct trauma. However, this association is confounded by the fact that operative delivery is often done because of fetal distress, which is itself associated with neonatal arterial ischaemic stroke. Isolated single case reports suggesting the occurrence of arterial dissection do not provide definitive evidence, including those with pathological post-mortem examination.[32,33] Although vascular imaging in the neonate can be challenging,[13] a large proportion of the more than 1000 neonates with neonatal arterial ischaemic stroke reported in the scientific literature have undergone angiography, and not one report has shown arterial dissection. Without dissection, and given that the cerebral arteries involved are located deep in the brain, the hypothesis that superficial external trauma could cause direct arterial injury and neonatal arterial ischaemic stroke is not plausible.

Several additional specific causes that can be definitively diagnosed are commonly considered. Cardiac disease, most commonly complex congenital heart disease, is an established risk factor for neonatal arterial ischaemic stroke. Echocardiogram investigation is standard; however, mounting evidence suggests that echocardiography with a normal clinical examination is unlikely to change management and is not predictive of stroke recurrence.[25] Although disordered thrombosis might have a role acutely, prothrombic evaluations for neonatal arterial ischaemic stroke are typically no longer indicated in the absence of other risk factors, as three studies have shown no association with neonatal arterial ischaemic stroke.[25,34,35] Bacterial meningitis must always be considered, and stroke complicates up to 43% of paediatric cases[36] and 33% of neonatal cases (unpublished). Clinical factors associated with arterial ischaemic stroke in paediatric meningitis include a delay in presentation, seizures, and infection with group B streptococcus (unpublished). Diffusion MRI can show recognisable patterns of meningitis-associated neonatal arterial ischaemic stroke, including bilateral involvement of the basal ganglia and cortex.[37] Treatment of meningitis is paramount and intravenous antibiotics should be promptly initiated. Anticoagulation is considered safe in paediatric patients,[38] but studies focused on anticoagulation for neonatal arterial ischaemic stroke are scarce. The use of steroids remains controversial, but should be considered when there is evidence of artieropathy. Mortality for meningitis complicated by stroke in children was 25% in one study (unpublished data).

Acute therapy for neonatal arterial ischaemic stroke focuses on neuroprotection. Emergency recanalisation strategies are precluded, because precise timing can never be known, the infarct is typically well established, and the affected artery is often open.[39] Management is supportive, with antiseizure therapy comprising the mainstay, and levetiracetam and phenobarbital are most commonly used.[36,40] Seizures can be serious and status epilepticus is not uncommon, suggesting a role for continuous electroencephalogram monitoring. However, in most patients, seizures resolve within days, and experts agree that with no evidence of efficacy and possible harm to the developing brain, most children can and should be

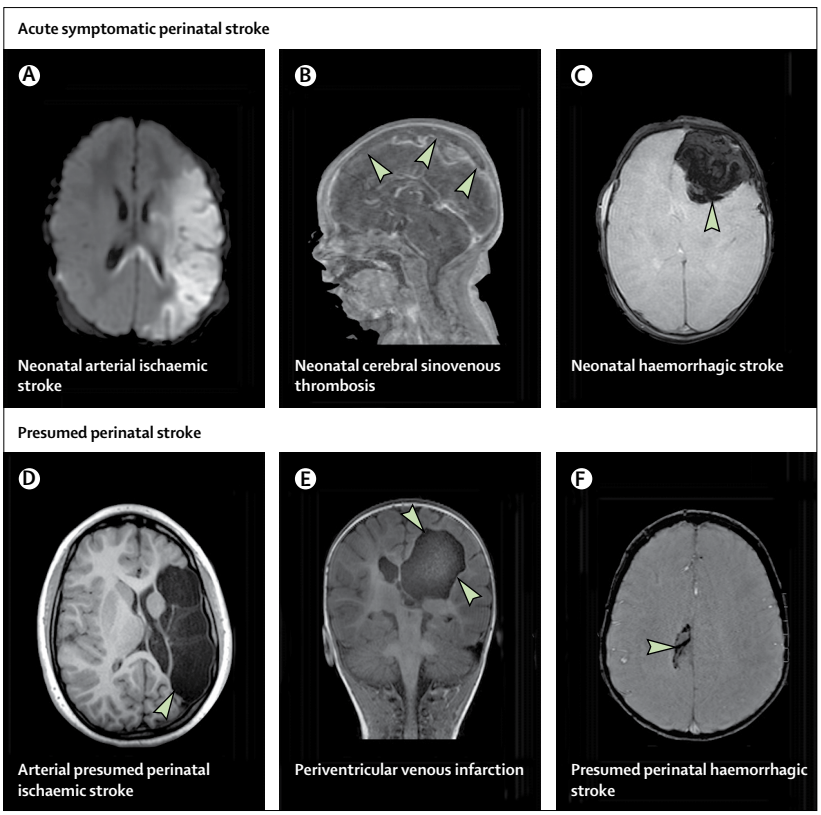

Figure 2: **Perinatal stroke diseases by MRI**
(A) Neonatal arterial ischaemic stroke features acute restriction on axial diffusion-weighted MRI in an arterial territory; diaschisis of the splenium of the corpus callosum is also evident. (B) Neonatal cerebral sinovenous thrombosis is evident as a filling defect on sagittal magnetic resonance venogram (shown), in this case, in the superior sagittal sinus (arrows). (C) Neonatal haemorrhagic stroke detectable on gradient echo or susceptibility weighted MRI (arrow). (D) Arterial presumed perinatal ischaemic stroke in a child with hemiparesis is diagnosed by focal encephalomalacia on CT or MRI (axial T1-weighted MRI shown) in an arterial territory (arrow). (E) Periventricular venous infarction presents with congenital hemiparesis with a focal lesion affecting the periventricular white matter with sparing of the cortex and basal ganglia, shown on coronal T1-weighted MRI (porencephaly indicated with arrows). (F) Presumed perinatal haemorrhagic stroke a focal area of remote parenchymal injury showing haemorrhage (gradient echo, arrow).

	Estan and Hope (1997)[18]	Harteman et al (2012)[19]	Chabrier et al (2010)[20]	Martinez-Biarge et al (2016)[21]	Darmency-Stamboul et al (2012)[22]*	Lee et al (2005)[8]*
Number of cases	12	52	100	79	32	40
Number of controls	24	156	45 508	239	96	111
5 min Apgar score <7	NA	19·5 (4·4–86·4)†	21% cases and 7·4% controls†	35·7 (1·9–653)†‡	NA	4·0 (1·7–9·2)†
Early-onset sepsis (within 7 days of birth)	NA	7·0 (1·8–27·1)†	5% cases and 2·9% controls	NA	NA	NA
Resuscitation at birth	50% cases and 12·5% controls†	NA	19% cases and 5·1% controls†	18·5 (4·0–85·6)†	NA	4·5 (2·1–9·9)†
Fetal heart rate abnormality	NA	8·2 (3·5–19·1)†	NA	7·3 (3·9–13·7)†	4·5 (1·7–12·1)†	5·0 (2·2–11·6)†
Emergency caesarean section	NA	18·0 (5·3–61·1)†	40% cases and 17% controls†§	6·8 (3·8–12·5)†	1·6 (0·5–5·1)	3·8 (1·6–8·9)†
Intrapartum fever	NA	7·5 (1·5–38·7)†	NA	5·3 (2·0–14·3)†	NA	NA
Meconium stain	50% cases and 25% controls	4·5 (2·1–9·8)†	NA	4·6 (2·2–9·3)†	4·9 (1·9–12·9)†	1·8 (0·9–3·9)
IUGR or SGA	NA	3·0 (0·9–10·4)	NA	3·9 (1·0–15·1)†	2·4 (0·5–11·2)	NA
Prolonged second stage of labour	NA	1·5 (0·3–8·2)	NA	3·7 (1·8–7·3)†	6·7 (0·6–76·8)	8·9 (2·1–41·9)†
Nulliparity	NA	2·0 (1·0–3·8)†	46% cases and 33% controls†	3·0 (1·7–5·2)†	1·0 (0·5–2·3)	3·4 (1·5–7·6)†
Male sex	50% cases and 50% controls	NA	61% cases and 51% controls	2·2 (1·3–3·8)†	NA	NA
Pre-eclampsia or pregnancy-induced hypertension	NA	1·0 (0·4–2·7)	4% cases and 3% controls	1·5 (0·6–3·7)	0·8 (0·1–7·6)	4·9 (1·2–21·0)†
Prolonged rupture of membranes	NA	0·6 (0·2–2·0)	6% cases and 2% controls†	11·5 (4·0–33·0)†	0·6 (0·2–2·3)	4·9 (1·7–14·1)†
Vacuum	NA	NA	NA	9·4 (2·9–30·6)†	0·8 (0·3–2·5)	2·7 (1–6·8)†
Cigarette smoking	NA	NA	16% cases and 15% controls	NA	NA	NA
Gestational diabetes	NA	NA	7% cases and 5% controls	NA	4·4 (1·1–17·7)†	0·8 (0·2–2·9)

Risks are presented as proportions or odds ratio (95% CI). NA=not assessed. IUGR=intrauterine growth restriction. SGA=small for gestational age. *Cases include both neonatal arterial ischaemic stroke and arterial presumed perinatal ischaemic stroke. †Results significantly different from OR=1, Mann-Whitney test $p<0·05$,[18] or χ^2 test $p<0·05$.[20] ‡Apgar score at 5 min of <5. §Any caesarean delivery.

Table: **Case-control studies of risk factors in neonatal arterial ischaemic stroke**

discharged without antiseizure medication.[41] Emerging treatment research includes erythropoietin, which has strong preclinical evidence for neuroprotection,[42,43] and improving behavioural performance in phase 2 trials in hypoxic-ischaemic encephalopathy and a phase 1 trial in neonatal arterial ischaemic stroke;[44] a placebo-controlled phase 2 trial of darbepoetin (NCT03171818) is ongoing. Whether the preclinical excitement for cell-based therapies in adult stroke and other cerebral palsy models[45] can translate to perinatal stroke is receiving ongoing consideration.[46]

Neonatal cerebral sinovenous thrombosis

Neonatal cerebral sinovenous thrombosis is the presence of a thrombus in one or more of the cerebral veins or dural sinuses (figure 1). This presence alone is not a stroke, but more than 50% of affected neonates will incur parenchymal venous infarction that is often haemorrhagic in nature.[47] Neonatal cerebral sinovenous thrombosis has an estimated incidence of 1–12 per 100 000 livebirths.[47,48] Again, the most common presenting sign is seizures in the first days of life.[47] Diagnosis is confirmed with combined parenchymal and vascular imaging. MRI and magnetic resonance venography can confirm a cerebral venous filling defect and characterise associated parenchymal changes ranging from venous congestion, to infarction (restricted diffusion), to haemorrhagic conversion, where haemosiderin-sensitive sequences are highly sensitive (figure 2B). Pattern recognition informed by cerebral venous drainage patterns is essential. For example, deep cerebral sinovenous thrombosis often features thalamic haemorrhage with intraventricular extension and distinctive diffusion restriction patterns for bilateral deep white and grey matter areas.[49,50]

With evidence limited to uncontrolled registry studies and case series, causal associations for neonatal cerebral sinovenous thrombosis are poorly understood. Clear risk

factors include sepsis and infection (including meningitis), dehydration, mechanical sinus compression, and cardiac surgery, and less clear associations include factors associated with difficult transition and perinatal asphyxia.[51–53] Evidence for thrombophilia conditions remains possible but incompletely defined.[54] Prothrombotic conditions can be assessed in at-risk individuals after clot resolution.[55]

Anticoagulation with low-molecular-weight or unfractionated heparin is generally considered safe, and should be considered on a case-by-case basis.[56] It is routinely recommended at many international centres; however, its use is inconsistent both among practitioners and across countries.[57] There is logical reticence in treating with anticoagulation in the presence of haemorrhage. However, an appreciation for the cause of haemorrhage (back pressure from venous stasis) helps to clarify why anticoagulation treatment might actually prevent worsening of haemorrhage and progression of thrombus, and safety data are now substantial.[58] Best available evidence suggests the absence of antithrombotic therapy is strongly associated with thrombus propagation and subsequent infarction.[58] Complete recanalisation occurs by 3 months in 90% of patients.[57,58] Randomised trials of anticoagulation are in development and are required to standardise therapy, to reduce morbidity and mortality.

Neonatal haemorrhagic stroke

Neonatal haemorrhagic stroke is defined as a focal accumulation of blood within the brain parenchyma (confirmed by autopsy or imaging) presenting with encephalopathy, seizures, altered mental status, or neurological deficit in the first 28 days following delivery (figure 1).[59] It refers specifically to term-born children and not the germinal matrix and intraventricular haemorrhages common in preterm infants. Evidence suggests that neonatal haemorrhagic stroke affects at least one in 6300 livebirths.[59] These estimates include both primary intracerebral haemorrhage as well as haemorrhagic transformation of focal or global ischaemic infarction, but not extra-axial (subdural or epidural) bleeds. The incidence for idiopathic intracranial haemorrhage alone was 1 in 9500 livebirths.

The most common clinical presentation is encephalopathy, followed by seizures and hypotonia, within the first days of life.[59] Haemorrhagic stroke is best diagnosed by MRI with dedicated sequences for blood, such as gradient echo and susceptibility-weighted imaging, complementing standard anatomical sequences, which themselves might provide information about the age and timing of bleeding (figure 2C). Additional sequences can analyse possible causes, including vessel imaging with magnetic resonance angiography and magnetic resonance venography, as well as diffusion-weighted imaging, to assess for primary, underlying ischaemic injury in the case of haemorrhagic transformation. Thalamic or intraventricular haemorrhage, in particular, should prompt suspicion of deep cerebral sinovenous thrombosis.[60] Haemorrhage is thought to be related to underlying weakness in the vessel wall, and the temporal lobe is the most common location for idiopathic haemorrhagic stroke in newborn babies.[59]

Evidence of possible causative risk factors for neonatal haemorrhagic stroke is limited to two studies, one of which relied on administrative data.[59,61] Several definitive causes are identified in these and additional case series, such as structural lesions like arteriovenous malformations and bleeding diatheses, including inherited (eg, haemophilia) and acquired (eg, neonatal alloimmune thrombocytopenia) conditions. Accordingly, initial investigations include complete blood count with platelet count and coagulation evaluations (international normalised ratio and partial thromboplastin time)[62] in addition to imaging. If haemorrhagic transformation of an ischaemic injury cannot be excluded, the additional evaluations for neonatal arterial ischaemic stroke and cerebral sinovenous thrombosis might also be pertinent.

However, such definitive causes account for few cases and the mechanisms of most idiopathic neonatal haemorrhagic stroke are not well understood. Similar to risk factors for neonatal arterial ischaemic stroke, two population-based, controlled studies[59,61] did observe associations with non-specific markers of difficulty with transition, including small for gestational age, fetal bradycardia, emergency caesarean section, and low Apgar scores. Whether these risk factors are related to inherent differences in the child, the effects of a brain injury that has already occurred, or additional factors is unknown.

Intrapartum trauma is often assumed to be a cause of perinatal haemorrhagic stroke.[62,63] However, carefully defined variables for trauma are not associated with neonatal haemorrhagic stroke. In fact, all previous studies examining risk factors of neonatal haemorrhagic stroke either inaccurately recorded trauma or described no causative association.[63,64] The highest level of evidence from the largest case-control study of haemorrhagic stroke in full-term neonates that carefully defined trauma found that only 4% of cases had experienced intrapartum trauma.[59] Furthermore, no association was observed with any obstetrical variables, including induction, assisted delivery, or forceps.[59] Therefore, objective evidence of severe and unusual trauma, such as a skull fracture, should be present before trauma is considered as potentially causative of neonatal haemorrhagic stroke.

Severe mass effect, herniation, or other need for urgent surgical intervention is rare,[59] and management of neonatal haemorrhagic stroke is mostly supportive, including neonatal neurointensive care and seizure monitoring. Repeat imaging after about 3 months, once blood products have resorbed, might be helpful in illuminating underlying pathologies, such as tumour[65] or arteriovenous malformation.[66] Intraventricular extension might be complicated by posthaemorrhagic hydrocephalus

that requires continuing surveillance of head circumference, imaging, and possible shunting. Morbidity with haemorrhage is high and can include cognitive challenges.[59] Opportunities for treatment and prevention are scarce, as idiopathic neonatal haemorrhagic stroke most likely represents rare events in uniquely susceptible individuals.

Presumed perinatal strokes

Arterial presumed perinatal ischaemic stroke

Arterial presumed perinatal ischaemic stroke is typically diagnosed in children who have early motor asymmetry or handedness and chronic, arterial infarction on neuroimaging in infancy.[1,67,68] It represents roughly 50% of perinatal ischaemic stroke, with an estimated incidence of about one in 3600 livebirths. The most common presentation is hemiparesis, usually evident before age 1 year.[69,70] Subtle early handedness can be missed from diagnosis for years.[71] Less commonly, arterial presumed perinatal ischaemic stroke can present in the preschool or school-aged years (3–10 years) with learning disabilities, cognitive, visual, or other focal deficits, or remote symptomatic epilepsy.[69] Either no indication of seizures, or failure to witness them, might explain why some children with arterial perinatal stroke present acutely with seizures (neonatal arterial ischaemic stroke), while others present outside the neonatal period as arterial presumed perinatal ischaemic stroke.[72]

With similar presentations, imaging findings, and outcomes, arterial presumed perinatal ischaemic stroke is likely to represent the same condition as neonatal arterial ischaemic stroke (figures 1, 2D). Accordingly, pathophysiology might be similar, although no controlled risk factor studies exist. Comparisons with periventricular venous infarction, another presumed perinatal stroke, support the idea that arterial presumed perinatal ischaemic stroke and neonatal arterial ischaemic stroke probably reflect different presentations of the same disease.[70] Investigations are of limited utility as echocardiography is almost always normal[25] and chronic thrombophilia evaluations have been shown to be non-contributory.[25,34,35]

Because the presentation of arterial presumed perinatal ischaemic stroke is so remote from the time of injury, therapies focus on rehabilitation. Management is centred around the presenting complaint and evolution of morbidities through development. In keeping with their clinical presentation, most children have motor deficits, while cognitive and behavioural outcomes can be partially predicted by lesion characteristics on MRI.[67]

Periventricular venous infarction

Similar to other types of presumed perinatal stroke, periventricular venous infarction is typically diagnosed in term-born children with congenital hemiparesis and specific neuroimaging findings (figures 1, 2E). The established mechanism of periventricular venous infarction in preterm infants is germinal matrix haemorrhage before 34 weeks gestation, leading to compression of the medullary veins and focal venous infarction of the periventricular white matter.[73] Periventricular venous infarction in term children is thought to represent an in-utero version of the same stroke.[67] Its incidence is difficult to determine, but multiple studies suggest that it accounts for about half of presumed perinatal ischaemic strokes.[70,72]

Parents of patients with periventricular venous infarction recognise motor asymmetry at an average age of 6 months, but median diagnosis is typically delayed to age 18 months, later than arterial presumed perinatal stroke.[70] The most common presentation is early hand preference and asymmetric motor development, and the lower extremity might be relatively more involved compared with arterial lesions.[70] As a pure subcortical lesion with no cortical involvement, seizures and non-motor delays are typically not seen.[70] Like all perinatal stroke, periventricular venous infarction is a clinical and radiographic diagnosis. MRI shows unilateral, porencephalic enlargement of the lateral ventricle with T2 prolongation of the periventricular white matter and internal capsule but sparing of the cortex and basal ganglia.[74] Evidence of the remote, fetal germinal matrix haemorrhage that underlies periventricular venous infarction on haemorrhage sensitive sequences adds further certainty to the diagnosis.[74]

Despite being a leading cause of hemiparetic cerebral palsy, dedicated studies of periventricular venous infarction are scarce and no data from case-control studies have been reported that estimate possible causative factors. Some case series[70] have suggested possible risk factors of maternal hypertension, recurrent miscarriage, antepartum bleeding, and prenatal infection, but none are established. Because periventricular venous infarction occurs months before birth, it is unsurprising that it has not been associated with intrapartum complications or a difficult transition.[70] By avoiding the critical care and other medical complications incurred by delivered preterm infants, periventricular venous infarction represents a unique opportunity to study mechanisms of germinal matrix haemorrhage. The probable germinal matrix haemorrharge and lesion similarity to known connective tissue disorders, like *COL4A1* mutations,[75] suggests that a unique genetic predisposition might be responsible for some periventricular venous infarction cases. Aside from this consideration, no standard investigations are required. Management is focused around motor rehabilitation, because most children with periventricular venous infarction do not have other perinatal stroke morbidities, such as cognitive delays or epilepsy.

Presumed perinatal haemorrhagic stroke

Presumed perinatal haemorrhagic stroke was defined after a large population-based study of neonatal haemorrhagic stroke revealed a few patients presenting after the first 28 days of life, analogous to the ischaemic presumed

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perinatal strokes.[59] Although such lesions have certainly been noted before, advances in haemorrhage-sensitive MRI sequences have increased the ability to detect and confirm remote parenchymal haemorrhage (figure 2F). The pathophysiology of presumed perinatal haemorrhagic stroke is assumed to be similar to that of symptomatic neonatal haemorrhagic stroke, although few data have been reported. Patients might have genetic conditions such as hereditary haemorrhagic telangiectasia, haemophilia, or acquired bleeding diatheses, such as immune thrombocytopenia. Such risks suggest that patients or mothers of children with presumed perinatal haemorrhagic stroke might have a greater risk of recurrence than those without, and thorough investigations of cause should occur accordingly. Additionally, small presumed perinatal haemorrhagic stroke could possibly occur without symptoms outside the perinatal period in early infancy and only be detected on later imaging. Similar to arterial presumed perinatal ischaemic stroke, clinical presentations can include seizures, developmental delay, or early motor asymmetry. Presumed perinatal haemorrhagic stroke is diagnosed by MRI with the same sequences as acute symptomatic neonatal haemorrhagic stroke used to identify associated risk factors such as arteriovenous malformation. A thorough systemic examination of the child and family members has been suggested for conditions such as hereditary haemorrhagic telangiectasia, and bloodwork should be done to exclude a bleeding diathesis. Management is directed towards symptoms such as epilepsy.

Outcomes, rehabilitation, and neuroplasticity

Overall, outcomes from perinatal stroke are poor, with most patients developing lifelong neurological disabilities (figure 3). With such lasting consequences and essentially no prevention strategies, a focus on rehabilitation is crucial. Although many lessons can be borrowed from the management of adult stroke, there are unique ramifications in the developing brain, including how affected children must develop around such injuries and learn, rather than relearn, functions that might be affected. Evidence for rehabilitation is also growing from studies of cerebral palsy, in which the focal injury in an otherwise healthy brain represented by perinatal stroke could provide a particularly valuable model.[5] Published guidelines are available for stroke rehabilitation that include children.[76,77]

Motor outcomes

Impaired motor development is the leading cause of disability in children with perinatal stroke. It usually takes the form of hemiparetic cerebral palsy affecting both the arms and the legs, although patterns might vary depending on the location, size, and number of lesions. Motor deficits are present in 50–60% of neonatal arterial ischaemic stroke cases and more than 80–90% of children with presumed perinatal ischaemic strokes.[78] Many motor rehabilitation strategies have emerged in the past 10 years, with a steady increase in the number and power of clinical trials, some of which are specific to perinatal stroke while others include all hemiparetic cerebral palsy (most of which are stroke).

The aims of outpatient upper extremity therapy include engaging in tasks that are meaningful, repetitive, progressively adapted, specific, goal oriented, and, ideally, incorporate activities of daily living. Therapies undergoing evaluation in clinical trials include constraint and bimanual therapies, as well as non-invasive brain stimulation (eg, NCT03216837, NCT02250092, NCT01189058). Most therapies have focused on the upper extremities, which are typically most affected in perinatal stroke and associated with

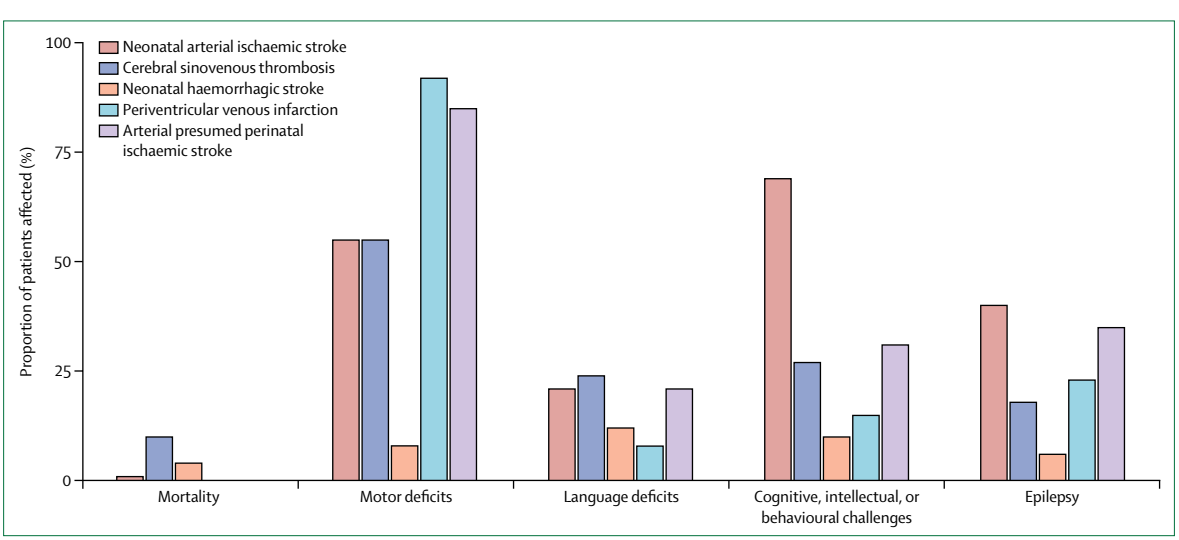

Figure 3: **Perinatal stroke outcomes, by stroke type**
See appendix for more details.

See Online for appendix

quality of life. Such therapies aim to take advantage of the dynamic nature of the developing brain, which is incompletely understood although models are improving. Both preclinical and human studies have shown that the relative balance of control from the healthy and lesioned hemisphere is related to motor disability.[5] Therapeutic strategies that focus on improving the activity of the lesioned hemisphere or decreasing control by the contralesional hemisphere are suggested but remain unproven.[78] Randomised sham-controlled trials of repetitive transcranial magnetic stimulation and transcranial direct current stimulation[79,80] have shown safety, tolerability, and possible efficacy in improving therapy-induced gains in hand function. These approaches are challenging the idea that cerebral palsy is a static brain injury that cannot be changed.

Language outcomes

Although language outcomes are not always unaffected, language functions show a remarkable ability to reorganise following perinatal stroke. Difficulties range from less than 10% for periventricular venous infarction[67] to 33% for stroke associated with meningitis (unpublished data). Children with neonatal arterial ischaemic stroke and presumed perinatal ischaemic stroke have similar language performance compared with their typically developing peers; however, some children with right hemisphere injury might be less expressive with their affective language.[81] Adolescents with a history of left hemisphere arterial stroke are more likely to make morphological errors, use less complex syntax, and use fewer syntactic types compared with controls, while those adolescents with right hemisphere lesions might also have reduced use of complex syntax.[82] Functional MRI studies of children with left hemisphere arterial stroke have reported variable plasticity in language localisation, with some children showing persistent left hemisphere activation, although some others are predominantly right sided, and others are bilateral. One study suggested that patients with bilateral activation of the superior temporal-inferior parietal regions had better language function than those with unilateral activation of either hemisphere.[83] Children might also have challenges with writing morphology when compared with controls, but have otherwise similar performance for written tasks.[84] Language outcome from other forms of perinatal stroke are not well defined. Early involvement of speech language pathology specialists can be helpful for children manifesting language delays. A lack of language development, or a loss of language ability, should prompt immediate investigation to exclude electrographic status epilepticus in sleep.[85]

Cognitive, intellectual, and behavioural outcomes

Contrary to motor and language outcomes, which can usually be estimated in the first 2 years after perinatal stroke, cognitive, intellectual, and behavioural challenges might only manifest many years later as deficits become more apparent with age. The prevalence of such deficits is not well defined, but are as high as 69% for patients with neonatal arterial ischaemic stroke.[86] A study of 40 children with neonatal arterial ischaemic stroke and presumed perinatal stroke (arterial presumed perinatal ischaemic stroke and periventricular venous infarction) found that their average intelligence was in the low–normal range, but significantly lower than the normative cohort.[87] Average scores were also lower for attention, verbal retrieval, inhibitory control, flexibility and shifting, planning and organisation, and processing speed. Working memory was the only domain that was not different from the control group. Unlike adults with stroke, cognitive performance does not seem to be strongly affected by lesion size or side.[88] However, the presence of epilepsy is associated with adverse cognitive outcomes, and potentially treatable epileptic encephalopathy should be screened for in any child not following normal developmental curves.

Given that cognitive, intellectual, and behavioural challenges are common in children with perinatal stroke, formal neuropsycholgical testing upon entry to school is recommended to determine any need for educational support and learning strategies. Comorbidities, such as attention-deficit hyperactivity disorder (ADHD), should be screened for with standard measures. Although care providers can be reluctant to treat ADHD with stimulants in the setting of epilepsy, there is no evidence that treating ADHD worsens seizures,[89] and improving attention might be crucial to the child's academic and other successes. Cognitive rehabilitation strategies specific to perinatal stroke have not yet been developed.

Epilepsy

Although most children who present with symptomatic seizures can be weaned from antiseizure medications before discharge, remote symptomatic epilepsy often occurs years after perinatal stroke. Epilepsy prevalence ranges from approximately 6% for neonatal haemorrhagic[59] stroke to 40–50% for neonatal arterial ischaemic stroke[86] and arterial presumed perinatal ischaemic stroke.[67] In one study, neonatal seizures increased the risk of remote seizures or epilepsy with a cumulative incidence of 69% over 10 years and an overall prevalence of epilepsy of 54%.[90] In another study of neonatal arterial ischaemic stroke, epilepsy was present in only 16% of patients presenting with seizures,[91] suggesting substantial variability, which might relate to factors such as the size and location of infarcts and associated comorbidities. Lesions involving the cortex are more likely to be associated with epilepsy.[67] Epilepsy has been associated with poor neurodevelopmental outcomes in children with perinatal stroke, and thus identification and treatment of seizures remain important.[88,92] Any developmental delays should prompt additional investigations, particularly

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Search strategy and selection criteria

We searched MEDLINE for articles from before March 6, 2018, using the terms "stroke" or "brain ischaemia" combined with keywords "perinatal" or "neonatal" and limited the search to English-language articles about humans, which produced 448 results. We reviewed titles for relevance, excluding articles about hypoxic ischaemic encephalopathy, brain injury specific to premature infants, case studies, childhood stroke, and pregnancy-related maternal stroke, resulting in 203 articles for review. We did another MEDLINE search for cerebral sinovenous thrombosis, including perinatal, neonatal, and newborn terms with terms for cerebral thrombosis ("sinus thrombosis", "intracranial thrombosis" or "intracranial thrombosis CSVT", and "CVST") and limited the search to English-language publications and humans, producing 236 articles, which we then evaluated for exclusion criteria, including maternal complications, other stroke types, perisurgical complications, adult cases, preterm infants, and duplicate articles from the neonatal stroke search, resulting in 84 articles for review. Additionally, we screened the reference sections of the identified papers for potentially overlooked articles.

electroencephalogram monitoring with sleep to assess for epileptic encephalopathy, such as electrographic status epilepticus in sleep, which might be particularly common after thalamic haemorrhage secondary to deep cerebral sinovenous thrombosis.[93] For patients with medically refractory epilepsy, surgical resection of the injured area can result in seizure freedom and improved quality of life.[94] These interventions should be considered early, because ongoing seizures might negatively affect neuroplasticity and neurodevelopmental outcomes.

Parental and family outcomes

Parents of children with disabilities have increased stress and anxiety, and reduced quality of life, which appears to be proportional to the degree of disability.[95] In the case of perinatal stroke, anxiety can be compounded by knowledge of the timing of the stroke (in utero or at birth) but an inability of physicians to assign specific causative explanations, which can often lead to misplaced emotions of guilt in the mother, with consequences for the entire family, including post-traumatic stress disorder, depression, and marital discord.[6] The degree of blame regarding the cause of a child's disability can affect the association between the severity of the cerebral palsy and degree of caregiver depression.[6] One of the most meaningful interventions takes only a few minutes: explicitly educating the parents and informing the mother that the child's stroke could not have been prevented and is no way her fault. Numerous support groups are also available, which can be useful to families.

Conclusions

Perinatal stroke can now be defined as one of six specific disease states, on the basis of clinical presentation and neuroimaging findings. Acute symptomatic varieties typically present with seizures, presenting challenges for early recognition and prompt imaging diagnosis that can afford opportunities for neuroprotection and improved outcomes. Presumed perinatal stroke varieties usually present with hemiparetic cerebral palsy well after the inciting injury, shifting the focus of efforts towards neurorehabilitation to improve function and minimise lifelong disability. Across all forms of perinatal stroke, causative mechanisms are poorly understood, highlighting the need for additional studies as well as caution in assigning causation. Complex morbidities must be considered for all forms of perinatal stroke, including epilepsy, cognitive and behavioural disorders, and adverse effects on the mental health of the individual and entire family, who must remain at the centre of care.

Contributors

MD did the literature search and conducted the analysis, wrote the first draft and edited subsequent drafts, and generated the figures and table. AK edited the text, figures, and table, provided oversight and mentorship, and assumes full responsibility for the final publication.

Declaration of interests

We declare no competing interests.

References

1 Raju TNK, Nelson KB, Ferriero D, Lynch JK, NICHD-NINDS Perinatal Stroke Workshop Participants. 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* 2007; **120:** 609–16.

2 Nelson KB, Lynch JK. Stroke in newborn infants. *Lancet Neurol* 2004; **3:** 150–58.

3 Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. *Stroke* 2007; **38:** 2234–40.

4 Chabrier S, Husson B, Dinomais M, Landrieu P, Tich SNT. New insights (and new interrogations) in perinatal arterial ischemic stroke. *Thromb Res* 2011; **127:** 13–22.

5 Kirton A, Deveber G. Life after perinatal stroke. *Stroke* 2013; **44:** 3265–71.

6 Bemister TB, Brooks BL, Dyck RH, Kirton A. Predictors of caregiver depression and family functioning after perinatal stroke. *BMC Pediatr* 2015; **15:** 75.

7 Shepherd E, Middleton P, Makrides M, McIntyre S, Badawi N, Crowther CA. Neonatal interventions for preventing cerebral palsy: an overview of Cochrane systematic reviews. *Cochrane Database Syst Rev* 2017; **9:** CD012077.

8 Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA* 2005; **293:** 723–29.

9 deVeber GA. Canadian Pediatric Ischemic Stroke Registry: analysis of children with arterial ischemic stroke. *Ann Neurol* 2000; **48:** 514 (abstr).

10 Benders MJNL, Groenendaal F, Uiterwaal CSPM, de Vries LS. Perinatal arterial stroke in the preterm infant. *Semin Perinatol* 2008; **32:** 344–49.

11 Bernson-Leung ME, Rivkin MJ. Stroke in neonates and children. *Pediatr Rev* 2016; **37:** 463–77.

12 Rafay MF, Cortez MA, Deveber GA, et al. Predictive value of clinical and EEG features in the diagnosis of stroke and hypoxic ischemic encephalopathy in neonates with seizures. *Stroke* 2009; **40:** 2402–07.

13 Siddiq I, Armstrong D, Surmava A-M, et al. Utility of neurovascular imaging in acute neonatal arterial ischemic stroke. *J Pediatr* 2017; **188:** 110–14.

14 Husson B, Hertz-Pannier L, Adamsbaum C, et al. MR angiography findings in infants with neonatal arterial ischemic stroke in the middle cerebral artery territory: a prospective study using circle of Willis MR angiography. *Eur J Radiol* 2016; **85:** 1329–35.

15 Kirton A, Armstrong-Wells J, Chang T, et al. Symptomatic neonatal arterial ischemic stroke: the International Pediatric Stroke Study. *Pediatrics* 2011; **128:** e1402–10.

16 Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. *Stroke* 2004; **35:** 1769–75.

17 Govaert P, Zingman A, Jung YH, et al. Network injury to pulvinar with neonatal arterial ischemic stroke. *Neuroimage* 2008; **39:** 1850–57.

18 Estan J, Hope P. Unilateral neonatal cerebral infarction in full term infants. *Arch Dis Child Fetal Neonatal Ed* 1997; **76:** F88–93.

19 Harteman JC, Groenendaal F, Kwee A, Welsing PMJ, Benders MJNL, de Vries LS. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. *Arch Dis Child Fetal Neonatal Ed* 2012; **97:** F411–16.

20 Chabrier S, Saliba E, Nguyen The Tich S, et al. Obstetrical and neonatal characteristics vary with birthweight in a cohort of 100 term newborns with symptomatic arterial ischemic stroke. *Eur J Paediatr Neurol* 2010; **14:** 206–13.

21 Martinez-Biarge M, Cheong JLY, Diez-Sebastian J, Mercuri E, Dubowitz LMS, Cowan FM. Risk factors for neonatal arterial ischemic stroke: the importance of the intrapartum period. *J Pediatr* 2016; **173:** 62–68.e1.

22 Darmency-Stamboul V, Chantegret C, Ferdynus C, et al. Antenatal factors associated with perinatal arterial ischemic stroke. *Stroke* 2012; **43:** 2307–12.

23 Golomb MR, Dick PT, MacGregor DL, Curtis R, Sofronas M, Deveber GA. Neonatal arterial ischemic stroke and cerebral sinovenous thrombosis are more commonly diagnosed in boys. *J Child Neurol* 2004; **19:** 493–97.

24 Michoulas A, Basheer SN, Roland EH, Poskitt K, Miller S, Hill A. The role of hypoxia-ischemia in term newborns with arterial stroke. *Pediatr Neurol* 2011; **44:** 254–58.

25 Lehman LL, Beaute J, Kapur K, et al. Workup for perinatal stroke does not predict recurrence. *Stroke* 2017; **48:** 2078–83.

26 Bernson-Leung ME, Boyd TK, Meserve EE, et al. Placental pathology in neonatal stroke: a retrospective case-control study. *J Pediatr* 2018; **195:** 39–47.

27 Elbers J, Viero S, MacGregor D, Deveber G, Moore AM. Placental pathology in neonatal stroke. *Pediatrics* 2011; **127:** e722–29.

28 Fluss J, Garcia-Tarodo S, Granier M, et al. Perinatal arterial ischemic stroke related to carotid artery occlusion. *Eur J Paediatr Neurol* 2016; **20:** 639–48.

29 Giraud A, Guiraut C, Chevin M, Chabrier S, Sebire G. Role of perinatal inflammation in neonatal arterial ischemic stroke. *Front Neurol* 2017; **8:** 612.

30 Guiraut C, Cauchon N, Lepage M, Sebire G. Perinatal arterial ischemic stroke is associated to materno-fetal immune activation and intracranial arteritis. *Int J Mol Sci* 2016; **17:** 1980.

31 Cheong JLY, Cowan FM. Neonatal arterial ischaemic stroke: obstetric issues. *Semin Fetal Neonatal Med* 2009; **14:** 267–71.

32 Lequin MH, Peeters EAJ, Holscher HC, de Krijger R, Govaert P. Arterial infarction caused by carotid artery dissection in the neonate. *Eur J Paediatr Neurol* 2004; **8:** 155–60.

33 Roessmann U, Miller RT. Thrombosis of the middle cerebral artery associated with birth trauma. *Neurology* 1980; **30:** 889–92.

34 Curtis C, Mineyko A, Massicotte P, et al. Thrombophilia risk is not increased in children after perinatal stroke. *Blood* 2017; **129:** 2793–800.

35 Arnaez J, Arca G, Martín-Ancel A, Agut T, García-Alix A. Neonatal arterial ischemic stroke: risk related to family history, maternal diseases, and genetic thrombophilia. *Clin Appl Thromb Hemost* 2018; **24:** 79–84.

36 Pryde K, Walker WT, Hollingsworth C, et al. Stroke in paediatric pneumococcal meningitis: a cross-sectional population-based study. *Arch Dis Child* 2013; **98:** 647–49.

37 Hernández MI, Sandoval CC, Tapia JL, et al. Stroke patterns in neonatal group B streptococcal meningitis. *Pediatr Neurol* 2011; **44:** 282–88.

38 Boelman C, Shroff M, Yau I, et al. Antithrombotic therapy for secondary stroke prevention in bacterial meningitis in children. *J Pediatr* 2014; **165:** 799–806.

39 Monagle P, Chan AKC, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; **141** (suppl): e737S–801S.

40 Chang CJ, Chang WN, Huang LT, et al. Cerebral infarction in perinatal and childhood bacterial meningitis. *QJM* 2003; **96:** 755–62.

41 Shellhaas RA, Chang T, Wusthoff CJ, et al. Treatment duration after acute symptomatic seizures in neonates: a multicenter cohort study. *J Pediatr* 2017; **181:** 298–301.

42 Wang L, Zhang Z, Wang Y, Zhang R, Chopp M. Treatment of stroke with erythropoietin enhances neurogenesis and angiogenesis and improves neurological function in rats. *Stroke* 2004; **35:** 1732–37.

43 Osredkar D, Sall JW, Bickler PE, Ferriero DM. Erythropoietin promotes hippocampal neurogenesis in in vitro models of neonatal stroke. *Neurobiol Dis* 2010; **38:** 259–65.

44 Benders MJ, van der Aa NE, Roks M, et al. Feasibility and safety of erythropoietin for neuroprotection after perinatal arterial ischemic stroke. *J Pediatr* 2014; **164:** 481–86.

45 van Velthoven CTJ, Sheldon RA, Kavelaars A, et al. Mesenchymal stem cell transplantation attenuates brain injury after neonatal stroke. *Stroke* 2013; **44:** 1426–32.

46 Wagenaar N, de Theije CGM, de Vries LS, Groenendaal F, Benders MJNL, Nijboer CHA. Promoting neuroregeneration after perinatal arterial ischemic stroke: neurotrophic factors and mesenchymal stem cells. *Pediatr Res* 2018; **83:** 372–84.

47 Berfelo FJ, Kersbergen KJ, van Ommen CHH, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. *Stroke* 2010; **41:** 1382–88.

48 deVeber G, Andrew M, Adams C, et al. Cerebral sinovenous thrombosis in children. *N Engl J Med* 2001; **345:** 417–23.

49 Teksam M, Moharir M, deVeber G, Shroff M. Frequency and topographic distribution of brain lesions in pediatric cerebral venous thrombosis. *AJNR Am J Neuroradiol* 2008; **29:** 1961–65.

50 Carvalho KS, Bodensteiner JB, Connolly PJ, Garg BP. Cerebral venous thrombosis in children. *J Child Neurol* 2001; **16:** 574–80.

51 Fitzgerald KC, Williams LS, Garg BP, Carvalho KS, Golomb MR. Cerebral sinovenous thrombosis in the neonate. *Arch Neurol* 2006; **63:** 405–09.

52 Tan M, Deveber G, Shroff M, et al. Sagittal sinus compression is associated with neonatal cerebral sinovenous thrombosis. *Pediatrics* 2011; **128:** e429–35.

53 Claessens NHP, Algra SO, Jansen NJG, et al. Clinical and neuroimaging characteristics of cerebral sinovenous thrombosis in neonates undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2018; **155:** 1150–58.

54 Kenet G, Lütkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation* 2010; **121:** 1838–47.

55 Somma J, Sussman II, Rand JH. An evaluation of thrombophilia screening in an urban tertiary care medical center: a 'real world' experience. *Am J Clin Pathol* 2006; **126:** 120–27.

56 Lebas A, Chabrier S, Fluss J, et al. EPNS/SFNP guideline on the anticoagulant treatment of cerebral sinovenous thrombosis in children and neonates. *Eur J Paediatr Neurol* 2012; **16:** 219–28.

57 Jordan LC, Rafay MF, Smith SE, et al. Antithrombotic treatment in neonatal cerebral sinovenous thrombosis: results of the International Pediatric Stroke Study. *J Pediatr* 2010; **156:** 704–10.

58 Moharir MD, Shroff M, Pontigon A-M, et al. A prospective outcome study of neonatal cerebral sinovenous thrombosis. *J Child Neurol* 2011; **26:** 1137–44.

59 Cole L, Dewey D, Letourneau N, et al. Clinical characteristics, risk factors, and outcomes associated with neonatal hemorrhagic stroke: a population-based case-control study. *JAMA Pediatr* 2017; **171:** 230–38.

60 Merlini L, Hanquinet S, Fluss J. Thalamic hemorrhagic stroke in the term newborn: a specific neonatal syndrome with non-uniform outcome. *J Child Neurol* 2017; **32:** 746–53.

61 Armstrong-Wells J, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Prevalence and predictors of perinatal hemorrhagic stroke: results from the Kaiser Pediatric Stroke Study. *Pediatrics* 2009; **123:** 823–28.

62 Brouwer AJ, Groenendaal F, Koopman C, Nievelstein R-JA, Han SK, de Vries LS. Intracranial hemorrhage in full-term newborns: a hospital-based cohort study. *Neuroradiology* 2010; **52:** 567–76.

63 Looney CB, Smith JK, Merck LH, et al. Intracranial hemorrhage in asymptomatic neonates: prevalence on MR images and relationship to obstetric and neonatal risk factors. *Radiology* 2007; **242:** 535–41.

64 Towner D, Castro MA, Eby-Wilkens E, Gilbert WM. Effect of mode of delivery in nulliparous women on neonatal intracranial injury. *N Engl J Med* 1999; **341:** 1709–14.

65 Buetow PC, Smirniotopoulos JG, Done S. Congenital brain tumors: a review of 45 cases. *AJR Am J Roentgenol* 1990; **155:** 587–93.

66 Tekkök IH, Ventureyra ECG. Spontaneous intracranial hemorrhage of structural origin during the first year of life. *Childs Nerv Syst* 1997; **13:** 154–65.

67 Kirton A, Deveber G, Pontigon A-M, MacGregor D, Shroff M. Presumed perinatal ischemic stroke: vascular classification predicts outcomes. *Ann Neurol* 2008; **63:** 436–43.

68 Golomb MR, MacGregor DL, Domi T, et al. Presumed pre- or perinatal arterial ischemic stroke: risk factors and outcomes. *Ann Neurol* 2001; **50:** 163–68.

69 Kocaman C, Yilmaz Y. Etiological analysis of presumed perinatal stroke. *Brain Dev* 2012; **34:** 133–39.

70 Kirton A, Shroff M, Pontigon A-M, Deveber G. Risk factors and presentations of periventricular venous infarction vs arterial presumed perinatal ischemic stroke. *Arch Neurol* 2010; **67:** 842–48.

71 Gacio S, Muñoz Giacomelli F, Klein F. Presumed perinatal ischemic stroke: a review. *Arch Argent Pediatr* 2015; **113:** 449–55.

72 Ilves P, Laugesaar R, Loorits D, et al. Presumed perinatal stroke: risk factors, clinical and radiological findings. *J Child Neurol* 2016; **31:** 621–28.

73 de Vries LS, Roelants-van Rijn AM, Rademaker KJ, van Haastert IC, Beek FJ, Groenendaal F. Unilateral parenchymal haemorrhagic infarction in the preterm infant. *Eur J Paediatr Neurol* 2001; **5:** 139–49.

74 Kirton A, Wei X. Teaching neuroimages: confirmation of prenatal periventricular venous infarction with susceptibility-weighted MRI. *Neurology* 2010; **74:** e48.

75 Yoneda Y, Haginoya K, Kato M, et al. Phenotypic spectrum of COL4A1 mutations: porencephaly to schizencephaly. *Ann Neurol* 2013; **73:** 48–57.

76 Hebert D, Lindsay MP, McIntyre A, et al. Canadian stroke best practice recommendations: stroke rehabilitation practice guidelines, update 2015. *Int J Stroke* 2016; **11:** 459–84.

77 Pediatric Stroke Working Group. Stroke in childhood. London: Royal College of Paediatrics and Child Health, 2017.

78 Kirton A. Advancing non-invasive neuromodulation clinical trials in children: lessons from perinatal stroke. *Eur J Paediatr Neurol* 2017; **21:** 75–103.

79 Gillick B, Rich T, Nemanich S, et al. Transcranial direct current stimulation and constraint-induced therapy in cerebral palsy: a randomized, blinded, sham-controlled clinical trial. *Eur J Paediatr Neurol* 2018; **22:** 358–68.

80 Kirton A, Ciechanski P, Zewdie E, et al. Transcranial direct current stimulation for children with perinatal stroke and hemiparesis. *Neurology* 2017; **88:** 259–67.

81 Lai PT, Reilly JS. Language and affective facial expression in children with perinatal stroke. *Brain Lang* 2015; **147:** 85–95.

82 Reilly JS, Wasserman S, Appelbaum M. Later language development in narratives in children with perinatal stroke. *Dev Sci* 2013; **16:** 67–83.

83 Raja Beharelle A, Dick AS, Josse G, et al. Left hemisphere regions are critical for language in the face of early left focal brain injury. *Brain* 2010; **133:** 1707–16.

84 Woolpert D, Reilly JS. Investigating the extent of neuroplasticity: writing in children with perinatal stroke. *Neuropsychologia* 2016; **89:** 105–18.

85 Mineyko A, Qi W, Carlson HL, Bello-Espinosa L, Brooks BL, Kirton A. Neuropsychological outcome in perinatal stroke associated with epileptiform discharges in sleep. *Can J Neurol Sci* 2017; **44:** 358–65.

86 Lehman LL, Rivkin MJ. Perinatal arterial ischemic stroke: presentation, risk factors, evaluation, and outcome. *Pediatr Neurol* 2014; **51:** 760–68.

87 Bosenbark DD, Krivitzky L, Ichord R, Jastrzab L, Billinghurst L. Attention and executive functioning profiles in children following perinatal arterial ischemic stroke. *Child Neuropsychol* 2016; **24:** 106–23.

88 Ballantyne AO, Spilkin AM, Hesselink J, Trauner DA. Plasticity in the developing brain: intellectual, language and academic functions in children with ischaemic perinatal stroke. *Brain* 2008; **131:** 2975–85.

89 Santos K, Palmini A, Radziuk AL, et al. The impact of methylphenidate on seizure frequency and severity in children with attention-deficit-hyperactivity disorder and difficult-to-treat epilepsies. *Dev Med Child Neurol* 2013; **55:** 654–60.

90 Fox CK, Glass HC, Sidney S, Smith SE, Fullerton HJ. Neonatal seizures triple the risk of a remote seizure after perinatal ischemic stroke. *Neurology* 2016; **86:** 2179–86.

91 Suppiej A, Mastrangelo M, Mastella L, et al. Pediatric epilepsy following neonatal seizures symptomatic of stroke. *Brain Dev* 2016; **38:** 27–31.

92 Bosenbark DD, Krivitzky L, Ichord R, et al. Clinical predictors of attention and executive functioning outcomes in children after perinatal arterial ischemic stroke. *Pediatr Neurol* 2017; **69:** 79–86.

93 Kersbergen KJ, de Vries LS, Leijten FSS, et al. Neonatal thalamic hemorrhage is strongly associated with electrical status epilepticus in slow wave sleep. *Epilepsia* 2013; **54:** 733–40.

94 Ghatan S, McGoldrick P, Palmese C, et al. Surgical management of medically refractory epilepsy due to early childhood stroke. *J Neurosurg Pediatr* 2014; **14:** 58–67.

95 Bemister TB, Brooks BL, Dyck RH, Kirton A. Parent and family impact of raising a child with perinatal stroke. *BMC Pediatr* 2014; **14:** 182.