Imaging of Perinatal Stroke

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The main neonatal stroke syndromes discussed in this review are: arterial ischemic stroke (AIS), including perinatal arterial ischemic stroke (PAIS) and “presumed” perinatal AIS; cerebral venous thrombosis (CVT), including cortical vein and venous sinus thrombosis and germinal matrix hemorrhage/periventricular hemorrhagic infarction; and intraparenchymal hemorrhage. Cerebral infarction in neonates may also occur as a result of cerebral hypotension causing hypoxic-ischemic brain injury, multiple vascular occlusions in meningencephalitis and cerebritis, and in some rare congenital disorders such as incontinentia pigmenti. Infarctions due to abnormal metabolism at a cellular level may occur in neurometabolic disorders such as molybdenum cofactor deficiency, organic acidemias, and hypoglycemia. These other causes of cerebral infarction are beyond the scope of this article.

The World Health Organization defines stroke as “a clinical syndrome of rapidly developing focal or global disturbance of brain function lasting more than 24 hours or leading to death with no obvious nonvascular cause.” This definition of stroke as a clinical syndrome with acute onset of a neurologic deficit is not readily applicable to strokes occurring in early life, either in children or in neonates. It is recognized that by this definition, children will have a nonvascular cause for their neurologic presentation in 1 out of 3 cases. Furthermore, neonates with an acute stroke may be asymptomatic, particularly preterm infants, or they may have a nonspecific clinical presentation such as lethargy, hypotonia, apnea, or feeding difficulties. The published series that have reported the highest rates of neonatal stroke are those in which the diagnosis was made by detecting an infarct on neuroimaging performed during routine screening rather than in symptomatic infants. For these reasons the diagnosis of stroke in neonates, as in children, relies on radiologic (or pathologic) confirmation. It is also recognized that some strokes occur in utero before birth. In the published literature perinatal stroke has been inconsistently defined as a focal cerebrovascular insult sustained at any time between 20 and 28 gestational weeks and 7 to 28 days of neonatal life. In an attempt to reach some consensus of definition, at least for the purposes of research, the National Institute of Child Health-National Institute of Neurological Disorders and Stroke (NICHD-NINDS) perinatal workshop defined perinatal stroke as a “a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombus or embolization” occurring “between 20 weeks of fetal life through the 28th postnatal day and confirmed by neuroimaging or neuropathological studies.” Their imaging criteria defined stroke as either

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- Germinal matrix hemorrhage-intraventricular hemorrhage
- Periventricular hemorrhagic infarction
- Intraparenchymal hemorrhage

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a partial or complete occlusion of a vessel with a focal brain lesion in that territory or brain imaging corresponding to infarction in a recognized vascular territory. By this definition an acute neurologic presentation is no longer necessary, while neuroimaging has become essential in making the diagnosis of perinatal stroke.

Some children in whom stroke is not detected in the neonatal period may present later with signs such as asymmetry of reach and grasp, failure to reach normal milestones, postnatal seizures, and congenital hemiplegia. In these children, in whom the presentation of hemiplegia or seizures is not acute, the diagnosis of presumed perinatal AIS is made based on neuroimaging appearances of a chronic arterial territory infarct. Hence the timing of the AIS is remote from the clinical presentation. It is assumed to be perinatal on the basis that beyond the neonatal period, stroke is likely to have presented as an acute focal or global neurologic deficit, and also on the presence of characteristic imaging features that establish that the stroke most likely occurred in early life.

The NICH-NINDS classification separates perinatal stroke into 3 groups: (1) fetal ischemic stroke diagnosed before birth using imaging or in stillbirths on the basis of postmortem pathologic examination, (2) neonatal ischemic stroke diagnosed after birth and before the 28th postnatal day (including preterm infants), and (3) presumed perinatal ischemic stroke, diagnosed in infants older than 28 days in whom it is presumed (but not certain) that the ischemic event occurred sometime between the 20th week of fetal life through the 28th postnatal day.2

Cranial ultrasonography, computed tomography (CT), and magnetic resonance (MR) imaging are the 3 main imaging techniques available to image the neonatal brain. Ultrasonography is readily available, inexpensive, portable, and can be performed at the bedside. It is usually the first-line brain-imaging technique performed on the neonatal unit, and allows serial examinations to be performed without transfer of the sick neonate to the radiology department. However, ultrasonography lacks sensitivity for all types of neonatal stroke, particularly lesions at interfaces with bone such as posterior fossa lesions and peripherally based cortical lesions. It is dependent on the level of skill and experience of the operator. CT has some advantages over MR imaging in that it is a quicker examination with less need for sedation. CT depicts venous sinus thrombosis and hemorrhage well. However, potential concerns regarding radiation effects on the developing neonatal brain and increased lifelong risk of cancer limit its use to neonates who are acutely deteriorating clinically and in whom neurosurgical intervention is being considered, or when there is limited access or contraindication to MR imaging. Multislice brain CT should be performed according to low-dose pediatric protocols that vary dose according to weight and age. The authors do not recommend the use of currently commercially available portable CT scanners for imaging the neonatal or infant brain because diagnostic quality is less good and a greater radiation dose is required compared with departmental scanners. Overall, CT is less sensitive for the detection and characterization of brain lesions, and MR imaging is the modality of choice for evaluating the neonatal brain. However, it is important that MR imaging and sedation protocols are optimized to allow multiplanar imaging, multiple sequences (T1, T2, and diffusion-weighted imaging) providing differing tissue contrasts, and vascular imaging (MR angiography, MR venography) without artifacts from motion.

PERINATAL ARTERIAL ISCHEMIC STROKE

Incidence

Eighty percent of perinatal stroke is attributable to AIS; this differs from the relative incidence of AIS in children in whom ischemic stroke (AIS and cerebral sinovenous thrombosis [CSVT]) and hemorrhagic stroke occur with the same frequency. The incidence of perinatal AIS is estimated to occur in around 1 in 1600 to 5000 births in populations from the United Kingdom, Switzerland, the United States, and Estonia.5–8 The United Kingdom study found that acute PAIS was more common in boys than in girls whereas presumed PAIS was more common in girls.5

These variations in incidence may be explained by differing diagnostic criteria and use of MR imaging, as well as different study populations. For example, the Estonian study included all neonatal stroke, including hemorrhagic stroke, in its cohort. Both this and the United States study included retrospectively diagnosed, presumed PAIS as well as neonatal AIS. These two studies had the highest incidences and showed that many perinatal strokes (42%,5 68%6 of all PAIS) are not diagnosed until later in life. This figure may still be an underestimate of the true incidence of PAIS, as it is likely that some PAIS is asymptomatic or associated with very mild deficits and therefore may go undetected during life. A hospital-based study by Benders and colleagues9 found that PAIS is not uncommon in preterm infants under gestational age of approximately 34 weeks, with an even greater incidence of 7 in 1000. Two possible explanations for this relatively high incidence may be the use of routine cranial
ultrasonography in this population and their exposure to more invasive procedures during their stay in the neonatal intensive care unit.

Perinatal stroke affects 20 to 62.5 per 100,000 live births. This high incidence compares with an annual incidence rate of stroke in children after the first month of life of 2.3 to 13 per 100,000 per year, similar to the incidence of pediatric brain tumor. The peak incidence of AIS is in the first year of life, and does not rise to these levels again until much later in life. The risk is highest in the perinatal period soon before birth and in the month after. This increased risk of neonatal AIS is mirrored by a parallel increased risk of ischemic stroke in the mother that is up to 5 times greater just before and for the day after delivery than earlier in pregnancy or when not pregnant. This increased maternal and neonatal risk of ischemic stroke is related to the activation of coagulation cascades during normal birth, likely to be an evolutionary adaptation to reduce the risk of blood loss during delivery.

Pathophysiology and Risk Factors

The majority of PAIS is most likely to be caused by thromboembolism passing from the placenta through the patent neonatal foramen ovale, although other potential sources include the fetal/neonatal heart and extracranial vessels (Box 1 and Fig. 1). By the end of the embryonic period the developing cerebral arterial system is already anatomically to that of the adult, and therefore the arterial territories that are affected in PAIS are the same as those in adults. Most PAIS occurs in the middle cerebral artery (MCA) territory, typically either a complete MCA infarct or a posterior truncal infarct, and the left MCA is affected 3 to 4 times more commonly than the right. This bias has been explained as the result of hemodynamic arterial flow; placental emboli or systemic venous emboli in the fetus or neonate may pass through a patent foramen ovale or patent ductus arteriosus directly into the left common carotid artery and hence to the left MCA. The sick newborn is also at risk from right-to-left shunting associated with respiratory disease, pulmonary hypertension, or congenital heart disease.

Hence most of the associated risk factors for perinatal stroke appear to be related to an increased propensity for thromboembolism. The physiologic activation of the coagulation cascade in the fetus and mother around delivery is normally a transient phenomenon, which may explain why the recurrence risk of neonatal stroke is extremely low, and then mainly seems to recur in children in whom there is an underlying procoagulation

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<th>Box 1</th>
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<td><strong>Risk factors for perinatal stroke</strong></td>
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<td><strong>Maternal factors</strong></td>
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<td>Autoimmune disorders</td>
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<td>Coagulation disorders (Protein C deficiency, Protein S deficiency, Factor V Leiden)</td>
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<td>Anticardiolipin antibodies</td>
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<td>Twin-to-twin transfusion syndrome</td>
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<td><strong>Cardiac disorders</strong></td>
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<td>Patent ductus arteriosus</td>
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<td>Pulmonary valve atresia</td>
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<td>Cardiac surgery (associated with cardiac bypass, atrial balloon septostomy)</td>
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<td><strong>Fetal and neonatal blood and lipid disorders</strong></td>
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<td>Disseminated intravascular coagulopathy</td>
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<td>Factor V Leiden mutation</td>
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<td><strong>Vasculopathy</strong></td>
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<td><strong>Trauma and catheterization</strong></td>
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<td>Dehydration</td>
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<td>Extracorporeal membrane oxygenation</td>
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This situation differs from that in AIS in children, in whom the recurrence risk is 6% to 13% with an even higher recurrence risk of transient ischemic attack (TIA) or “silent infarct.”

While thromboembolism is also a risk factor in pediatric stroke, it appears there is a greater range of underlying etiological factors for stroke in children; arteriopathy is one of the commonest causes of childhood stroke and is associated with recurrence risk, a feature that has not been recognized (or systematically studied) in neonatal stroke. Beyond a few case reports in which the diagnosis of dissection was presumptive and made without pathognomonic radiological evidence of a dissection flap or intramural thrombus, there is little evidence that arterial dissection is a common cause of PAIS, unlike in older children.

Risk factors for thromboembolism for PAIS include fetal/neonatal, maternal, and placental factors, and are found in 42% to 78% of PAIS. In one study thromboembolic risk factors were found in 68% of PAIS compared with 24% of normal controls. Multiple risk factors for thromboembolism may coexist. Normal neonates already have several risk factors for thrombus formation in the perinatal period, including a raised hematocrit, presence of fetal hemoglobin, high procoagulant proteins, and increased blood viscosity. Additional blood and lipid disorders are also associated with PAIS. Twin pregnancies have a greater risk of PAIS, which appears to be independent of twin-twin transfusion syndrome or co-twin demise.

Congenital heart disease is an independent risk factor for perinatal stroke. White matter lesions are more common than arterial territory cortical infarcts. In studies investigating brain MR imaging abnormalities in children with congenital heart disease, periventricular white matter injury was seen on MR imaging in 16% to 43% of patients with congenital heart disease prior to any operative procedure. The changes were focal and asymptomatic, and were seen in children without any acute postnatal hypoxic-ischemic event. Although established lesions do not appear to progress postoperatively, additional ischemic lesions are found after cardiac surgery. Impairment of brain development during the fetal period in children with congenital heart disease (measured by quantitative advanced MR imaging techniques) is recognized. It is suggested that the brains of children with congenital heart disease...
disease are immature and behave in a similar way to the brains of preterm babies affected by hypoxic-ischemic injury, and that the white matter is particularly susceptible. In these studies risk factors associated with acquired postoperative brain injury included risk factors for cerebral hypotension, such as cardiopulmonary bypass (CPB) with regional cerebral hypoperfusion, lower intraoperative cerebral hemoglobin oxygen saturation during the myocardial ischemic period of CPB, and low mean blood pressure during the first postoperative day. However, neonates with congenital heart disease are also at risk of AIS. Preoperative AIS is typically arterial territory branch cortical infarction and is associated with balloon atrial septostomy, whereas white matter injury is not. Children are also at risk of thromboembolic AIS from cardiac catheters and other vascular catheters. Extracorporeal membranous oxygenation (ECMO) is a specific thromboembolic risk. Specific artificial devices such as the Berlin Heart, a pediatric mechanical ventricular assist device, are also associated with neonatal AIS (Fig. 2).

Although an association with hypoxic-ischemic encephalopathy (HIE) in term babies has been described, there is actually little evidence for HIE as a cause when strict diagnostic definitions are used. The more usual scenario is a term baby born in good condition after an uncomplicated pregnancy and labor or elective cesarean section. Hypoglycemia is recognized as an independent risk factor for PAIS in preterm babies but not in term babies, in whom hypoglycemic brain injury usually manifests as bilateral parieto-occipital lobe infarction.

The placenta itself has an important role in the etiology of thromboembolism in perinatal stroke; placental disorders include thrombosis, abruption and fetomaternatal hemorrhage, placental infection, and chorioamnionitis. Placental thrombotic vasculopathy is a commonly recognized finding, and may be linked to maternal prothrombotic conditions. Emboli may also arise from umbilical vascular catheters.

Maternal factors associated with PAIS include maternal procoagulation tendencies and autoimmune disorders. Factor V Leiden deficiency, increased lipoprotein(a) and antiphospholipid antibodies, and heterozygosity or homozygosity of methyltetrahydrofolate reductase mutations are seen with greater frequency in neonates with PAIS and their mothers. Other maternal factors include a history of infertility, infection, preeclampsia, maternal trauma, diabetes, in utero cocaine use, prolonged labor, and instrumented delivery. Primiparity has been identified as a risk factor in 30% to 75% of cases of PAIS in term infants but not in preterms. This finding may be more closely related to a prolonged second stage of labor, as primiparity did not remain a statistically significant independent risk factor on multivariate analysis.

Clinical Presentation

Acute presentation in the neonatal period

Although epidemiologic data may be less accurate given the limitations of missed or later diagnoses, approximately 60% of cases of PAIS do present acutely in the neonatal period, mostly with recurrent focal seizures in the first 3 days of life.

Fig. 2. CT brain scans of a 5-week-old baby with congenital heart disease presenting with seizures, who had received a Berlin Heart ventricular assist device and was therefore unable to have MR imaging. Unenhanced CT brain scans (left, middle) show bilateral low-density lesions in the basal ganglia and right thalamus in keeping with arterial perforator territory infarcts, with some hyperdensity due to secondary hemorrhagic transformation. Contrast was also given (right), showing enhancement in the regions of hemorrhagic transformation indicating disruption of the blood-brain barrier.
Therefore about 40% of the children do not have specific symptoms in the neonatal period, and are only recognized later with the emergence of motor impairment, developmental delay, specific cognitive deficiency, or seizures. Twenty-five percent to 40% of term infants with PAIS present with seizures. After hypoxic ischemia, perinatal arterial ischemic stroke is the second most common cause of neonatal seizures in term newborns; this differs from AIS in childhood whereby the most common presentations are an acute focal deficit (91%), seizures (23%), or headache (44%).

Typically PAIS occurs in a term baby with a normal antenatal course who appears generally well. The baby usually has a normal neurologic examination with preserved primitive reflexes, and no or minimal signs of encephalopathy. Usually the seizures in PAIS are focal with clinical recovery in between, matched by electroencephalography (EEG) changes of focal spikes and/or sharp waves during seizures, but usually a normal background EEG. In other neonates there may be subtle, nonspecific neurologic signs of hypotonia, lethargy, poor feeding, duskniness, or apnea. Hemiparesis is rarely found on neurologic examination at this age. Hence the diagnosis of PAIS is made only when neuroimaging confirms a lesion consistent with focal infarction in an arterial vascular territory.

**Presumed diagnosis of PAIS made retrospectively**

Infants and children with presumed PAIS are diagnosed after the neonatal period; they do not have clinical signs during the neonatal period or may have signs that are so subtle that they escape detection. Such patients may present later with hemiplegia, focal hand weakness, or pathologic early hand preference occurring when younger than 1 year of age. These motor deficits are usually only detected from the middle of the first year of life onward, when coordinated voluntary motor activity is developing. Children may present with other long-term neurologic problems such as cognitive impairment and seizures. In these children the diagnosis is presumptive, and relies on confirmation of neuroimaging findings of a chronic arterial territory infarct.

**Fetal or preterm ischemic stroke**

Fetuses may be diagnosed with AIS based on a routine early second-trimester anomaly screening ultrasound scan (ideally confirmed by MR imaging), on ultrasound scans done later in pregnancy for other reasons, or on postmortem examination. PAIS in preterm infants is more likely to be asymptomatic than in term babies, and is often detected as the result of routine cranial ultrasonography or brain MR imaging in the (sick) preterm infant. In one study PAIS was detected in 10% of all preterms who had routine cranial ultrasonography as part of their assessment. Equally PAIS was found in 10% of preterms who were symptomatic with apneas that were subsequently confirmed as seizures using amplitude-integrated EEG.

**Imaging**

The role of imaging is to make or confirm the diagnosis of PAIS and to exclude stroke mimics such as encephalitis, hypoglycemia, and hypoxic ischemia. Neuroimaging can be used to help time the onset of the infarct and to confer information regarding prognosis. Neuroimaging definition criteria for PAIS are: (1) imaging evidence of a partial or complete occlusion of an artery in relation to a focal brain lesion, or (2) distribution of parenchymal lesion(s) that can only be explained by occlusion of a specific brain artery.

**Site**

The developing arterial system is already similar to the mature arterial system by the end of the embryonic period, the major differences being in the watershed sites between arterial territories, which have shifted from the germinal matrix and periventricular regions to more lateral parasagittal cortex by term. Hence the lesion pattern caused by occlusion of a particular artery is already established by 20 gestational weeks and is consistent throughout life.

Any arterial territory may be involved; however, most infants with PAIS show involvement of the MCA territory (75%) and usually of the left hemisphere (55%). Posterior circulation infarction is relatively unusual, and this is comparable with the distribution in children in whom isolated anterior circulation infarcts (73%) are much more common than posterior circulation infarcts (21%). Multiple arterial territories may be involved in thromboembolic disease, and 6% to 25% of perinatal arterial ischemic strokes are bilateral. The most common MCA branches affected in term infants are the main branch of the MCA, resulting in complete MCA territory infarction, and the posterior MCA trunk, causing posterior temporal and parietal lobe infarction. After this, in decreasing order of frequency, are infarcts in the territories of the internal carotid, anterior cerebral, posterior cerebral, posterior communicating, and anterior choroidal arteries. As in the term population, the majority of strokes in preterm infants involve the MCA (81%); however, the involvement of different branches of the MCA appears to change...
with gestational age. Involvement of one or more lenticulostriate branches was most common among infants with a gestational age of 28 to 32 weeks.41

**Evolution of infarction on neuroimaging**

Magnetic resonance imaging Swelling of astrocytes is seen on pathologic studies within 30 minutes of onset of ischemia, and by 4 to 6 hours swelling of oligodendrocyte nuclei and cytoplasm is seen microscopically.42 MR imaging, particularly diffusion-weighted imaging, is more sensitive than both cranial ultrasonography and CT for the detection of acute AIS, and MR imaging is the modality of choice in the neuroimaging evaluation of suspected neonatal stroke.

Animal experiments show restricted diffusion on brain MR imaging scans within the infarcted parenchyma minutes after ischemia.43 The exact mechanism accounting for the appearances of restricted diffusion in acute ischemia is not completely understood. In tissue ischemia energy depletion leads to disruption of the energy-dependent ion pump, which causes increased intracellular sodium and water and results in cytotoxic edema. There is a net shift of water from the extracellular space to the intracellular space, with reduced free water movement within the interstitial fluid. This shift is not the only contribution to the signal hyperintensity on diffusion-weighted images, as increased signal due to T2 effects becomes more important later when cytotoxic edema has already occurred.

On diffusion-weighted imaging the earliest changes of infarction are seen as signal hyperintensity in the affected arterial territory, and can be seen before changes on T2-weighted sequences are appreciated. The signal hyperintensity is maximal until 4 days after birth and slowly declines, but remains higher than in normal brain for up to 1 to 2 weeks.44–46 These earliest diffusion-weighted signal hyperintensity changes are matched by low signal on calculated apparent diffusion coefficient (ADC) maps. The ADC values in infarction progressively decrease over the first 3 days before beginning to increase again, reaching normal values, or pseudonormalization, by 4 to 10 days.47,48 It is suggested that this ADC change broadly correlates with the presence of cytotoxic edema. Thereafter, ADC values progressively increase as vasogenic edema develops. The evolution of these changes with time is probably similar to those changes described in adults though has not been systematically studied. However, the signal hyperintensity seen on diffusion-weighted images in adults often persists for longer, often appearing hyperintense weeks after the initial event. In adults the cortical gray matter shows a smaller drop in measured ADC values and a slightly faster rate of increase in ADC than white matter, hence pseudonormalization occurs slightly earlier in the cortical gray matter.49 This appearance is also probably similar in neonates.

The cortex in the region of infarction is initially hyperintense on T2-weighted imaging for the first 6 days. It is seen as loss of the normal, relatively darker signal of the cortical ribbon in comparison with the unmyelinated white matter (Fig. 3). On T1 weighted imaging the cortex may appear relatively dark with respect to normal cortex. During this time the white matter also appears hyperintense on T2-weighted imaging, and this persists for 2 to 3 weeks or so before declining to eventually appear similar to unaffected brain. The white matter appears mildly hyperintense on T1-weighted imaging during the first 8 to 9 days compared with the normal cerebral white matter (though not as bright as the T1 shortening seen with subsequent haemorrhagic transformation or cortical highlighting). This feature is particularly apparent in acute neonatal AIS, possibly because of the relatively greater contrast between the normal low signal of the neonatal unmyelinated cerebral white matter and adjacent cortex.

Neonates have smaller vessels with lower blood flow velocities than children or adults, making MR angiography and MR venography of the neonatal brain more technically challenging for assessment of the vascular anatomy, vessel diameter, and flow. Three techniques are available: time-of-flight, phase-contrast, and contrast-enhanced MR angiography. Each has its advantages and disadvantages, but the first 2 techniques may be successfully used in the neonate without the need for contrast. In PAIS, MR angiography may show medium-vessel or large-vessel occlusion, supporting the pathogenesis of thromboembolism (Fig. 4), but may also be normal.

**Ultrasonography** Although relatively insensitive for the diagnosis of AIS, cranial ultrasonography is usually the first neuroimaging test that will be performed, either in symptomatic term infants or on routine screening of sick preterm infants. The typical appearances are a well-defined wedge-shaped region of increased echogenicity affecting cortex and white matter in a recognized arterial territory. Doppler studies in MCA infarcts may, or may not,50 show transient reduced flow and pulsatility on the affected side that becomes similar to the contralateral unaffected side by 24 hours.51 The exact reason for this is not known; possible explanations for the subsequent improved flow include migration of arterial embolus and
compensatory cross-flow. Most neonatal strokes have a patent MCA by the time of presentation. The sensitivity of ultrasonography for the detection of AIS increases with the age of the infarct (68% sensitive in the first 3 days compared with 87% between days 4 and 10\textsuperscript{52}) but it is well recognized to miss small, peripherally located cortical infarcts, and posterior circulation infarcts, even when these are retrospectively diagnosed following a positive MR imaging study. Repeated imaging may be required to detect a lesion. Typically an MCA infarct is easier to diagnose when mass effect is at its greatest, around the third day, where ultrasonography may have some advantage over MR imaging in the detection of small perforator territory AIS such as those seen in preterm infants.\textsuperscript{9}

Necrosis and organization From 6 hours to 6 days coagulation necrosis is associated with damage to the endothelium and breakdown of the blood-brain barrier, leading to vasogenic edema and brain swelling. Swelling of the affected brain is usually maximal at 3 days and is evidenced by sulcal effacement, and in large anterior circulation infarcts by subfalcine and uncal herniation with shift of midline structures. If the cerebral swelling progresses, contralateral hydrocephalus may develop. Although not routinely given, contrast enhancement may be seen as a consequence of disruption of the blood-brain barrier. Hemorrhage may be seen as the result of reperfusion of the infarct. Increased flow velocities such as diastolic arterial flow with a lowered resistance index and increased venous flow may be seen on ultrasonography as a result of regional luxury perfusion.

The pathologic description of laminar necrosis is of necrosis in the cortex; this may affect all layers or just the middle to deeper cortical layers (pseudolaminar necrosis). The imaging correlate of this is

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Fig. 3. MR axial T2-weighted images (top row), diffusion-weighted image, and calculated apparent diffusion coefficient (ADC) map (bottom row) of a term baby boy whose mother noticed jerking movements of his right limbs at 6 hours of life resolving within 20 minutes. While on the neonatal unit the baby again developed jerking movements of the right upper and lower limbs. Electroencephalography (EEG) showed left-sided focal seizures. MR imaging on day 3 of life showed bilateral multiple acute cortical branch MCA territory infarcts. Note the cortical and white matter signal hyperintensity on T2-weighted images with loss of normal cortical ribbon in some regions (arrows). The diffusion-weighted imaging increases the conspicuity of the lesions; these show restricted diffusion with signal hyperintensity on the diffusion-weighted image (left) matched by low signal on the ADC map (right).
believed to be cortical highlighting, or T1 shortening localized to the cortex. This is seen from days 5 to 6 after onset; from this time the cortex also becomes dark on T2-weighted imaging. These cortical changes are generally thought to be related to petechial hemorrhage or increased paramagnetic substances, release of myelin lipids, or calcification.53,54 Susceptibility-weighted imaging has been used in attempts to differentiate the changes seen on T1-weighted imaging from hemorrhage; in one study the cortical highlighting did not correspond with dark signal on susceptibility imaging, and the assumption was made that the changes are not due to hemorrhage.55 However, this study did not differentiate extracellular met as in methemoglobin hemoglobin, which is bright on both T1-weighted and T2-weighted sequences, from the other molecular forms of hemorrhage that do demonstrate susceptibility effects.

From 3 days to 6 weeks the infarct organizes, a process in which central liquefaction develops in necrotic areas with gliosis, breakdown of myelin, microcyst formation, calcification, and peripheral neovascularization. During this time the infarct shows signal changes in keeping with increased water content compared with unaffected brain, but has not yet cavitated. Strands of tissue may be seen crossing the infarct.

Tissue loss Cystic cavitation and atrophy in the affected arterial territory are seen from approximately 4 weeks after onset. Typically the cyst is lined by a gliotic scar, and there may be hemosiderin. On MR imaging this is seen as regions of cystic cavitation or encephalomalacia with surrounding signal change in keeping with gliosis. When imaged later in life, as in a presumed large perinatal MCA infarct the whole of the cerebral hemisphere appears smaller, and there may be compensatory expansion of the calvarial diploic space and paranasal and mastoid sinuses (Fig. 5).
Acute secondary neuronal pre-Wallerian and Wallerian degeneration Secondary signal intensity changes remote from the infarction are seen in the brainstem and thalamus in the first week. In some MCA infarcts, restricted diffusion occurs outside the MCA territory within the more caudal ipsilateral corticospinal tract within the brainstem (Fig. 6). These diffusion changes occur earlier than the signal hyperintensity on T2-weighted images and focal swelling seen subsequently. Within a few weeks these changes progress to mature injury with evidence of atrophy and gliosis, sometimes with T1 shortening, as a secondary neuronal degenerative or Wallerian-type phenomenon. Similarly, acute changes of restricted diffusion with subsequent T2 signal changes and swelling are also seen within the medial thalamus, which are likely attributable to secondary degeneration of corticothalamic projections. Contralateral cerebellar hemisphere atrophy may be seen as a result of crossed cerebellar diaschisis following MCA infarction.

Treatment

Although there are currently 3 international evidence-based stroke guidelines for the investigation and management of stroke in children, only the American Heart Association (AHA) Stroke Council guideline (2008) specifically addresses neonatal stroke. There is no specific treatment for stroke, and management is supportive and directed at modification of etiological factors as well as treatment of the complications of stroke such as epilepsy. Recommendations for surgery are ventricular drainage of hydrocephalus complicating hematoma evacuation or shunting if hydrocephalus persists (Class I recommendation), and hematoma evacuation in the presence of raised intracranial pressure, though this may not necessarily improve outcome (Class II recommendation). Anticoagulation may be considered for recurrent thromboembolic stroke, but specific recommendations are not made. Thrombolytic agents are not recommended in neonates while...
more information about the safety and effectiveness of these agents is awaited.

**Predicting Outcome**

The main adverse outcomes following PAIS are hemiplegia, epilepsy, visual impairment, cognitive impairment, and behavioral difficulties. However, some children (33%–40%) will have a normal outcome, presumably due to plasticity of the neonatal brain. There is no evidence of an increased risk of death in neonates with AIS unless there are additional complicating factors such as congenital heart disease or HIE. All of the outcome studies to date show that the outcome for babies with stroke is better than that for older children and adults.

**Motor Impairment**

Up to 50% of neonates with PAIS will develop subsequent hemiplegia. Hemiplegia is usually not evident in the neonate or infant, but may be detected in later life. Children with PAIS may also develop more subtle motor impairments, which may present even later. Nevertheless, most children will still be able to achieve independent walking. Early MR imaging performed around the time of the acute infarct can be used to predict the subsequent development of hemiplegia. In general, small infarcts of the posterior cortical branches of the MCA or posterior cerebral artery are associated with a better prognosis than large main-branch MCA infarcts. Involvement of 3 sites of cerebral infarction (basal ganglia, posterior limb of the internal capsule, and temporoparietal cortical infarction) as seen in main-branch MCA infarction predicts future hemiplegia, whether occurring at term or preterm. Acute pre-Wallerian secondary neuronal degeneration with restricted diffusion in the corticospinal tract caudal to the infarct also predicts future hemiplegia. Combining these findings further refines motor outcome prediction. In their study of 73 infants with PAIS...
affecting the MCA territory, Husson and colleagues found that 72% of babies with superficial cortex, basal ganglia involvement, and restricted diffusion of the corticospinal tract (CST) developed later motor impairment by age 2 years.62 Mixed infarctions involving superficial cortex and basal ganglia (P<.001) and CST involvement (P<.001) were highly predictive of hemiplegia, whereas most babies (88%) with isolated superficial cortical infarcts did not develop future motor impairment. Absence of CST involvement predicted normal motor outcome in 94%.

The risk of epilepsy for a child with PAIS increases with time, and PAIS is a common cause of epilepsy in children referred for consideration of epilepsy surgery. Epilepsy may be seen in up to 50% of children, whereas cognitive outcome is more frequently impaired in PAIS than in childhood stroke, and ranges from 25% to 40%. However, the success of early brain MR imaging in predicting subsequent epilepsy, cognitive outcome, and behavioral difficulties is more limited.63 Some studies suggest that cognitive impairment is worse when there are more extensive main-branch infarcts involving superficial cortex and deep gray matter.20,64 Other studies suggest that cognitive outcome is more closely associated with hemiplegia and epilepsy than extent of MCA lesion, and may occur with smaller infarcts when there are additional neonatal factors.65 Preterm infants with PAIS had more associated problems, such as language delay, than term infants.

**Recurrence Risk**

The recurrence risk for stroke appears to be very low. The Childhood Stroke Study Group followed up 215 neonates with arterial ischemic stroke for a median time of 3.5 years, during which time 7 children (3.3%) developed symptomatic thromboembolism (AIS, CSVT, or deep vein thrombosis of the leg). Four children developed a second AIS (~2%). Five children had a prothrombotic risk factor, and the second event was often triggered by a specific underlying problem such as infection, cardiac abnormality, or moyamoya disease.13

**Cerebral Sinovenous Thrombosis**

**Incidence**

The Canadian registry, one of the largest cohorts of pediatric stroke, estimated the incidence of cerebral venous thrombosis as at least 0.67 per 100,000 children per year.66,67 whereas a German study estimated this at a higher rate of 2.6 per 100,000.68 Neonates were the most frequently affected age group and accounted for 43% of cases in the Canadian registry. The estimated incidence of neonatal CSVT was 40.7 per 100,000 live births per year. This figure is likely to be an underestimate of the true incidence because the clinical presentation is nonspecific, the diagnosis may be missed clinically in the presence of coexistent illnesses occurring in the sick neonate, and the radiological diagnosis itself is not always straightforward, though it is easier to make in the acute phase. Not all CSVT is recognized to be symptomatic, and some CSVT clearly remains undiagnosed in neonatal or later life. In some cases the diagnosis is made on the basis of imaging performed for other reasons. A high index of suspicion is required to make the clinical and radiological diagnosis.

**Pathophysiology and Risk Factors**

CSVT has been associated with all the thrombotic risk factors that have been implicated in PAIS, such as Protein C or Protein S deficiency, G20210A prothrombin mutation, factor V Leiden mutation, antiphospholipid antibodies, infection, and polycythemia. Prothrombotic abnormalities have been reported in 15% to 20% of neonates with CSVT. A recent study comparing presumed PAIS and venous infarction in neonates found that there were no differences in prothrombotic conditions between the two groups.69 However, children with presumed perinatal AIS were more likely to have acute perinatal risk factors (66% vs 17%, P = .002) including fetal distress, emergency cesarean section, or neonatal resuscitation. This finding is supported by a meta-analysis of 1764 patients in published observational studies, which reviewed the impact of thrombophilia on risk of first childhood stroke.70 A statistically significant association with first stroke was demonstrated for each thrombophilia trait evaluated, with no difference found between AIS and CSVT. Venous sinus thrombosis and venous infarction may coexist with AIS in the same patient (Fig. 7).

In CVST there is often a history of an acute neonatal illness, for example an infection, meningitis, or dehydration, and other comorbidities such as neonatal congenital heart disease are common. Associated acute systemic illnesses at the time of diagnosis were present in the majority (61%–84%) of cases. Five percent of all infants with ECMO have evidence of CSVT. Complicated delivery is a common finding in CSVT, and traumatic delivery may disrupt the superior sagittal sinus or cortical veins. Maternal factors such as maternal diabetes and preeclampsia are also recognized.

The lesions detected in cerebral venous thrombosis are thrombus within an occluded or partially occluded vein or venous sinus, venous ischemia, venous infarction, and hemorrhage. Following
venous sinus thrombosis there is retrograde transmission of raised venous pressure proximal to the level of venous obstruction. This process increases both the venular and capillary hydrostatic pressure, which results in leakage of the capillary fluid into the interstitial space, causing vasogenic edema. The fluid leakage is often accompanied by red blood cells and is the usual cause of hemorrhagic venous infarcts in CSVT. Most of the edema is vasogenic and hence reversible but, if the process progresses, the capillary hydrostatic pressure and interstitial pressure can exceed the arteriolar pressure. This process can sometimes cause true venous infarction in which impairment of both arterial inflow and venous outflow occur.

Clinical Presentation
The diagnosis of CSVT should be considered in neonates presenting with seizures and encephalopathy, but the presentation may be more subtle and nonspecific and may include lethargy, apnea, and poor feeding, much like PAIS in this period. Around half of neonates present within the first 2 days of life and another 25% in the first week of life. Seizures may be subtle and focal or generalized. Some infants have relatively mild symptoms of encephalopathy despite extensive thrombosis within the venous sinuses. It is also recognized that venous sinus thrombosis may be detected as an incidental finding on brain MR imaging performed for other reasons.

Imaging
CSVT may be detected and missed on all imaging modalities, and in general isolated cortical vein thrombosis is not reliably and consistently diagnosed on any modality. However, because of the greater coverage achievable of the deep and superficial venous structures and superior evaluation of the brain parenchyma, CT and MR imaging are preferable to ultrasonography. MR imaging remains the modality of choice, as it does not involve ionizing radiation and is the most sensitive technique for detecting parenchymal lesions.

On unenhanced CT in the acute stage the involved venous sinuses appear hyperdense and expanded, the “dense triangle” or “cord sign” (Fig. 8). It can sometimes be difficult to discriminate
between normal appearances of the neonatal venous sinuses, in which blood appears relatively hyperdense compared with the adjacent brain (Fig. 9). This normal appearance in the neonate is the result of a combination of persistent fetal hemoglobin and raised hematocrit; together they increase electron density in blood within the venous sinuses and hence increase the attenuation of x-rays. In addition, there is greater contrast between the relatively hyperdense normal neonatal venous sinus and the relatively low-density unmyelinated neonatal brain. The use of contrast, either a delayed postcontrast CT of the brain or a CT venogram, may facilitate the detection of nonenhancing thrombus, the “empty delta” or “empty triangle” sign.

On MR imaging a combination of T1-/T2-weighted sequences in multiple planes, as well as MR venography, are often necessary to make the diagnosis and avoid artifacts. Reliance on a single sequence, including MR venography, may lead to underdiagnosis or overdiagnosis (Fig. 10). One observation and potential pitfall of 2-dimensional time-of-flight MR venography in neonates is that there seem to be more gaps in flow in the venous sinuses, particularly the posterior aspect of the superior sagittal sinus, which has been attributed to the age-related smaller size of the sinus, reduced venous flow, and skull molding.

The brain itself may appear normal, or there may be diffuse cerebral swelling secondary to venous hypertension and ischemia. Lack of focal brain lesions or venous infarcts may not correlate with a good outcome (see Fig. 10). Enlargement of the ventricles can occur as a result of impaired venous outflow or be secondary to obstruction from associated intraventricular hemorrhage in deep venous infarction. Typically focal edematous brain parenchymal lesions involve the cortex and white matter, are seen in a typical venous tributary, and often have large intralesional hemorrhagic components early on or at presentation. There is some evidence that both brain lesions and hemorrhage are more common in neonates and infants than in children with CSVT. It has been suggested that the mechanisms for compensation of raised intracranial pressure in neonates, such as opening up of reserve capillaries (increasing cerebral blood volume) or end-to-end meningeal anastomoses allowing alternative venous drainage, are immature in the neonate, making them more susceptible to venous ischemia and hemorrhage.

These edematous parenchymal lesions may have a mixed pattern of signal changes on diffusion-weighted imaging, with regions of increased and reduced diffusion on diffusion-weighted imaging/ADC maps. In the acute phase, imaging does not reliably

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Fig. 8. CT scan (top row) in a 6-week-old infant with acute cerebellar hemorrhages causing marked cerebellar swelling presumed to be secondary to idiopathic thrombocytopenic purpura (no underlying structural lesion was found on follow-up MR imaging or angiography). A CT scan the day after the posterior fossa hematoma resection shows there is new acute thrombus in the straight sinus, torcular, and superior sagittal sinus.
discriminate between venous ischemia and venous infarction, even when diffusion-weighted imaging shows evidence of restricted diffusion. Unlike most AIS, these lesions have the potential to reverse with the development of alternative venous drainage pathways or recanalization of the venous sinus. Serial imaging should be considered if there is neurologic deterioration or hemorrhage in order to detect propagation of thrombus as well as progression of brain changes, as both may affect decisions to treat with anticoagulation. In a consecutive cohort study, asymptomatic thrombus propagation occurred in 25% of untreated neonatal CSVT compared with 3% of those who were treated with anticoagulation. The AHA guideline also considers it reasonable to repeat imaging to assess for recanalization of the venous sinus in order to guide management.

Site
The venous drainage of the cerebral hemispheres is divided into the superficial and the deep systems. The superficial system consists of the superior sagittal sinus, the transverse sinuses, torcular, sigmoid sinuses, and the internal jugular veins. The deep system consists of the deep basal veins draining into the paired internal cerebral veins that unite with the inferior sagittal sinus and then drain into the vein of Galen, the straight sinus, and the torcular. Thrombus may propagate along the course of either system and may interconnect. As for the arterial tree in the neonate, the anatomic structure and distribution (though not necessarily the dynamic flow) of the major cerebral veins and venous sinuses are already established by the end of the first trimester. However, there is greater normal variation in the anatomic venous drainage and collateral venous drainage than in the arterial system, which leads to some variability in the distribution of parenchymal lesions in CSVT. Specific patterns of involvement include parasagittal subcortical hemorrhage with superior sagittal sinus thrombosis (the most common), thalamic and intraventricular hemorrhage with occlusion of the internal cerebral vein (Fig. 11), striatohippocampal hemorrhage with basal vein thrombosis, temporal lobe or cerebellar hemorrhage with transverse sinus thrombosis, temporal lobe anterolateral hemorrhage with tentorial sinus or temporal diploic vein rupture, and temporal lobe

Fig. 9. Normal CT brain studies at 3 and 6 weeks of life. There is lower density within the white matter (WM) and gray matter (GM) on the earlier neonatal scan compared with the later one (visually and as measured in Hounsfield units). The venous sinuses appear relatively hyperdense in contrast to the lower-density brain. The sinus itself is also slightly more dense than on the later scan. However, there is no expansion of the sinus on any of the scans. CSF, cerebrospinal fluid. (Courtesy of WK “Kling” Chong, Great Ormond Street Hospital.)
hemorrhage with vein of Labbe thrombosis. Deep venous anomalies may also thrombose in the presence of other risk factors (Fig. 12).

**Treatment**

The optimal treatment for neonatal SVT remains under debate. The mainstay of treatment is supportive with correction of dehydration, sepsis, anemia. Investigation of prothrombotic disorders and septic screening should be instituted. Kenet and colleagues suggest anticoagulation should be given on an individual basis in children with newly identified SVT and high risk of recurrence. A recent Cochrane review in all patients with CSVT concluded that evidence was limited, but that anticoagulant treatment of cerebral venous sinus thrombosis appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency, although this did not reach statistical significance. Treatment of neonatal CSVT with anticoagulation has not been universally accepted, and in the AHA guideline on pediatric stroke it was recognized that many neonates with CSVT are not treated, even in the presence of a thrombophilic disorder. The current AHA recommendation is that anticoagulation is a reasonable treatment option, even in the presence of hemorrhage, for 3 to 6 months. A clear distinction between symptomatic and asymptomatic infants is not made. Thrombolytic therapy with tissue plasminogen activator may be considered in selected children with CSVT (Class IIb, level of evidence C). The American College of Chest Physicians guideline (2008), however, concluded that, as for AIS, there are insufficient data to

![Image](image-url)

*Fig. 10. A term male neonate who was unexpectedly hypotonic at birth with poor respiratory effort requiring resuscitation, and who developed seizures at 12 hours of life. His mother had reported unusual movements in utero. Initial CT (top row) on day 2 of life shows diffuse brain oedema, with expanded and hyperdense transverse and sagittal sinuses, torcular, and internal cerebral veins as well as the cerebral cortical veins. CT performed on day 9 (middle row) shows resolution of the cerebral oedema, increased density of the thrombus within the transverse sinus, torcular, and superior sagittal sinus. MR imaging on day 9 (bottom left, images 1–4) shows mild diffuse cerebral atrophy but no focal venous infarcts, with persistent thrombus and no flow on the MR venography (stars). Follow-up MR imaging on day 15 shows evolution of thrombus signal intensity to methemoglobin. Note the effect of T1 shortening within the thrombosed sagittal and transverse sinuses and torcular, mimicking flow within the sinuses (arrow). His seizures continued and were refractory to medical treatment. EEG continued to show interictal burst suppression pattern with multifocal epileptiform abnormalities. He subsequently died following uncontrolled seizures and respiratory arrest.*
Outcome

CSVT is associated with significant morbidity and mortality. Adverse outcomes include postnatal epilepsy, cerebral palsy, visual deficits, cognitive impairments, posthemorrhagic hydrocephalus requiring shunting, and death.\textsuperscript{57,76,77} It is not clear how outcomes in neonates differ from those in children, although one study found higher mortality rates of CSVT in neonates.\textsuperscript{78} A recent study showed that in 52 neonates with SVT, moderate to severe neurologic sequelae were present in 58% and 19% (10 infants) died. Normal neurodevelopment was seen in only 45%.\textsuperscript{79} Neurologic deficits appear to be related to the presence of multiple venous sinus involvement and the presence of venous infarctions.

Recurrence

There are few data on the recurrence risk of CSVT in neonates. In the cohort of 396 children with CSVT studied by Kenet and colleagues,\textsuperscript{80} none of the 22 children with recurrent thrombosis were younger than 2 years at the time of the initial thrombosis, implying that the risk of CSVT recurrence is low among very young children. However, children with more than one inherited thrombophilic factor who had venous thrombosis in the neonatal period may be at increased risk of future thrombotic events.\textsuperscript{81} Additional data on the recurrence risk in different age groups are needed.
GERMINAL MATRIX HEMORRHAGE-INTRAVENTRICULAR HEMORRHAGE AND PERIVENTRICULAR HEMORRHAGIC INFARCTION

Definition and Classification

Germinal matrix hemorrhage (GMH)-intraventricular hemorrhage (IVH) is bleeding that is confined to the germinatal matrix or associated with uncomplicated intraventricular hemorrhage, with no evidence of ventricular enlargement. This terminology clearly separates GMH-IVH from parenchymal lesions. Periventricular hemorrhagic infarction refers to hemorrhagic necrosis of the periventricular white matter. This lesion frequently coexists with IVH; approximately 15% of all infants with GMH-IVH also exhibit periventricular hemorrhagic infarction. The traditional Papile classification graded hemorrhagic lesions in the preterm brain on a scale of I to IV on the basis of a single CT scan, and assumed parenchymal hemorrhage was simply the extension of blood from the ventricles. This classification has been abandoned by some investigators because it does not allow for changes on serial imaging (improvement or progression) and assumes there is a continuous spectrum of abnormalities with hydrocephalus seen only with more severe lesions, and with grade IV parenchymal hemorrhage seen as the end stage of disease.

Incidence

The incidence of GMH-IVH is inversely related to gestational age and birth weight. The incidence overall has been declining in Europe and the United States from around 50% in the 1970s to approximately 20% now, due to improved care of preterm babies, unlike the incidence of periventricular leukomalacia. However, this overall reduction has not been seen in very low birth weight infants (<750 g), for whom periventricular hemorrhagic infarction (PVHI) is a particular problem. It remains a bigger problem at all gestational ages outside Western countries; in one recent study from Syria the incidence of GMH-IVH was 44% of all neonates younger than 37 weeks. GMH-IVH and PVHI mostly occur during early neonatal life, and 80% to 90% develop within the first 96 hours after birth with less than 20% being already present at birth. Only a minority (3%) have established lesions with porencephalic cysts on neonatal cranial ultrasound scans.

Pathophysiology and Risk Factors

The ganglionic eminence is thickest at 20 to 26 weeks gestational age and has involuted by 34 to 36 weeks. Proliferative cells are numerous in both the ventral and dorsal ganglionic eminences until 18 weeks, after which there is a marked reduction in proliferative cells within the dorsal ganglionic eminence, while proliferative cells are still seen in the ventral ganglionic eminence until 28 weeks.

The developing neocortex is recognized to have several layers including the deep proliferative zones, which are clearly seen on postmortem MR imaging of the fetus. By 7 gestational weeks, the ventricular zone immediately surrounding the ventricular cavity gives rise to a secondary proliferative region, the subventricular zone (as well as the preplate, a precursor to the cortical layer). The...
intermediate zone, a precursor of the white matter, appears by 8 weeks. By 14 gestational weeks, the outer subplate and cortical plate have developed. Cortical projection neurons with long axons are generated from the ventricular zone mainly during the embryonic and early fetal period. The subventricular zone becomes the predominant site of cell generation after 15 weeks when it begins to expand rapidly in some sites, forming prominent ganglionic eminences along the lateral walls of the frontal horns, and to a lesser extent the temporal horns of the lateral ventricles. The ganglionic eminence (germinall matrix) is the source of neocortical γ-aminobutyric acid–ergic inhibitory interneurons, produced until at least 20 gestational weeks, and neurons for the adjacent basal ganglia, produced until 25 weeks. Neuron production for the thalamus, likely to be from the ventral ganglionic eminence, continues until 34 weeks. The subventricular zone also generates precursors of oligodendrocytes and astrocytes well into the third trimester. The germinall matrix then regresses gradually, with eventual involution of the ganglionic eminence by 34 to 36 gestational weeks.

GMH most often arises from the ganglionic eminence, which lies between the frontal horn of the lateral ventricle and the head of the caudate nucleus. The germinall matrix vasculature seems to be inherently vulnerable to reduced cerebral blood flow, due to factors such as discontinuous glial end feet of the blood-brain barrier, relative lack of pericytes, immature basal lamina, relatively thin vessel walls, and increased angiogenicity with increased endothelial turnover.88

In animal models there is evidence of direct toxicity of plasma, serum, thrombin, and plasmin on the perinatal subventricular zone in rats; these affect proliferation, differentiation, and migration in oligodendrocyte precursor cell cultures. In another animal experiment, unilateral injection of autologous blood into the periventricular region led to bilateral reduced cell proliferation in the germinall matrix from 8 hours to 1 week following injection, leading to increased cell death in the ipsilateral striatum by 2 days, with peak astrocytic and glial reaction seen at 2 days and persisting for up to 4 weeks. Three mechanisms are suggested for GMH: inherent fragility of the germinall matrix vasculature, disturbance in cerebral blood flow, then additional platelet and coagulation disorders that result in expansion (rather than initiation) of a spontaneous GMH.89

Again maternal, neonatal, and obstetric risk factors may all play a part. GMH-IVH is associated with vaginal delivery, low birth weight, low Apgar scores, hypoxia and hypercapnia, feto-maternal infection, and expression of inflammatory cytokines. Very low birth weight infants who are carriers for Factor V Leiden or prothrombin gain-of-function mutations are also at increased risk for development of GMH-IVH. Genetic factors act as independent risk factors of the same magnitude as other known risk factors.90

PVHI is thought to arise following bleeding into the germinall matrix, and not as extension of hemorrhage from IVH into the adjacent parenchyma.91 Essentially this is a venous infarct. The medullary veins have a fanlike appearance within the frontal lobe white matter adjacent to the basal ganglia, and converge to a single draining terminal vein within the germinall matrix. GMH causes obstruction to the medullary venous outflow, and thrombus within the medullary veins may develop. Venous ischemia and eventually infarction with hemorrhagic necrosis may occur as a consequence of impaired venous outflow. The hemorrhagic component of the infarction tends to be most concentrated near the junction of the frontal horn with the body of the lateral ventricle. At this location the fan-shaped medullary veins draining the cerebral white matter converge, forming a sharp angle to join the terminal vein running along the wall of the lateral ventricle. PVHI is a pathologic entity distinct from periventricular leukomalacia, in which secondary hemorrhage may occur as the result of a reperfusion injury following watershed ischemic damage to the white matter in the preterm infant, and also from the white matter injury that may be seen with untreated hydrocephalus. Because neuroimaging may not always clearly delineate the underlying mechanism, some investigators prefer usage of the simpler term intraparenchymal lesion, which does not attribute any particular etiology to the lesion.

**Imaging**

Ultrasonography is usually the first neuroimaging study performed on the preterm brain. The main limitations of cranial ultrasonography are the subjectivity of interpretation and lack of interobserver correlation. Accurate interpretation depends on training and experience.92 The detection of parenchymal lesions and intraventricular hemorrhage demonstrates greater agreement between observers than for GMH. Another study found that compared with MR imaging, ultrasonography accurately predicted the presence of GMH, IVH, and hemorrhagic parenchymal infarction on MR imaging.93 However, intraobserver agreement is greater for MR imaging than for ultrasonography, and some studies have shown greater agreement than ultrasonography of postmortem findings.
GMH is typically seen on ultrasonography as an echogenic region in the caudothalamic groove, and must be distinguished from the mildly echogenic appearance of the normal choroid plexus, which may also be seen in the caudothalamic groove and is potentially a cause of misdiagnosis. Associated intraventricular hemorrhage may be seen as intraventricular echogenic areas extending from the caudothalamic groove, often forming dependent blood-cerebrospinal fluid levels or casts of hemorrhage around the choroid plexus within the lateral ventricles. Associated ventricular dilatation due to either hydrocephalus secondary to obstruction at the foramina of Monro/cerebral aqueduct or generalized white matter loss may be present.

MR imaging used for prognostic purposes is ideally performed in preterm infants at term gestational age. Imaging at this time allows comparisons with the published MR imaging literature for detection of abnormality versus the normal neonatal brain at term. On MR imaging the germinal matrix is most prominent in the second trimester fetus at 24 and 26 weeks of gestation, and forms a band of low intensity on T2-weighted MR images along the lateral margin of the lateral ventricles. GMH is seen typically as darker linear regions on T2-weighted sequences in the caudothalamic region or along the lateral ventricular ependyma, due to either deoxyhemoglobin or more usually hemosiderin. Acute hydrocephalus is most accurately distinguished from white matter volume loss by the presence of temporal horn distension and distension of the inferior and posterior recesses of the third ventricle. Unlike ultrasonography, MR imaging may clearly show the obstructive hemorrhagic lesion, for example as a focus of hemorrhage obstructing the cerebral aqueduct or foramina of Monro, and also may show intraventricular septations that may help to guide placement of ventricular drains and third ventriculostomy.

PVHI or parenchymal venous infarction is seen as a focal region, typically fan shaped, extending from the level of the caudothalamic groove into the adjacent brain. More than half of cases are asymmetric. The thrombosed veins may be demonstrated. On ultrasonography the PVHI is seen as a region of echogenicity in the basal ganglia and thalami with its apex at the caudothalamic groove, and on MR imaging as a region of signal change in keeping with either hemorrhage, edema, or a combination of the two. It is asymmetric in most cases. As the coagulation necrosis resolves there is tissue loss and a porencephalic cyst develops, which is usually, but not exclusively, in continuity with the lateral ventricle (Fig. 13). If the lesion has occurred in the early preterm period (<26 weeks gestational age) when the brain does not respond to insults with gliosis, then this cyst is typically smooth walled with no evidence of surrounding signal abnormality. Later than this there may be evidence of white matter scarring adjacent to the cyst (Figs. 14 and 15). The main differential diagnosis is from the cysts or white matter scars of focal periventricular leukomalacia; these are usually smaller, bilateral, and not so asymmetric, are seen more posteriorly within the white matter, and are more often associated with a worse outcome. Cerebellar hemorrhages are frequently seen in the presence of supratentorial GMH, PVHI, and white matter injury (Fig. 16).

PVHI is well described in infants delivered preterm but may occur in utero; it may also be detected prenatally or may present as presumed perinatal ischemic stroke in infancy following term birth. Familial porencephaly is an autosomal dominant condition in which leukoencephalopathy, macrohemorrhages and microhemorrhages, and porencephalic cysts occur, while adults may present with hemorrhages, small vessel disease, and intracranial aneurysms. It is a cause of strokes at any age, may also affect infants and fetuses and may mimic the appearances of PVHI. Recently a mutation in the gene encoding a protein of collagen type 4 A1 has been identified that impairs the structural integrity of the vascular basal membrane, rendering vessels susceptible to rupture. The porencephalic cysts are presumed to have occurred as a consequence of preterm hemorrhage and have an appearance similar to the mature injury seen following PVHI, but in the absence of a clinical history of preterm delivery or neonatal illness. An additional clue may be the presence of cataracts (Fig. 17).

Outcome

The traditional Papile ultrasound grading predicts morbidity and mortality, with ultrasonographic grades III (intraventricular hemorrhage with ventricular dilatation) and IV (intraventricular hemorrhage complicated by periventricular hemorrhagic infarction). Grade III hemorrhage has survival rates of 67% and 40%, respectively. Neurologic sequelae are seen in 50% of Grade III and 75% of Grade IV hemorrhages.

More than half of babies who have a porencephalic cyst will develop a contralateral hemiplegia in childhood. The majority of surviving preterm children with periventricular hemorrhagic infarction in one study had cerebral palsy with limited functional impairment at school age. Infants with unilateral PVHI had better motor and cognitive outcomes than infants with bilateral PVHI. This finding seems to be related to the anatomic site...
of the cyst and whether it involves the CST. Hence anterior cysts have a better prognosis than posterior frontal or parietal cysts, and MR imaging does have some advantages here in both accurately localizing the cyst and its relation to the corticospinal tract as well as in the detection of abnormal signal in the CST within the posterior limb of the internal capsule (see Fig. 14). This finding correlates with a higher incidence of contralateral hemiplegia in such infants compared with babies who have normal-appearing myelin within the CST. Abnormal signal may be seen remote from the cyst itself along the course of the CST, and is presumably caused by Wallerian degeneration. If there is coexistent ventricular enlargement due to white matter loss (e.g., following untreated hydrocephalus or additional hypoxic-ischemic white matter injury), the risk of cognitive impairment is increased. Decreased cortical thickness has been found in uncomplicated GMH (without PVHI). GMH-IVH has an increased risk of major depressive disorder and obsessive-compulsive disorder by age 16 years.

**INTRACEREBRAL HEMORRHAGE**

Hemorrhagic stroke is less common than ischemic stroke in children, and likely also less common in neonates, although the data on its incidence rate are lacking. Much of the difficulty of estimating the prevalence of neonatal intracranial hemorrhage (ICH) in general is related to frequent occurrence of asymptomatic hemorrhages that may not come to clinical attention, and variable results attributable to different populations studied and sensitivity of diagnostic imaging tools. Two reports estimated the regional incidence of symptomatic ICH in full-term infants at 4.9 and 5.9 per 10,000 live births, respectively. However, another case-control study based on a northern California health maintenance practice from 1993 to 2003 estimated a lower prevalence for symptomatic perinatal hemorrhagic stroke (including intracerebral and subarachnoid hemorrhage) of 6.2 per 100,000 live births, about one-fifth the prevalence of symptomatic PAIS. In recent years identification of ICH with intraparenchymal involvement has increased in neonates because of improved imaging techniques and increased.

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**Fig. 13.** Ultrasound images of one of twins born at 25 gestational weeks showing evolution of an acute left basal ganglia, intraventricular and frontal white matter hemorrhage into a region of porencephaly in continuity with the ventricle (top row day 3, middle row day 16, bottom row day 54). (Courtesy of Cornelia Hagmann, Neonatal Unit, University College Hospital, London.)
use of diagnostic imaging. In this discussion, neonatal hemorrhagic stroke is mainly defined as acute stroke with intraparenchymal hemorrhage in infants during the first month of life.

**Clinical Presentation**

The most frequent presenting symptoms in both preterm and term newborns with ICH are neonatal seizure and decreased level of consciousness. Depending on the site of hemorrhage, there may be cranial nerve palsy, hemiparesis, and apnea. Frequently there are also nonspecific signs such as lethargy, irritability, fever, cyanosis, crying, vomiting, or diarrhea. In a retrospective analysis of 33 symptomatic term infants with ICH, 24 of 33 infants (73%) presented with seizure, respiratory distress, or apnea. A subset of 4 patients who had lobar hemorrhage all manifested with seizures. In another neuroimaging series of 53 term infants who had ICH with parenchymal involvement, seizures were found to be the most common presenting symptom (71.7%), and another 18.9% presented with apneic seizures while 5 infants (9.4%) had no clinical signs.

**Risk Factors**

In children, a few risk factors for cerebral hemorrhage have been identified, including underlying
Fig. 15. MR brain scans (top and middle rows) in a term baby who had difficulty feeding after delivery, developed weight loss, and presented with apneic episodes. He was found to have hypernatremic dehydration, then developed left femoral vein thrombosis after vascular catheter insertion. EEG showed bilateral focal changes. Low Protein S level was found and confirmed 3 months later. There is thrombus within the left ependymal vein extending into the internal cerebral vein and vein of Galen. There is maturing left frontal lobe white matter infarction with linear signal abnormality, suggestive of thrombosis in the medullary veins. Follow-up imaging 2 years (bottom row) later shows mature white matter scarring, extending from the periventricular into the left frontal subcortical white matter with focal volume loss. This appearance could incorrectly be interpreted as periventricular leukomalacia, but the latter is usually bilateral, though it may be asymmetrical.

Fig. 16. MR images of a preterm infant scanned at term showing extensive cerebellar atrophy and mature cerebellar hemorrhages as well as bilateral germinal matrix hemorrhages. A focal region of porencephaly is seen on the right associated with greater enlargement of the right lateral ventricle.
coagulopathy, vascular malformation, malignancy, and trauma. A large population-based study of childhood stroke over a 10-year period from the 1970s identified 45% (31 of 69 all stroke cases) of hemorrhagic stroke comprising both subarachnoid and intracerebral hemorrhage.\textsuperscript{108} The study included infants and children ranging in age from 0 to 14 years, and arteriovenous malformation (AVM) was cited as the most common cause of hemorrhagic stroke in children (18.8%) when stroke related to birth, intracranial infection, or trauma was excluded. Other vascular malformations that carried the risk of hemorrhage included cavernous malformation and aneurysm, the latter contributing to 8.7% of all hemorrhagic strokes in the same study.\textsuperscript{108} Hemorrhage and venous ischemia may be seen in vein of Galen aneurysmal malformations (Fig. 18).

Fig. 17. Brain MR imaging in a boy with epilepsy and a 4-limb motor disorder who was 7 months at the time of his scan, showing multiple bilateral asymmetrical porencephalic cysts with scattered mature white matter hemorrhages. He has left microphthalmia and a congenital cataract, and a confirmed de novo mutation in the ColIVA1 gene.

In neonates, the primary risk factors for hemorrhagic stroke include prematurity, underlying coagulopathic disorders (whether genetically predisposed or iatrogenically induced), trauma, and also underlying vascular malformations or malignancies. Of note, in a case-control study\textsuperscript{105} using multivariable analysis, fetal distress and postmaturity were found to be the strongest independent predictors of perinatal hemorrhagic stroke. ICH and, in particular, intraventricular hemorrhage are most commonly seen in preterm newborns with low birth weight (<1500 g), most likely related to immature vasculature. In term newborns, on the other hand, intracranial hemorrhage is considered uncommon and often has a different, nonintraventricular (more frequently subdural, subarachnoid followed by intraparenchymal) location, etiology, and clinical presentation, as well as more variable
In the perinatal period, GMH is most frequently encountered in premature infants and is fully discussed in the previous section. The most advanced GMH, classified as Grade IV hemorrhage, includes a parenchymal component in addition to intraventricular hemorrhage. This periventricular hemorrhagic pattern may also be seen in term neonates, and was found in 9 of 33 (27.3%) term infants in the series of Harnigan and colleagues. Coagulopathy is a major risk factor for intracranial hemorrhage in both preterm and term neonates. A diagnosis of underlying coagulopathic disorder (whether due to production defects or functional abnormalities) should always be considered in neonates presenting with ICH.

Coagulopathies tend to make intracranial hemorrhage much more severe and devastating. Failure to give Vitamin K at birth is a recognised cause. Hemophilia A (due to deficiency of factor VIII) and hemophilia B (due to factor IX deficiency) are the most common severe inherited coagulopathies, and can both cause ICH. Hemophilia C, due to deficiency of factor XI, is much less common. Von Willebrand disease is rarely a cause of neonatal cerebral hemorrhage because the factor typically follows a physiologic elevation at birth, providing protection from bleeding.

Some of the genetic causes of coagulopathic disorders include glutaric aciduria type 1, a metabolic disorder that presents with retinal and intracranial (most often subdural) hemorrhages that
are not nonaccidental. Congenital disorders of glycosylation is a spectrum of disorders that affects multiple organ systems with increased susceptibility to bleed, and several rare inborn errors of metabolism such as galactosemia (which can present with progressive lethargy, irritability, poor feeding, and liver dysfunction), tyrosinemia type I (worsening liver function with elevated transaminases, lethargy, and poor feeding that can progress to coagulopathy, distress, coma, and death), and carnitine/acylcarnitine translocase deficiency (liver failure and resultant hyperammonemia). Carnitine palmitoyltransferase 2 deficiency (CPT2 deficiency) has a severe neonatal form whereby there is evidence of liver failure with hypoglycemia, cardiomyopathy, and arrhythmias that presents within days of birth and can lead to seizures, and focal malformations of specific organs.

Much more frequently coagulation problems are acquired, and hemorrhagic stroke occurs because of sepsis or iatrogenic factors, for example, the use of anticoagulation in ECMO. Thrombocytopenia is the most common condition causing ICH in term newborns, and has many causes including drug-induced, infectious, genetic, immune-mediated, disseminated intravascular coagulation, or placental insufficiency. In the Kaiser pediatric stroke study based in northern California, thrombocytopenia accounted for 20% of perinatal hemorrhagic stroke while 75% were deemed idiopathic.

**Associated Pathophysiology**

Based on previously published studies and the authors’ own experience in examining intraparenchymal hemorrhage in term newborns, the underlying etiological factors remain unknown in many, sometimes up to 50%, of cases. It is noteworthy that none of the cases in several reported studies involved an underlying arteriovenous malformation or neoplasm, while cavernous malformation accounted for 1 in 20 cases of the Kaiser study in a 10-year span. The absence of AVM was documented in the series by Bergman and colleagues by negative contrast CT scan and/or cerebral angiograms at the time of acute symptoms or on follow-up, and appears to be the common experience shared by other investigators. Hence it seems that AVM, while a relatively common cause of hemorrhage in children, should not be generally be considered a cause of ICH in the neonate.

HIE and hemorrhagic injuries often occur concomitantly in both preterm and term newborns, and share many similar pathophysiologic and clinical features. In the Bergman series it was thought that most cases of intraparenchymal hemorrhage resulted from hemorrhagic infarction. In their retrospective review of patients under 1 month old with ICH within a span of 10 years since 1975, 18 term neonatal infants were identified, among whom 6 presented with primarily intraparenchymal hemorrhage. Two patients sustained hypoxic-ischemic injury, while one had hyperviscosity of blood predisposing to infarction. Three of these 6 patients did not have any identifiable precipitating conditions, but were postulated to have suffered from embolic hemorrhagic infarctions based on the distribution of haemorrhage and subsequent areas of cerebral damage seen on follow up CT. However hemorrhagic transformation of AIS can usually be excluded on MRI. Some lobar hematomas may be seen in association with thrombosed medullary veins or cortical veins (such as vein of L’Abbe in temporal lobe hematomas). However often the underlying cause is not identified.

**Imaging**

Neuroimaging is important in the evaluation of these neonates, and allows prompt and accurate diagnosis. Cranial ultrasonography is most frequently used as the first line of imaging modality, and has distinct advantages of portability, low cost, lack of ionizing radiation, and ease of operation for serial examinations. Ultrasonography is particularly useful in following preterm neonates, who are prone to GMH, and in infants treated with ECMO, without removing them from the intensive care unit or requiring sedation to be used. Hemorrhage is depicted on ultrasonography as increased echogenicity (Fig. 19), but the low contrast against the choroid plexus and adjacent brain tissue makes it difficult to resolve the small amount of hemorrhage and diffuse parenchymal abnormalities. CT and MR imaging are more sensitive in the detection of ICH than ultrasonography, and have superior capability of delineating blood in different compartments in addition to depicting other parenchymal abnormalities, such as those resulting from ischemia, with much greater interobserver agreement. Fig. 20 illustrates the conspicuous wedge-shaped hypodensity on CT representing arterial infarct, which subsequently undergoes hemorrhagic transformation with curvilinear hyperattenuation. MR imaging is even superior to CT in evaluating brain parenchyma particularly for concomitant ischemic changes, which have been found to be an important predictor of neurodevelopmental outcomes. Susceptibility-weighted imaging can highlight petechial hemorrhage that may offer clues to underlying pathophysiology (Fig. 21). In the same MR examination, MR angiography and MR
Fig. 19. A male infant born at 38 weeks with congenital diaphragmatic defect and pulmonary hypoplasia, treated with extracorporeal membrane oxygenation. (A) Baseline head ultrasonography is normal. (B) On day 15, ultrasonography shows increased echogenicity within the choroid plexus in the right lateral ventricle with ventricular dilation, suggesting IVH. (C) Noncontrast head CT performed on day 20 confirms hemorrhage casting the right lateral ventricle, in addition to a small amount of IVH in the left occipital horn, as well as moderate ventricular dilation. (D) Head CT also shows a new right temporal hematoma with surrounding vasogenic edema.

Fig. 20. A newborn baby boy with normal delivery and Apgar scores of 8 (1 minute) and 9 (5 minutes) presented with jerky movements of clonic nature suggestive of seizure at 2 hours of life. (A) Head CT shows a wedge-shaped hypodensity in the right parietal lobe consistent with right MCA territory infarct. (B) On day 10 of life, curvilinear densities are identified within the area of infarct, reflecting hemorrhagic conversion.
venography can also easily be incorporated to allow interrogation of vascular abnormalities.

The hemoglobin products evolve with time through several forms including oxyhemoglobin, deoxyhemoglobin, and intracellular methemoglobin, and finally get broken down to ferritin and hemosiderin, which are sequestered by macrophages and scavenger cells in the chronic stage. T1 shortening occurs in methemoglobin as a result of paramagnetic dipole–dipole interactions, whereas the magnetic susceptibility effect accounts for T2 shortening observed with deoxyhemoglobin, methemoglobin, and hemosiderin (see Fig. 21).115 Five stages of hemorrhage are described on conventional MR imaging:

1. Hyperacute (intracellular oxyhemoglobin, long T1, long T2)
2. Acute (intracellular deoxyhemoglobin, long T1, short T2)
3. Early subacute (intracellular methemoglobin, short T1, short T2)
4. Late subacute (extracellular methemoglobin, short T1, long T2)
5. Chronic (ferritin and hemosiderin, short T2).

Fig. 21. A 35-week preterm baby boy born by cesarean section who had an uncomplicated delivery but developed pulmonary hypertension of newborn, resulting in hypoxic damage of his liver and kidney, and subsequently disseminated intravascular coagulation and intracranial hemorrhage. (A) T1-weighted sagittal MR image shows a peripherally hyperintense and centrally isointense hematoma in the occipital lobe. (B) T2-weighted axial image shows the right occipital hematoma is dark, reflecting acute hemorrhage with deoxyhemoglobin blood products and peripheral rim of intracellular methemoglobin. (C) T2*-weighted axial image shows several foci of parenchymal hemorrhage, possibly mixed with intraventricular blood.

Fig. 22. Term baby delivered by cesarean section for thick meconium and late decelerations, Apgar scores of 1, 6, and 8 (at 1, 5, and 10 minutes), presented with neonatal seizures at night of first day of life. EEG showed bilateral hemispheric origin, all cultures were negative, and there was no evidence of venous sinus thrombosis. (A, B) Axial head CT images show bilateral frontal, parietal, and scattered occipital hemorrhages in the periventricular and subcortical white matter, the largest in the frontal centrum semiovale.
The pattern and location of hemorrhage may also offer some clues to the underlying etiology. For example, by examining the hematoma location and clinical factors in 25 term infants with ICH, Hanigan and colleagues found periventricular hemorrhage (28% of all cases) and peripheral cortical hemorrhage (24%) predominantly associated with hypoxic-ischemic injury or coagulopathy. By contrast, lobar hemorrhage (16%) and extra-axial hemorrhage (32%) were often associated with trauma or coagulopathy. It would be of interest to confirm this association in a larger cohort of patients.

**Outcomes**

HIE has been cited as a major contributor to or associated clinical factor of intracranial hemorrhage. Perinatal asphyxia and findings of cerebral ischemia are associated with a high mortality rate and poor neurodevelopmental outcomes. The majority of infants with parenchymal hemorrhage from unknown causes had good Apgar scores. Long-term clinical outcome was found to be variable: 50% of those infants who suffered ICH had a normal development and 50% had moderate to severe disability. The lobar type of hemorrhage described in the small series by Hanigan and colleagues showed normal development in 3 out of 4 infants, but severe mental retardation in 1.

**REFERENCES**


**Fig. 23.** A 1-day-old full-term female infant born via normal spontaneous vaginal delivery with forceps assistance, who was found to have a right frontal lobe hematoma following seizure activity at 15 hours of life. Axial head CT shows a hyperdense hematoma in the right frontal lobe.


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