Neuroimaging in Perinatal Stroke and Cerebrovascular Disease

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Abstract: Approximately one-quarter of childhood strokes occur in the perinatal period, which includes both fetuses and neonates, affecting between one in 2300–5000 births and representing the primary cause of cerebral palsy. Although the pathogenesis is incompletely understood, risk factors for perinatal stroke are often unique from strokes at other ages, with a combination of maternal, obstetric, anatomic, and genetic factors or predispositions leading to infarct. Clinical presentations of perinatal stroke differ from strokes in older children and adults, often presenting as encephalopathy, seizure, altered mental status, or neurologic deficits. However, neuroimaging remains equally indispensable for diagnosis and prognostication. Here, we provide a comprehensive review of perinatal strokes occurring in fetal and neonatal periods, and discuss the etiologies, diagnosis, management, and prognosis, with a focus on neuroimaging utilization and findings. Understanding the appropriate use of imaging in the distinct clinical entity of perinatal stroke is important for guiding appropriate clinical management.

Keywords: arterial ischemic stroke; hemorrhagic stroke; perinatal stroke; sinovenous thrombosis; venous infarct
INTRODUCTION

Stroke is an important cause of morbidity in the perinatal period, occurring in both fetuses and neonates. Accounting for approximately one quarter of all pediatric strokes, it occurs in one in 2300–5000 live births and is the leading cause of cerebral palsy (1–3). The presentation of stroke in the perinatal period may be different from that in older children and adults, more often presenting with seizures than focal neurologic deficits (2). The etiologies of perinatal stroke are also distinct, resulting from maternal, placental, obstetric, anatomic, and genetic risk factors unique to the perinatal period, albeit with lower risks of recurrence (4). The extrapolation from the paradigms guiding management of stroke in adults may be imperfect and remain largely untested or inconclusive. Accurate recognition of perinatal stroke is nevertheless critical for appropriate management and prognostication, although a clinical diagnosis may not be straightforward. In this chapter, we discuss the unique causes of arterial ischemic, hemorrhagic, and venous stroke in fetuses and neonates and the role of imaging in diagnosis and long-term prognosis. Imaging of diffuse ischemic brain injury, such as in hypoxic ischemic encephalopathy and white matter injury of prematurity, are beyond the scope of this chapter and thoroughly reviewed elsewhere (5, 6).

DEFINITIONS

The temporal classification of perinatal stroke divides them into three distinctive forms, delineated by age of symptom onset and distinguished by differing clinical presentations (7):

(i) Fetal stroke occurs between 18 gestational weeks and onset of labor resulting in delivery. It is diagnosed by prenatal imaging or on the basis of neuropathologic examination in the case of stillbirth (2).

(ii) Neonatal stroke is diagnosed between birth and 28 days of life; it presents with acute encephalopathy and seizures in newborns (2).

(iii) Presumed perinatal ischemic stroke (PPIS) is diagnosed in infants older than 28 days of age, in whom it is presumed that the ischemic event occurred sometime within the perinatal period, with clinically cryptic presentation and/or without neuroimaging at the time for definite diagnosis (2).

In addition, perinatal stroke can be divided into ischemic and hemorrhagic types. Ischemic perinatal stroke (IPS) represents a heterogeneous group of conditions characterized by a focal disruption of cerebral blood flow caused by arterial or cerebral venous thrombosis or embolization. Perinatal hemorrhagic stroke is defined as a nontraumatic intracerebral hemorrhage in the parenchymal, intraventricular, and/or leptomeningeal locations.

CLINICAL PRESENTATION

Fetal stroke presents with chronic encephalopathy in the newborn (7). Neonatal stroke most often presents with focal or generalized seizures (occurring in
80–90%), as well as apnea, hypotonia, or episodes of duskiness, irritability, and poor feeding (2, 4, 8). PPIS can present as early hand preference in infancy, contrary to the typical absence of hand preference prior to the age of 1 year, or as developmental delay, motor impairment, or congenital hemiplegia (3, 9). Approximately 30% of congenital hemiplegia cases result from PPIS (2). It remains unclear why some children present acutely while others present outside the neonatal period, although it may be related to the difficulty of diagnosing seizures in neonates or that some neonates may not seize at all (10, 11). Because the clinical presentation of stroke in neonates can be subtle, imaging is essential for definitive diagnosis.

**IMAGING**

Neuroimaging is performed to confirm a diagnosis of perinatal stroke, to identify a potential etiology, suggest the timing of insult, follow stroke evolution, exclude stroke mimics, assist in treatment decisions, and provide prognostic information.

**Choice of imaging modality**

The choice of radiologic study depends on multiple patient-specific and environmental variables, including advanced imaging access and subspecialty expertise. Fetal imaging usually begins with ultrasound, although evaluation of the brain is often limited by a restricted field of view and suboptimal soft tissue contrast. Fetal MRI provides improved soft tissue contrast and adds valuable information undetected on ultrasound in 30–55% of cases (12–14). It is especially important in regard to fetal cerebral ischemia, which is essentially undetectable on sonography. Diffusion weighted imaging (DWI), which may depict acute ischemic injury in the fetal brain, should be a routine part of fetal MR protocol.

As neonates generally present with acute but nonspecific symptoms, ultrasound is often the first study performed at most institutions. When properly performed with high-frequency probes, and when the studies are performed four days from onset, ultrasound detects up to 87% of neonatal strokes involving the basal ganglia and large supratentorial vascular territories (15). However, ultrasound is less sensitive in the detection of small white matter infarctions, small cortical infarctions over the cerebral convexities, or those in the posterior fossa. Although ultrasound can detect intraventricular hemorrhage, it is insensitive for subarachnoid and small parenchymal hemorrhage. Duplex Doppler sonography can be useful for the diagnosis of dural venous sinus thrombosis in neonates with an appropriate acoustic window. Echogenic clot is seen in the affected sinus and Doppler analysis shows alterations in flow.

Noncontrast head CT (NCCT) may be the initial study in a neonate presenting with possible stroke due to the widespread availability, speed, and sensitivity for detection of intracranial hemorrhage, despite its dependence upon ionizing radiation; however, NCCT suffers low sensitivity for small and posterior fossa infarcts, with the unmyelinated neonatal brain masking subtle hypodensity and further compounded by commonly prescribed “low-dose” imaging protocols. However, in neonates who are medically unstable, in whom
MRI is contraindicated, or in centers without MRI capabilities, NCCT with or without contrast, CT angiography (CTA), or CT venography (CTV), remain considerations.

MRI, supplemented by MR arteriography (MRA) and MR venography (MRV), is the imaging modality of choice in neonatal stroke. It can firmly establish diagnosis of either ischemic or hemorrhagic lesions, as well as identify arterial occlusion or stenosis, vascular malformations, and cerebral sinovenous thrombosis (CSVT). Imaging critically ill or preterm neonates, who often require an incubator or high-frequency ventilation, presents a challenge for safe and timely neuroimaging. Infants may be transported in an MRI-compatible incubator, while some facilities possess MRI machines within the NICU to reduce the need for transport. Imaging of neonates requires thorough optimization of MR sequences, because of higher water content and lower protein and lipids components of neonatal brain, compared with older children and adults. It is therefore important to optimize scan parameters to improve grey-white contrast and increase signal-to-noise (16). While the need for sedation may further delay the scan, neonates are particularly receptive to the “feed and wrap” method of sedation in which the infant is fed and swaddled (17).

Although rarely performed in neonates, catheter angiography can be considered in complex cases or persistent clinical conundrums, particularly when high clinical suspicion of an arteriopathy or vascular malformation remains (18).

**Arterial ischemic perinatal stroke**

Although arterial IPS may result from specific identifiable risk factors, many cases lack a definable cause. Risk factors for IPS are summarized in Table 1, which are identified in approximately 78% of cases (2, 3, 19). Major risk factors include intrapartum fever, preeclampsia, oligohydramnios, use of instrumentation in delivery, fetal distress, emergency Caesarean section, tight nuchal cord, resuscitation at birth, hypoglycemia, and a birthweight small for gestation age (20). These factors exacerbate the combination of the physiological hypercoagulable state of pregnancy and the prothrombotic nature of neonatal blood related to increased hematocrit, fetal hemoglobin, and procoagulant proteins, leading to thrombus formation (21). Although the exact etiology and interplay between various risk factors is not known, and likely to be multifactorial, thromboembolism from the placenta is widely held as a contributor to perinatal AIS (22, 23). Fetal asphyxia, leading to increased flow across the patent ductus arteriosus into the left heart, along with placental pathology therefore poses increased risk of AIS. Complex congenital heart disease and the associated procedures, as well as rare congenital vasculopathies, are also well-established risk factors (24). Bacterial meningitis is complicated by stroke in 17–43% of cases, resulting in obliterative vasculopathy from exudative collections in the basal cisterns (25, 26). Disorders of coagulation, which include deficiencies of proteins C and S, and factor V Leiden, as well as the presence of anticardiolipin antibodies, are rare causes of stroke in this age group, and testing for such sources of thrombophilia may be low yield in neonates without other systemic thromboses or congenital cardiac diseases because recurrence risk is reportedly low (27–34).
| Maternal factors                      | Fetal/infant factors                                      | Placental factors |
|--------------------------------------|----------------------------------------------------------|-------------------|
| Chorioamnionitis                     | • Infection                                              | Thrombosis        |
|                                      |   ○ CNS infection                                        |                   |
|                                      |   ○ Systemic infection                                   |                   |
| Acquired or Inherited Thrombophilia  | • Blood disorders                                        | Abruption         |
|                                      |   ○ Polycythemia                                         |                   |
|                                      |   ○ Disseminated intravascular coagulopathy              |                   |
|                                      |   ○ Factor-V Leiden mutation                              |                   |
|                                      |   ○ Protein-S deficiency                                  |                   |
|                                      |   ○ Protein-C deficiency                                  |                   |
|                                      |   ○ Prothrombin mutation                                  |                   |
|                                      |   ○ Homocysteine                                          |                   |
|                                      |   ○ Lipoprotein (a)                                       |                   |
|                                      |   ○ Factor VIII                                           |                   |
| Preeclampsia                         | • Cardiac etiologies                                     | Insufficiency     |
|                                      |   ○ Congenital heart disease                             |                   |
|                                      |   ○ Patent ductus arteriosus                             |                   |
| Autoimmune conditions and autoantibodies (platelet alloantigen-1) | • Need for resuscitation or low Apgar score at 5 minutes | Chorioamnionitis  |
| Infertility and infertility treatment| • Trauma or birth asphyxia                               | Infarction        |
| Prolonged rupture of membrane (>24 h) | • Twin-to-twin transfusion syndrome                      | Inflammation      |
| Cocaine use during pregnancy         | • Neonatal hypoglycemia (in preterm infants)             | Decreased placental reserve |
| Nulliparity                          | • Persistent fetal circulation and extracorporeal membrane oxygenation therapy |                   |
|                                      |   • Intrauterine growth restriction                      |                   |
|                                      | • Congenital vascular abnormalities/vasculopathy         |                   |
|                                      |   ○ Vascular maldevelopment                              |                   |
|                                      |   ○ Vasculopathy (collagen 4A1 mutation, generalized arterial calcification of infancy) |                   |
|                                      | • Dehydration                                            |                   |
|                                      | • Extracorporeal membrane oxygenation                    |                   |
|                                      | • Male sex                                               |                   |
More than half of perinatal AIS occur in the middle cerebral artery territory (MCA), more often on the left due to preferential flow in fetal and neonatal right-to-left shunts, such as patent foramen ovale and ductus arteriosus (22, 35). Perforator strokes in the basal ganglia or thalami in newborns are commonly associated with difficult deliveries, sepsis, or presence of a central venous catheter (36). Multiple arterial territories may be involved in neonates with meningitis, embolic showers, thrombophilia, vasospasm, and congenital vasculopathies (such as COL4A mutation and generalized arterial calcification of infancy) (35). Stroke in preterm and extreme preterm neonates more often involves lenticulostriate and posterior inferior cerebellar artery territories (37, 38).

Acute phases of fetal stroke, such as in case of congenital heart disease or twin-twin transfusion syndrome (TTTS), may only rarely be detected prenatally. Fetal stroke often manifests with the chronic features of unilateral ventriculomegaly and volume loss with or without associated hemorrhage (Figures 1 and 2). Cranial ultrasound is usually the first brain imaging study performed in neonates for screening if they are symptomatic (39). Although not as sensitive as MRI, large ischemic lesions, perforator strokes, and thrombus in the superior sagittal sinus can be identified. Posterior fossa infarctions are difficult to detect unless quite large, although imaging through the posterolateral fontanelle improves sensitivity. Smaller infarcts in the cerebral cortex or white matter may be difficult to detect (40). The sensitivity for the depiction of perinatal AIS is 68% in the first 3 days, increasing to 87% between days 4 and 10 (41). Cerebral infarction appears as an ill-defined, hyperechogenic focus in a vascular distribution that slowly develops for several days after the event (42). Differentiation of hemorrhagic from bland infarction can be difficult, however, more focal areas of hyperechogenicity within the echogenic area may suggest hemorrhage. Cystic degeneration develops over 2–4 weeks with associated ex vacuo enlargement of the ipsilateral ventricle (Figure 3) (40). Color and power Doppler sonography show changes in regional cerebral blood flow after infarction, as well as asymmetric blood flow with loss of pulsatility in the MCA in the hyperacute phase (43, 44).

Although CT is often the first imaging modality performed, MR is generally preferred for its greater sensitivity, specificity, tissue contrast, and non-reliance on ionizing radiation or, in most cases, exogenous contrast agents. CT is nevertheless sensitive for acute intracranial hemorrhage in the acute setting. Cerebral infarction in the neonate has a similar appearance to that in the older child or adults, manifesting as a well-defined region of hypointensity in an arterial distribution (Figure 4), although small lesions can be difficult to identify on routine imaging due in part to unmyelinated brain masking subtle hypointensity. Additionally, certain areas in the posterior temporal and occipital cortices can have low attenuation on CT in normal infants and the risk for false positive classification of stroke merits circumspection. The “hyperdense artery sign” representing acute intraluminal thrombus is infrequently observed in neonates, and may relate to varying clot compositions, including potential differences in the presence, concentration, or composition of red blood cells and iron within the heme moiety of hemoglobin (45).

On MRI, acute infarcts demonstrate reduced diffusivity within minutes, exhibiting high signal on DWI and low computed diffusivity on ADC maps (Figure 5) (46). Diffusivity remains reduced for about 6 days, peaking at about 3 days, before pseudonormalization occurs, with diffusivity then increasing to
above normal by the second week (47–50). Timing of DWI changes can be affected by the age of the patient, size of the stroke, and how quickly collateral blood flow is recruited. DWI also detects early or pre-wallerian degeneration in infants (also referred to as “acute network injury”), characterized by injury to the antegrade white matter tracts following acute infarct and manifests as reduced diffusivity in white matter pathways affected by the infarction within a few days.

Figure 1. Acute and chronic fetal infarctions. 29 weeks of gestation fetus with a chronic stroke in the right hemisphere. (A) Axial HASTE (Half Fourier Singleshot Turbo Spin-Echo) and (B) Gradient Recall Echo (GRE) images showing unilateral enlargement of the right lateral ventricle, with periventricular white matter loss (white arrow) and linear blood staining (black arrowhead). 21 weeks of gestation fetus with congenital heart disease with acute stroke in the right hemisphere. (C) Axial DWI and (D) ADC map showing areas of reduced diffusion in the left ACA and MCA territories (black arrow) with questionable infarct in the right MCA territory (white arrowhead). Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.
of the injury (Figure 5) (51). Common pathways affected by acute network injury include the corpus callosum, thalamus, and descending corticospinal tract. When seen along the corticospinal tracts, acute network injury is highly predictive of poor motor outcomes (52, 53).

Due to the immaturity of the brain, MRI appearance of the infarct can evolve uniquely in infants. In newborns, the combination of cytotoxic and vasogenic

Figure 2. Three-day-old girl with chronic encephalopathy. Pregnancy complicated by maternal HELLP (H: Hemolysis, E: elevated liver enzymes, L: low platelet count) syndrome. Sagittal T1- (A) and coronal T2-weighted images (B) show microcephaly and bilateral chronic MCA-territory infarctions. Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.

Figure 3. Coronal brain US in ex-premature 31-week boy. A. At 11 days of life and (B), 2 weeks later showing evolution of periventricular infarction. Small arrow in (A) indicates an ill-defined subacute infarction in the left frontal white matter. Arrowhead in (B) indicates evolution of infarcted area into the focally cystic encephalomalacia. Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.
edema results in increased signal in the cortex and white matter on T2-weighted imaging 24–48 hours after infarct (54). As the signal increases within the cortex, it becomes isointense to the underlying unmyelinated white matter, known as the “missing cortex sign” (55). In infants, infarcts may be difficult to see on FLAIR images due to unmyelinated white matter. In the subacute phase (1–3 weeks), infarcted gray matter may show high signal intensity on T1-weighted images because of petechial hemorrhage, lipid laden microglia, high protein content, and manganese accumulation related to astrocytes (“cortical highlighting”) and low signal intensity on T2-weighted images because of petechial hemorrhages, lipids, and calcification (46, 56–58). Contrast enhancement of the infarct is typically seen related to neovascularization with immature “leaky” vessels lacking well-formed blood brain barriers (55). Earlier phases of contrast enhancement following blood brain barrier ischemia, developing several hours after infarction, are commonly uncaptured due to persistent vascular compromise, but may rarely be identified if reperfusion occurs early (59, 60).

The chronic stage (beginning by 3 weeks) is characterized by volume loss and varying degrees of gliosis. The final appearance of the infarct is related to the timing of insult, the maturity of the infarcted brain, and the degree of astrocytic response to injury, and may span from none (infarct earlier in gestation) to mild (infarct later in gestation and early prenatal period). If injury occurs before 20 weeks of gestation, schizencephaly will often develop, with the cleft lined by

**Figure 4. A 14-day-old boy with seizures.** Axial non-contrast CT image showing unilateral diffuse hypodensity in the right PCA distribution (arrows). Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.
dysplastic gray matter. Porencephaly results when the insult occurs between approximately 20 and 24 weeks from liquefactive necrosis, appearing as a smooth-walled, fluid-filled cavity isointense to CSF that may or may not communicate with the ventricular system. The surrounding white matter typically demonstrates normal signal. Encephalomalacia and gliosis results when the insult occurs in the late second trimester and onward, as the brain is able to mount an astrocytic response to injury, and demonstrates surrounding parenchymal signal abnormality, best depicted on FLAIR (Figure 6).

While MRA is technically more challenging to perform in neonates due to smaller blood vessels and lower blood velocities, it can help define the site of stenosis or large vessel occlusion and define anatomic variation non-invasively (61–64). Most neonates (62%) with AIS have been shown to have findings on MRA, including occlusion or thrombus-type flow defect (Figure 3) (65). Additionally, some neonates show increased flow in insular MCA branches, which has been proposed to be related to early dissolution of clot with loss of autoregulation and hyper-perfusion (54).
Perfusion imaging is not routinely used in neonatal stroke for technical reasons—dynamic susceptibility contrast-enhanced (DSC) imaging requires a large, generally power-injected contrast bolus and noncontrast arterial spin labeling (ASL) perfusion is technically challenging in neonates in part due to the faster heart rate—and because it does not presently alter patient management in most cases, although paradigms for use of neonatal perfusion are emerging (19). ASL can be used to assess perfusion without the need for intravenous contrast, with pseudocontinuous tagging schemes (pCASL) and ideally flexible prescription of post-label delays preferred (66). Compared to the core and penumbral hypoperfusion seen in older children and adults, neonates often demonstrate hyperperfusion within the region of decreased ADC (Figure 7), with little evidence of adjacent hypoperfusion, which may be related to reperfusion or seizure-associated neuronal hyperexcitability (67). Hypoperfusion may be more common in venous stroke (67).

Hemorrhagic stroke

The incidence of perinatal hemorrhagic stroke is approximately 1 in 6000–9000 live births (68–71). Compared with PIS, fairly little is understood about its risk factors, etiologies, and outcomes. While intraventricular hemorrhage in premature neonates originates from a fragile germinal matrix, the mechanisms responsible for late preterm and term hemorrhagic strokes remain unclear, and the majority are described as idiopathic (69, 70). In term infants, isolated intraventricular hemorrhage is less common than intraparenchymal hemorrhage and, if present, may be the result of CSVT (72–74). Causes of hemorrhagic stroke include congenital and acquired coagulopathy, CSVT (particularly cerebral medullary veins thrombosis), vascular malformations, and hemorrhagic conversion of ischemic infarct (arterial or venous) (69). Hemorrhagic disease of the newborn is more prevalent in infants who have not received vitamin K at birth and in infants.
of mothers taking blood thinning medications, such as warfarin, phenytoin, or barbiturates, during pregnancy (75, 76). Acquired coagulopathies include neonatal alloimmune thrombocytopenia or disseminated intravascular coagulation. Some genetic arteriopathies associated with both fetal and neonatal hemorrhagic stroke include collagen IVA and JAM3 mutations, which can appear identical to hemorrhagic venous infarctions (77–84). In addition to hemorrhages occurring later in life, fetal and neonatal patients may present with subpial hemorrhages (Figure 8), which may be related to local venous thrombosis or birth trauma (85–87). In these cases, blood is seen between the pia mater and the displaced brain parenchyma, often accompanied by venous infarction and subarachnoid or parenchymal blood.

Although NCCT is sensitive for acute hemorrhage, MRI is the imaging modality of choice when clinically feasible due to the diagnostic accuracy and lack of ionizing radiation. MRI can diagnose hemorrhage, differentiate hemorrhagic transformation of arterial or venous infarction from primary hemorrhages, and is well-suited to evaluation of the brain parenchyma for an underlying mass or large vascular malformation. SWI uses magnitude and phase data to create high-resolution images to visualize intravascular venous deoxygenated blood and blood breakdown products and can help differentiate hemorrhage from calcification (88). The paramagnetic effects of blood products contribute to the heterogeneity of diffusion characteristics. Hemorrhage varies from large subcortical hematomas to petechial hemorrhages within edematous brain parenchyma (89, 90).

Catheter angiogram is rarely used in the setting of hemorrhagic infarct, except in the diagnosis and management of vascular malformations, due to demand for high operator technical expertise and the attendant risks to manipulation of small, fragile neonatal vessels (91). Repeat imaging once blood products have resorbed

**Figure 7. Neonatal arterial ischemic infarction.** DWI (A) demonstrates reduced diffusion in the right PCA territory (white arrow), from acute infarct, as well as the callosal splenium (white arrowhead), representing acute network injury, with increased perfusion on Arterial Spin Labeling (ASL) perfusion (black arrow) (B). Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.
Perinatal Stroke Imaging

(approximately 3 months) may be helpful to exclude subtle underlying pathology such as arteriovenous malformations or tumor (92, 93).

**Venous infarct/CSVT**

Pediatric venous infarcts secondary to CSVT/thrombosis of medullary veins occur most often (more than 40%) in the neonatal period (88, 89). The reported incidence of venous thrombosis is 2.6 per 100,000 (1, 88, 90). Approximately 50–60% percent suffer venous infarction, of which about 75% are hemorrhagic (21). The suggested pathophysiology of venous thrombosis encompasses “Virchow’s triad”, including: stasis of blood flow, injury to the endothelial lining, and hypercoagulability of blood components (94). As in perinatal AIS, multiple risk factors in both the mother and fetus may play a role in neonatal venous thrombosis, including gestational diabetes, preeclampsia, chorioamnionitis, neonatal sepsis, dehydration, difficult or instrumented delivery, and underlying prothrombotic state (95, 96). Venous thrombosis should be suspected in the setting of an unexplained hemorrhage or a brain parenchymal injury that does not fit an arterial vascular distribution, in the absence of trauma or infection (73, 97). Venous sinus occlusion initially reduces venous outflow with resultant vasogenic edema, and if adequate collateral venous outflow is not established, venous infarction will ensue (98). CT is sensitive for detecting hemorrhage, although the risk of ionizing radiation should be considered. On CT, venous infarcts are usually poorly delimited, hypodense, or mixed-attenuation, likely related to the presence of cerebral edema and hemorrhage, without respecting arterial territories (Figure 9) (42). The thrombosed vein may be seen overlying the infarction as a curvilinear region of high attenuation, depending upon the age of the thrombus. Infarctions occur in the territory of thrombosed venous, with parasagittal injuries in superior sagittal sinus thrombosis, temporal lobe hematomas in transverse sinus thrombosis, and thalamic hemorrhage in vein of Galen and straight sinus thromboses (99).

Periventricular venous infarction occurs in preterm infants as a consequence of germinal matrix hemorrhage, typically prior to 32 weeks of gestation (11). Germinal matrix hemorrhage may secondarily cause compression of the medullary veins, resulting in focal venous infarction in the periventricular white matter (100).
Primary thrombosis of deep medullary vein can also be seen in full term neonates with congenital heart disease or with dehydration/metabolic acidosis, in the absence of germinal matrix hemorrhage, hypothesized to be related to hypoperfusion or impaired cerebral blood flow, and resulting in periventricular white matter venous infarct, often hemorrhagic (101–103). The “iris sign,” a fan-shaped appearance of restricted diffusion or hemorrhage, most prominent in the deep frontal white matter, is a pathognomonic imaging sign of medullary vein thrombosis (Figure 10) (104). Delayed findings of periventricular venous infarction include periventricular white matter volume loss sparing the cortex and basal ganglia, focal irregularity of the ventricular margin, and hemosiderin staining (105). If spontaneous venous thrombosis is identified, the patient should be evaluated for disorders of coagulation (30, 97, 106–113).

On MRI, routine T1- and T2-weighted images should be obtained, in addition to DWI, GRE or SWI images, and MRV. Acute venous thrombus (<7 days old) exhibits marked hypointensity with apparent expansion of the affected sinus on GRE or SWI (114). Subacute thrombosis (6 - 15 days) demonstrates high intensity on T1-weighted images (115). Multiple MRI techniques have been developed to detect venous thromboses, including 2D Time-of-Flight and phase contrast angiography, both of which are performed without the use of gadolinium, as well as contrast-enhanced techniques. Contrast-enhanced MRI is more accurate for diagnosing CSVT than non-contrast-enhanced flow-related and native contrast MR sequences, likely due to superior performance where flow-related enhancement is diminished due to extremely slow flow or where flow is parallel to the imaging plane on 2D time-of-flight sequences (116).

In neonates with venous thrombosis, follow-up MRI/MRV may be performed between age 6 weeks and 3 months following initiation of anticoagulation (96).

Figure 9. Venous thrombosis and hemorrhagic venous infarction. A three-day-old girl with right sided seizures. Axial non-contrast CT images show left frontal hemorrhagic venous infarction (arrow) and hyperdense clot in the superior sagittal sinus (arrowheads). Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.
Follow-up imaging may guide therapy, since persistence or extension of the clot may lead to extension of full-dose anticoagulation, while resolution of the clot may prompt discontinuation of therapy. If anticoagulation is not initiated, short-term follow-up within one week, or sooner if symptoms worsen, can be considered and may lead to the subsequent initiation of treatment (19).

**STROKE MIMICS**

Clinically diagnosing stroke in neonates can be difficult due to the non-localizing and nonspecific signs of stroke, such as lateralized weakness after seizure or ataxia, are often overlooked (117). Other neurologic diagnoses can have a similar presentation, including congenital and acquired metabolic disorders, hypoglycemia, in addition to epilepsy, intracranial infection or inflammation, focal lesions, and drug toxicity (Figures 11 and 12) (118, 119).

**TREATMENT**

Unlike in adults, no standard acute therapy exists for neonatal AIS, since, by the time of presentation, the infarct is often well established, and the affected artery is often patent (120). Management is therefore focused on neuroprotection, including seizure control (121). Early seizures often cease within days of onset and some children can be weaned from antiepileptic medications prior to discharge. Experimental neuroprotective therapies, including erythropoietin and stem cell therapy, show promising results (122, 123). Anticoagulation is used in patients with CSVT who do not have substantial intracranial hemorrhage. In neonates, CSVT often resolves without aggressive therapy and without neurologic residua.

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**Figure 10. Medullary vein thrombosis and periventricular venous infarctions.** Ex-premature at 32 weeks of gestation neonate, axial T2-weighted image (A) shows intraventricular hemorrhage (Black arrowhead), medullary veins thrombosis, and periventricular venous infarctions (arrows). A 7-day-old full-term neonate with severe dehydration. Sagittal T1-weighted (B) and axial GRE (C) images shows acute thrombus in the straight sinus (black arrow) and torcular and extensive thrombosis of the deep periventricular medullary veins (white arrowheads). Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.
However, since about 30% of CSVTs propagate and result in worsening infarction, the risks and benefits of preventing further infarction and hemorrhage by anticoagulation and worsening the existing hemorrhage by withholding treatment must be carefully weighed.

**PROGNOSIS**

Over half of patients affected by perinatal stroke will have long-term neurological disabilities (124). Motor deficits occur in up to 60% of the cases, with hemiplegic cerebral palsy being the most common outcome. The upper extremity is often

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**Figure 11.** A 20-day-old boy with classic-type of maple syrup urine disease (MSUD). Axial DWI images showing symmetric pattern of acute restricted diffusion in the basal ganglia, thalami, brainstem, characteristic of exacerbation of MSUD. Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.

**Figure 12.** A three-weeks-old girl with seizures and hypoglycemia. Axial CT (A) and axial DWI (B), and ADC (C) MR images show low density and loss of gray-white matter differentiation in the posterior half of the cerebral hemispheres on CT and reduced diffusion on MRI. The extent of the signal abnormality is much greater than usually seen with watershed infarction in the border zone between the MCA and PCA. Case courtesy of Dr. Tamara Feygin, Department of Radiology, Children’s Hospital of Philadelphia.
more involved than the leg in arterial lesions, with the reverse true for periven-
tricular venous infarction. Poor motor outcome is associated with basal ganglia
involvement and with periventricular venous infarction (9). Other neurodevelop-
mental problems include recurrent seizures, cognitive disabilities, and behavioral
disorders (4). Seizures, poor cognition, and delayed development are associated
with cortical involvement (9, 125). Patients with larger infarctions or infarctions
involving eloquent regions of cortex have larger residual deficits than do those
with smaller infarcts and those involving less eloquent regions (126, 127). In
neonates, hemiparesis typically does not develop unless the cortex, basal ganglia,
and internal capsule are all affected, whereas later in childhood, hemiparesis may
develop even if only one or two of those sites are affected (128). In the absence of
epilepsy, many functions normally performed by the injured regions of the brain
may be subsumed in regions that have been spared due to neuroplasticity; although,
when epilepsy develops, cognitive recovery may be impaired (127). Although congenital hemiplegia can result from prenatal periventricular venous
infarctions, these patients are less likely to present with seizures or cognitive
delays due to sparing of the cortex (129, 130). Language development potentially
maintains a relatively normal trajectory due to neuroplasticity of the developing
brain. Since the pregnancy-related circumstances that lead to perinatal stroke
resolve, the risk of recurrent stroke in neonates is considered comparatively low
(0–1.8%), except in neonates with congenital heart disease or other predisposi-
tions (14%) (4, 131). Important imaging features indicative of poor long-term
neurological outcome may be demonstrated by reduced diffusion in the descend-
ing white matter tracts, preceding Wallerian degeneration, while notably T1- and
T2- weighted sequences often fail to depict this early injury in the maturing brain.

CONCLUSION

A significant cause of morbidity, perinatal stroke results from a combination of
maternal, obstetric, anatomic, and genetic factors. Understanding the unique eti-
ologies and presentation is important for accurate and timely diagnosis. The use
of appropriate neuroimaging is essential for making the correct diagnosis, direct-
ing treatment, excluding alternative diagnoses, and determining prognosis. As the
understanding of the mechanism of neonatal stroke progresses and treatments
improve, neuroimaging will continue to be an essential component of patient
management and will evolve.

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