

Perinatal Ischemic Stroke

Etiology and Imaging



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KEYWORDS

- Perinatal stroke • Neonatal arterial ischemic stroke
- Periventricular venous infarction • Presumed perinatal arterial ischemic stroke

KEY POINTS

- Perinatal ischemic stroke is a common cause of acute neonatal neurologic symptoms. It can be most effectively diagnosed in the acute period with imaging, preferably MRI if available.
- Perinatal ischemic stroke can cause lifelong morbidity, including hemiparesis, language impairment, and cognitive disability.
- The risk for poor outcome in perinatal stroke can be predicted early on acute imaging and managed with proactive referral to rehabilitation services.

INTRODUCTION

Perinatal ischemic stroke is common, exceeding the risk of childhood stroke 10-fold.¹ Most cases of unilateral hemiparesis are due to perinatal stroke.² Early identification of affected patients and prediction of their risk for future morbidity on acute imaging can aid in determining rehabilitation strategies and clinical follow-up. This review will provide an overview of perinatal ischemic stroke, including clinical features, imaging, and outcome.

DEFINITIONS

A workshop was convened in August 2006 by the National Institute of Child Health and Human Development (NICHD) and the National Institute of Neurologic Disorders and Stroke (NINDS) to review the topic of stroke in the perinatal period and create research goals. The proceedings noted that various terms have been used to define both stroke and the perinatal period, leading to numerous different labels for the condition. Thus, the workshop specifically chose the term ischemic perinatal stroke (IPS) and defined it

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as “a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life and the 28th-day postnatal day, confirmed by neuroimaging or neuropathologic studies.”³ They further defined various subsets of IPS based on the time of diagnosis, to include (1) fetal ischemic stroke diagnosed before birth, (2) neonatal ischemic stroke diagnosed in either term or preterm infants after birth and on or before the day of life 28, (3) presumed perinatal ischemic stroke (PPIS) diagnosed in patients greater than 28 days of age, in whom it is inferred that an ischemic event occurred sometime between 20th week of fetal life and the 28th postnatal day, with said inference typically made from the interpretation of imaging and clinical history.³

More recent publications have further refined the classification of perinatal stroke. The current standard is to categorize perinatal stroke based on whether it is arterial or venous in origin, whether it is purely ischemic or contains hemorrhage, and age at diagnosis.⁴ This leads to 6 commonly used categories of perinatal stroke. In this review, we will focus on the ischemic stroke subtypes, which are currently typically termed neonatal arterial ischemic stroke (NAIS), synonymous with neonatal ischemic stroke as defined above, presumed perinatal arterial ischemic stroke (PPAIS), synonymous with PPIS as defined above, and periventricular venous infarction (PVI), another presumed perinatal ischemic stroke subtype.⁴ Of note, NAIS is synonymous with perinatal arterial ischemic stroke (PAIS) as used in much of the literature on neonatal stroke, but for consistency in this review, the term NAIS will be used.

NEONATAL ARTERIAL ISCHEMIC STROKE

Epidemiology

Neonatal arterial ischemic stroke (NAIS) incidence estimates range from 17.8/100,000 to 35/100,000.^{5–8} Incidence estimates have increased over time, and it is unclear whether this is due to a true increase in disease or improved detection. Perinatal stroke overall accounts for 25% of stroke in children,⁹ and NAIS represents 71% of all perinatal strokes.¹⁰ Most of the reported NAIS cases are male, ranging up to 70%.¹¹ NAIS was the etiology of 15% of neonatal seizures in one study.¹² Mortality is generally considered rare, with incidence estimates ranging from 2.67/100,000 to 3.49/100,000 live births,⁵ although more recent case series have reported no deaths.⁷

Table 1 Risk Factors of NAIS		
Maternal	Fetal/Intrapartum	Placental
First pregnancy	Male sex	Maternal vascular malperfusion
Twin pregnancy	Congenital heart disease	Fetal vascular malperfusion
Prolonged second stage	Hypoglycemia	Amniotic fluid inflammation
Emergency caesarean section	Perinatal hypoxia	Chronic villitis
Preeclampsia	Infection/inflammation	Large placenta with chorangiosis
IUGR	Need for resuscitation	
Maternal Smoking	Apgar <7 at 5 min	
Maternal Fever	Arteriopathy	
PPROM	Presence of meconium	
Family history of seizures		

Data from Refs. ^{10,11,13–15,54}

Risk Factors

Most sources separate NAIS risk factors into maternal, fetal, and placental categories (**Table 1**). The most commonly reported risk factors include first pregnancy, perinatal infection/inflammation, prolonged second stage, need for resuscitation, male sex, and congenital heart disease.^{10,11,13–15} In many cases, multiple risk factors are present and increase the likelihood of NAIS.⁶

Although global hypoxia is considered a risk factor for NAIS, it and HIE are typically considered separate entities. One study did identify an overlap of multiple risk factors for NAIS and neonatal hypoxic-ischemic encephalopathy (HIE), including male sex, premature rupture of membranes (PROM), presence of meconium, and need for resuscitation.¹¹ Intrapartum inflammatory complications such as PROM and maternal fever are still more common in NAIS, which further implicates inflammation as an important risk factor.¹⁵

Evidence regarding thrombophilia as a risk factor is mixed. Some reports have strongly implicated thrombophilia in infants and/or mothers in NAIS,^{16,17} although more recent studies have not found an association.^{18,19} Curtis and colleagues thus do not recommend routine testing for thrombophilia in patients with NAIS.

Causes

Regardless of the risk factor background, NAIS likely occurs due to some of the same underlying mechanisms as stroke at older ages. These include embolus (of either cardiac or aortic origin), arteriopathy, and thrombosis due to disordered hemostasis.²⁰ Emboli can result from either congenital heart disease or placental pathology (both known risk factors), arteriopathy can result from either genetic causes or neonatal meningitis causing nearby arteritis, and thrombosis can be caused from systemic perinatal infection and/or inflammation.²¹

Clinical Presentation

Patients with NAIS will present before 28 days of life in 58% to 68% of cases.^{6,14} Seizures are the classic and most common presentation of NAIS, occurring in up to 88% of neonates, and they are most often focal although they can be generalized.²² Focal motor seizure presenting after 12 hours of life in the neonate strongly favors NAIS over HIE.²³ Neonates can also present with other neurologic deficits, including encephalopathy, abnormal tone, and feeding and respiratory difficulties.²²

Imaging

Cranial ultrasound

Cranial ultrasound (CUS) is frequently the first diagnostic imaging test undertaken on the neurologically compromised NICU patient. A study of CUS in term infants with NAIS found that the modality detected 68% of cases in scans performed between days 1 to 3 of life, and 87% of cases performed between days of life 4 to 14.²⁴ However, in a major series of childhood stroke patients from Canada, CUS was the first test to diagnose NAIS in only 7%.²²

Infarcted tissue on neonatal CUS is typically abnormally echogenic relative to surrounding normal brain. CUS is superior at detecting areas of infarction that are within the view of the ultrasound probe, including the lenticulostriate territory, the medial anterior cerebral artery, and more lateral middle cerebral artery territories (**Fig. 1A, B**). Small infarctions, particularly over the more superior convexities outside of the probe range, can be missed (**Fig. 1C, D**). As alluded to above, CUS sensitivity increases in the earlier subacute period compared with the acute period (<3 days).²⁴

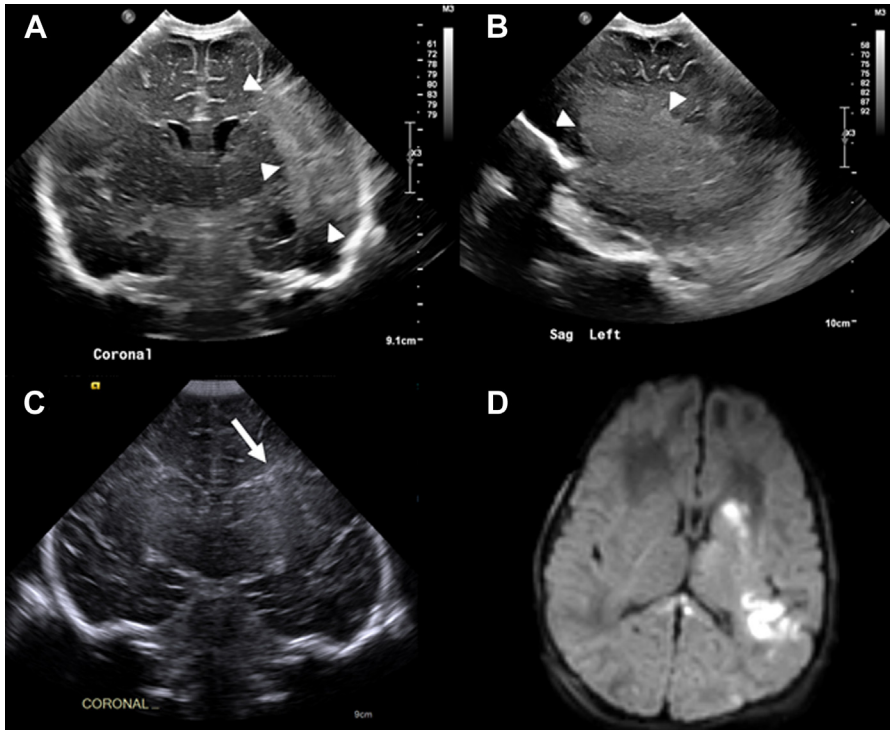


Fig. 1. Cranial US coronal (A) and sagittal (B) images were obtained in an infant at DOL 7 who was already diagnosed with stroke on MRI at DOL 1 after presenting with seizures. Images demonstrate a roughly wedge-shaped area of increased echogenicity in the left MCA territory compatible with infarction (arrowheads). Coronal cranial US (C) in a different patient at DOL 1 was called normal. In retrospect, there is a subtle area of increased echogenicity near the left caudate head (arrow). The areas of infarction are demonstrated on the follow-up DWI MRI performed at DOL 2 (D).

Head computed tomography

Head computed tomography (HCT) is often not the first-choice modality for imaging of neonatal neurologic symptoms for several reasons. CUS is more easily and quickly obtained as it can be performed at the bedside in critically ill neonates. HCT generally requires transport to the CT scanner, which entails extra risk for neonates in the NICU. Further, if transport is required, MRI (if available) is a more sensitive modality for most neurologic diseases, including NAIS. HCT is also less sensitive to parenchymal disease in the neonate due to its generally unmyelinated state.

However, HCT is still a reasonable alternative to MRI in those neonates who are so critically ill that they cannot undergo a (generally longer) MRI examination or in institutions whereby MRI is not available. In fact, HCT was the first test to diagnose NAIS in 87% of patients in a large national series of patients with stroke.²²

The HCT findings of acute arterial ischemic stroke in the neonate are the same as in older children and adults—an area of hypodensity corresponding to an arterial territory (Fig. 2A, B). The characteristic hypodensity of acute infarction is more difficult to detect on HCT in neonates, because the relatively unmyelinated neonatal brain is more diffusely hypodense, creating less inherent contrast between normal and

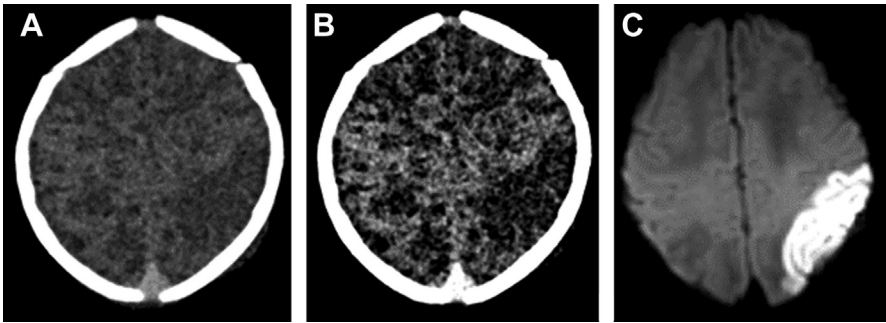


Fig. 2. Term newborn with focal seizures. Axial CT image at DOL 0 displayed with routine brain windowing (A) demonstrates a very subtle area of hypodensity in the left parietal lobe that is better seen on a narrower stroke window (B). DWI at DOL 1 (C) shows the area of restricted diffusion compatible with arterial ischemic stroke to much better advantage.

infarcted brain. Using a narrower “stroke” window setting increases the contrast between infarcted and normal brain (see Fig. 2B). Also, like older patients, HCT is less likely to show a stroke less than 12 to 24 hours old compared with DWI on MRI (see Fig. 2C).

Brain magnetic resonance imaging

General considerations. MRI is the gold standard for imaging of neurologic disease at any age. It is particularly valuable in imaging neonates with concern for central nervous system pathology for many reasons, including avoidance of ionizing radiation and superior depiction of tissue contrast. Furthermore, multiple different types of anatomic and physiologic imaging can be performed during a single MR examination, including multicontrast imaging of the brain parenchyma, luminal imaging of the intracranial arterial and venous systems, MR spectroscopy, and perfusion-weighted imaging (Fig. 3).

MRI does present specific challenges in neonatal imaging compared with other modalities. There are safety concerns with the high magnetic field strengths necessary for clinical MRI. Although these are routinely managed by MRI staff, additional MR safety

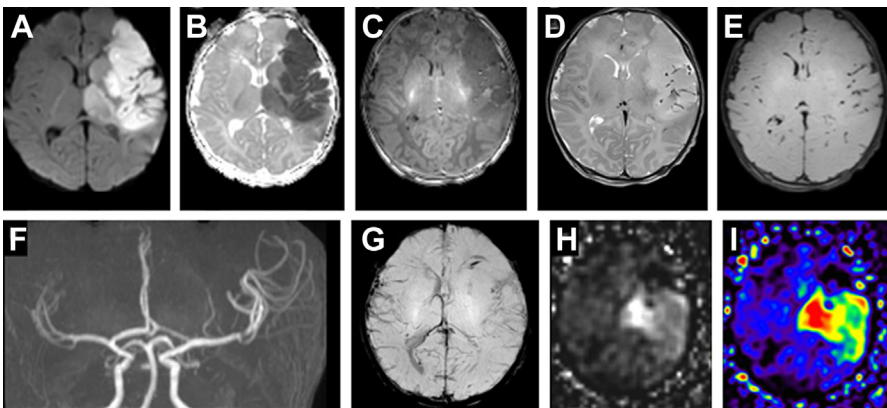


Fig. 3. This figure illustrates the different types of MRI sequences commonly used to image perinatal arterial ischemic stroke, including DWI (A), ADC (B), T1 (C), T2 (D), FLAIR (E), time of flight MRA (F), SWI minIP (G), grayscale (H) and color-coded (I) pCASL.

training is usually necessary for NICU staff transporting the patient. In most institutions, transport from the NICU to the MRI suite and a transition from the incubator to the MRI scanner table is required. Some institutions have acquired MRI scanners in the NICU, obviating the need for lengthy transport, and many other children's hospitals have used MRI compatible incubators to maintain neonatal life support without the need to move the patient to a separate table.²⁵ Finally, MRI requires a relatively motionless subject for diagnostic imaging. While general anesthesia is often used in pediatric MRI examinations to ensure patients remain motionless, most neonates can be imaged safely and easily without anesthesia using a feed and sleep technique.^{26,27} Multiple new MRI techniques have also been developed to acquire images more quickly and to decrease motion artifacts.²⁸

Diffusion-weighted imaging. While most routine MR sequences generate image contrast by varying parameters to accentuate differences in local proton magnetic environments (known as the T1 and T2 tissue times), diffusion-weighted imaging (DWI) uses a specific sequence of strong magnetic gradients to ensure that only relatively stationary protons will return signal. Protons in brain tissue tend to return the signal on DWI in several pathologies, but most often in cytotoxic edema, which is a state of intracellular swelling often brought about by metabolic derangements such as ischemia.²⁹

DWI is thus extraordinarily sensitive to acute arterial ischemic stroke in both adults and children, and it can demonstrate changes in infarction earlier than most other imaging modalities. Areas of infarction are hyperintense on DWI. An apparent diffusion coefficient (ADC) map is routinely generated with DWI to show diffusion restriction in a quantifiable manner and to remove the effects of T2 hyperintensity. Thus, any areas of hyperintensity on DWI should be correlated with hypointensity on ADC maps to confirm true restricted diffusion indicative of infarction.²⁹

Several publications have studied the time course of DWI and ADC changes after infarction (Fig. 4). While usually positive soon after symptom onset, DWI can underestimate the extent of infarction and the degree of associated network injuries if performed within 24 hours of presentation.³⁰ The time course of diffusion-weighted changes has also been studied on ADC maps, showing that the lowest ADC values are usually seen 3 to 4 days after presentation, with so-called pseudonormalization (apparent return to normal ADC values) at approximately 7 to 9 days.³¹

T1 and T2-weighted imaging. In general, T1-weighted images depict areas with higher lipid content (such as the myelin sheath) as hyperintense, and T2-weighted images depict areas with higher water content as hyperintense. In the unmyelinated neonatal brain, this results in the normal cortex being relatively T1 hyperintense and T2 hypointense, and normal white matter being T1 hypointense and T2 hyperintense.

Loss of gray/white differentiation is the first sign of infarction in the neonatal brain on T1 and T2-weighted images, manifesting as abnormal cortical T1 hypointensity and T2 hyperintensity. This occurs after findings are apparent on DWI/ADC, usually greater than 12 to 24 hours after presentation. This persists through approximately day 6 to 7, after which the cortex gradually becomes more T1 hyperintense and T2 hypointense through the first or second month after infarction³² (see Fig. 4G, H). Tissue atrophy and cyst formation begin approximately 1 month after the initial insult, and the area of infarction will usually take on its chronic appearance within 2 to 3 months (see Fig. 4K, L).

Although a mainstay for diagnosis in older children and adults, FLAIR imaging (see Fig. 3E) is of limited utility for parenchymal evaluation and NAIS in neonates,

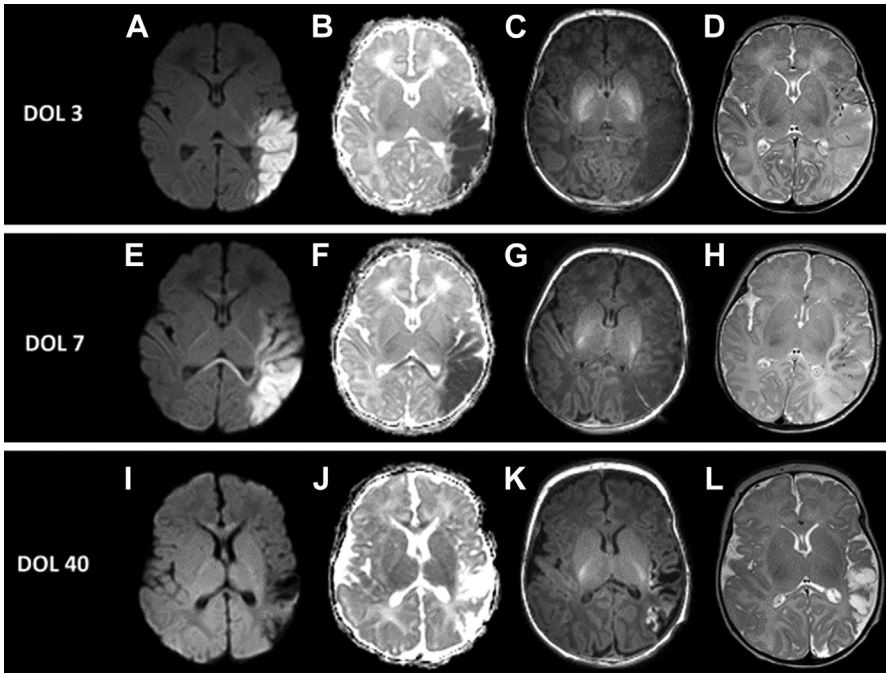


Fig. 4. Lettering is off. D is on their twice. Term neonate who presented at DOL 2 with seizures. Successive DWI, ADC, T1, and T2-weighted images demonstrate the maturation of signal changes in a perinatal arterial ischemic stroke single patient over time. On the patient's first examination performed at DOL 3, DWI image (A) depicts a circumscribed area of marked hyperintensity in the left posterior temporal lobe with corresponding decreased ADC values (B), compatible with restricted diffusion. In this context, the diffusion restriction indicates cytotoxic edema from acute arterial ischemic stroke. T1 (C) and T2 (D) images show the area of infarction as a homogeneous area of loss of gray/white differentiation. On DOL 7, the area of infarction is still hyperintense on DWI (E) and shows persistently decreased ADC values (F), although they have slightly increased since DOL 3. DWI image also demonstrates diffusion restriction in the corpus callosum splenium, compatible with an associated network injury. The involved white matter in the left posterior temporal lobe has become more T2 hyperintense, and the cortex has become slightly more T1 hyperintense (G) and T2 hypointense (H). By DOL 40, diffusion restriction on DWI (I) has resolved, and ADC values in the area of infarction have become diffusely increased relative to normal brain (J). Associated cortical T1 hyperintensity throughout this region has become even more conspicuous (K) and cystic changes and atrophy of the affected parenchyma have already developed on T2-weighted images (L).

secondary to their unmyelinated white matter. It is, therefore, not a routine part of many neonatal brain imaging protocols, although it can aid in the detection of extra-axial hemorrhage.

Magnetic resonance angiography. Most routine intracranial magnetic resonance angiography (MRA) techniques are designed to use the signal from fast-moving blood flowing into the area of interest to generate images of the arterial lumen; thus, no intra-venous contrast is necessary.

MRA findings in NAIS can range from stenosis or occlusion of involved arterial segments (Fig. 5A, B, C), to paradoxical enlargement and hyperintensity of involved

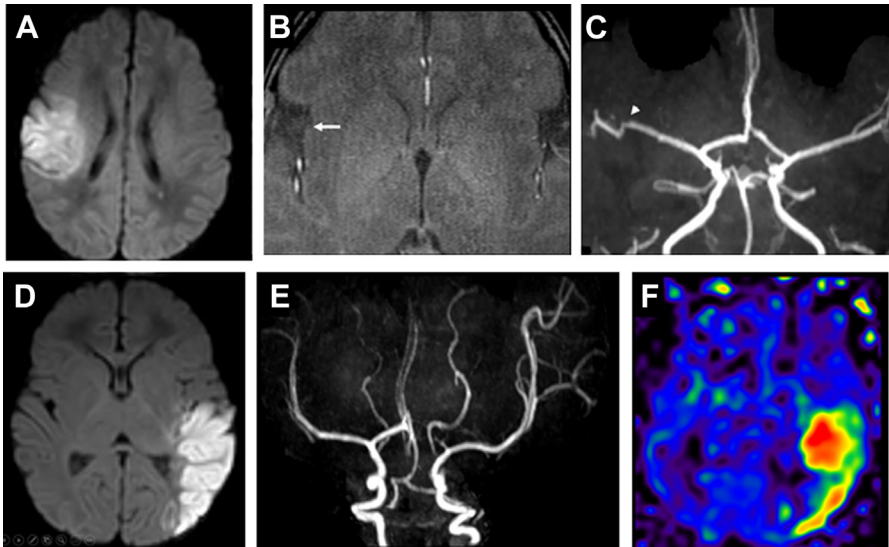


Fig. 5. DWI (A) of a 2-day-old woman presenting with seizures demonstrates acute infarction in the right posterior frontal lobe. MRA source image (B) shows the asymmetric absence of flow-related enhancement in right MCA M2 branches (arrow), also seen on a frontal MIP projection (C, arrowhead). DWI image (D) obtained at DOL 3 in a different patient (same infant as depicted in Fig. 4) redemonstrates the left posterior temporal lobe acute neonatal arterial ischemic stroke. Time of flight MR angiography from DOL 3 (E) shows increased caliber and intensity of flow-related enhancement in left MCA branches supplying the area of infarction. Color pCASL image (F) demonstrates that the area of infarction is correspondingly hyperperfused.

segments, a phenomenon sometimes referred to as reperfusion or luxury perfusion (Fig. 5D, E). In one study of 37 patients with NAIS, 23 had abnormalities on MRA, including occlusion in 6, thrombus formation in 9, and increased flow in 8.³³ Those patients with NAIS with MRA abnormalities also demonstrated worse outcomes, especially those with occlusion. These findings may provide additional evidence that embolism is a frequent cause of NAIS.

Arterial spin labeling. Arterial spin labeling (ASL) perfusion techniques are increasingly used in routine brain imaging to depict changes in cerebral blood flow without the need for intravenous contrast. Various ASL techniques are available that vary by manufacturer, including continuous, pulsed, and pseudocontinuous. Each technique has its own advantages, disadvantages, and availability, although pseudocontinuous ASL (pCASL) has been shown to be superior to pulsed ASL (PASL) in neonates.³⁴ Regardless of the available technique, ASL can be technically challenging in neonates due to their size and smaller volume of circulating blood. Modification of default parameters to optimize the detection of neonatal cerebral blood flow is often necessary and may require vendor support.

ASL in NAIS often depicts an area of increased blood flow corresponding to the area of infarction (Fig. 5F), corresponding to findings often seen on MRA. In one large series of neonatal stroke imaged with ASL, 8/11 NAIS cases demonstrated hyperperfusion, and a penumbra was seldom seen,³⁵ in contrast to older patients.

Network injury. Secondary neuronal degeneration in a part of the brain distant from an injury has been called diaschisis, Wallerian degeneration, or network injury by various authors. All these terms refer to the structural and/or functional changes that can occur in the central nodes of the various neuronal networks distant from a site of injury. This phenomenon is perhaps most famously recognized in crossed cerebellar diaschisis, whereby hypoperfusion or atrophy occurs in the cerebellar hemisphere contralateral to a large cerebral insult,^{36,37} although it has also been described in the striatum and thalami of adults following surgery.³⁸

The unmyelinated neonatal brain may be particularly vulnerable to this sort of secondary neuronal degeneration.^{39,40} Network injuries in neonates most often manifest as areas of mild diffusion restriction (with higher ADC values than the area of infarction) in central areas of the brain not supplied directly by the middle cerebral artery, including the corpus callosum splenium, thalamus, and corticospinal tracts in the cerebral peduncle (Fig. 6). Recognition of these sites of diffusion restriction as network injury and not additional sites of infarction is important to accurately determine the extent of injury and to aid in the prognostication of outcome. Notably, network injuries on DWI are more likely to be demonstrated on imaging performed more than 48 hours after presentation, which has implications for outcome prediction (see Fig. 4A, E).³⁰

Stroke evolution. Large territory AIS in adults and older children can result in malignant edema, causing significant midline shift and transfalcal herniation that can require decompressive hemicraniectomy.⁴¹ In contrast, even very large territory arterial ischemic strokes in neonates do not swell to a significant degree (see Fig. 6A, C). As is often the case with any difference noted between neonatal and childhood stroke, this could be attributable to the lack of myelination in the neonatal brain. Open sutures in the neonate can also better accommodate degrees of brain swelling than older children and adults.

After several months, the infarcted tissue in NAIS takes on a chronic appearance of largely cystic volume loss,³² in contrast to cortical infarctions in older children and adults that more often manifest at least partially as gliosis. As is the case with any injury occurring early during brain development, the affected hemisphere is often smaller, and the calvarium over it is also smaller to accommodate the difference in cerebral hemisphere size (see Fig. 6B, D). Atrophy of central structures such as the thalami that are involved in network injuries also often occurs. Recurrence risk of NAIS is very low outside of the context of congenital heart disease. Therefore, follow-up imaging is not indicated for stroke follow-up, although it is sometimes performed for secondary complications such as seizures or developmental delays.

PRESUMED PERINATAL ISCHEMIC STROKE

Some children with brain imaging compatible with a remote infarction only come to clinical attention after the neonatal period. These are typically categorized as either presumed perinatal arterial ischemic stroke (PPAIS) or periventricular venous infarction (PVI).

Presumed Perinatal Arterial Ischemic Stroke

PPAIS is diagnosed in patients older than 28 days of age who lack significant perinatal neurologic history and who usually require imaging for hemiparesis or seizures in infancy.³ Imaging in these patients is indistinguishable from the chronic imaging of NAIS diagnosed symptomatically in the neonatal period. The injured areas of brain demonstrate cystic volume loss and contain thin membranes, central structures such as the thalamus are often correspondingly atrophied, and the affected

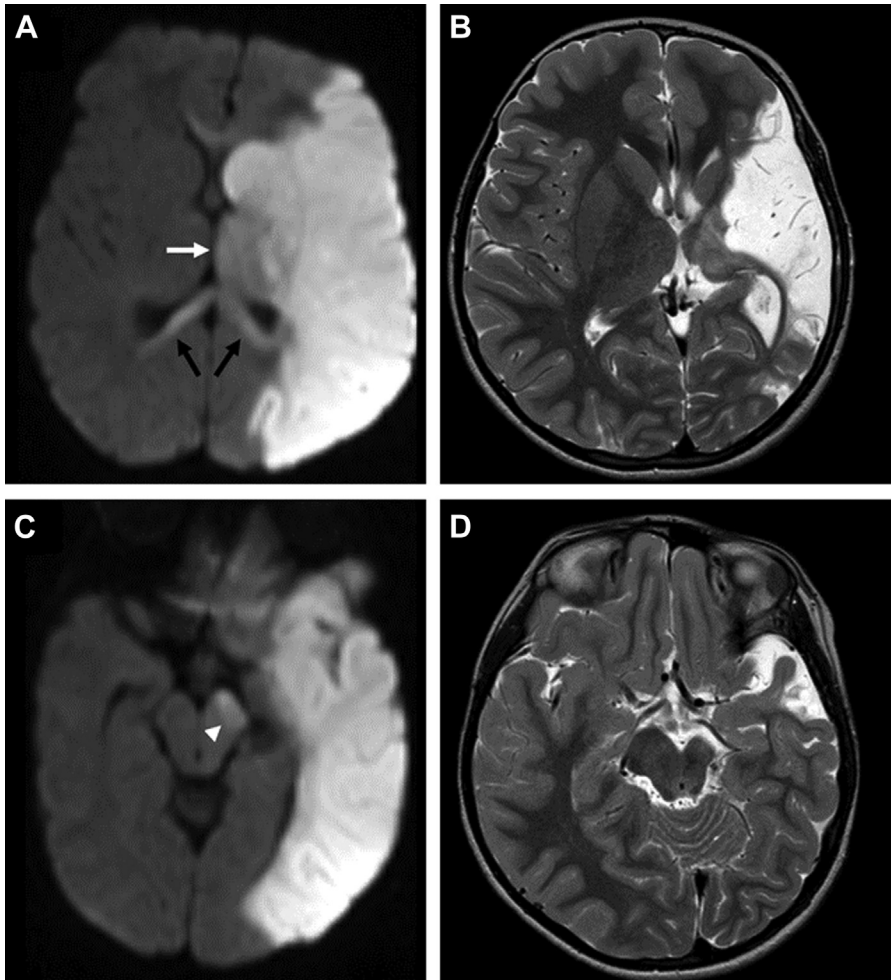


Fig. 6. Axial DWI images (A, C) obtained in a term neonate at DOL 3 demonstrate a large area of marked diffusion restriction in the left MCA territory, compatible with an acute neonatal arterial ischemic stroke. Areas of milder diffusion restriction not in the left MCA territory, including the thalamus (A, *white arrow*) corpus callosum splenium (A, *black arrow*) and cerebral peduncle (C, *white arrowhead*) indicate areas of network injury. Note that despite the large territory of infarction, there is no significant midline shift or swelling of the large area of infarcted tissue. Axial T2 images (B, D) from a follow-up MRI obtained at 7 years of age demonstrate marked cystic volume loss of the left MCA territory infarction, marked atrophy of the ipsilateral thalamus and cerebral peduncle as a result of the network injury. Further, the left cerebral hemisphere is much smaller than the left overall, and the calvarial vault accommodates this different size.

hemisphere is usually smaller with a correspondingly smaller cranial vault volume (Fig. 7). For these reasons, the putative etiology is NAIS which was simply not diagnosed in the neonatal period.

Debate exists over the reasons why NAIS presentation is sometimes delayed. Possible explanations include neonatal seizures that are missed clinically, an insult that occurred in utero with missed hemiparesis in the neonatal period, or a smaller

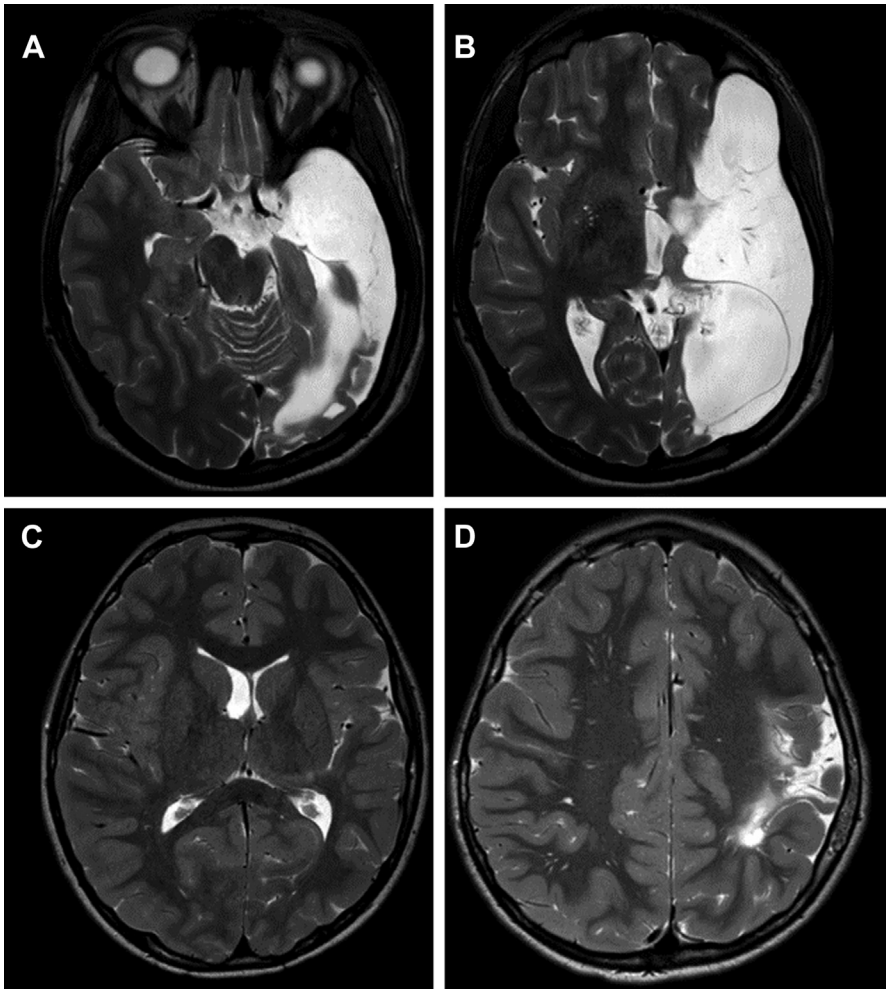


Fig. 7. Axial T2 images (A, B) are from a 15 year old with presumed perinatal arterial ischemic stroke. The extensive area of left MCA territory cystic infarction, associated atrophy of the thalamus and cerebral peduncle, and smaller left cerebral hemisphere size are nearly identical in appearance to the perinatal arterial ischemic stroke diagnosed in the neonatal period acutely in the patient in [Fig. 6](#). Axial T2 images (C, D) from a patient with mild right hemiparesis first imaged at 7 years of age demonstrate a smaller area of chronic infarction in the left posterior MCA territory, with milder volume loss in the left thalamus and cerebral hemisphere. This was also diagnosed as a presumed perinatal arterial ischemic stroke as symptoms had been present as infancy but not imaged until later in life.

infarction that correspondingly lacked seizures.⁴² However, most studies of PPAIS find that the risk factors are very similar to acute symptomatic cases of NAIS, which argues against many cases occurring in utero.⁴³

Periventricular Venous Infarction

Some patients presenting during the first year of life with hemiparesis have a different pattern of abnormality on brain imaging, consisting of cystic periventricular white

matter volume loss focally dilating the ventricular margin (porencephaly) and occasionally lined by chronic blood products indicating remote hemorrhage (Fig. 8). As the appearance is identical to the chronic evolution of periventricular white matter infarctions seen in preterm infants, it is presumed to represent a similar mechanism of infarction occurring in utero, and thus has been termed periventricular venous infarction (PVI).^{44,45} In fact, with the growing use of fetal MRI for diagnosis of in utero brain abnormalities, more cases of PVI are diagnosed in the fetus that otherwise appears like what is seen in the preterm infant⁴⁶ (Fig. 9). In keeping with their proposed differing mechanisms, patients diagnosed with PVI are more likely to have antenatal or maternal risk factors such as preeclampsia, small for gestational age or primigravida, while those with PPAIS are more likely to have acute peripartum risk factors such as low Apgar and prolonged rupture of membranes.^{2,42}

An important differential consideration for porencephaly diagnosed in infancy is a mutation in the COL4A1 gene that encodes type IV collagen. These mutations can cause weakening of the basement membranes whereby type IV collagen is located, including blood vessels of the brain, eyes, and muscles.⁴⁷ Thus, the clinical phenotypes are broad, but they can include intracerebral hemorrhages in infancy that present with a similar appearance as periventricular venous infarction (Fig. 10A). Some of these patients will also have a distinctive type of congenital cataract with a characteristic lens shape⁴⁷ (posterior lenticonus, Fig. 10B, C).

OUTCOME PREDICTION IN PERINATAL ISCHEMIC STROKE

Mortality and stroke recurrence are rare in NAIS.⁴² Siblings are also at no greater risk than the general population.⁴² The risk of epilepsy is high and likely varies with the location and size of the infarction, with rates ranging historically from 9% to 16%,⁴² although a recent meta-analysis noted an overall epilepsy rate of 27.2%.⁴⁸ A recent study found the risk of infantile spasms in NAIS increases with larger infarct volume and involvement of deep cerebral structures.⁴⁹ Other studies have correlated larger stroke volumes with the development of cerebral palsy.⁵⁰

The presence and location of network injuries have been used for outcome prediction on acute imaging of NAIS. One study quantifying the diffusion restriction in the cerebral peduncle on acute imaging of NAIS found that the percentage of cerebral peduncle involvement and length and volume of the abnormal corticospinal tracts

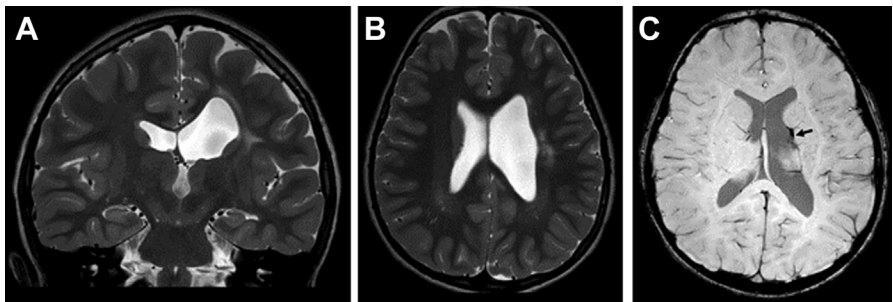


Fig. 8. 5-year-old with hemiparesis and seizures. Coronal (A) and axial (B) T2-weighted images demonstrate focal enlargement and outward scalloping of the left lateral ventricular surface, with small areas of nearby abnormal T2 hyperintensity. Axial SWI image (C) demonstrates a small area of hemosiderin along the ependymal surface near the caudothalamic notch (black arrow).

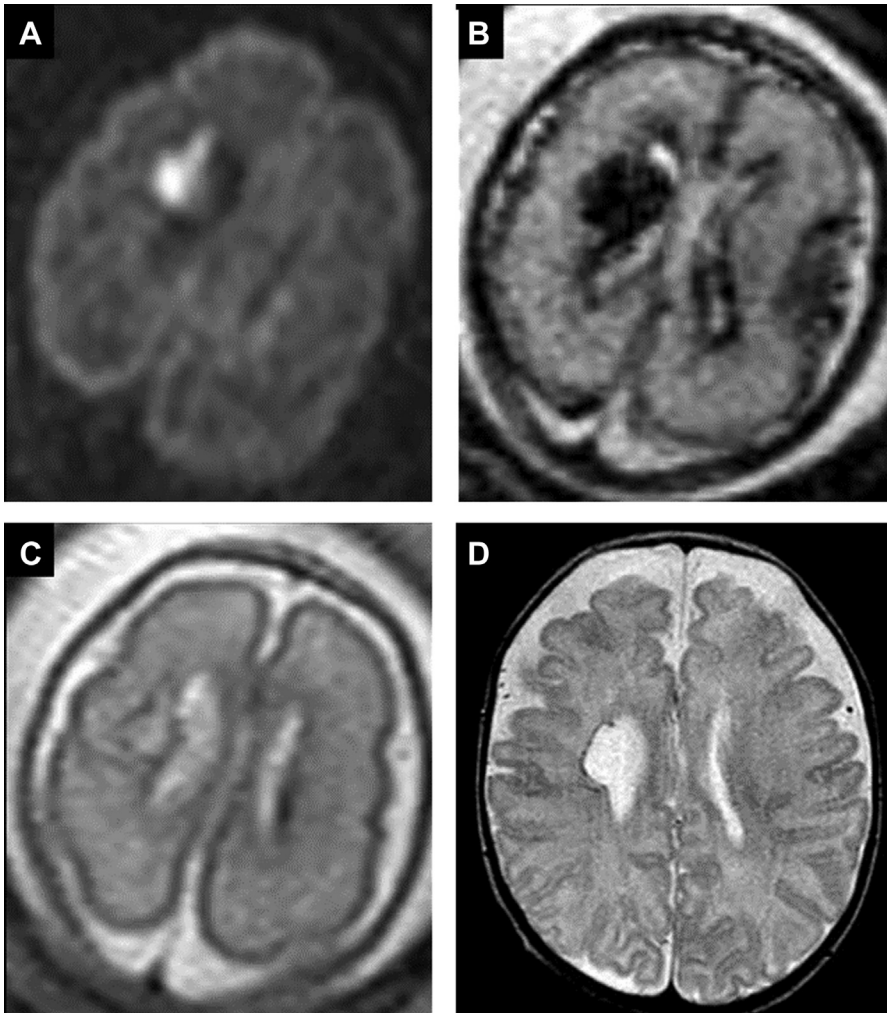


Fig. 9. Images from a fetal MRI performed at 26 weeks gestation (A–C) demonstrate a focal area of diffusion restriction in the right periventricular white matter on DWI (A), with corresponding susceptibility on an EPI T2*-weighted sequence compatible with internal hemorrhage (B), and faint T2 hyperintensity with a hypointense rim (C). An axial T2-weighted image (D) from a follow-up MRI performed at DOL 3 shows the typical appearance of a chronic periventricular venous infarction.

correlated with poor motor outcome.³⁹ Another study of diaschisis in NAIS measured thalamic volumes in patients with NAIS after 6 months of age and compared them to control patients. While the thalamic volume of patients with NAIS ipsilateral to the stroke did not correlate with motor deficits, an inverse correlation was found between their contralateral thalamic volume and motor function. This implies that the thalamus is involved in the mechanisms of plasticity that occur in the healthy cerebral hemisphere after a unilateral infarction.⁵¹

A recent study of cognitive outcomes in NAIS and PPAIS found that deficits in attention and executive function correlated with a diagnosis of PPAIS, larger infarct

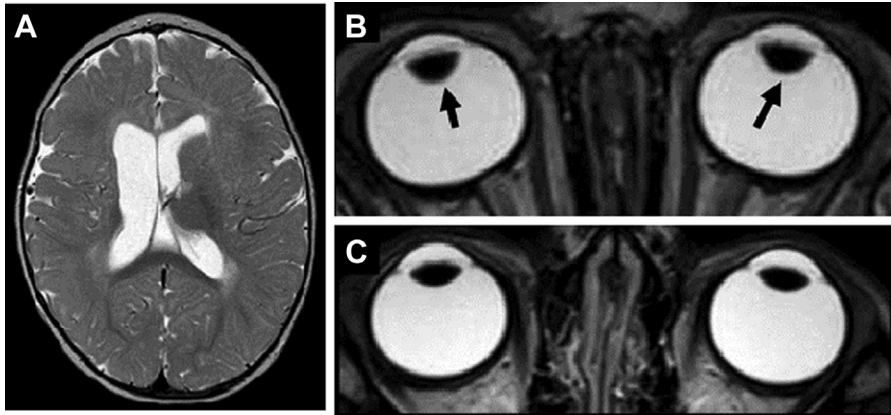


Fig. 10. An axial T2-weighted image (A) from a 9 month old with a COL4A1 mutation demonstrates a similar appearance of periventricular volume loss and T2 hyperintensity as seen in periventricular venous infarction. Axial T2-weighted image through the globes in this patient demonstrates the typical appearance of posterior lenticonus (B, *black arrows*). Normal appearance of the lenses in a control (C) for comparison.

volumes, and history of epilepsy.⁵² The unexpectedly worse outcomes noted in PPAIS could be due either to referral biases, or the potential for earlier intervention in NAIS as diagnosed in the neonatal period.

Wagenaar and colleagues classified areas of infarction in NAIS on acute DWI into 1 of 8 territories (main MCA, anterior MCA, middle MCA, posterior MCA, cortical MCA, perforator, PCA, ACA), and included injuries in the thalamus, basal ganglia, and posterior limb internal capsule. Adverse outcomes were defined as cerebral palsy, language delay, epilepsy, behavioral issues, and visual deficits. Main MCA branch strokes were associated with universally adverse outcomes, basal ganglia/thalamic injuries were correlated with cognitive deficits and behavioral difficulties, and lesions in the cerebral peduncles and bilateral lesions were correlated with increased risk for epilepsy.⁵³

Differences in outcomes between PPAIS and PVI have also been studied.⁴⁴ The amount of cortical involvement, as seen in PPAIS but not PVI, is correlated with increased risk of seizures, language disorders, and poor cognitive outcomes. Both presumed ischemic stroke subtypes carry a risk of poor motor outcomes, although PVI has a greater risk of spasticity than some patients with PPAIS.⁴⁴

SUMMARY

Acute imaging in NAIS is preferentially performed with MRI, whereby it can be promptly diagnosed and managed. Patients who are diagnosed with perinatal stroke either in the neonatal period or later in childhood experience a range of morbidities, often hemiparesis and epilepsy. Both acute and chronic imaging can be used to estimate the risk of various long-term complications, and aid in the determination of rehabilitation strategies.

Best practices

What is the current practice for perinatal arterial ischemic stroke?

Acute imaging with MRI, DWI, MRA, and MR perfusion is recommended for the best assessment of stroke size and location, and to provide the optimal opportunity for outcome prediction.

Best Practice/Guideline/Care Path Objective:

What changes in current practice are likely to improve outcomes?

Adoption of methods to predict poor neurodevelopmental and motor outcomes, such as the detection of network injuries and classification of stroke location and size, will enable improved patient surveillance and earlier rehabilitation referral.

Pearls/Pitfalls at point-of-care:

Do not mistake network injuries for new or additional sites of infarction.

CLINICS CARE POINTS

- CUS and CT have been used in acute diagnosis of NAIS, although both can miss acute infarction when performed within 1-2 days.
- MRI is the preferred modality for diagnosis of NAIS and PVI, due to its superior contrast resolution, ability to diagnose stroke earlier, and multimodality capabilities such as MRA and ASL.
- Network injuries detected on MRI acutely can be used in outcome prediction.
- Risk of adverse outcomes can be also predicted based on arterial territory involvement and stroke subtype (NAIS vs PPAIS, PPAIS vs PVI).

DISCLOSURE

The author has nothing to disclose.

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