Position Statement

Imaging the term neonatal brain

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Abstract

Brain imaging is important for the diagnosis and management of sick term neonates. Although ultrasound and computed tomography may provide some information, magnetic resonance imaging is now the brain imaging modality of choice because it is the most sensitive technique for detecting and quantifying brain abnormalities and does not expose infants to radiation. This statement describes the principles, roles and limitations of these three imaging modalities and makes recommendations for appropriate use in term neonates. The primary focus is the brain of term infants with neonatal encephalopathy, many of whom are diagnosed with hypoxic-ischemic encephalopathy.

Keywords: Brain imaging; Encephalopathy; Newborn

Brain imaging is an important step in the diagnosis and management of sick neonates and especially for infants presenting with neonatal encephalopathy (NE), seizures, unexplained apneas, infections, metabolic disorders, birth injuries and suspected structural brain abnormalities. Information from imaging can help to define an underlying diagnosis, determine management and predict neurodevelopmental prognosis. This statement describes the principles, roles and limitations of three brain imaging modalities: cranial ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). Recommendations for choosing the best investigation in common clinical situations are made, with focus on term infants with NE, many of whom are ultimately diagnosed with hypoxic-ischemic encephalopathy (HIE) [1].

METHODS

The literature on brain imaging in term infants published between 2000 and 2015 was identified using PubMed. Reference lists of publications were also reviewed. Original articles on diagnosis and prognosis were rated, and the strength of recommendations in this statement was graded according to classifications and levels described by the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society in their practice parameter for neonatal neuroimaging (Table 1) [2].

IMAGING MODALITIES

Ultrasound (US)

US imaging uses high-frequency sound waves emitted by a transducer to reflect off body structures. Returning sound waves (echoes) create an image, based on the frequency and strength of the signal and the time it takes to return to the transducer.

In newborns, the fontanelles provide an acoustic window for cranial imaging. US has several advantages over CT and MRI. It is safe (no ionizing radiation), technology is portable and usually readily available, and imaging is easily repeated, economical and does not require special preparation. However, in term infants with NE, US has limitations as a sole imaging modality, in part because the convex surfaces and posterior fossa may not be well visualized [3,4]. US is operator-dependent and subtle gray/white matter anomalies may be missed in less experienced hands. Transcranial Doppler US can measure cerebral blood flow noninvasively, which is helpful in diagnosing intracranial
vascular malformations. Abnormal intracranial Doppler measurements can be early signs of hypoxic-ischemic injury. In centres where cranial US can be performed by experienced technologists and radiologists, US can be a useful initial evaluation tool of the term newborn brain.

**Computed tomography (CT)**
CT combines a series of x-ray images using a computer to create cross-sectional images. Although cranial CT has been used to assess for hemorrhage, brain injury and edema secondary to hypoxia-ischemic injury, venous sinus thrombosis, masses and structural abnormalities, MRI has generally supplanted CT for most of these indications.

In one comparison of neuroimaging findings for 48 term newborns with NE uniformly scanned with CT and MRI, MRI more readily detected cortical injury and focal/multifocal lesions, such as strokes and white matter injury (5). CT and MRI similarly identified injury to the deep gray nuclei (basal ganglia and thalamus). A recent retrospective study showed that CT was less likely to detect injuries to the deep gray nuclei, brainstem and cerebellum, as well as strokes (P<0.001 for each) (6). CT requires ionizing radiation, which should be avoided as much as possible in infants. Furthermore, because of lack of myelination in the newborn brain, gray/white matter contrast on CT is poor (7). Nevertheless, when newborns are too unstable to adjust to necessary modifications in care or to undergo a long MRI procedure, CT can be considered as an alternative—at least initially—to detect the basal nuclei pattern of injury, which poses the most significant risk for adverse neurodevelopmental outcomes (5).

**Magnetic resonance imaging (MRI)**
MRI produces images using the body’s natural magnetic properties (8). The scanner’s magnetic field makes the axes of hydrogen atom protons line up uniformly. Energy pulses from radio waves knock these axes out of alignment, followed by realignment or relaxation when this energy is turned off. The relaxation times produced by different tissues vary, creating contrast. T1 and T2 are relaxation constants that apply to the time taken for proton realignment. In T1-weighted images, water appears darker and fat lighter. In T2-weighted images, water appears lighter.

The water content of white matter is high in the nonmyelinated neonatal brain and signs of edema may be subtle but are usually still detectable using both T1 and T2 sequences. Diffusion MRI, such as diffusion-weighted imaging (DWI), measures the motion of water molecules when a magnetic gradient is applied in a particular direction, forcing the molecules to move in that direction (9–11). Following acute cellular injury with resultant cytotoxic edema, the movement of water molecules is impeded, restricting diffusion. The rate of diffusion is expressed as the apparent diffusion coefficient (ADC). ADC maps are used to determine site and extent of injury. Areas with restricted diffusion have low ADC values and appear hyperintense or brighter on DWI and hypointense or darker on ADC maps. Fractional anisotropy measures directionality of diffusion, with higher values implying more directionality. Increasing myelination of white matter, seen as the brain matures, is one factor increasing fractional anisotropy (12–15).

Magnetic resonance spectroscopic imaging (MRSI) assesses regional brain metabolism by measuring the concentration of different biochemical compounds. N-acetylaspartate (NAA) and lactate are useful metabolites when evaluating metabolic changes associated with brain development and injury. NAA is normally found in high concentrations in neurons, and levels increase further as the brain matures (16). When injury is present, NAA levels decrease with neuronal dysfunction or death. By contrast, brain lactate levels increase as cerebral oxidative metabolism is disturbed and energy sources fail, as seen with HIE or inborn errors of metabolism (17).

In term neonates, MRI has become the brain imaging modality of choice due to its superior sensitivity and specificity for detecting and quantifying brain abnormalities (18). Also, MRI does not expose infants to ionizing radiation. Improved diagnostic accuracy and patient safety far outweigh the higher costs of MRI, including the transfer of at-risk newborns to a higher level of care. There are few contraindications to MRI because neonates rarely have implanted medical devices or metallic foreign bodies. However, it is essential to make sure that nearby equipment or objects do not contain ferromagnetic material that could become magnetized in the vicinity of an MRI system. Appropriate positioning, swaddling and timing of feeds can help to optimize effective scanning without the need for pharmacological sedation or general anaesthesia for most newborns. The development of MRI-compatible transport and monitoring equipment has increased accessibility and safety of MRI for critically ill neonates (19). The standardized MRI sequences used for adults must be adapted for neonates because their brains have a higher water content and lower levels of proteins and lipids (20).

The brain develops dramatically in the third trimester of pregnancy and early extra-uterine life. Injury during this critical period can significantly alter function, including motor, cognitive, language and behavioural skills. However, it is important to recognize the neonatal brain’s potential for recovery and repair. MRI techniques are important for identifying the etiology and severity of brain abnormalities in the neonatal period as well as for understanding the scope for recovery and repair.

**DISEASE PROCESS AND NEUROIMAGING**

**Neonatal encephalopathy (NE)**
NE describes ‘a clinically defined syndrome of disturbed neurological function in the earliest day of life in the term infant’ (21).
Later, injury is best seen on T1-weighted images as increased T1-weighted images of the basal ganglia, even at this stage. On DWI in the basal ganglia/thalamic region. In severe total watershed injuries, restricted diffusion is maximal around the cortex, such as the sensorimotor (perirolandic) cortex. As with rate and the greatest need for energy substrates. They sustain (30). Deep grey matter structures have the highest metabolic severity and extent based on individual circumstances.

The watershed or border zone pattern affects areas between the brain’s major arterial supplies and deep in the sulci, leading to edema, necrosis of the cerebral cortex and focal or regional infarction. On MRI performed between days 3 and 5 of life, this pattern is best seen as areas of restricted diffusion on DWI. MRSI may show a lactate peak in white matter in watershed areas (28). Conventional T1- and T2-weighted images may still be normal at this point. Typically, from about day 8 and beyond, increased signal intensity on T1-weighted images is observed in the sulcal depths near the central and interhemispheric fissures, which indicates cortical necrosis. Deeper white matter can also be affected (29). Maximal injury is evident at 10 to 14 days postinjury on T1- and T2-weighted images. This injury pattern is thought to be associated with prolonged partial hypoxia-ischemic (Class II to III studies).

The second pattern of injury in HIE is basal ganglia/thalamic, which is more often seen in acute, profound hypoxia-ischemia (30). Deep grey matter structures have the highest metabolic rate and the greatest need for energy substrates. They sustain injury first, followed by the most active regions of the cerebral cortex, such as the sensorimotor (perirolandic) cortex. As with watershed injuries, restricted diffusion is maximal around the third day after the insult and is seen as a hyperintense signal on DWI in the basal ganglia/thalamic region. In severe total hypoxia-ischemia, higher signal intensity may present on T1-weighted images of the basal ganglia, even at this stage. Later, injury is best seen on T1-weighted images as increased signal intensity, initially in the ventro-lateral nuclei of the thalami, but also in all deep grey matter structures if injury is severe. A helpful neuroradiological sign in neonates more than 37 weeks’ gestation is loss of normal signal intensity in the posterior limb of the internal capsule (PLIC) (31) (Class II to III studies).

These two ‘pure’ pathways of injury are conceptual. In reality, the type, pattern, duration and variability in severity of hypoxia-ischemia are a continuum, and imaging yields mixed appearances. In one group of term neonates with the full range of NE, MRI was done at a median age of 6 days: 52% of infants had a watershed lesion of white and gray matter, 22% had basal ganglia/thalamic injury and 26% had a normal MRI (30). When infants experienced a known sentinel event and an MRI was performed within the first 6 weeks of life (median age 10 days), similar patterns of injury were identified, with more infants having basal nuclei damage predominantly, as might be expected by the mechanism of injury (32).

When HIE is severe, generalized brain edema, which peaks 72 hours after the insult, can be seen on both CT and MRI. Identifiers include effacement of sulcal markings, closure of the Sylvian fissures, narrowing of the interhemispheric fissure and compression of the anterior horns of the lateral ventricles, giving a slit-like appearance. Similar changes may also be seen on US (Class II to III studies) T1-weighted images and DWI can show abnormal grey/white matter differentiation due to infarction and edema in the first week postinjury. DWI is more sensitive to acute brain injury than conventional MRI in the first days of life. Physiological factors, such as hypoglycemia, can modulate the pattern of hypoxic-ischemic injury (33).

Brain changes consistent with HIE take time to evolve and the extent of injury can be underestimated when imaging is performed too early (28). In most cases, changes are present on MRI with DWI by day 3, worsening up to day 5, then normalizing (28,34). Optimally, based on the experience of multiple investigators, both MRI with DWI and MRSI should be obtained in term newborns with NE between 3 and 5 days of life to confirm diagnosis and determine the extent of hypoxic-ischemic injury. This time frame is relevant for optimizing early management decisions (5,28,35–37) (Class I to III studies). A repeat MRI at 10 to 14 days is a helpful adjunct when clinical examination or clinical evolution is not consistent with early MRI findings or when diagnostic ambiguity persists.

Both main patterns of brain injury are clinically relevant predictors of neurodevelopmental outcome. Basal ganglia/thalamic lesions as well as abnormal signal intensity in the PLIC are associated with severe motor and cognitive disability, while watershed patterns are more closely associated with cognitive impairment than motor disability (30,31,38–40). In one large study cohort, 60% to 70% of infants who sustained moderate basal ganglia/thalamic injury had cerebral palsy and 35% had a developmental quotient less than 70 (40). Cerebral palsy was identified in 98% of infants with.
severe basal ganglia/thalamic injury (40,41). The watershed pattern of injury also appears to predict language outcomes (29,42).

In the absence of MRI abnormalities, the likelihood of severe neurodevelopmental impairment is low (30,41,42). In one study, a normal MRI was predictive of normal outcome (43). One recent meta-analysis involving MRI scans acquired over the first weeks of life showed that deep gray matter lactate/NAA was the most accurate quantitative MRI biomarker for predicting neurodevelopmental outcome after NE (36). The pooled sensitivity and specificity of lactate/NAA ratios were 82% and 92%, respectively; for conventional MRI they were 91% and 51%, respectively. Performance of MRSI, however, varies in different practice settings. Background noise, qualitative nature of data, varying performance on different machines and different methods of semiquantification make accurate assessment and evaluation of MRSI images a challenge.

Therapeutic hypothermia can affect MRI results and should be considered when determining image timing. MRI of cooled neonates detects most abnormal findings and patterns of brain injury follow similar evolution patterns to those observed in infants who are not cooled, although appearance of injury may be delayed (37,44) (Class II studies). Importantly, therapeutic hypothermia does not appear to affect the predictive value of conventional MRI for subsequent impairment (43,45,46). Because most infants are cooled for 72 hours, MRI can be performed on days 4 to 5 of life, after rewarming.

Other imaging modalities for HIE
When performed on day 1 with careful attention to technique, US can identify significant antenatal brain injury (3). Used meticulously, US has been shown to have high sensitivity and accuracy in detecting certain parenchymal lesions, although MRI shows more extensive lesions (47) (Class I study). Rebound increases in cerebral blood flow, which usually occur 24 hours to 36 hours after an hypoxic-ischemic insult, may be captured with Doppler studies of the anterior cerebral artery and provide additional evidence of brain insult (47). These findings are more likely to be present with moderate-to-severe prolonged partial hypoxia-ischemia, when most of the cerebral hemisphere is involved, and less likely following acute profound asphyxia.

When MRI is not accessible, CT may be used for imaging neonates with HIE. However, the machine must be well calibrated to detect water and standardized imaging parameters must be used, both for kilovoltage and milliamperes per second (CT dose indices). The ‘window’ for accurately quantifying brain injury depends on identifying the extent of cerebral edema and is narrower with CT than for MRI (48). Ideally, CT imaging should be performed 72 ± 12 hours after a suspected insult. Imaging performed earlier or later increases the risk of underestimating the extent of injury. When the timing is optimal and standardized imaging parameters are used, central grey matter, white matter and cerebral cortex involvement is seen as increasing edema (decreased attenuation). Basal ganglia/thalamic injury or total injury following acute profound hypoxia-ischemia is the lesion most accurately diagnosed with CT (5). Even under optimal conditions, CT underestimates the severity of white matter and cerebral cortex injury (6) (Class II study).

OTHER CAUSES OF NE

Neonatal stroke
Arterial infarction (stroke) is more common in the neonatal period than at any other time in childhood (18). Neonates typically present with seizures. Although US and CT may be useful, the consensus is that MRI is the most sensitive modality for neonates with suspected acute ischemia (49,50). MRI may be used to identify the vessel and branch involved, the left middle cerebral artery being the most commonly affected. Acutely, stroke is seen as loss of grey/white matter differentiation on T1-weighted images, with hyperintense signal on DWI indicating restricted diffusion in the area of infarction. By the end of the first week, the lesion is clearly seen on conventional MRI, eventually evolving into tissue loss and cysts at 1 to 2 months of age (51,52). The vascular classification of stroke in neonates is an important predictor of neurodevelopmental outcome (53).

Inborn errors of metabolism
Metabolic disease may be suspected from biochemical abnormalities or presenting signs. Recognizing characteristic imaging features may help with diagnosis. Cranial US can detect a variety of abnormalities, including cysts, calcification, white matter changes and structural abnormalities, which suggest metabolic abnormality (54). However, MRI is considered the optimal modality. DWI and MRSI may be of diagnostic value with particular disorders, such as maple syrup urine disease, nonketotic hyperglycinemia or creatine deficiency (52,54). When clinical signs and biochemical abnormalities suggest a metabolic disorder that requires urgent management, treatment should not be delayed to perform neuroimaging.

Traumatic brain injury
US can be used to identify intracranial hemorrhage, as can CT. The latter modality can also identify bone abnormalities and fractures, and better delineate hemorrhage. Subdural, subarachnoid and posterior fossa bleeds, as well as small intracranial hemorrhages, are not well visualized with US. MRI can be used to delineate injury further and is the modality of choice for assessing parenchymal injury. Newer MRI techniques have enhanced the detection of hemorrhage.
CT is the modality of choice in trauma, when detection of bony fractures is a priority (2,7).

Cerebral dysgenesis and structural brain abnormalities
MRI is the preferred modality for assessing brain developmental abnormalities after birth due to its superior imaging of the cerebral cortex relative to US and CT (55).

Bilirubin encephalopathy
MRI has been used to assess infants with severe hyperbilirubinemia, with variable results. In newborns with acute bilirubin encephalopathy who develop chronic encephalopathy, increased T1 signal may be seen early on in both the globus pallidus and subthalamic nuclei. Later, increased T2 signal in the globus pallidus and subthalamic nuclei are typical findings associated with kernicterus (56). Because of the risk for false-positive scans early on and poor predictive value, MRI should not be done routinely for neonates with severe hyperbilirubinemia in the absence of encephalopathy.

Congenital infection
Congenital infections, including syphilis, toxoplasmosis, rubella and cytomegalovirus, can cause CNS injury with subsequent developmental abnormalities. MRI is the preferred modality for assessing neonates with suspected or proven congenital infection, and should be performed in all infants with established cytomegaloviral infection (57,58). Compared with US or CT, MRI has greater sensitivity in detecting CNS abnormalities in such cases (59). While MRI may miss calcifications evident on CT, a normal MRI can predict favourable psychomotor development (59), and is recommended for all infants with symptomatic congenital cytomegaloviral infection as well as for infants with an abnormal US (57).

RECOMMENDATIONS
1. Magnetic resonance imaging (MRI) is the preferred imaging technique for examining the brain of term neonates who present with encephalopathy or a suspected brain injury or abnormality (Level A recommendation).
2. Ultrasound (US) may be a useful first imaging modality, provided that trained and experienced technologists and radiologists are available. Although US can help identify hemorrhage, major structural anomalies or calcification, it is not recommended as the sole imaging modality in term neonates who present with moderate-to-severe encephalopathy, seizures or neurological signs suggestive of inborn errors of metabolism, brain injury or brain malformation, because the extent of injury is underestimated relative to MRI (Level A recommendation).
3. Computed tomography (CT) may a useful first imaging modality in urgent situations, when MRI is not available, when an infant is too unstable to undergo MRI or when trauma or skull fracture is suspected (Level A recommendation).
4. For infants presenting with hypoxic-ischemic encephalopathy (HIE), MRI should be performed at day 3 to 5 of life or, if the infant has received therapeutic hypothermia, once rewarming has taken place. Within practice settings, consistent timing of MRI scans is recommended to facilitate recognition of injury patterns on the specific sequences applied. Appropriate timing of the MRI is crucial for accurate diagnosis, for counselling parents about their infant’s prognosis and potential outcomes, and for guiding decisions about care. A repeat MRI at 10 to 14 days of age should be considered when the imaging and clinical features are discordant or when diagnostic ambiguity persists (Level A recommendation).
5. When CT is used for imaging infants with HIE, it should be performed as close to 72 hours of the suspected insult as possible, ideally within 72 ± 12 hours. A subsequent MRI is also recommended (Level B recommendation).
6. When a paediatric radiologist or neuroradiologist is not on site or it is not practical or possible to transfer an infant, images should be sent electronically for interpretation.

Table 1. Strength of recommendations

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<tr>
<th>Level</th>
<th>Description</th>
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<tr>
<td>Level A</td>
<td>Useful/predictive or not useful/predictive for given condition in specified population</td>
</tr>
<tr>
<td>Level B</td>
<td>Probably useful/predictive or not useful/predictive</td>
</tr>
<tr>
<td>Level C</td>
<td>Possibly useful/predictive or not useful/predictive</td>
</tr>
<tr>
<td>Level U</td>
<td>Data inadequate or conflicting. Test/predictor is unproven</td>
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Based on ref. (2)

Abbreviations

ADC apparent diffusion coefficient
CT computed tomography
DWI diffusion-weighted imaging
HIE hypoxic-ischemic encephalopathy
MRI magnetic resonance imaging
MRSI magnetic resonance spectroscopic imaging
NAA N-acetylaspartate
NE neonatal encephalopathy
PLIC posterior limb of internal capsule
US ultrasound


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