Head Ultrasound in Neonatal Hypoxic-Ischemic Injury and Its Mimickers for Clinicians: A Review of the Patterns of Injury and the Evolution of Findings Over Time

Jacqueline Salas^{a, b} Aylin Tekes^{b, c} Misun Hwang^{b, d} Frances J. Northington^{a, b}
Thierry A.G.M. Huisman^{b, c}

^aDivision of Neonatology, Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ^bNeurosciences-Intensive Care Nursery Group, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ^cSection of Pediatric Neuroradiology, Division of Pediatric Radiology, Russell Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA; ^dDivision of Pediatric Radiology, Russell Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA

Keywords

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Abstract

Hypoxic-ischemic injury (HII) of the neonatal brain and resulting clinical hypoxic-ischemic encephalopathy remains a significant cause of morbidity and mortality in the neonatal population. Ultrasound (US) has emerged as a powerful screening tool for evaluation of a neonate with suspected HII. The pattern of injury on brain imaging has crucial implications in therapies and predicted neurodevelopmental outcomes. US has become increasingly effective at determining the pattern, timing, and extent of injury in HII as well as differentiating these findings from a host of diagnoses that can result in a similarly appearing clinical picture. Repeated US studies over a patient's course can define the evo-

lution of findings from the acute through chronic phase in addition to identifying any complications of therapy. US also has the added benefits of easy portability, no need for patient sedation, and a relatively low cost when compared to other imaging modalities like magnetic resonance imaging (MRI). It is crucial that clinicians understand the full capabilities of advanced US in identifying an underlying diagnosis, directing appropriate therapy, monitoring disease progress, and finally in predicting outcomes, thus improving the care of neonates with encephalopathy. The following article demonstrates the breadth of uses for US in the full-term neonate with encephalopathy, its limitations, the patterns of injury seen, and their evolution over time. We will also briefly review several clinical mimickers of HII for comparison.

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We dedicate this work to the memory of Dr. Andrea Poretti.

Fig. 1. Normal head ultrasound of a full-term neonate 1 day after birth. Coronal view through the anterior fontanelle (**a**) demonstrating a normal configuration of the bodies of the lateral ventricles (arrows). The lateral ventricles may appear somewhat small on the initial head ultrasound in the term neonates. Note the normal echogenicity of the brain parenchyma: in the full-term neonate, gray and white matter echogenicities blend in without distinctive discrimination. **b** Sagittal view through the anterior fontanelle demonstrating the mid-line structures. Normal corpus callosum (arrow) and thalamus (star). The belly of the pons (thick arrow) and the vermis (line) demonstrate normal hyperechogenicity. Parasagittal view (**c**) through the anterior fontanelle demonstrating the caudothalamic notch (arrow), the most common location for residual germinal matrix. The arrowhead points to the caudate head and the star denotes the thalamus. Coronal view through the mastoid fontanelle (**d**) showing the cerebellar hemispheres with the highest detail as the probe is closest to the posterior fossa on this view. The cerebellar vermis is in the middle with a relatively high echogenicity. Cerebral peduncles can be seen in the midline immediately above the vermis (arrows).

Ultrasonography in Hypoxic-Ischemic Injury

Hypoxic-ischemic injury (HII) of the neonatal brain and subsequent clinical hypoxic-ischemic encephalopathy (HIE) affects 1–3 per 1,000 live births in developed countries and is responsible for a significant burden of morbidity and mortality in the pediatric population [1]. Different imaging modalities, including ultrasound (US) and magnetic resonance imaging (MRI), have been used to classify patterns of cerebral injury within the realm of HIE-related injury. Correct classification of injury informs treatment options, allows monitoring of treatment progress, and often predicts motor and neurocognitive outcomes. MRI is predictive of long-term outcomes in patients with HII/HIE in multiple studies [2–5]. However, MRI is costly, lacks portability, is time consuming, and, consequently, is limited in its utility in nonacademic centers, in low-income countries, and with critically ill patients who are too unstable to be moved. Brain US has emerged as a powerful, inexpensive adjunctive and alternative tool to MRI. US is widely available, can be per-

formed bedside without sedation, can be repeated as often as necessary, has no side effects, and, when performed by an experienced sonographer using high-end equipment, provides a wealth of anatomical and functional information. Figure 1 is an example of a normal head US of a neonate born at term. It demonstrates the high level of detail that can be achieved with US.

The use of multiple acoustic windows and variable-frequency US transducers has greatly improved the diagnostic sensitivity and specificity of US [6]. Variable-frequency transducers allow the sonographer to focus on near-, mid-, and far-field pathologies. Many lesions such as subdural hematomas or deep gray matter abnormalities once poorly visualized by US are now more readily apparent [7]. With optimal technique and view, US can delineate multiple focal intracranial pathologies such as intracranial hemorrhages, calcifications, ischemia, and brain abscesses. In addition, a wide array of developmental disorders such as Chiari and Dandy Walker malformations and corpus callosum agenesis/dysgenesis, as well as vascular anomalies such as vein of Galen aneurysmal

malformation, ventriculomegaly, and migrational abnormalities can also be revealed [8]. Detection of posterior fossa pathologies has been greatly enhanced by the addition of posterior and mastoid fontanel views to the standard anterior fontanel approach [9, 10].

Cranial US has many roles in evaluating patients when there is a concern for neonatal HII. US findings evolve over time just as the injury itself does [11]. Thus, specific patterns of injury and focal findings can provide important clues as to the severity and duration of the injury [12]. By repeating studies over time, one can see the full evolution of the disease process from the acute to the chronic phase [13, 14]. Once the pattern of brain injury is detected, it can help determine prognosis [13]. Focal findings on US can sometimes explain specific clinical presentations, such as the presence of unilateral seizures in the setting of a focal arterial stroke. US detection of stroke is improving but remains less sensitive when compared to MRI [15]. In addition, US is a quick and easy tool which can be used to assess the patient during an acute clinical deterioration, allowing the practitioner to implement appropriate therapies more rapidly [14]. Importantly, US can also redirect the diagnostic workup if findings are not consistent with HII [16]. There are several mimickers of HIE and having a fast screening tool available at bedside to guide diagnosis and decision-making is helpful.

Therapeutic Hypothermia and Imaging

Therapeutic hypothermia (TH) is currently the only therapy for infants with moderate to severe encephalopathy due to HII. TH has been shown to improve neurodevelopmental outcomes and reduce the severity of imaging findings on MRI [17, 18].

Other than a reduction in neuropathology due to presumptive limitation/improvement of the brain injury, it is not yet fully understood how TH affects imaging findings, in particular conventional and diffusion MR imaging findings. There is some evidence that it delays the conspicuity of MRI changes. For example, the appearance and evolution of diffusion-weighted imaging findings, in particular the so-called pseudo-normalization of diffusion restriction, is delayed for several days following TH [19]. Given that a proposed neuroprotective mechanism of injury of TH is a reduction in secondary injury, there is a biologic basis for a delay in imaging changes which has been observed clinically. Others have found no difference in MRI findings during or after hypothermia [20]. The prognostic value of MRI does not appear to be affected by TH [21].

US can be performed at or before the initiation of TH to evaluate for the presence of established injury from an insult prior to the time of delivery or from a particularly severe perinatal event. Importantly, pretreatment US should evaluate for brain pathology that clinically mimics HIE or pathology that would be a relative contraindication to TH such as focal hemorrhage, focal arterial stroke, metabolic diseases, infections, or brain malformations. These are all relative contraindications because TH has been used in focal arterial stroke and is being considered as treatment for some metabolic diseases [22, 23]. Caution must be taken because US imaging does not provide optimal information in some of these diseases [15]. Correlation with clinical status must always be considered. US is usually repeated on completion of the TH to assess persistence of initial indicators of injury or appearance of new findings. During TH, US can be used to quickly detect abnormalities such as an acute hemorrhage when there is a significant clinical change.

Doppler Ultrasonography and Resistive Indices

Duplex US with spectral analysis of the blood flow curves during systole and diastole allows calculation of the resistive index (RI). It provides a measurement of cerebral vascular dynamics and the integrity of cerebral autoregulation. Abnormalities in RI have been correlated with prognosis. An abnormal RI (equal to or less than 0.55), in the first 72 h after birth, has been found to be highly predictive of a poor prognosis with either death or severe disability [24–28]. Of note, these studies were performed in the pre-TH era. In a study performed in 2011 [29], the positive predictive value of a low RI value for a poor outcome decreased from approximately 84% for patients who did not undergo hypothermia therapy to only 60% in those who did. A normal RI in the early phase of injury (within the first 6–12 h) can be deceiving as these patients can still develop significant disability or death [24, 25]. This may be due to the confounding effect of increased intracranial pressure, patent ductus arteriosus, or cardiac dysfunction. If an RI is performed early enough after admission and before or simultaneous with the onset of TH, a low RI value may retain some of its prognostic value [30]. Its predictive value returns once the infant is rewarmed [31]. The reason for a loss of the predictive value of a low RI during TH is not well understood. Hypotheses include a relative vasoconstriction in the cerebral circulation or changes in metabolic demands with TH [29, 32, 33].

Fig. 2. Central pattern of injury. Full-term neonate with complete placental abruption. Coronal (**a**) and parasagittal (**b**, **c**) images through the anterior fontanelle. **a**, **b** Images were obtained 2.5 h after birth. Note the bilateral symmetric increased echogenicity in thalami extending into the cerebral peduncles representing ischemic injury. Ventricles are slit-like due to edema from the central structures. Follow-up head ultrasound within 48 h on (**c**–**f**)

demonstrate interval evolution/maturation of ischemia, now settled in the entire basal ganglia and thalami again in a bilateral symmetric fashion (**d**, **e**). Some echogenicity may be due to hemorrhage following reperfusion injury in addition to ischemia. Note the hyperechogenicity in the perirolandic region in **f**. This infant died 3 days after birth.

Evolution and Pattern of Injury in HII

Acute Phase

The acute phase of HII begins when the injury occurs and continues for 6 to 15 h [34]. It is characterized by primary neuronal cell death due to hypoxia-ischemia, with contributions from oxidative stress, excitotoxicity, and inflammation [35]. This leads to additional cell death and the development of cerebral edema initially [15, 16, 35]. Secondary energy failure propagates the initial injury, causing further damage of brain tissue [34].

Cerebral edema takes time to develop and can be very mild in the early stages. Accordingly, US findings can be negative for 24–48 h following the insult. It should also be noted that in some cases the insult may be remote from the time of delivery and so edema may have already developed and resolved by the time of birth. Findings typically become apparent on US after 24–48 h after HII, with some variability dependent on the severity of the

injury and the presence of coexistent complications [11, 25, 36]. White matter edema is demonstrated on US by enhanced gray-white matter differentiation. The echogenicity of the white matter increases in relation to the less echogenic, more compact cortical gray matter [37]. An elevated quantitative ratio of white to gray matter echogenicity has been associated with HII and with markers of white matter injury on DTI [30, unpubl data]. Other indicators of parenchymal edema include effacement of the cerebral sulci, compressed slit-like ventricles, and narrowing of the intrahemispheric fissure and basal cisterns. It is important to note that ventricles may be small in the first 36 h after birth in neonates without injury or with edema so care must be taken in the interpretation of this finding [38]. Edema is observed in Figures 2–4 along with additional findings corresponding to individual patterns of injury. Duplex sonography typically shows decreased RI values, i.e., less than 0.60 with significant edema.

Fig. 3. Near total gray and white matter injury in a full-term neonate. Head ultrasound performed 17 h after birth in a full-term neonate with severe hypoxic-ischemic encephalopathy. Edema is represented by the relatively high signal throughout the white matter in comparison to the marked low signal of the cortex, best appreciated in the cingulate gyrus region (long arrows). Note slit-like ventricles (a) due to diffuse brain edema. Resistive index values in the anterior cerebral artery were also decreased at 0.34–0.4 in this patient (not shown), another indication of this edema. Also note the high echogenicity of the thalami bilaterally best noted in a

(stars). MRI of the brain performed on day of life 10. The axial T2-weighted image (d) demonstrates generalized parenchymal volume loss. The dark T2 signal along the cortex indicates cortical laminar necrosis (thin arrows). Note the cystic changes in the subcortical white matter (thick arrow). Generalized high T2 signal of the white matter and thalami reflecting edema. Diffusion tracer image (e) and apparent diffusion coefficient map (f) demonstrating restricted diffusion in the genu (star) and splenium (arrowhead) of the corpus callosum and internal capsules bilaterally (arrows) reflecting wallerian degeneration.

Subacute Phase

With the evolution of primary and secondary injury over a few days after birth, the injury advances into the subacute stage. In term infants, subacute injury is marked by progressive demarcation of central gray matter and white matter injury/edema. Four distinct patterns of injury can emerge based on the type and duration of HII. Myers [39] described the most widely utilized system in the current literature. The presence of multiple patterns of injury (and multiple different classification systems) likely reflects the complexities of human brain injury and differences in timing, insult type, and severity in various clinical scenarios. For the purpose of this review the Myers classification will be used.

Near Total Asphyxia

Placental abruption or cord prolapse are typical precipitants to the severe compromise in fetal blood flow that is seen with near complete asphyxia. The brain regions most vulnerable to near total asphyxia are the basal ganglia, the thalamus sparing the internal capsule, the brainstem, and the cerebellum [40, 41]. This type of injury is characterized by extensive gray and white matter regions of hyperechogenicity on US and it is commonly described as a central pattern of injury (Fig. 2). It is common to observe a hyperechoic putamen or thalamic structure juxtaposed to a relatively less echogenic internal capsule [42]. These findings can be bilateral, unilateral, or focal. Typically, findings become more pronounced after the first 24–48 h before which time US can appear negative.

Fig. 4. Near total white and gray matter injury in a full-term neonate. Head ultrasound images through the anterior fontanelle on coronal (**a**, **c**) and parasagittal (**b**) planes within the first 24 h after birth. The “swollen” appearance of the supratentorial brain is due to bilateral symmetric and significant cytotoxic edema affecting the white matter. There is marked differentiation between gray matter and white matter, well seen throughout the entire brain both in anterior and posterior distributions. The increased echogenicity of the basal ganglia and thalami with poor distinction of

their borders again reflect edema. On magnetic resonance images obtained 4 days after birth, the T2-weighted image (**d**) shows a diffuse increased signal of the white matter, cortex, basal ganglia, and thalami with poor gray-white matter differentiation. Apparent diffusion coefficient maps (**e**, **f**) reveal diffuse supratentorial restricted diffusion (diffusion trace image not shown). The diffuse symmetric parenchymal injury of the supratentorial brain in comparison to normal cerebellum, as seen in **e**, is critical in identifying this injury. This is also known as the white cerebellar sign.

On average, infants with near total asphyxia have a higher risk of death when findings are severe compared to those with watershed injuries. If they survive, children with this type of injury have a significant risk of cognitive and motor impairment [2, 42, 43]. In particularly severe cases, brainstem involvement is an independent risk factor for death in the neonatal period [44, 45].

Watershed Injury

Watershed injury typically occurs following partial prolonged asphyxia with a concurrent hypoxic acidotic state [39, 46]. Hypoperfusion to the cortex occurs at the periphery of major arterial perfusion territories [47, 48]. This can become apparent on head US in several ways. It typically manifests as a wedge-shaped region of hyperechogenicity at border zones. Border zones occur in the frontal lobe, near the posterior horn, in the parafalcine

region in the subcortical white matter, and in the parieto-occipital region. Cortical injury may also appear as general peripheral edema. Compared to the near complete asphyxia, patients with border zone injury tend to have milder clinical signs and less severe outcomes [2]. However, cerebral palsy is observed in this patient population when focal gyral atrophy occurs on US [42]. MRI is generally superior to US at detecting this type of injury [42].

Primary White Matter Injury

Primary white matter injury occurs with a history of partial asphyxia in the setting of sustained hypoxia [39]. The classic US finding is subcortical and periventricular white matter hyperechogenicity underlying the relatively dark cerebral cortex, resulting in increased cortico-medullary differentiation on US [42].

In term infants, this type of injury, particularly in patients with internal capsule involvement, commonly precedes global developmental delay, visual impairment, and seizures [3]. However, this must be correlated to clinical findings when diagnosed with US as outcomes can be variable [42].

Concurrent Partial and Near Total Asphyxia

The basal ganglia is the primarily affected area, typically manifesting as bilateral hyperechogenicity on US [39]. Watershed cortical involvement, focal infarctions, or global injury often accompany the basal ganglia findings [42] (Fig. 3, 4). The combination of partial and total asphyxia is associated with more ominous outcomes than other patterns of injury. Bilateral involvement and a higher intensity of the echogenicity predict poorer neurodevelopmental and mortality outcomes in the short term, as well as worse cognitive and motor outcomes in the long term, than less extensive injuries [4, 5].

Chronic Phase

The chronic phase of the injury occurs weeks after the initial insult. Necrosis of the affected areas evolves into scarring of the initial injury sites. This often produces generalized atrophy of these regions in severe cases. Progressive volume loss of the central gray matter is most typically seen in term neonates. White matter volume loss is also possible and may result in an ex-vacuo ventriculomegaly, sometimes accompanied by widening of the subarachnoid space and microcephaly in the chronic phase.

Other Possible Findings

Cerebellar Involvement

Injury to the cerebellum was not a well-defined aspect of Myers' original classification; however, it deserves note. Abnormalities including focal hyperechogenicity require posterior and mastoid fontanel views to be performed. Injury in this region most often occurs with severe HII and has significant developmental implications [49, 50].

Normal US

It is important to note that infants with HII/HIE may have normal appearing anatomical US/MRI findings on follow-up. The lack of findings on imaging does not preclude the risk of developmental delay [51]. Detection of abnormalities may be improved by advanced imaging techniques as discussed later [52].

Potential Complications

In addition to the primary and secondary mechanisms of injury, several complications can worsen the disease process; however, they are rare in this population. Intracranial hemorrhage, including a choroid plexus bleed, a more profound intraventricular hemorrhage or, intraparenchymal hemorrhage, can occur at the time of initial injury. It can also occur with reperfusion after the primary episode of ischemia or with venous thrombosis [53, 54]. Acute hemorrhages present as hyperechogenic focal lesions that may become iso- and later hypoechogenic on follow-up during involution.

Mimics

There are several conditions that can present with neonatal encephalopathy and mimic HIE. US can reveal characteristic findings of these conditions to redirect a provider to the appropriate therapy. The following are a few common mimickers of HIE whose imaging patterns can be identified on US.

Hypoglycemia

Neonates with severe symptomatic hypoglycemia can have neurologic signs that mimic HIE. Cranial US in this setting typically reveals hyperechogenicity of posterior subcortical white matter and overlying cortex with sparing of the central gray matter. Detection is improved with posterior fontanel views. However, these findings are not specific and are not consistently observed on US despite the use of posterior fontanelle views. MRI should be performed to confirm suspected hypoglycemic brain injury. Severe hypoglycemia can also occur concurrently with HIE, producing a mixed pattern of injury.

Neonatal Stroke

Stroke can present with seizures, hypotonia, lethargy, and poor feeding, all of which could be mistaken for signs of HIE. Cranial US may initially only reveal a slight hyperechogenicity of the cortex and white matter in a vascular distribution, most commonly the middle cerebral artery territory [55]. Hyperechogenicity in the peripheral cerebral hemispheres, the basal ganglia, and the thalamus are all common findings. Sonographic abnormalities become more defined as the stroke evolves [15]. The focal nature of the lesion is key to diagnosis (Fig. 5). It is important to note that stroke and HIE can occur together in rare instances.

Fig. 5. Arterial stroke in a full-term neonate. Parasagittal image obtained 3 days after birth through the anterior fontanelle demonstrating a focal peripheral hyperechogenicity involving the cortex and subcortical white matter in the left parietal lobe representing a unifocal stroke (**a**). Note the high signal in the diffusion tracer image obtained 6 days after birth (corresponding apparent diffusion coefficient map not shown) secondary to restricted diffusion (**b**).

Infections

Meningitis with or without concurrent brain abscesses can present with an ill-appearing, lethargic, and hypotonic neonate possibly with simultaneous seizure activity. The most common US findings are a widening of the subarachnoid and subdural space, hyperechogenic pia mater, prominent subarachnoid vessels, layering debris within the subarachnoid space, and hyperperfusion of the meninges on power Doppler sonography. On follow-up, ventriculomegaly may result with adhesions/webs within the ventricles. Circular hyperemic foci scattered within the brain parenchyma can represent developing brain abscesses. Bacterial meningitis can present with cerebral infarctions secondary to an arterial vasculitis or thrombophlebitis [56].

Metabolic Diseases

Urea cycle disorders, nonketotic hyperglycinemia, and others can imitate HIE in symptomatology. Imaging findings of neonates with metabolic diseases can range from changes in white matter volume and echogenicity to cysts, calcifications, and structural abnormalities [16]. The following are specific examples.

Sulfite Oxidase Deficiency

Indications of sulfite oxidase deficiency on US include large cystic structures in the white matter, possible hypoplasia of the corpus callosum, and ventriculomegaly. Basal ganglia involvement is possible and may mimic certain patterns of HIE [57–59].

Molybdenum Cofactor Deficiency

Molybdenum cofactor deficiency frequently shows initial US findings of diffuse increased echogenicity and

then subsequent parenchymal hyperechogenicity and calcifications in the basal ganglia, white matter cysts, and later cerebral atrophy [60].

Zellweger Syndrome

Zellweger syndrome, a peroxisomal disorder with migrational abnormalities, can show subependymal cysts, ventricular enlargement, lenticulostriate vasculopathy, and gyral malformations on US. Though symptomatically similar, neonates with Zellweger syndrome are more easily differentiated from neonates with HII based on imaging findings [16, 61, 62].

Nonketotic Hyperglycinemia

US commonly shows hypoplasia of the corpus callosum in neonates with nonketotic hyperglycinemia [63, 64].

Maple Syrup Urine Disease

In maple syrup urine disease, edema, white matter hyperechogenicity, and central gray matter hyperechogenicity can be observed (Fig. 6), with corresponding white matter tract disease apparent on MRI. Neonates with maple syrup urine disease are frequently not symptomatic until 4–7 days after birth [65].

Reliability and Predictive Value of US Findings

US has value as a screening tool in infants with HIE as outlined above; however, it is not uncommon that significant abnormalities are not detected until 24–96 h after birth [11, 25, 36]. Thus HII may not be immediately apparent and the predictive value of a normal head US in this early phase is low. If there is a significant abnormal-

Fig. 6. Maple syrup urine disease. Full-term neonate who presented with poor feeding and lethargy at 6 days of life. Head ultrasound performed 16 days after birth. Coronal ultrasound (**a**) and sagittal ultrasound (**b**) through the anterior fontanelle revealing normal echogenicity of the white matter with a subtle increased echogenicity of the thalami. Brain magnetic resonance imaging was performed 20 days after birth. The axial T2-weighted image shows global white matter hyperintensity in the supratentorial brain involving the posterior limb of the internal capsules with a normal cortical signal. The diffusion tracer image (**d**) on the coronal plane mirrors these findings, with densely restricted diffusion in cortico-spinal tracts that extends from the bilateral internal capsule into the cerebellar tracts and brainstem (apparent diffusion coefficient map not shown).

ity already present at this stage (less than 24 h after birth), it is highly predictive of a poor outcome due to a particularly severe insult or because the injury occurred prior to the onset of labor [13].

Rutherford et al. [43] demonstrated that basal ganglia and thalamic changes are more likely to be visualized on MRI than US. Those infants who do have abnormalities on US develop significant motor deficits, particularly if abnormalities are also seen on MRI [43]. Infarcts and lesions at the convexity of the brain require a linear high-resolution probe (14–16 MHz) for evaluation on US. Lesions in the cortex are much less likely to be seen on US compared to MRI [43]. In comparison to autopsy findings, when US is performed less than 12 h before death, the sensitivity and specificity for thalamic lesions is 100 and 83%, respectively, and for lesions in the cortex it is 76.9 and 100%, respectively [36].

Many of the early studies particularly comparing US to MRI in neonates were performed with less sophisticated transducers and techniques than available today, likely inhibiting their ability to identify subtle findings

[6]. There were also frequent comparisons of early US to MRI done several days later. The injury typically becomes more apparent with time, partially explaining why MRI appears to be more diagnostic than US [66, 67]. High-end US done concurrently with MRI has 95% diagnostic accuracy compared to MRI [68].

In more recent studies, there is an improved correlation [13]; however, US and MRI are still not identical in their detection capabilities and their ability to determine the extent of lesions. There is only a slight difference in the positive predictive value for adverse outcomes between head US and MRI findings. However, normal or mildly abnormal findings were not strong prognostic factors for a good outcome, either in US or in MRI [13]. This reaffirms that early imaging is helpful for prognosis if significantly abnormal both in HUS and in MRI; however, normal findings are not definitive predictors of a favorable outcome. US performed a median of 2 days before MRI (the mean age at MRI was 5.4 days) was predictive of a favorable prognosis when the US was normal or had echogenic changes only in the cortex. Deep gray matter chang-

es on US had a positive predictive value of 67% and a negative predictive value of 100% for an adverse outcome. However, MRI remains more reliable in its identification of the extent of injury and association with outcomes [69]. MRI is the gold standard for determining the presence and extent of hypoxic-ischemic brain lesions; even so, additional quantitative imaging modalities are needed to improve the prediction of outcomes, especially in infants who have normal imaging on conventional sequences.

Diffusion-weighted MRI is utilized in HIE to detect injury in the early phase when it may not be apparent on other imaging, to quantitatively correlate brain injury with outcomes, and to more accurately differentiate mimickers such as ischemic injuries of other etiology like metabolic diseases and stroke [52, 70–72]. T1/T2 signal abnormalities may not be present or may be very subtle in the first 48 h after birth; however, apparent diffusion coefficient values are significantly lower than normal in the injured neonatal brain even within the first 48 h after birth [67, 73]. Diffusion abnormalities tend to evolve over time, starting as more localized findings in the first 48 h, becoming more diffuse and apparent by day 4–5, and then pseudo-normalizing about 7 days after birth. Infants treated with TH demonstrate more delayed pseudo-normalization around 8–10 days after birth [67, 74]. Apparent diffusion coefficient values have also been correlated with favorable or unfavorable outcomes [69, 75–77]. Proton MR spectroscopy has emerged as an adjunct imaging modality superior in its ability to detect the full extent of injury in the first 24 h. In particular, lactate to N-acetylaspartate ratios have been correlated with long-term prognosis [73, 75, 76, 78–80]. Arterial spin labeling noninvasively assesses cerebral blood flow by inverting arterial hydrogen protons and has recently been used more frequently in the pediatric population [81, 82]. Studies have used arterial spin labeling to characterize the timeline and pattern of changes in cerebral blood flow in neonates with HIE [83, 84]; arterial spin labeling perfusion values, particularly in the basal ganglia and thalamus, correlate with outcomes, especially when combined with MR spectroscopy information [85]. All of these additional modalities have the capability to enhance the power of imaging findings to reliably determine the severity of injury and predict outcomes.

Advances in Ultrasonography Techniques

Advanced neurosonography techniques have the potential to enhance the diagnostic sensitivity of conventional grayscale and color Doppler US. Contrast-en-

hanced US is a technique in which gas-filled microbubbles smaller than red blood cells create an acoustic impedance mismatch to generate a contrast signal within the intravascular compartment. The technique permits real-time quantification of tissue perfusion, specifically via generation of perfusion kinetics curves from which perfusion parameters including wash-in, time to peak, peak intensity, and area under the curve can be derived. The application of the contrast-enhanced US technique is in the preliminary stages due to off-label use in the neonatal brain, but it is showing promise based on the initial case series on neonatal HII [86]. Dynamic color Doppler sonography permits perfusion quantification of a region of interest without intravenous contrast. The method quantifies tissue perfusion by inferring the amount of blood flow through a specific region of tissue during a cardiac cycle based on the mean perfusion velocity of vessels and the mean perfused area, which then reflects the differences in small vessel perfusion between systolic and diastolic phases. It has been used recently in HII to quantify reperfusion injury [87].

Elastography is a technique in which tissue stiffness can be quantified based on the perpendicular acoustic waves produced by transient deformation of the tissue by a focused US pulse, and its application in neonatal brain for evaluation of HII is still to be studied [88]. Other perfusion quantification Doppler techniques include ultrafast Doppler, which has the benefit of quickly mapping the vascular dynamics of a large region of interest rapidly [89]. This may aid in identifying the full extent of injury in HII, but additional studies are needed to delineate the utility of this technique in practice.

Summary

Cranial US is a valuable screening tool in the diagnosis and management of encephalopathic neonates. In the acute time frame when it can be difficult to obtain more advanced imaging, US is helpful in determining the etiology of encephalopathy, whether it be due to HII or a host of mimickers which would warrant alternative therapies. Through repeated evaluations, it can further identify the pattern, timing, and severity of injury. It has the added benefits of being safe, cost-effective, and portable. Advances in US equipment and techniques have significantly improved its detection abilities. When present, abnormalities on high-quality US have proven helpful in predicting outcomes; therefore, medical decisions should not be postponed due to a lack of MRI imaging when the

US findings are consistent with the clinical picture. Imaging findings should always be combined with exam, electrophysiological data, and other clinical findings to guide management and prognosis determination. MRI remains the gold standard for evaluation of neonates with HII, stroke, and other mimickers, as US studies can sometimes miss or underestimate pathology. However, providers should understand the evolving capabilities and limita-

tions of high-end US in neonatal encephalopathy such that its utility can be optimized particularly in those patients in whom additional imaging is not feasible.

Disclosure Statement

The authors declare no conflict of interests.

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