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Easily Overlooked Sonographic Findings in the Evaluation of Neonatal Encephalopathy: Lessons Learned From Magnetic Resonance Imaging

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Findings of neonatal encephalopathy (NE) and specifically those of hypoxic-ischemic injury are frequently evident on magnetic resonance imaging (MRI). Although MRI has become more widely used and has gained widespread acceptance as the study of choice for the evaluation of NE in recent years, its costs are high and access to MRI is sometimes limited for extremely sick neonates. Therefore, head sonography (US) continues to be the first-line imaging modality for the evaluation of the brain in neonates with NE; furthermore, in many of these infants, the diagnosis of NE may have first been made or suggested using head US. US is noninvasive, inexpensive, and portable, allowing examinations to be performed without moving the infant. However, many of the telltale signs of NE on US are subtle and may be easily overlooked, contributing to diagnostic delay or misdiagnosis. We aim to illustrate the spectrum of US findings in NE, with emphasis on those findings that may be easily overlooked on US. Recognition of these findings could potentially improve detection rates, reduce errors, and improve patient management.

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Background

Neonatal encephalopathy (NE) is a serious health problem with a reported prevalence ranging from 1-6 per 1000 live term births.[1-3] The consequences are potentially devastating, as NE can lead to mortality or severe disability.[1] It is estimated that every year, approximately 900,000 neonatal deaths worldwide are attributed to birth asphyxia, representing 8% of all deaths occurring in children younger than 5 years of age and 23% of the approximately 4 million neonatal deaths occurring every year throughout the world.[4,5] However, it is unclear whether all of the 900,000 neonatal deaths are truly related to birth asphyxia, as, in many instances, the terms NE and birth asphyxia or hypoxic-ischemic injury (HII) are erroneously used interchangeably, despite an American College of Obstetricians and Gynecologists committee report published in December 2005[6] that strongly encourages physicians not to do so. In the experience of Pierrat et al,[7] HII was the main cause of NE in approximately half of the instances, whereas it was associated with other diagnoses in approximately 23% of cases. However, in the experience of Badawi et al[3,8] no evidence of intrapartum asphyxia could be demonstrated in nearly 70% of the cases of NE. These authors also found that the causes of NE are heterogeneous and mainly occur in the antenatal period.

NE is clinically defined as a neurologic syndrome occurring in the neonatal period; it manifests as a combination of a subnormal level of consciousness, decreased tone and reflexes, inability to initiate and maintain respiration, and seizures,[9] which may be the result of various conditions and not necessarily HII. HII is a specific subset of NE, defined as intrapartum hypoxia in the absence of any other

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abnormality. Involvement of multiple additional organs is a characteristic feature of HII. HII may present with multiorgan dysfunction, poor myocardial contractility, or abnormal renal or liver function.[10,11] Notably, the presence of renal dysfunction in infants with HII is associated with a poor long-term neurodevelopmental outcomes.[11] According to the guidelines of the American College of Obstetricians and Gynecologists and the American Academy of Pediatrics,[6,12] the following 4 criteria must be present to define an acute intrapartum hypoxic event sufficient to result in cerebral palsy (CP): (1) evidence of metabolic acidosis at birth (cord pH $<$ 7.0 and a base deficit of 12 mmol/L or more); (2) early onset of severe or moderate NE in infants born at $\geq$ 34 weeks' gestation; (3) quadriplegic or dyskinetic CP; and (4) exclusion of other identifiable etiologies, such as trauma, infection, coagulation, or genetic disorders. The document also comments on criteria that in conjunction suggest an intrapartum timing (within close proximity to labor and delivery), although they are not specific to asphyxial insults: (1) a sentinel hypoxic event taking place immediately before or during labor; (2) a sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations, usually after a hypoxic sentinel event when the pattern was previously normal; (3) Apgar scores of 0-3 beyond 5 minutes; (4) onset of multisystem involvement within 72 hours of birth; and (5) early imaging studies showing evidence of an acute nonfocal cerebral abnormality.

CP is a chronic neuromuscular disorder that appears early in life and is typified by an abnormal control of movement or posture that is not the result of a progressive neurologic disease. Although the injury is static or nonprogressive, clinical signs of CP become more apparent as time progresses because of the development of the child. CP has a prevalence of approximately 2 per 1000 live births.[13] Although CP is frequently attributed to asphyxia, most cases of CP are not associated with severe perinatal asphyxia and vice versa.[11,14,15]

The clinical manifestations and course vary depending on the severity of NE. Despite the existence of several scoring systems,[16,17] the staging system created by Sarnat and Sarnat[9] is most widely used. This system recognizes 3 stages of NE, which are each correlated with specific clinical outcomes. At one end of the spectrum, Sarnat stage 1, or mild encephalopathy, is characterized by irritability, poor feeding, hyperreflexia, and an exaggerated Moro reflex and has no long-term sequelae. On the other end of the spectrum, patients with Sarnat stage 3, or severe encephalopathy, have seizures and usually require ventilatory support; this stage is associated with a high mortality rate and severe neurodevelopmental impairment in survivors. Therapeutic hypothermia is a useful management strategy in HII in term infants to prevent secondary neuronal injury. If started within 6 hours of the insult, this therapy is associated with lower mortality without increasing neurodevelopmental disabilities.[18]

Imaging Features of NE

Perinatal asphyxia is among the most common causes of NE, ultimately leading to hypoxemia and hypercapnia. Hypotension results in impaired blood flow to the brain, triggering a cascade of detrimental effects and ultimately resulting in loss of autoregulation.

The precise pattern of brain injury in neonates depends on several factors, including brain maturity, the severity and duration of the hypoxic event, and the timing of the imaging study.[19,20] Although there can be significant overlap, there are 4 main patterns of HII lesions in relation to gestational age, insult duration, and insult severity: (1) mild to moderate hypotension in premature neonates; (2) severe hypotension in premature neonates; (3) mild to moderate hypotension in term infants; and (4) severe hypotension in term infants.[19]

Mild to Moderate Hypotension in Premature Neonates

Before 32 weeks of gestation, the brain circulation differs significantly from that in late gestation or in neonatal life, with blood vessels penetrating the cortex from the pial surface; these vessels consist of short penetrators (ending in subcortical white matter) and long penetrators (extending deeper into the brain) (Fig. 1). This pattern of circulation results in relatively poor vascularization of the periventricular white matter, which predisposes premature infants to periventricular ischemic injury,[21] manifesting as periventricular leukomalacia (PVL). PVL is often symmetrical and represents injury to the white matter of the developing brain. Further, PVL is thought to result from decreased blood flow to the white matter adjacent to the lateral ventricles and subsequent hyperemia during reperfusion. The areas that are most prone to injury include the

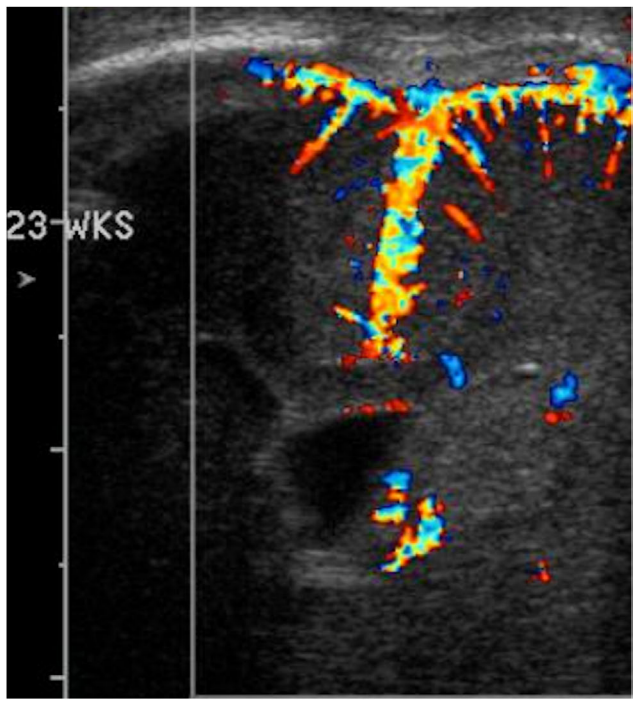

Figure 1 Color Doppler image in this 23 weeks premature infant depicts the normal short and long penetrators. The relative poor vascularization of the periventricular white matter should be noted. (Color version of figure is available online.)