Neuroradiology in the Perinatal period

The occurrence of birth related central nervous system injuries is an enormous problem and one that is of intense interest to both plaintiffs and defendants alike. Brain injuries affecting our youngest and most vulnerable population have devastating ramifications due to the personal, emotional, and economic toll that these may inflict.

Radiology expert witnesses and medical consultants must have a specialized familiarity with the complicated and oftentimes confusing nature of imaging findings in the perinatal population.

There is no question that, from the defense perspective, many of these injuries are simply unfortunate results in the setting of complicated medical circumstances, which do not necessarily imply substandard care or malpractice on the part of physicians, hospitals, and other caregivers.

From the plaintiff's position, many of these cases result from actions that were or were not taken in complicated medical circumstances, and that resulted in significant damages to the patient and their families.

Regardless of one’s point of view, the imaging features can be a crucial component in establishing a compelling case.

A central aspect of the overall evaluation of intracranial injuries is demonstrated by the imaging findings. The imaging findings are crucial because they provide some objectivity, confirmation and demonstrable findings that an injury is or is not present, prognostication as to future intellectual and functional capacity, characterization of the type of injury, and also timing the findings to correlate with the clinical course and medical record. The radiology expert witness can provide valuable insights into these considerations.

This review will attempt to provide a framework for thinking about imaging findings in the setting of perinatal hypoxic ischemic events, hemorrhagic, thrombotic, and traumatic conditions.

It must also be kept in mind that the infant, particularly the premature infant, is a work in progress and the structure of the brain may be quite immature and is subject to considerable variation and evolution as the age of the patient progresses.
The appearance of the brain in the very premature normal infant does not at all resemble the appearance of the brain in a 4 year old.

The neuronal structures of the brain are sheathed in a lipid rich covering called myelin. The presence or absence of this can result in differing imaging appearances and this is a function of the gestational age and maturity of the brain parenchyma.

Likewise, the convolutions of the brain surface evolve over time, and with respect to the gestational age, and an understanding this evolution is required for assessing the overall appearance.

The severely premature infant represents a distinct entity from the near-term gestation. Ischemic injuries in fetuses of second trimester age have very different manifestations of ischemia from those term or near-term infants.

Germinal matrix hemorrhage in the premature infant:

The most common type of acute intracranial pathology in the very premature infant is that of germinal matrix hemorrhage (GMH).

The germinal matrix is a site of neuronal call differentiation located centrally in the brain adjacent to the thalamus. Since it is a site of early cellular differentiation, it is only seen in the premature infant. Hemorrhages in this area are very common, occurring in approximately 80% of infants born at 23-24 weeks gestation, and 67% of infants born between 28-32 weeks.

Blood vessels in the germinal matrix region are very thin walled and are prone to rupture in the setting of any stress, including that of labor and delivery. Bleeding is initially periventricular, but if it persists, rupture into the ventricles may occur leading to intraventricular hemorrhage (IVH). Blood products within the ventricles will often produce ventricular enlargement and communicating hydrocephalus.

Ultrasound is the modality of choice for evaluation of GMH because of its sensitivity in identifying the abnormality, ease of conducting the exams at the bedside, and its convenience for obtaining serial studies to follow the course.

GMH is graded on a four-point scale with 1 being the most mild and limited to the germinal matrix, 2 with extension onto the ventricle without ventricular dilatation, 3 showing ventricular dilatation, and 4 demonstrating hemorrhage into the brain parenchyma. Grades 1 and 2 have relatively good prognoses, while grades 3 and 4 are usually associated with some degree of cerebral palsy, seizures and mental retardation.

Hypoxic Ischemic Encephalopathy

Terminology can sometimes be confusing. The terminology of hypoxic ischemic encephalopathy (HIE) specifically refers to a condition that is diagnosed on the basis of a constellation of clinical findings consisting of acidosis, poor Apgar score (0-3) at birth, seizures, coma, hypotonia and multi-organ dysfunction.

The term hypoxic ischemic injury can be used to diagnose any brain impairment that results from insufficient oxygenation or hypo-perfusion. This can be the result of hypoxic ischemic injury, trauma, metabolic abnormalities, infection or even congenital disorders.

The following excerpt is taken directly from the American College obstetrics and gynecology task force on neonatal encephalopathy and cerebral palsy (2003) and gives a succinct summary of the important clinical considerations:

“Neonatal encephalopathy is defined clinically on the basis of a constellation of findings, including a combination of abnormal consciousness, tone and reflexes, feeding, respirations, or seizures, which can result from many conditions. It may or may not result in permanent neurologic impairment and is not necessarily caused by intrapartum asphyxia. However, the pathway from intrapartum hypoxic-ischemic injury to subsequent cerebral palsy must progress through neonatal encephalopathy. Hypoxic-ischemic encephalopathy (HIE) is defined as neonatal encephalopathy with intrapartum hypoxia in the absence of any other abnormality.

Cerebral palsy is a chronic disability of central nervous system origin characterized by aberrant control of movement and posture, which appears in early life and is not a result of progressive neurologic disease. Spastic diplegia is the only type of cerebral palsy associated with an acute interruption of blood flow.

The historical factors used to define perinatal asphyxia (i.e., meconium, Apgar scores) are not specific to the disease process leading to the neurologic

damage. Using these nonspecific markers incorrectly identifies individuals as being exposed to "perinatal asphyxia."

The criteria to define an acute intrapartum event sufficient to cause cerebral palsy are listed in the report as follows:

Essential criteria (must meet all 4):

1. Evidence of a metabolic acidosis in fetal umbilical cord arterial blood obtained at delivery (pH
< 7 and base deficit ≥ 12 mmol/L)

2. Early onset of severe or moderate neonatal encephalopathy in infants born at ≥ 34 weeks gestation

3. Cerebral palsy of the spastic quadriplegia or dyskinetic type

4. Exclusion of other identifiable etiologies, such as trauma, coagulation disorders, infectious
conditions, or genetic disorders

Criteria that collectively suggest an intrapartum timing (within close proximity to labor and delivery, e.g. 0-48 hours) but are nonspecific to asphyxial insults:

1. A sentinel (signal) hypoxic event occurring 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

5. Early imaging study showing evidence of acute non-focal cerebral abnormality."

Peter S. Bernstein, M.D., MPH, et. al., *Neonatal Encephalopathy and Cerebral Palsy: Defining the Pathogenesis and Pathophysiology by the ACOG Task Force on Neonatal Encephalopathy and Cerebral Palsy*, 8(2) MEDSCAPE OB/GYN & WOMEN'S HEALTH 1 (2003): p. 1.

HIE results from a hypoxic or ischemic event, often in the setting of perinatal asphyxia, which leads to hypoxemia and hypercapnia.

Hypotension and the resulting decreased cerebral blood flow are thought to lead to acidosis, release of inflammatory mediators and excitatory neurotransmitters, and formation of free radicals. Loss of vascular autoregulation and biphasic energy failure, in which initial impairment of cell metabolism is followed by reperfusion and eventual neuronal cell death, may result.

Clinical history is important in determining etiology of hypoxic ischemic events. Pattern of injury in preterm infants, particularly early preterm, will differ from those of infants born at the appropriate gestational age. Ischemic events manifesting themselves at the time of delivery oftentimes have different etiologies than those that have their onset following the delivery itself with the latter being more likely infection or metabolic causes, rather than birth related trauma.

The most robust imaging modality for evaluation of hypoxic ischemic events is MRI. This will frequently show changes at a much earlier stage in onset and well the other 2 mainstays of imaging, namely, CT or ultrasound.

While all 3 modalities have strengths and weaknesses, MRI is clearly superior for detecting ischemic injury at the earliest stage. This is best accomplished with diffusion weighted imaging and this will be discussed later.

Ultrasound (US) is non-invasive and may be used to assess neonates at bedside. In positive cases involving the deep gray nuclei, areas of hyperechogenicity may be seen in the thalami, globi pallidi, putamina, and periventricular white matter and is most visible at 2–10 days of life.

Cerebral edema can be visualized and hemorrhage can also be demonstrated. Overall, US is suboptimal for evaluating HII because of its operator dependence, decreased sensitivity and specificity, and often subtle findings, which can sometimes be very subjective. Ultrasound is clearly of value in the premature infant with germinal matrix hemorrhage. In cases where there is ventricular dilatation or intra-ventricular hemorrhage, ultrasound is very useful in serially evaluating this in a noninvasive manner.

CT demonstrates its greatest strength in detecting foci of hemorrhage. Subcortical white matter normally has low attenuation because of the high

water content of the neonatal brain, a characteristic that may obscure edema or early signs of parenchymal injury.

Hypoxic events themselves can have different imaging manifestations. There are 2 distinct versions that have been described, severe total hypoxia and partial prolonged hypoxia. While these events can have different manifestations, there may often be significant overlap between the 2 and they are not always distinguishable entities.

The severe total hypoxia occurs in the setting of abrupt loss of oxygenation such as that which might be seen in a placental abruption. The partial prolonged variety is a process of longer onset and evolution and can be seen in such situations as prolonged difficult labor.

MRI findings in the neonate with severe total hypoxia:

The basal ganglia are hypermetabolic regions which makes them sensitive to hypoxia and this area may show increased T1-weighted signal intensity. However, this finding may be somewhat subjective.

The thalamus is also an area with a high metabolic rate and this region is also susceptible to hypoxic injury, again showing high signal intensity on T1-weighted images.

A particularly sensitive indicator of hypoxia in the neonate is also the posterior limb of the internal capsule which becomes isointense with the adjacent parenchyma on T1-weighted images. This so called "absent posterior limb sign" is a reliable marker of brain hypoxia when demonstrated on imaging.

Diffusion-weighted imaging which is an MRI pulse sequence that images restricted diffusion can be one of the earliest indicators of the presence of hypoxia. Restricted diffusion refers to water molecules that have escaped the normal cellular environment and are located in an extracellular space from which they are unable to migrate. In the normal circumstances, water is located within axonal structures which allow water molecules to diffuse along the elongated axonal structures. In the post hypoxic state, cellular damage has occurred and water has leaked out into an extracellular space where it is relatively static.

Restricted diffusion is particularly important in the timing and dating of a hypoxic event because it will frequently be positive within the first several

hours following the onset of hypoxia and will persist for approximately 7-10 days at which time it normalizes. Therefore, a study positive for demonstration of restricted diffusion can give important information as to the point of onset.

Additional findings of cerebral injury that can be identified include that of profound global injury which involves both the white matter and gray matter, as well as a findings manifest by abnormalities in the parasagittal gray and white matter.

MRI findings in prolonged partial hypoxia:

This group of patients has generally suffered a prolonged and difficult delivery and is often hypoxic at birth. These patients frequently have patchy or diffuse cortical signal abnormalities and often do not manifest findings in the deeper thalamic and basal ganglia structures. Part of the reason for this is that compensatory mechanisms of blood flow can occur when there is time to equilibrate in the more gradual and prolonged hypoxic events occurring in this subgroup of patients. As such, autoregulatory mechanisms within the intracranial circulation tend to augment blood flow to the hypermetabolic areas of the basal ganglia and thalamus at the expense of the cerebral cortex, which then exhibits MRI findings of abnormal signal due to the ischemia.

CT findings in hypoxic ischemic events:

Some of the deep structures within the brain are relatively hyper-dense compared with the nearby white matter. In the setting of ischemia, this contrast difference can be minimized and there is lack of good gray-white differentiation. Grey-white differentiation refers to the contrast difference between two distinct anatomical areas, and the result is a more uniform appearance. Similar loss of gray-white differentiation can occur in the cortical/subcortical regions of the brain. In some instances cortical edema can be seen which may produce some effacement, or smoothing, of the normal sulcal pattern of the brain surface, particularly in the region of the sylvian fissure. This can be seen as early as 8 hours after onset of the event, peaks at about 3-4 days and gradually subsides after that.

Benjamin Y. Huang, M.D., MPH, et. al., *Hypoxic-Ischemic Brain Injury: Imaging Findings from Birth to Adulthood*, 28 RADIOGRAPHICS 417 (2008)

Timing of Ischemic events:

The timing of the hypoxic event can be estimated based upon the imaging findings.

Ultrasound will show hyper-echogenicity within the brain parenchyma within about 2 days following the event. Cystic degeneration may take 2 to 4 weeks to develop and this may be associated with ventricular enlargement.

Computed tomography will show evolution of infarcts similar to that in the adult with hypo-density being seen after 12 to 24 hours.
Contrast enhancement can be seen about five days following the injury and disappears after two weeks. Hemorrhage on CT is hyper-dense initially and becomes iso-dense after 7 to 10 days.

Timing of the event is best seen with MRI which shows increased signal on diffusion weighted imaging within two hours after the event. This lasts for approximately one week and up to 10 to 12 days, at which time the findings will normalize. T1 or T2 weighted images will show abnormality after about 8 to 12 hours. If contrast is given, the enhancement pattern and timing is similar to that of CT.

Intracranial Hemorrhage:

Hemorrhage itself constitutes a distinct entity that undergoes a predictable pattern of evolution. This is due to a complicated series of interactions that occur between blood breakdown products and the high magnetic field environment of the MRI scanner.

A detailed description of the physics of MRI, the magnetic properties of blood breakdown products and the resulting signal intensities are beyond the scope this presentation. Suffice it to say, that the evolution of hemoglobin, the principal component of red blood cells and the molecule responsible for transport of oxygen through the bloodstream is the primary mitigator of the MRI appearance of hematoma.

When intravascular blood leaves the circulation and forms a hematoma, the initial state of the hematoma consists of oxygenated hemoglobin. As the hematoma evolves, it goes through the following sequence of blood breakdown products: oxyhemoglobin (the normal oxygen carrying molecule

within red blood cells) degrades to a de-oxygenated form, deoxyhemoglobin, and this ultimately degrades into a substance called methemoglobin. To make matters even more complicated, these breakdown products exist in either intracellular or extracellular environments, each of which results in different imaging characteristics.

In a chronic hematoma there is further degradation of the iron containing molecules into a substance called hemosiderin, which has entirely different imaging characteristics.

Based upon a predictable time course of the evolution of the blood breakdown products, the signal characteristics of a hematoma in the MRI environment can be correlated with the timing of hematoma formation, which can help to pinpoint the onset of the injury.

It should be noted, that intracranial hemorrhage in the term infant is not an unusual event. Hemorrhage was seen in approximately 26% of asymptomatic neonates delivered vaginally. While such findings may be thought to be indicative birth trauma, it may also be viewed as a normal consequence of a stressful life event in transitioning from the intra uterine environment to the world at large.

Christopher B. Looney BS, et. al., *Intracranial Hemorrhage in Asymptomatic Neonates: Prevalence on MRI Images and Relationship to Obstetric and Neonatal Risk Factors*, 242 RADIOLOGY 535 (February 2007): p. 538.

Cerebral sinovenous thrombosis is a less common entity and is usually seen in the term infant. Specific risk factors include infections and hematologic disorders. Clinical features are quite variable and can include decreased level of consciousness, focal neurologic signs and cranial nerve policies as well as diffuse seizures.

Gabrielle DeVeber, M.D., et. al., *Cerebral Sinovenous Thrombosis in Children*, 345 N. Engl. J. Med. 417 (August 2001): p. 421.

Perinatal arterial ischemic stroke (PAS) represents a cerebrovascular event occurring in the early newborn period which represents an ischemic event related to a specific vascular territory, in contradistinction to the global anoxia resulting from HIE. Symptoms in the neonate are very nonspecific and suspicion of this entity is usually heightened with the onset of seizures or sometimes hypotonia or apnea. Since clinical examination in this population is limited, diagnosis of this entity rests almost entirely with neuroimaging.

Janet Lee, MS, et.al., *Maternal and Infant Characteristics Associated With Perinatal Arterial Stroke in the Infant*, 293 JAMA 723 (February 2005): p. 727

Stroke is 17 times more common in the perinatal period then in later childhood and these patients often may exhibit cerebral palsy in later life. Etiologies of this entity may be due to vascular thrombosis or possibly embolism such as that seen with cardiac shunting, eclampsia or pre-eclampsia, placental disease, antiphospholipid antibody syndrome or ematologic/thrombotic conditions. Other reported causes include chorioamnionitis, polycythemia, and systemic infection.
Janet Lee, MS, et.al., *Maternal and Infant Characteristics Associated With Perinatal Arterial Stroke in the Infant*, 293 JAMA 723 (February 2005): p. 727-728.

Importantly, from the defense perspective, intrapartum complications are more common in infants with PAS than in control infants. Although fetal distress and low Apgar scores often lead to a clinical diagnosis of birth asphyxia, these complications do not always reflect a global hypoxic-ischemic event, as implied by the term *birth asphyxia*. Infants with PAS who are diagnosed with birth asphyxia may actually have a focal arterial infarction as opposed to the more typical neuroimaging findings of hypoxic-ischemic brain injury, such as deep gray-matter or arterial-watershed injury, reminding us that the clinical diagnosis of birth asphyxia is not specific for any single pathogenic mechanism of brain injury.
Janet Lee, MS, et.al., *Maternal and Infant Characteristics Associated With Perinatal Arterial Stroke in the Infant*, 293 JAMA 723 (February 2005): p. 728.

Finally, child abuse constitutes a very important component of neuroimaging in the newborn in as well as in the later stages of life. Skeletal fractures in the newborn infant are almost invariably associated with child abuse and trauma. Intracranial abnormalities in this patient population are also frequently due to inflicted trauma.

“Two forms of head trauma occur in the settings of abusive head trauma (AHT). The term “impulsive loading” refers to nonimpact forces generated by alternating angular acceleration and deceleration of the cranial vault. The term “impact loading” refers to direct application of forces to the head. Each mechanism is believed to result in distinct—but potentially overlapping—injury patterns.

Impulse loading results in shearing injury to the brain and meninges. In early studies, authors described the association of a shaking-type injury with the

triad of subdural hematoma (SDH), retinal hemorrhage (RH), and focal or diffuse parenchymal injury often in the absence of external signs of injury. This association has been supported by additional articles in the literature.

Impact loading typically results in skull fracture and parenchymal contusions with associated focal extra-axial and sub-periosteal hemorrhage. Impact injuries are less common in infants with AHT and are more frequent in older children.

Subdural Hematoma: SDH is considered the cardinal cranial in jury in AHT; SDH was present at imaging in almost 90% of children in a recent prospective study. SDH is of only moderate specificity for AHT because it is common in AHT, accidental (non-abusive) head trauma, and non-traumatic conditions. The specificity of SDH for AHT is increased when associated with RH and underlying diffuse parenchymal injury."

Other patterns of neuro-radiological injury may occur such as diffuse or focal parenchymal injury, skull fractures and spine injuries, particularly at the cranio-cervical junction.
Jason N. Wright, *CNS Injuries in Abusive Head Trauma,* 208 American Journal of Radiology 991 (May 2017)

In conclusion, the appearance of the brain in the newborn infant is a moving target. What is normal at 27 weeks does not necessarily correlate with the term infants imaged at four weeks of age. A variety of factors including the degree of myelination and the maturity of the brain reflect the imaging characteristics.

Parameters of imaging studies can reliably predict the timing of untoward events. Neuroradiology expert witnesses are important arbiters in identifying and classifying, and confirming perinatal intracranial injuries. Radiology expert witnesses can help to identify characteristic constellations of imaging findings that correlate with specific pathological insults such as birth trauma, HIE, child abuse, developmental anomalies, and congenital defects. These observations can significantly impact assertions regarding causality, occurrence and existence.

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