Hypoxic–Ischemic Encephalopathy (Preterm, Term, and Adult)

22

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Abstract

Hypoxic–ischemic injury (HII) to the brain is usually a devastating event and an important cause of morbidity and mortality in the United States and elsewhere in the world. Neuroimaging plays a pivotal role in diagnosis, treatment, and long-term prognosis determination for these patients. The correct diagnosis made on the basis of different imaging modalities requires knowledge of the different manifestations of this type of injury. Some of the factors that contribute to the different findings are brain maturity, duration and severity of the insult, underlying cause, and associated disorders.

Severe HII will result in preferentially deep gray matter damage in preterm and term infants, with peri-rolandic involvement more frequently observed in the latter age group. In these patients, a less profound insult will result in germinal matrix hemorrhages or periventricular leukomalacia (PVL) in preterm neonates and parasagittal watershed infarcts in term neonates. In the postnatal period, severe insults produce diffuse gray matter injury, with relative sparing of the peri-rolandic cortex and posterior circulation structures. In older children and adults, profound insults produce injury in the deep gray matter nuclei, cortices, hippocampi, and cerebellum.

The use of advanced MRI techniques such as DWI and MR spectroscopy is useful in

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making the diagnosis especially in the acute setting where conventional imaging might be less sensitive.

Keywords
HII • Hypoxic–ischemic injury • Brain ischemia • Global brain hypoxia

Introduction

Hypoxic–ischemic injury (HII) to the brain is usually a devastating event, still considered the third leading cause of death in the United States with approximately half a million new victims per year. Death will occur in nearly one third of these patients, while another third will end up suffering severe neurologic deficits with important functional impairment [1]. Even more, perinatal asphyxia is considered an important risk factor for cognitive and behavioral difficulties in surviving children [2].

This serious and life-threatening condition is most often caused by insults as cardiac arrest, asphyxia, poisoning (drug overdose or carbon monoxide intoxication), and head trauma. Supportive care is the most used primary treatment strategy, which in majority of cases fails to prevent the brain injury that quickly follows the primary insult. Other treatment techniques are being studied, including promising new targeted neuroprotective approaches such as hypothermia and excitatory amino acid antagonists. However, most of these new treatments have a limited window of time to be effective even as little as 6 h post insult [3]. For this reason, times spent in the transportation of patients to the hospital and early detection of this injury are extremely important to the final outcomes of these patients [4]. As treatment protocols seize being based on time and become based on tissue status, neuroimaging plays an important role with ultrasonography (US), computed tomography (CT), and magnetic resonance (MR) imaging permitting early intervention. Also, imaging in the subacute stages is useful in predicting long-term outcomes of these patients by providing precise information about the severity and extent of injury [5–8].

It is necessary to emphasize, however, that findings in HII are variable. They depend on many different factors such as age (brain maturity), duration, severity, and exact type of insult and also the modality and timing of the imaging studies. Because of this difficult imaging scenario and the necessity of making a fast and accurate diagnosis, the radiologist requires a thorough knowledge of the imaging patterns of HII and be able to identify subtle findings by looking for the specific areas most likely to be injured when HII is suspected clinically.

In this chapter, first the pathophysiologic features of HII and how they influence the imaging patterns are discussed. Then, the specific imaging manifestations in term (>36 weeks gestational age) and preterm (<36 weeks gestational age) neonates, postnatal infants, children, and adults are reviewed.

Physiopathology of HII and Factors Influencing the Patterns of Injury

Earlier in this chapter, some of the most important causes of HII were mentioned. Independent from the underlying causes, the main pathophysiologic processes that lead to HII are remarkably similar. The main two processes that cause HII are ischemia and hypoxemia. Depending on the type of injury, the duration of injury, and the patient's age (brain maturity), these two processes will play different roles influencing the pathologic and imaging findings.

In general, infants and small children are more inclined to suffer asphyxia, due to perinatal asphyxia or being traumatic in nature (pool accidents, etc.). In asphyxia, the chain of events that lead to brain HII starts with hypoxemia. If the hypoxemia is maintained long enough and if the redistribution of oxygenated blood fails to compensate for it, cardiac hypoxia and decreased cardiac output occur. After this, brain ischemia ensues due to decreased blood flow. For this reason, the type of brain injury caused by asphyxia is ischemia superimposed on hypoxia. Even more, there is evidence that ischemia superimposed on hypoxia is required for the HII to occur as acute

hypoxia alone is unlikely to cause damage to the neonatal brain unless it is prolonged. This reflects the resistance of the immature brain to hypoxia when compared to the adult brain as well as better compensatory mechanisms in babies [9]. In contrast to this, in adults, direct blood flow reductions as in cardiac arrest or cerebrovascular disease, which lead to primary ischemia with secondary hypoxia, are common underlying mechanisms.

Another important aspect of HII physiopathology is that not all brain structures are affected to the same degree in a global hypoxic–ischemic event. It is known that there are certain tissues more likely to be injured or injured earlier because of their different sensitivity to hypoxia. This concept is known as *selective vulnerability.* HII causes damage through a process called *excitotoxicity* [9]. This process refers to cellular death due to the excessive stimuli of certain amino acid receptors that normally mediate physiologic excitatory effects of dicarboxylic acid glutamate, a ubiquitous neurotransmitter in the brain. This stimuli end up triggering a complex cascade of biochemical events that finally produces selective death of certain populations of neurons. This process appears to be even more important in developing brains than in adults.

Brain ischemia, on the other hand, produces a change from oxidative phosphorylation to anaerobic metabolism which is inefficient. Rapid depletion of adenosine triphosphate (ATP) occurs, and lactate accumulates in cells with loss of normal functions in their membrane. The failure to produce ATP and the subsequent depolarization of the neuronal cell membranes cause excessive release of glutamate from nerve terminals, which in combination with the reduced activity of glial pumps that normally keep synaptic glutamate levels low produces a rapid increase in glutamate concentration. When this process occurs, neurons and other cells with the appropriate receptors die due to a complex neurotoxic cascade. In immature brains, glutamate and reduced membrane potential contribute to the opening of *N*-methyl-D-aspartate (NMDA) receptors which cause a massive influx of calcium (Ca^{2+}) into neurons. Direct effects of Ca^{2+} include generation of oxygen free radicals such as nitric oxide and peroxynitrite. Also, damage to the mitochondria may diminish their capacity of handling multiple oxidation reactions and results in further loss of ATP enabling the production of more free radicals and perpetuating the cycle of membrane depolarization and NMDA receptor channel opening. Finally, delayed depletion of energy and elevated brain lactate levels are associated with neuronal death and resultant neurodegeneration after asphyxia.

Finally, from all of these biochemical and pathophysiological data mentioned before, there are some important conclusions to be kept in mind when analyzing the imaging patterns of HII. First, some areas of the brain are more susceptible to ischemic injury than others primarily because of their concentrations of glutamate and other excitatory amino acid receptors (primarily located in the gray matter), a concept known as *selective vulnerability.* Second, there are some areas of the brain with more energy demand than others. In these, energy will be depleted faster and therefore the injury will ensue earlier. Third, due to delayed neuron death (apoptosis), not all of the injury is evident until days after the initial insult.

It is important to realize that in any given patient, the sites of the brain that are most vulnerable and are first affected by HII will be determined by the degree of maturity of the brain, which depends on the age of the patient. This is one of the reasons why HII manifestations in the perinatal period (up to 1 month of age) differ from those seen in older infants and in adults. Even between term and preterm infants, there are important differences in patterns of injury. It is relevant to be cognizant of the degree of brain maturity to correctly interpret the studies for suspected HII. Another important factor determining the distribution of injuries is the severity and duration of the HII. Severe episodes of hypoxia–ischemia produce different injury patterns when compared to lesser ones. In insults of short duration, usually there is no brain injury especially in the immature brain due to its enhanced resistance to hypoxia. In the pediatric population, the time of hypoxia–ischemia required to produce brain injury has been

estimated to be approximately 15 min and in adults 3–4 min [10]. With all these factors that influence the patterns of injury in mind, we can now review the different manifestations of HII in imaging studies in preterm, term, and older children and adults.

HII in the Preterm Neonate

Preterm neonates are susceptible to suffer HII, and this type of injury is more common in this group than in term neonates. The consequences of HII can be devastating, as at least 5 % of infants born before 32 weeks gestational age and approximately 19 % of preterm neonates less than 28 weeks develop cerebral palsy. If one takes all cases of cerebral palsy, approximately 50 % of them occur in preterm neonates [11]. This situation can be explained mainly by two reasons. First, in this group, there is increased frequency in events leading to HII, such as respiratory distress syndrome, pneumothorax, patent ductus arteriosus, pregnancy infection, etc. Second, preterm infants have less autoregulation and compensatory capacity when compared to term neonates. Also, in this age group, making a diagnosis is more difficult because the clinical examination is limited, signs of HII may be lacking, or if present, they can be mistaken for developmental immaturity. Furthermore, preterm infants not uncommonly have transient neurological abnormalities and decreased muscle tone as part of their immature central nervous system, and most of these patients do not develop long-term deficits. For this is the reason, imaging is the key to arrive at the correct diagnosis.

Imaging manifestations of HII in preterm babies differ from those seen in term infants, mainly because of their degree of immaturity. In terms of the imaging findings, HII can be divided in two groups: those with severe and those with mild-to-moderate asphyxia. One must realize that this is an arbitrary and somewhat simplistic division because in any given patient, there is a continuous range of insults that are variable in terms of duration and severity, and therefore it is not surprising to have different imaging features in the same patient.

Severe Asphyxia

The injury pattern of preterm babies following a severe but brief hypoxic event resembles the pattern seen in term infants (see below) but with some differences [12]. These patients often show lesions in the basal ganglia, thalami, brainstem structures, cerebellum, and corticospinal tracts, as well as decreased cerebral hemispheric white matter. Although basal ganglia injury is frequent, it is less severe than the involvement of the thalami in this age group and especially among those less than 32 weeks of age. When involved, the basal ganglia tend to atrophy without scarring. Overall, the thalami, anterior vermis, and dorsal brainstem are the most commonly involved structures when profound asphyxia happens [3, 13]. The peri-rolandic cortex is usually spared in these patients. Germinal matrix hemorrhages and periventricular white matter injuries may also be seen in this group.

The reason for the differences in the extent of injury between the putamen and thalamus that is seen in these patients is likely related to the degree of myelination of these structures. The thalamus, the pallidothalamic fibers of the posterior internal capsule, and globus pallidus myelinate at about 24–25 weeks of gestation, whereas the corpus striatum (caudate nucleus and putamen) does not myelinate until 35–36 weeks. Myelinated structures are more metabolically active, as shown in F-18 FDG positron emission tomography studies [14], when compared to less myelinated areas, as the putamen and caudate, and therefore they are more susceptible to hypoxic injury [15].

Usually, the first imaging study performed in preterm neonates is a cranial transfontanelle US. As this is a noninvasive, bedside examination, it can be easily used in the intensive care unit as a screening tool to determine significant brain injury. The findings in US suggesting HII include increased echogenicity in the thalami at 2–3 days following the insult; nevertheless, US may appear normal, especially in the first 2 days. MRI is generally the next study performed in preterm neonates with suspected HII and is complimentary to US and necessary to accurately assess the extent of the injury and predict outcomes especially cognitive delay [16].

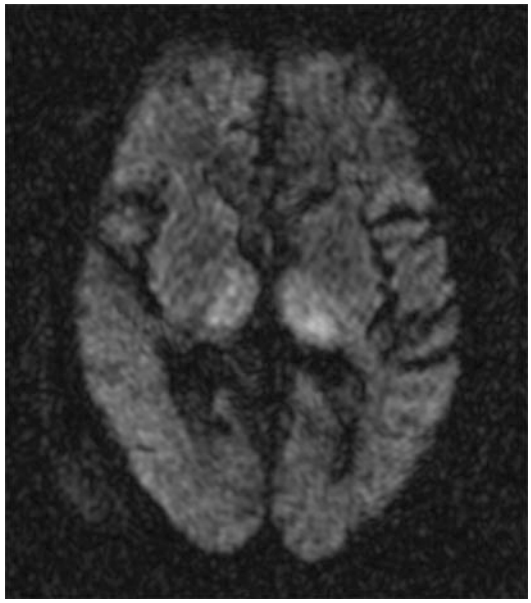

Fig. 1 Severe asphyxia in a preterm neonate. DWI image shows hyperintensity in the thalami

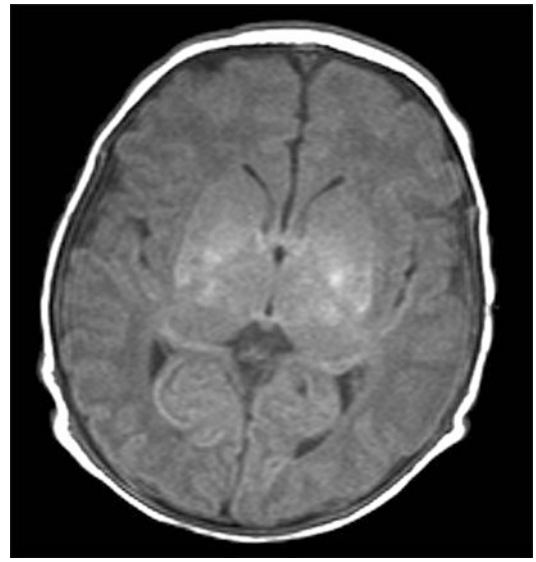

Fig. 2 T1WI in a preterm neonate who suffered severe asphyxia shows hyperintensity in the thalami and posterior lentiform nuclei. The high signal in T1 can persist into the chronic stage

Conventional MRI sequences can be normal or show only subtle abnormalities within the first day after injury. DWI is the most sensitive sequence in the first 24 h showing abnormalities in the thalami (Fig. 1). Then, after approximately 2 days post injury, T2 hyperintensity can be seen in the thalami and basal ganglia. By the third day, T1 shortening ensues in the injured areas. As in term infants, the DWI abnormalities peak at about 3–5 days and then tend to pseudo-normalize [3, 10, 17]. Thereafter, T2 hyperintensity appears at approximately 7 days and T1 shortening persists into the chronic stage (Fig. 2).

Mild-to-Moderate Asphyxia

The most characteristic pattern of injury in mild-to-severe asphyxia in preterm babies is determined by direct injury and hemorrhage of the germinal matrix. The germinal matrix is a highly cellular region that lines the walls of the lateral ventricles in fetal life and from where neurons and glia arise and migrate. It is most active between the second half of the first trimester and the first half of the second trimester. Thereafter, it starts to involute by the first half of the third trimester so that by the 34th week, the germinal zones have almost completely involute. For this reason, germinal matrix hemorrhages are infrequent before this age [3]. A very important anatomic landmark to recognize is the caudothalamic notch. The caudothalamic notch is a groove where the last remnant of the germinal matrix to involute – the ganglionic eminence – is located. The caudothalamic notch is a groove located between the caudate head and the thalamus and is where most of germinal matrix hemorrhages originate. The pathogenesis of germinal matrix hemorrhage is related to the relative higher vascularization of this region and the properties of the vascular bed in it. The capillaries in this region are fragile, mainly because they are lined only by simple endothelium and lack the muscular or collagenous layers that are present in the larger blood vessels. Second, cells that compose their endothelium have high concentration of mitochondria reflecting their high oxidative metabolic requirements. This makes them susceptible to hypoxic conditions. It is believed that first, this fragile endothelium suffers a loss of integrity due to

hypoxia and then with restoration of the normal circulation by resuscitation, bleeding ensues. This hemorrhage can be localized in the caudothalamic notch or extend to the ventricles. The prevalence of intraventricular hemorrhage in preterm neonates weighting less than 2 Kg has been estimated at approximately 25 % and most of them are related to hemorrhages of the germinal matrix. Also, it is known that most hemorrhages happen within the first 24 h of life and that infants who are very premature and with a very low birth weight are at higher risk for developing intraventricular hemorrhage [18, 19].

Germinal matrix hemorrhages are divided in four grades reflecting their locations and degree of dilatation of the ventricles (Table 1).

Grades I–III are hemorrhages that arise from the germinal matrix and have variable extension to the lateral ventricles. Grade IV hemorrhages are not germinal matrix hemorrhages but are parenchymal periventricular hemorrhagic infarcts, probably venous in origin, with extension to the ventricular system. There is a correlation between higher hemorrhage grade and higher perinatal mortality rates as well as a higher prevalence of long-term neurological sequelae [10].

Table 1 Germinal matrix hemorrhage (GMH) – periventricular hemorrhage (IVH) grading

Grade I	Subependymal GMH (mostly in the caudothalamic groove)
Grade II	GMH and IVH with or without mild ventriculomegaly
Grade III	GMH and IVH with ventriculomegaly
Grade IV	Above + periventricular parenchymal hemorrhagic infarction (not true GMH)

Germinal matrix and intraventricular hemorrhages can be adequately evaluated with cranial US (Figs. 3, 4, and 5), keeping in mind that sometimes the findings can be subtle and difficult to visualize. US of the posterior fossa by a posterior fontanelle approach, as a complement to the classic anterior fontanelle examination, can help to better visualize the posterior supra- and infratentorial structures. This can help to diagnose subtle intraventricular hemorrhages when the ventricles are not dilated and cerebellar hemorrhages that are believed to be underdiagnosed. These last types of hemorrhages are clinically silent but are not uncommon and are recognized in 10–20 % of autopsies. In fact, cerebellar hemorrhages are believed to be no different in origin than caudothalamic notch hemorrhages also arising from germinal matrix remnants within the external granule cell layer of the cerebellum and in the subependymal layer of the roof of the fourth ventricle [3, 20, 21]. Cerebellar hemorrhages are seen as lentiform or crescent-shaped hyperechoic lesions located posterior and peripheral in the cerebellar hemispheres. MRI is usually the next

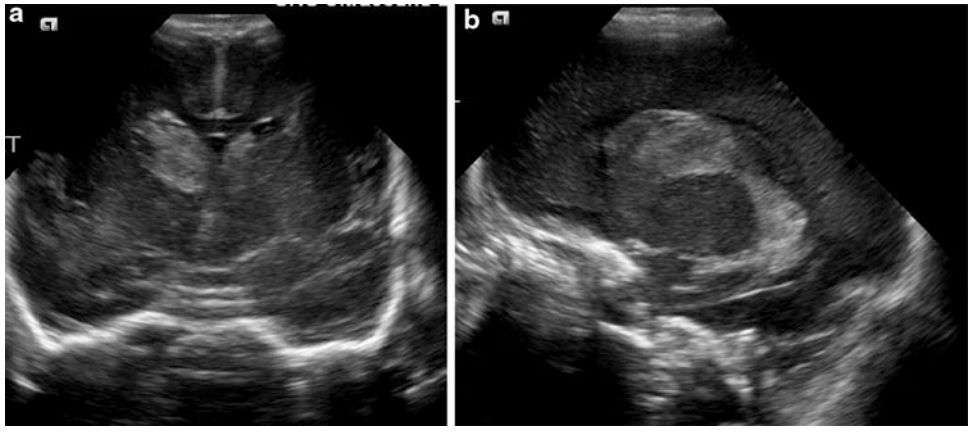

Fig. 3 US image in a preterm patient. Coronal (**a**) and sagittal (**b**) images demonstrate bilateral areas of subependymal echogenicity, right greater than left. The sagittal image confirms the location in the caudothalamic groove. Choroid plexus is large and thought not to be related to the hemorrhage. GMH grade I

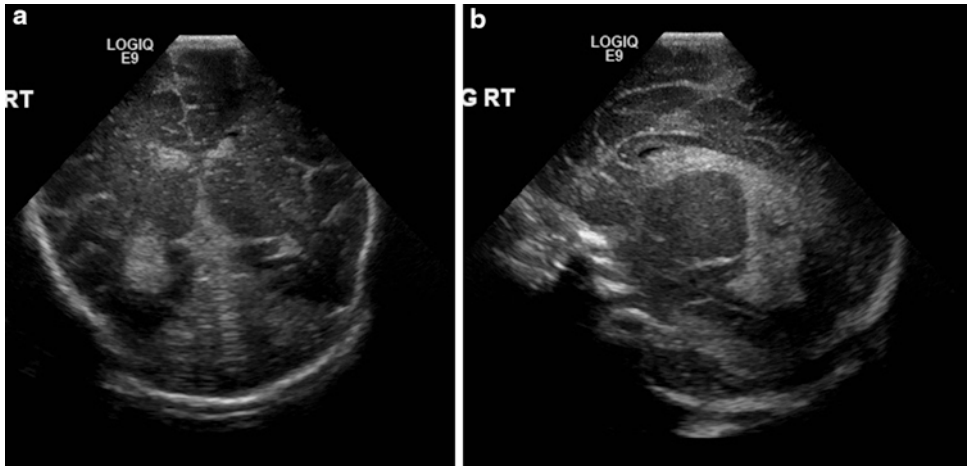

Fig. 4 US coronal (**a**) and sagittal (**b**) images in a preterm neonate demonstrate extension of the left side hemorrhage into the lateral ventricles, right greater than left. The ventricles are not enlarged. GMH grade II

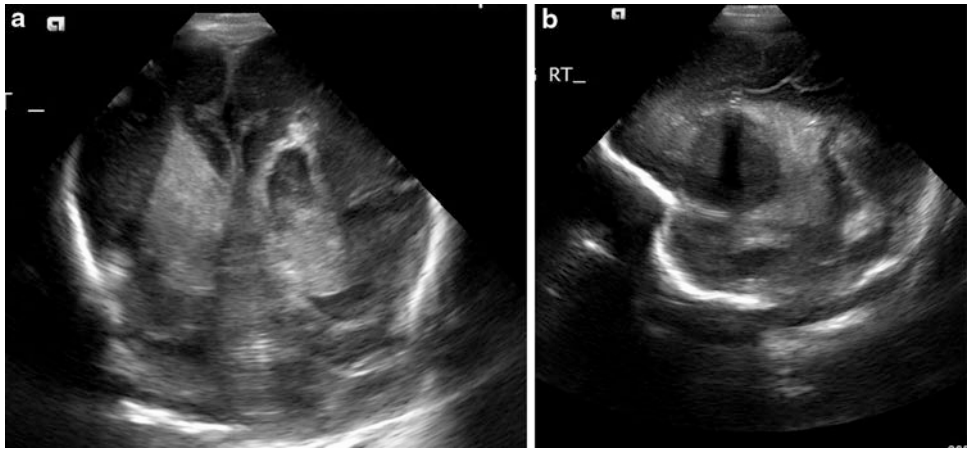

Fig. 5 US coronal (**a**) and sagittal (**b**) images in a preterm neonate demonstrate bilateral intraventricular hemorrhage with enlargement of the lateral ventricles. GMH grade III

study used most of the times to detect concomitant injuries such as white matter injury of prematurity or deep gray matter injury.

Another common manifestation that can be seen in mild-to-moderate asphyxia in preterm babies is periventricular leukomalacia (PVL), also known as white matter injury of prematurity. This type of injury also appears to be inversely related to gestational age at birth. Its pathogenesis is believed to be related to selective vulnerability of oligodendrocyte precursors and to perturbations in cerebral blood flow in a context of anatomic and physiological immaturity of the blood vessels in preterm patients [22, 23]. These oligodendrocyte precursors are late precursors known as preoligoendrocytes, and the white matter in the period prior to myelination is populated with them. This is the period of higher risk for PVL, as these late precursor cells are believed to be even more susceptible to hypoxia than the earlier precursor cells or the mature oligodendrocytes [24]. This explanation is supported by the fact that the prevalence of PVL declines after 32 weeks, the same time that the population of

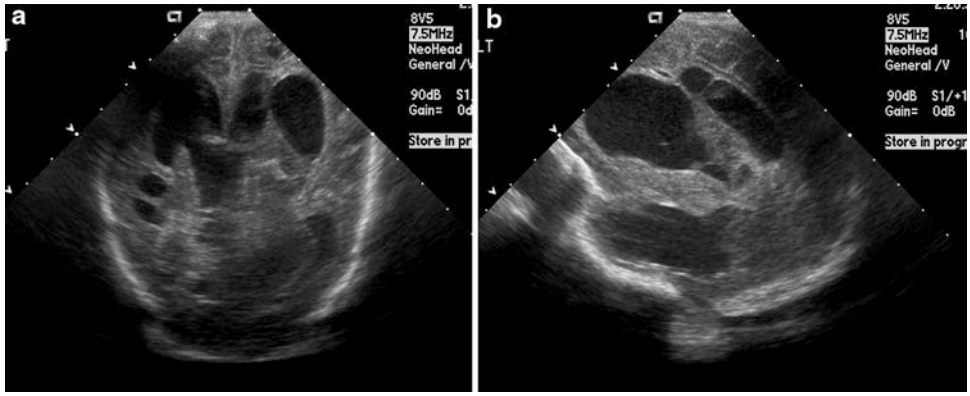

Fig. 6 US coronal (**a**) and sagittal (**b**) images in a preterm neonate demonstrate the third stage of PVL with the development of bilateral periventricular cysts

these late precursors in the periventricular white matter maturates into oligodendrocytes. Also, damage to a particular subpopulation of vulnerable neurons plays a role in the development of PVL. These are called subplate neurons and they contribute to cortical development and in particular to the formation of thalamocortical connections. They form a transient cell population that peaks at approximately 24 weeks (the onset of the developmental window of vulnerability) and later undergoes apoptosis [25]. The subplate which can reach up to four times the width of the cortical plate has been shown by MRI to be affected by hypoxic injury.

PVL is most commonly seen in the peritrigonal region and adjacent to the foramina of Monro [33, 37]. It can have a cavitary or non-cavitary presentation, this last type being more frequent. The most commonly encountered neurological sequelae are motor and visual impairments because of the direct injury to the corticospinal tracts and geniculocalcarine tracts that pass through affected regions in the periventricular white matter [3, 26]. Spastic diplegia is also a common motor sequelae of PVL, in which the degree of motor impairment is greater in the lower extremities, and occurs more frequently in preterm infants with PVL than in term infants [3, 11]. At a histological level, PVL evolves first with necrosis and cavitation that thereafter progress to porencephalic cysts. Later, these cysts collapse resulting in gliosis and loss of white matter volume that is seen in imaging studies [3, 26].

By US, there are four stages of PVL that somewhat correlate with its histological characteristics. First, there is congestion in the periventricular white matter, which in US is seen as increased echogenicity that usually adopts an elongated and globular morphology, sometimes referred as "flares." This increased echogenicity usually is seen in the first 48 h. In the second stage, there is a relative return to normal which occurs mostly by the 2–4 weeks. In the third stage, the development of cysts is evident in US at approximately 3–6 weeks (Fig. 6). Finally, in the fourth and last stage, there is resolution of the cysts, with evidence of volume loss with enlargement of the lateral ventricles. This last stage happens at approximately 6 months of age [27].

US is usually used as the first examination in evaluating suspected HII cases. Nevertheless, it lacks the sensitivity and positive predictive value and, as mentioned before, the study can be normal in patients that develop PVL. Conversely, in other cases, US shows increased echogenicity in the periventricular areas of normal neonates. The presence of prolonged hyperechogenicity of the periventricular white matter has a fairly low sensitivity and positive predictive value for the detection of PVL [28]. Serial US examinations improve substantially the detection of transient cystic

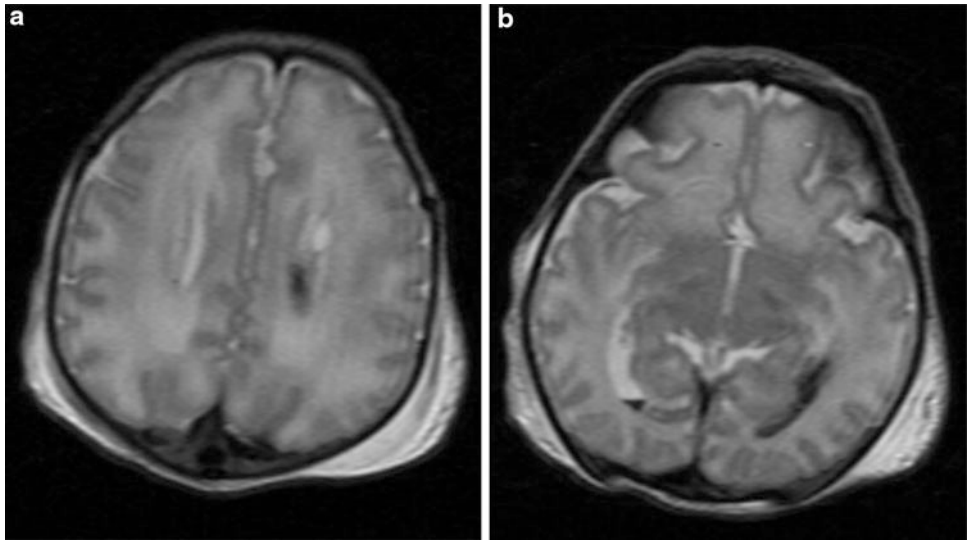

Fig. 7 (**a**, **b**) T2WI of a preterm neonate who suffered mild-to-moderate asphyxia shows T2 hyperintensity in the periventricular white matter in the setting of PVL. Also, dark fluid levels can be seen inside the lateral ventricles compatible with intraventricular hemorrhage. Small left side periventricular cyst is present

lesions and can be better than MRI studies for this purpose. This is important because it has prognostic value as most of patients with cystic changes present neurological sequelae [29]. For these reasons, the primary roles of US are to detect germinal matrix hemorrhages in the immediate postnatal period and detect cystic changes later in perinatal life [3].

MRI allows better visualization of the periventricular white matter lesions and is a useful complement to cranial US especially among patients without cystic lesions. It also allows better depiction of hemorrhages and/or white matter volume loss which also has prognostic value [29]. In MR images, early injury to the white matter appears as foci of T1 hyperintensity in the larger areas of T2 hyperintensity. These T1 hyperintense foci must be distinguished from hemorrhages, and they do not produce T2 shortening. These T1 abnormalities may represent focal areas of mineralization, while in the white matter reactive gliosis develops [30]. These changes are usually evident at the third–fourth days post injury, and then they give way to a mild T2 shortening of the white matter at days 6–7. The high T2 signal is most evident in the peritrigonal regions (Figs. 7 and 8).

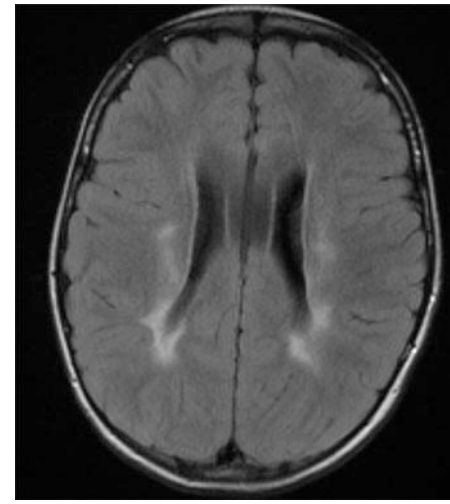

Fig. 8 T2WI of a preterm neonate who suffered moderate asphyxia demonstrates characteristic hyperintensity in the periventricular white matter, more pronounced at the level of the peritrigonal regions compatible with PVL. Also, note the "wavy" appearance of the ventricular walls

CT is usually avoided in neonates because of the exposure to ionizing radiation. It does not provide much more information than the US and MRI, but it could be important and helpful in confirming PVL end-stage injuries later in life. In the last stage of PVL, MRI and CT show a

characteristic loss of volume of the periventricular white matter and centra semiovale with secondary enlargement of the lateral ventricles in particular their trigones. MRI and CT also show the characteristic irregular outline and wavy appearance of the outer wall of the lateral ventricles. MRI better shows the loss of volume in the corpus callosum, particularly in the posterior aspect of the body and splenium [31].

Table 2 HII in preterm neonates

Severe	Injury in the deep gray matter, mostly the thalami but also the basal ganglia, dorsal brainstem, cerebellum, and corticospinal tracts as well as a diminished volume of the cerebral hemispheric white matter
Mild to moderate	Germinal matrix hemorrhage
	IVH
	PVL

HII in the Term Neonate

As mentioned before, HII is also considered an important cause of death, neurodevelopmental disorders, and disability in term neonates, although its incidence and prevalence has declined over the last decade and is now estimated to be between 2 and 4 per 1,000 live term births [3, 32, 33]. Risk factors for HII can be divided in antepartum factors and intrapartum factors. Antepartum risk factors include maternal hypotension, infertility treatment, multiple gestation, prenatal infection, gestation $\geq$41 weeks, and thyroid disease. Among the most important intrapartum factors are forceps delivery, breech extraction, umbilical cord prolapse, abruptio placentae, tight nuchal cord, maternal fever, prolonged membrane rupture, abnormal cardiotocography, shoulder dystocia, and thick meconium. The most popular hypothesis is that most of the HII cases are attributable only to antepartum risk factors; however, there are new reports that point to the intrapartum factors as necessary to develop this condition. In approximately 10 % of HII cases, there are postnatal complications such as sepsis, shock, and/or severe respiratory distress [33–35].

The clinical manifestations at birth of HII in term infants include nonspecific signs and symptoms that evolve over a period of days. Data suggest that the infants at risk for severe HII can be reliably identified by a group of clinical manifestations that include evidence of intrapartum distress (e.g., fetal heart rate abnormality), severe functional depression (low 5 min Apgar score), need for resuscitation in the delivery room, severe fetal acidemia, abnormal early neurologic examination, and abnormal electroencephalogram. These patients, in the first hours after a severe insult, may present with depressed consciousness, periodic breathing or apnea, or bradycardia. In cases where severe injury to cortical regions has ensued, hypotonia and seizures may occur. In patients that survive, severe HII typically develops including quadriparesis, choreoathetosis, severe seizure, and/or mental retardation. In cases of moderate HII, spastic diplegia or quadriplegia almost always develops and is usually referred to as cerebral palsy. On the other hand, in mild cases of HII, term infants may develop mild developmental delay or recover completely.

The imaging patterns can be subdivided depending on the severity of the hypoxic injury into severe and partial asphyxia (Table 2).

In term neonates, transfontanelle US is the first imaging study to be obtained when HII is suspected. Although some abnormalities can be detected by US, it has a low sensitivity and therefore a negative study should not be used as a definite evidence of an absence of hypoxic injury. If there is strong clinical suspicion of HII and US is negative, MR imaging should be obtained to evaluate the presence and severity of the injury. It is important to remember that, as mentioned before, the biochemical and histological features of HII that influence the imaging findings vary with time so that a study performed only hours after the event will be different from one done several days later.

Severe Asphyxia

In term neonates, severe asphyxia results mainly in a central pattern of injury that usually involves

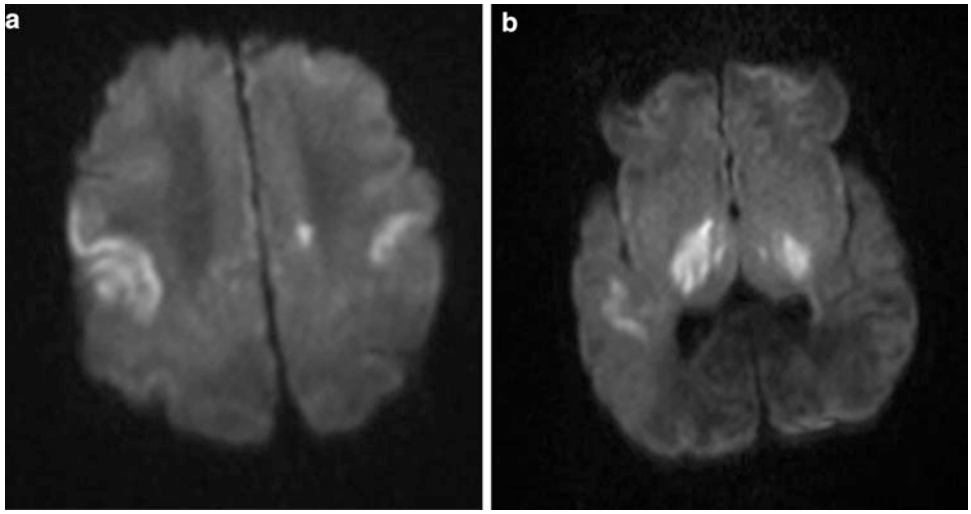

Fig. 9 (**a**, **b**) DWI in a term neonate with severe asphyxia demonstrates diffusion restriction in the ventrolateral thalami and peri-rolandic cortex

the deep gray matter including the putamina, ventrolateral thalami, hippocampi, dorsal brainstem, and lateral geniculate nuclei. Occasionally, the peri-rolandic cortex is also involved. The explanation for this pattern of injury is, as we mentioned before, the active state of myelination of these areas and the high concentration of NMDA receptors which makes them more susceptible to neonatal HII [6, 36]. The rest of the cortex is usually spared or shows mild abnormalities since it is generally less metabolically active. However, if the injury is prolonged, the remaining cortex will be injured and portrays a worse prognosis [10].

Transfontanelle US, although it is the most commonly used technique and usually the first one in cases of suspected HII, is less sensitive (about 50 % in the first week of life) and specific compared with CT and MRI and carries less interobserver agreement [3, 37, 38]. Its sensitivity increases when it is performed after 7 days. Early US findings include a generalized increase in cerebral echogenicity and diffuse cerebral edema with obliteration of the cerebrospinal fluid (CSF) containing spaces. Subtle increased echogenicity in the basal ganglia, thalami, and brainstem can be seen in the first week but are more apparent after 7 days [38, 39]. The presence of thalamic hyperechogenicity generally suggests a severe insult and poor outcome [40]. At a later stage, the imaging pattern reflects the loss of volume including prominence of the ventricles and extra axial CSF-containing spaces, likely due to atrophy. Doppler US during the initial US examination may be useful and improves sensitivity and specificity by showing diminished resistive indexes (<60) in the anterior and middle cerebral arteries. These lower resistive indexes have been also associated with poorer clinical outcome, even in absence of other US abnormalities [41].

MRI is probably the most accurate modality to assess neonatal HII especially when performed with diffusion-weighted imaging (DWI) in the first 24 h, when DWI is most sensitive to detect injuries which may still not be visible in conventional T1- and T2-weighted images. DWI shows high signal (with corresponding low ADC values) in the ventrolateral thalami and basal ganglia (particularly the posterior putamina), peri-rolandic regions, and along the corticospinal tracts (Fig. 9). It is important to highlight the fact that even with the high sensitivity of this technique, the findings in DWI in the first 24 h usually underestimate the ultimate extent of the injury, and although rare, some reports of normal findings in the first 24 h have been reported [17, 42].

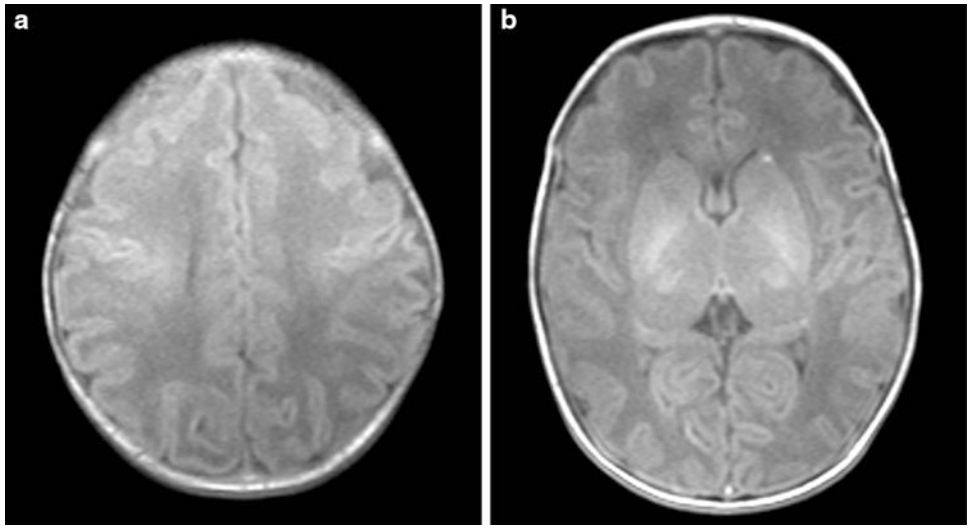

Fig. 10 (**a**, **b**) T1WI showing hyperintensity in the posterior lentiform nuclei, ventrolateral thalami, and pericentral cortex in a preterm neonate who suffered profound asphyxia

It is believed that the reason for this delay in showing the full extent of the injury may be based in the important role of apoptosis in HII, and as explained before, the time that takes for ATP to be depleted which precedes the death of neurons and the resultant neurodegeneration at a macroscopic level. Abnormalities on DWI peak at 3–5 days. By the end of the first week, the hyperintensity in injured areas in DWI tends to decrease, phenomenon known as "pseudo-normalization" [4, 6, 10, 20]. It is important to realize that although the images seemingly improve, this does not imply that there is a real reversal or improvement of the underlying injury, just resolution of signal abnormalities on DWI. Because of the rare possibility of a false-negative DWI study when performed in the first days, it is recommended to repeat the examination at 2–4 days when the signal abnormality is expected to be greatest or perform an evaluation with proton MR spectroscopy (MRS).

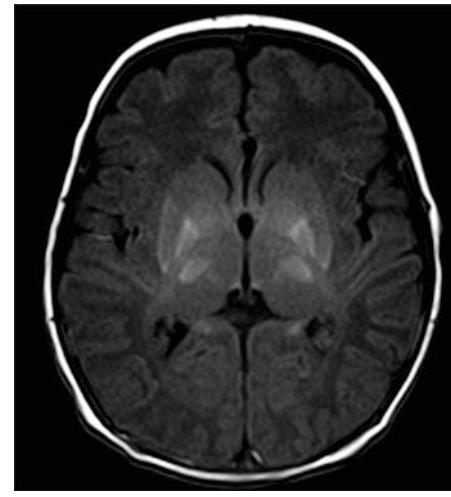

Fig. 11 T1WI. A different patient showing T1 hyperintensity in the posterior lentiform nuclei and ventrolateral thalami

It is well known that conventional MRI sequences with T1- and T2-weighted images obtained within the first day are frequently normal and therefore are less useful than DWI to diagnose acute HII. By the second day, conventional sequences, especially T1-weighted images, start to show hyperintensity in the posterior lentiform nuclei and ventrolateral thalami (Figs. 10 and 11). Sometimes, signal intensity changes may also be seen in the dorsal brainstem and basal ganglia [36]. The T2 hyperintensity usually develops later than the T1 shortening and usually by the second week, affects the thalami and posterior putamina. As mentioned before, cortical abnormalities can also occur.

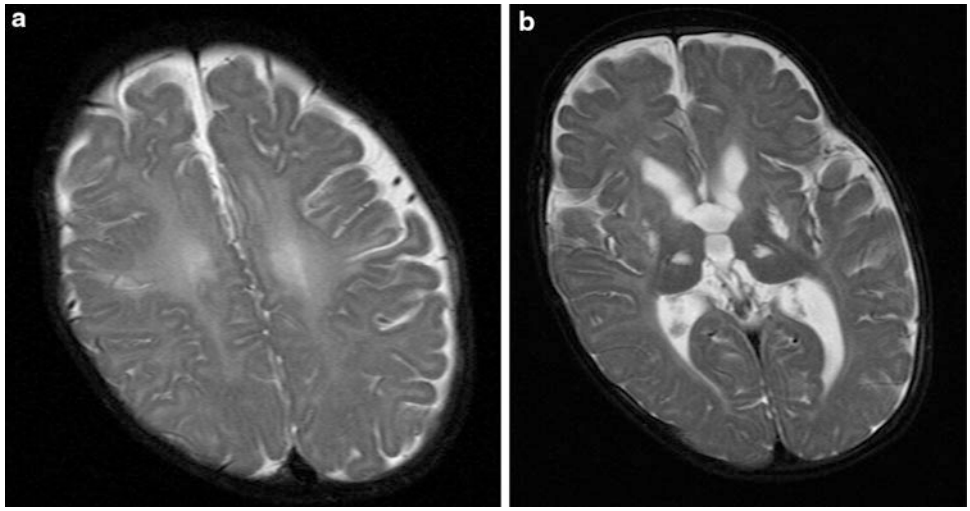

Fig. 12 (**a**, **b**) T2WI in a term neonate with chronic changes from HII shows hyperintensity in the corticospinal tracts, putamina, and ventrolateral thalami. Also, some loss of volume is noted

The cause of the abnormalities seen with the MRI conventional sequences in the basal ganglia and thalami remains incompletely understood, with possible explanations including hemorrhage, transient calcium deposition, lipid release from myelin breakdown, free fatty acids, and even paramagnetic effects from free oxygen radicals. In infants, cortical abnormalities are likely due to laminar necrosis [36, 43]. A possible explanation for the delay in appearance of the T2 hyperintensity changes is the high water content of the white matter, so subtle abnormalities are obscured and difficult to identify at first. The T1 shortening in posterior putamina, thalami, and peri-rolandic cortex can persist for several months. Because of all these reasons, DWI is very useful in the first days, especially in the first 24 h when conventional MR images are likely to be normal. On the other hand, conventional MRI sequences are useful at the end of the first week when the DWI images pseudo-normalize. Later, in the chronic phase, the imaging findings reflect atrophy of injured structures and T2 hyperintensity especially in the ventrolateral thalami, posterior putamina, and corticospinal tracts (Figs. 12 and 13) [36]. The major imaging differential diagnosis in newborns with bilateral basal ganglia lesions includes HII and inborn errors of metabolism. The latter ones are suspected if there is no history of HII and if other imaging features outside of the typical spectrum of HII, like localized white matter and cortical abnormalities, atrophy, or heterotopias, are seen.

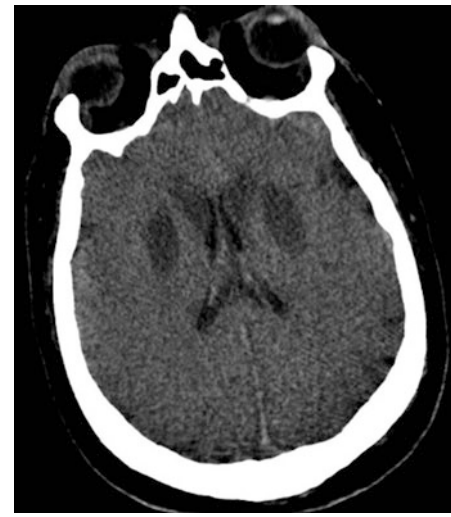

Fig. 13 NECT in acute severe HII shows hypodensity of the basal ganglia. CT is not usually the imaging modality of choice in these patients

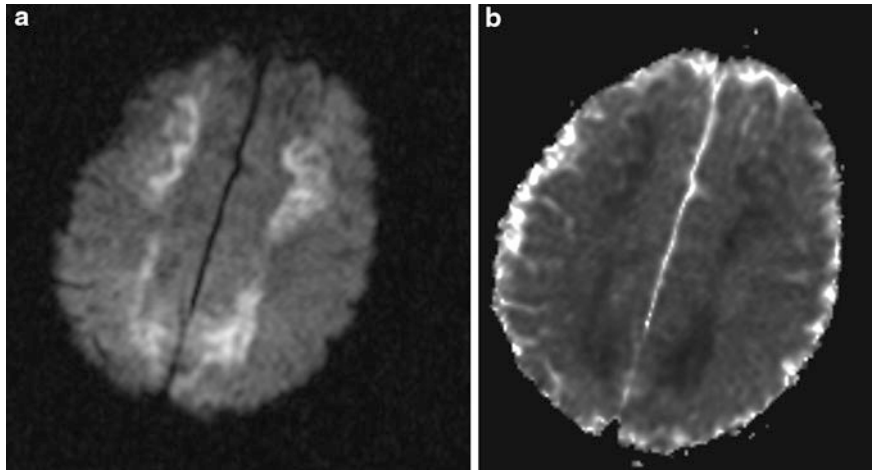

Fig. 14 (**a**, **b**) DWI in a term neonate who suffered partial asphyxia demonstrates hyperintensity in watershed areas with the corresponding low signal in the ADC map, compatible with watershed infarcts

Partial Asphyxia

When partial asphyxia occurs, the pattern of injury changes and as mentioned before, the neonatal brain is more resistant to hypoxia than the adult brain. For this reason, in mild or moderate insults of short duration, there may be little or no injury [10]. Compensatory mechanisms that take place when hypoxia is established have been well studied in animal models. With prolonged fetal hypoxia, blood shunting to vital brain structures occurs, including the brainstem, basal ganglia, hippocampi, and cerebellum. Thus, less metabolically active regions of the brain receive less blood and are more susceptible to injury, specifically the cortex and white matter. This is the reason why in mild-to-moderate HII, the brainstem, cerebellum, and deep gray matter are generally spared. When the autoregulatory mechanisms are exceeded, the result is injury to the watershed zones which become relatively hypoperfused. The clinical manifestations of this process generally are seizures, hypotension, and possibly proximal extremity weakness and/or spasticity [10].

US diagnosis of this type of injury is difficult as this technique has low sensitivity for examination of the cortical and subcortical areas that are close to the calvarium. For this reason, MRI is the modality of choice when studying term infants with suspected partial asphyxia. Regarding the MRI sequences that are more useful, again DWI are the most sensitive and the first to show abnormalities in the first 24 h. These abnormalities include hyperintensity with corresponding low ADC values (diffusion restriction) in the watershed territories (Fig. 14). Interpretation of DWI is sometimes difficult because of the high content of water of the brain at this age which makes the hyperintensity of HII subtle. To facilitate the correct diagnosis, it is important to interpret DWI with the corresponding ADC map which will show areas of low signal confirming true diffusion restriction [17]. T1 and T2 images may be normal in the first 24 h, but by the second day, they show T2 hyperintensity in the cortex and subcortical areas related to cortical swelling and loss of differentiation between the gray and white matter contrast. These findings are more evident in watershed zones but occasionally can be appreciated in the hemispheres [3]. Deep gray matter structures will be most likely spared in these patients. In the chronic stage, there are signs of atrophy with loss of volume of the white matter and cortical thinning predominantly in the parasagittal watershed zones (Table 3).

Table 3 HII in term neonates

Severe	Injury of the deep gray nuclei (putamina, ventrolateral thalami), hippocampi, dorsal brainstem, and lateral geniculate nuclei
	Occasionally, the peri-rolandic cortex
Partial or less severe asphyxia	Cortical watershed zones

HII in Postnatal Infants and Young Children

In this group of patients, the most common causes of HII are accidents such as drowning or choking and non-accidental trauma. There are differences between the pattern of injury seen in neonates and that in infants and young children. These differences occur mostly because of disparities in the brain maturation that advances rapidly during the perinatal period. It has been estimated that the myelination process is completed by about 2 years of age, and around this period, the pattern of injury starts to resemble the one encountered in adults.

Severe Asphyxia

Severe episodes of asphyxia in infants between 1 and 2 years of age result in injuries to the caudate nuclei, putamina, lateral geniculate nuclei, hippocampi, and cerebral cortex. The anterior frontal and parieto-occipital cortex will be most affected with relative sparing of the peri-rolandic cortex and thalami [36].

In patients who experience asphyxia after the immediate perinatal period, but before 1 year of age, findings are often a mixture between those of neonatal asphyxia and later infantile asphyxia and result in the involvement of the basal ganglia in particular the posterior putamina and lateral thalami and also in involvement of the dorsal midbrain and cortex. The reasons for these differences between neonates and older children are not entirely understood, but it has been suggested that the relative sparing of the thalami in older

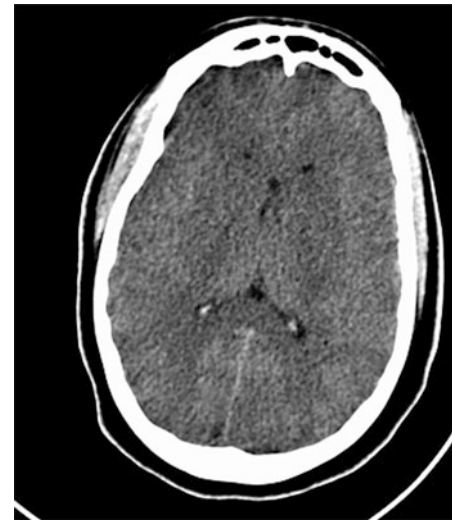

Fig. 15 NECT of severe diffuse anoxic injury shows the "reversal sign." Note the subtle decreased density of the cortical gray matter and basal ganglia relative to the denser white matter

infants may be due to redistribution of blood flow from the anterior circulation to the posterior circulation after asphyxia [36]. Also, some differences may be due to physiologic and biochemical changes that occur with maturation; this results in changes in regional energy requirements and thus also in changes in the regional susceptibility to hypoxia. By the time the anterior fontanelle closes (at approximately 4 months), US cannot be used anymore and CT becomes the study of choice. CT examinations that are done too early, before 24 h, can show only subtle hypodensity in the deep gray matter structures or be negative. Later, CT demonstrates diffuse basal ganglia abnormalities along with diffuse cortical hypoattenuation with loss of gray-white matter differentiation and sulcal and cisternal effacement, all of which are consequences of cerebral edema. The peri-rolandic cortex may be relatively spared [13, 44, 45]. At 4–6 days, hemorrhagic infarcts may be evident in the basal ganglia. In some patients, the "reversal sign" can be seen (Fig. 15). The reversal sign refers to a reversal in the normal CT attenuation patterns between gray and white matter probably due to the congestion of deep medullary veins secondary to obstruction of venous outflow by cerebral edema and

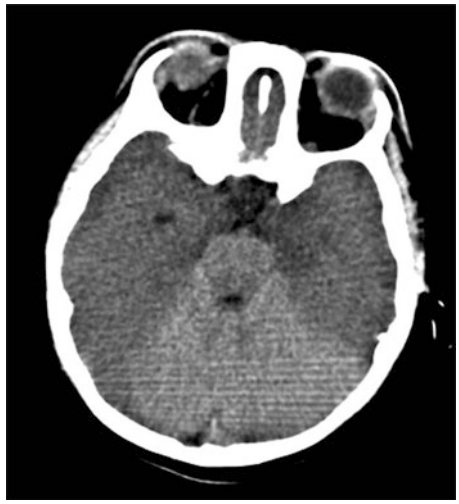

Fig. 16 NECT demonstrating the "white cerebellum" sign in a child with severe HII. Note the diffuse hypodensity of the cerebral parenchyma that makes the cerebellum look denser

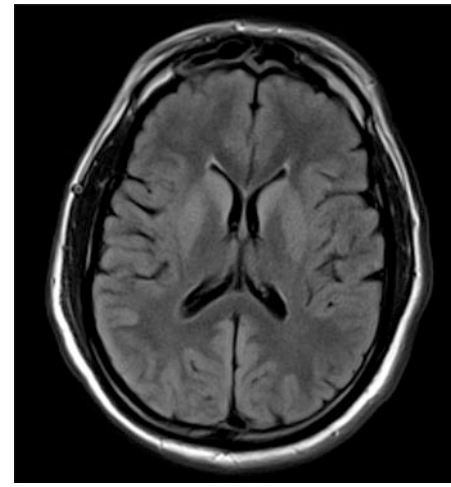

Fig. 17 FLAIR image demonstrates affectation of the basal ganglia with sparing of the thalami. The occipital cortex is also slightly hyperintense

subsequent compression of them. The other sign in CT studies is the "white cerebellum sign" (Fig. 16), in which the cerebral hemispheres are hypodense due to diffuse edema, making the cerebellum and brainstem appear relatively hyperdense. This finding may be related to blood flow redistribution to the posterior circulation that occurs during anoxia [44]. Both the "reversal sign" and "white cerebellum sign" are associated with a worst outcome [44–46].

In MRI studies, the abnormalities on DWI are evident in the first 12–24 h. First, images show high intensity in the posterolateral lentiform nuclei, and if the thalami are involved, usually the ventrolateral nuclei will be most affected. In the next 48 h, there is progression and involvement of the rest of the basal ganglia and cortex. Conventional T1- and T2-weighted images are usually normal during the first day and may remain normal for 48 h [43]. After this, T2-weighted images show diffuse basal ganglia and cortical hyperintensities with a relative sparing of the thalami and peri-rolandic cortex (Fig. 17). These T2 hyperintensities are believed to represent edema [3]. The differential diagnosis of bilateral basal ganglia abnormalities is wide and includes inborn errors of metabolism, hypoglycemia, osmotic myelinolysis, hemolytic uremic syndrome, toxic exposure, and infectious encephalitis.

Table 4 HII in postnatal infants and young children

Severe	1–2 years: injury to the caudate nuclei, putamina, lateral geniculate nuclei, hippocampi, and cerebral cortex (especially anterior frontal and parieto-occipital)
	<1 year: mixture of the features of neonatal asphyxia and later infantile asphyxia
Mild to moderate	Cortical watershed zones

Mild-to-Moderate Asphyxia

In mild hypoxic insults to older infants, watershed zone abnormalities in the cortex and subcortical white matter are seen. White matter lesions may also be seen but are more common in younger children (under 1 year of age) [7]. Relative sparring of the periventricular white matter is common [31] (Table 4).

HII in Older Children and Adults

In older children, just as in younger ones, the most common causes of asphyxia are drowning and choking accidents. In adults on the other hand, the causes of HII are different. The leading causes for hypoxic adult events are related to chronic diseases as cerebrovascular disease and/or cardiac arrest with secondary hypoxemia. In this group of patients, mild-to-moderate injury will manifest as watershed infarcts. More severe insults have deleterious effects in the cortical gray matter and deep gray structures. The cortex is usually diffusely affected predominantly in the peri-rolandic and visual areas, and the cerebellum and hippocampi may also be affected. The pathophysiology of this gray matter injury pattern is probably related to the fact that the gray matter contains most of the postsynaptic glutamate receptors and therefore is most susceptible to the excitotoxic effects of glutamate. Also, gray matter is more metabolically active than white matter.

Cerebellar injury is common in older patients. The reason for this is not completely understood, but it is believed that the relative immaturity of the Purkinje cells in neonates has a protective. These cells are particularly prone to ischemia because they are not able to generate energy during an anoxic event. The Purkinje cells die along with cells in the granular layer [13].

In older patients, the first imaging study performed for a suspected brain anoxic injury is commonly a CT. In CT, the most common findings are diffuse hypoattenuation of the cortex and basal ganglia, consistent with edema, effacement of the CSF-containing spaces, and loss of gray-white matter differentiation (Fig. 18). In older patients, as in children, the "reversal sign" and "white cerebellum" sign may be present and also indicate a poor prognosis (Fig. 19) [3].

As in other age groups, DWI is the earliest to show abnormalities, usually starting after a few hours after the injury. During the first 24 h, hyperintensity in DWI is evident in the basal ganglia, cerebellar hemispheres (Fig. 20), and cerebral cortex (especially in peri-rolandic and occipital areas), and the thalami, brains tem and basal ganglia may also be involved (Fig. 21) [7, 47, 48]. Abnormalities on T1- and T2-weighted images may be delayed in comparison with DWI. After the first 24 h, T2 images begin to show abnormalities that consist of hyperintensity and swelling of gray matter structures that may persist until the end of the second week (Figs. 22, 23 and 24).

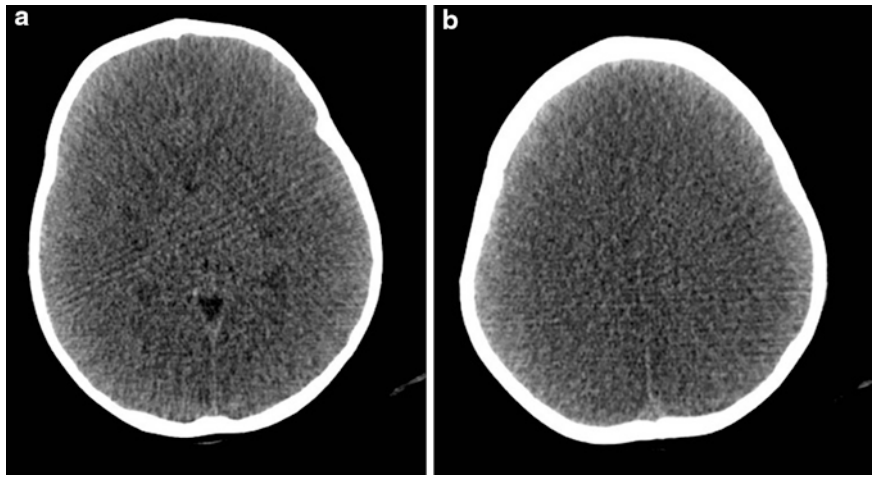

Fig. 18 NECT in severe HII injury after a cardiac arrest shows total loss of gray-white matter differentiation with hypoattenuation of the cortex and basal ganglia. There is also effacement of the CSF-containing spaces

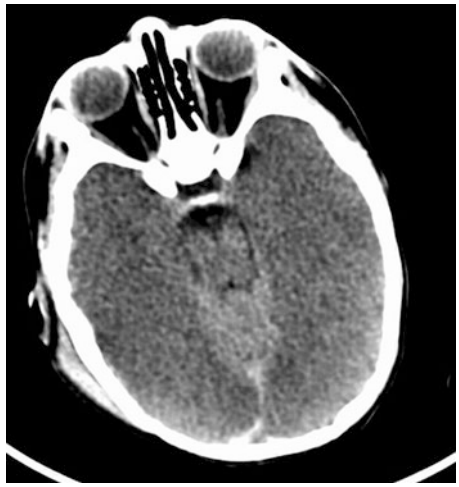

Fig. 19 NECT showing the "white cerebellum sign." The cerebellum appears "white" when compared with the abnormal hypodense brain

DWI images usually pseudo-normalize by the end of the first week. In the chronic stage, T2-weighted images demonstrate some residual hyperintensity in basal ganglia, and the T1 may show hyperintensity in the affected cortex, representing cortical laminar necrosis in addition to diffuse atrophy (Figs. 25 and 26) [48] (Table 5).

Delayed White Matter Injury

Delayed white matter injury, also known as postanoxic leukoencephalopathy, is a rare complication of global hypoxia and takes place weeks after the injury. It is an uncommon syndrome which may be seen in approximately 3 % of carbon monoxide intoxications. Patients usually present with a period of relative clinical stability

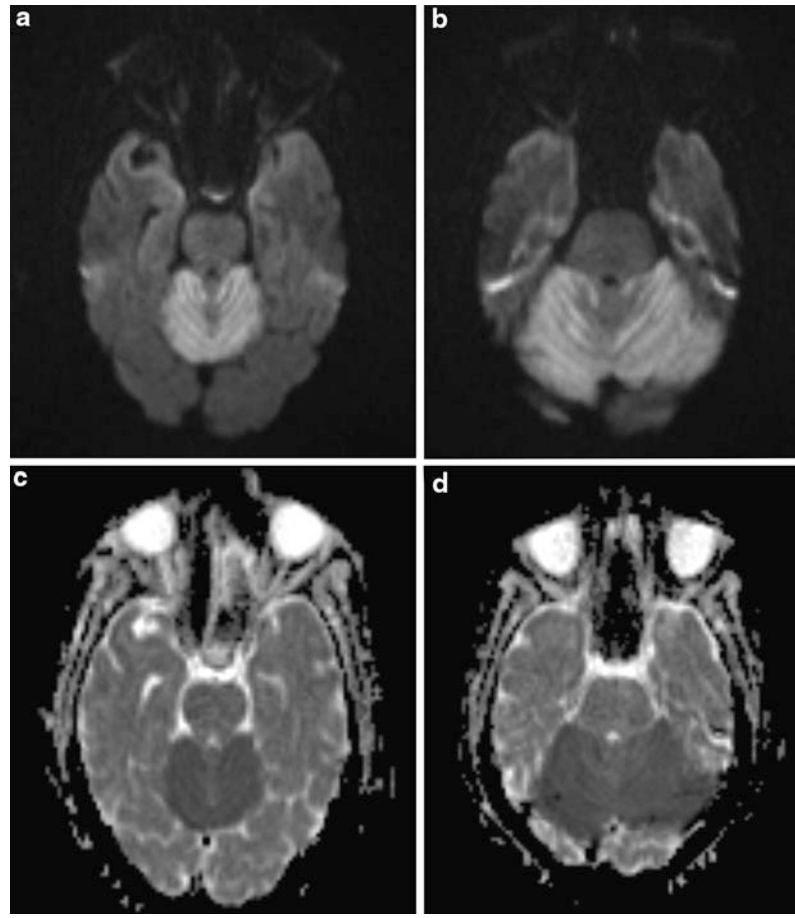

Fig. 20 (**a**–**d**) DWI in severe HII shows diffuse diffusion restriction of the cerebellar parenchyma with the corresponding ADC map hypointensity

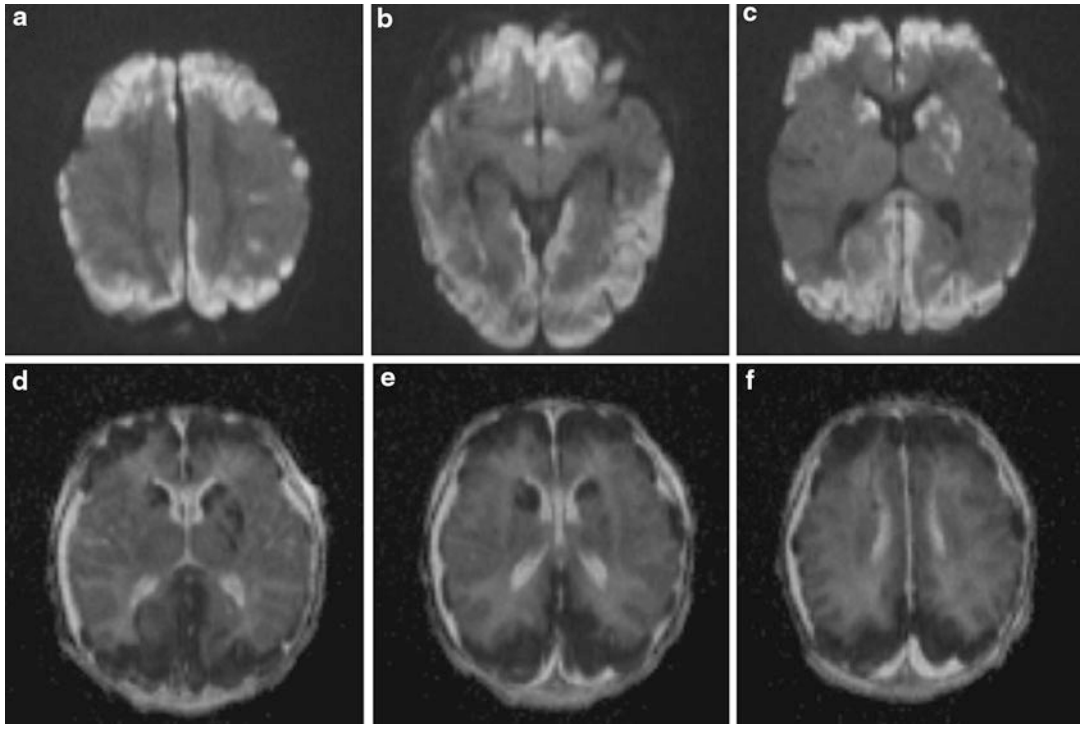

Fig. 21 (**a**–**f**) DWI showing diffuse diffusion restriction throughout the cortex, caudate nuclei, and *left* lentiform nucleus in a severe HII

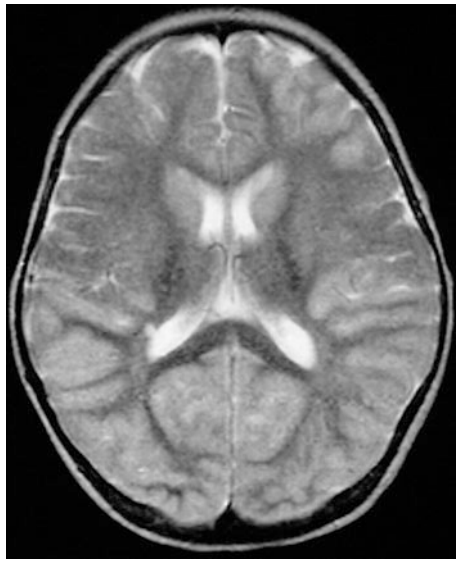

Fig. 22 T2WI shows hyperintensity and swelling of the parieto-occipital cortex in HII

or improvement, after which they develop acute neurologic deterioration 2–3 weeks after the initial hypoxic event. Symptoms include delirium, personality changes, intellectual impairment, movement disorders, and/or seizures [49, 50]. This condition has a relatively good prognosis with approximately 75 % of patients showing near-complete or complete recovery in 6–12 months. In the rest of patients, there maybe residual dementia or rarely the condition may progress to paresis, coma, or even death [3]. It is important to identify patients with this condition recognizing their clinical and imaging features to be able to provide them time to recover without abrupt withdrawal of care [51].

MR is the study of choice in suspected delayed white matter injury. DWI can fail to demonstrate abnormalities when performed immediately after the insult, but when performed during the period

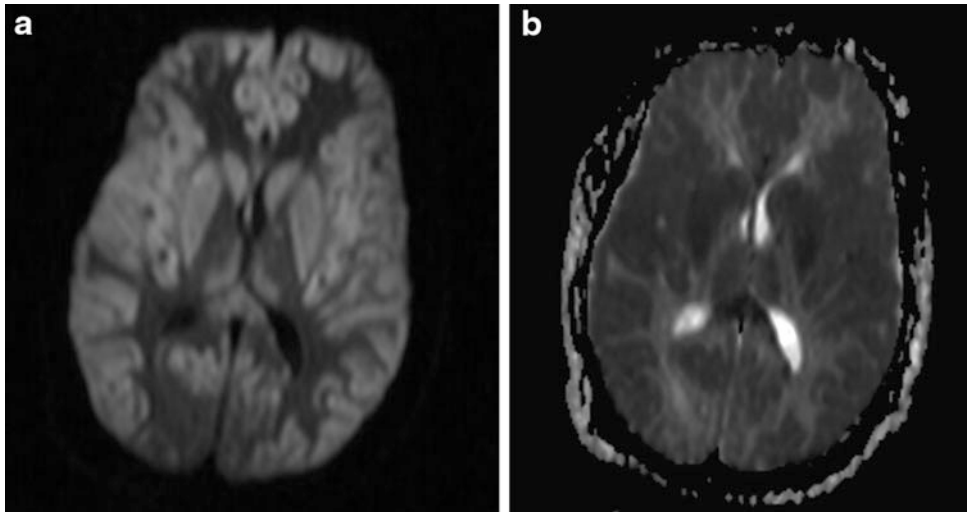

Fig. 23 (**a**, **b**) DWI in HII shows diffusion restriction in the cortex and basal ganglia, with the corresponding ADC map hypointensity

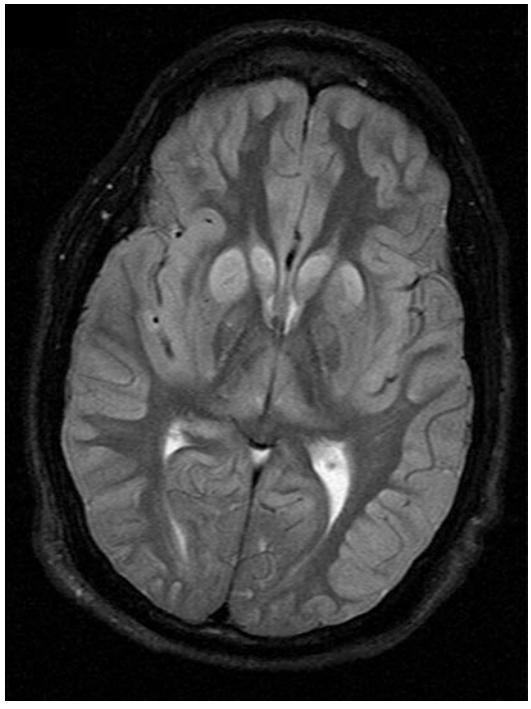

Fig. 24 T2WI of the same patient shows diffuse cortical and basal ganglia hyperintensity and swelling

of delayed neurologic decline demonstrate diffuse confluent areas of restricted diffusion in the white matter [3, 47–49, 52]. T2-weighted images also show corresponding hyperintensities in these areas.

Although this syndrome is typically a delayed process, it can present as a progressive leukoencephalopathy not separable from the primary injury and without an intervening lucid period. In these cases, the abnormalities seen in DWI appear as early as 2 days. In other cases, clinical findings may not be apparent and MRI may be the first to detect white matter injury. Clinical improvement appears to be associated with improvement of the signal intensity abnormalities in the white matter; however, some residual hyperintense areas may persist beyond 18 months [3, 53].

The pathophysiology of this delayed injury is not known. It is believed that the findings represent a process similar to Wallerian degeneration although apoptotic cell death may also play a role and help explain the delay in the presentation of the disease [47].

Role of Proton MR Spectroscopy in the Evaluation of HII

Magnetic resonance spectroscopy (MRS) is a technique that allows the identification and quantification of some metabolites in tissues. It differs from the conventional MR imaging in that it provides physiological and pathophysiological data

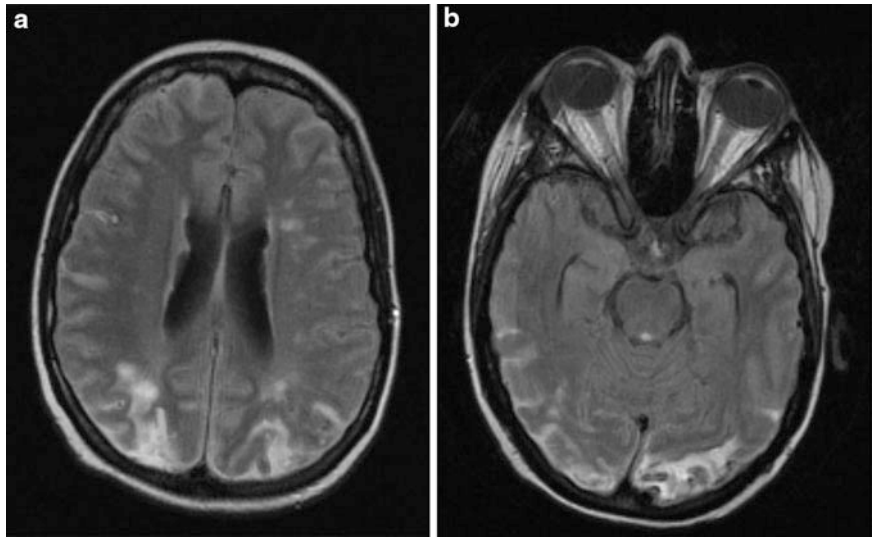

Fig. 25 (**a**, **b**) FLAIR images in HII demonstrate hyperintensity in the temporoparietal cortex

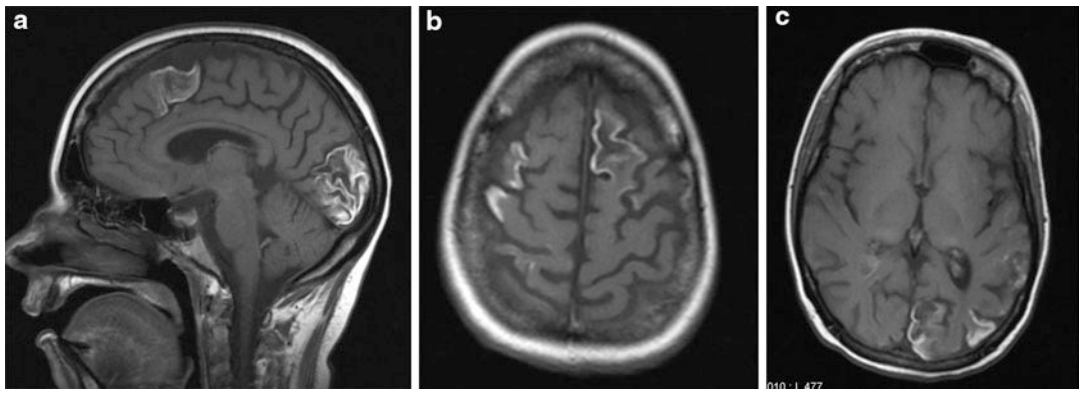

Fig. 26 (**a**–**c**) T1WI show areas of hyperintense cortex representing cortical laminar necrosis

instead of anatomic information. MRS has become a valuable tool in the identification of HII, especially in the perinatal period. Together with DWI, they are the most sensitive modalities for detecting HII in the acute period [3, 17, 54]. Furthermore, MRS is very useful in the first 24 h, being more sensitive than the conventional MR sequences and DWI in this period. MRS also has value in predicting the severity of injury [10, 17, 42].

The main alteration seen in MRS when HII ensues is elevation of lactate. Lactate is not normally present or seen only as a very small peak in normal newborns and only the first few hours of life [55]. In HII, MRS shows increased lactate levels which appear as a doublet at 1.3 ppm at 1.5 T in the deep gray matter, parieto-occipital regions, or watershed zones by 2–8 h [17, 54, 56]. A glutamine–glutamate peak may be detected at 2.3 ppm [54, 55] and could reflect the glutamate release that occurs in HII (Fig. 27). Evidence suggests that the elevation of lactate takes place in two different phases. A first elevation occurs very early in the acute stage of the injury and is probably due to hypoxemia and the secondary anaerobic glycolysis that takes place. Next, it returns to normal as perfusion is restored. Then, a second peak occurs over the following 24–48 h

Table 5 HII in older children and adults

Severe	The cortex usually diffusely affected, deep gray structures (basal ganglia and thalami), hippocampi, and cerebellum
Mild to moderate	Cortical watershed zones

which is believed to be caused by a process known as "secondary energy failure" in which surviving neurons suffer delayed energy depletion most probably due to mitochondrial failure. Injury caused by this mechanism results in lactate elevation after 24 h and is associated with poor prognosis [5, 6]; this partially explains the underestimation of injury seen in DWI during the first hours.

To correctly interpret the MRS studies in preterm and term infants, it is important to realize that the spectra of premature babies differ significantly from the one seen in term infants and adults. This is the result of the differences in the concentration of metabolites in the developing brain which does not become similar to the adult brain until 2 years of age [55]. In newborns, it is normal to have a lower N-acetylaspartate (NAA) and higher myo-inositol (Myo) and choline (Cho) levels compared with older children and adults. In preterm babies, a small peak of lactate is present and makes the interpretation of MRS in suspected HII more difficult. Lactate diminishes and NAA increases as the brain matures, but trace amounts of lactate may be present even in term infants [3, 55–57]. Because of this, it is very useful to take into consideration the gestational age of the infant at birth when interpreting the MRS to avoid false-positive interpretations.

One useful tool is using the lactate–NAA ratio in preterm neonates. The normal ratio in the thalami for normal control neonates (term and preterm) is around 0.25 [56]. In preterm and term neonates with HII, lactate–NAA ratios are greater than 0.4, while in more severe injury, ratios are greater than 0.5. When ratios are above the 95 % confidence limits, there is a clear association with major impairments or death at 1 year [56]. NAA is usually normal in acute HII. If it descends in the subacute phase, it is also associated with a poor neurologic outcome [5, 58]. In older children, the findings at MRS in HII are reduced NAA, elevated lactate, and elevated glutamine–glutamate. These alterations in the spectra correlate with a bad prognosis including persistent vegetative state or death [27]. Although HII cannot be completely ruled out with normal examinations until day 3–4, a normal MRS study and no abnormal findings in conventional MRI sequences correlate with a good outcome [6].

Imaging Choices in HII

As HII characteristics are variable, highly dependent on the time since onset and patient's age (CNS maturity), many factors must be taken into account when choosing the type of imaging study. Some of the most important considerations are the patient's condition, age, availability of imaging modalities, and concerns about ionizing radiation exposure.

Many neonates with suspected HII are in intensive care units and are hemodynamically unstable, making the transportation difficult. In this regard, performing cranial US may be best, taking in consideration that it is fast and easy to perform in a bedside setting, does not involve ionizing radiation, and may provide useful information. The major limitations of US are its operator dependence and its low sensitivity (especially in some areas such as the convexities). When US demonstrates HII, it is very helpful but if it is negative, another study is required.

In neonates, the next study should be MRI. CT is not recommended in these patients because it involves the use of ionizing radiation and is no more sensitive than US due to the high water content of the neonatal brain [3]. The MR protocol should include at least DWI, ADC map, and T1–T2-weighted images. MR spectroscopy can be performed in the acute stage, especially when DWI is negative and a clinical suspicion for HII is high. In these situations, long echo time (135 msec) and short echo time (30 msec) MRS with voxels positioned in the basal ganglia and centra semiovale are most useful. If the study is negative in the first 24 h, it should be repeated within 2–4 days. If subtle abnormalities are

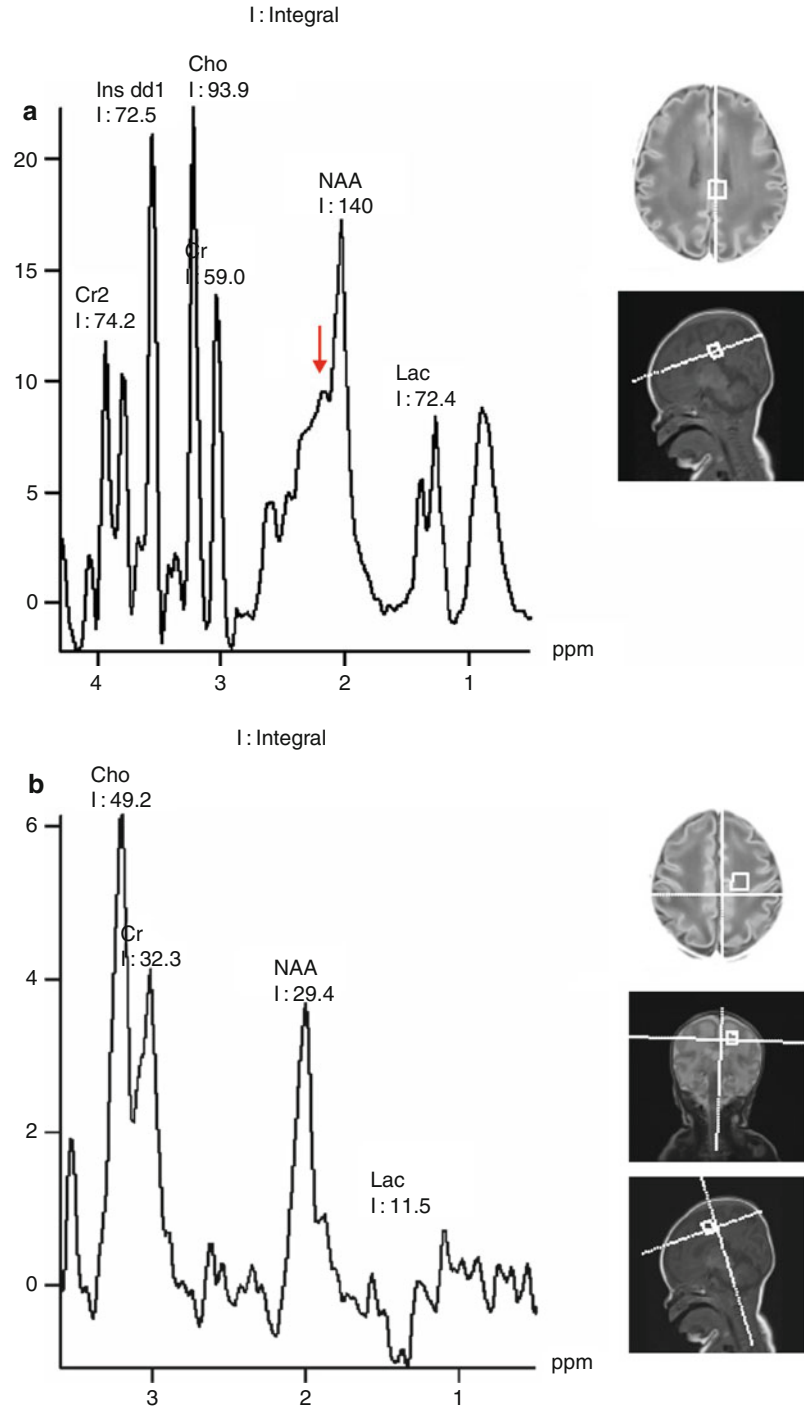

Fig. 27 (**a**, **b**) MR spectroscopy in a term neonate with HII. Short (top) and long (bottom) echo times show lactate doublet centered at 1.3 ppm in the short echo time and an inverted lactate doublet in the long echo time. There is also elevated glutamine–glutamate (*red arrow*) in the short echo time and reduced NAA in the long echo time

present on MRI in the acute setting, follow-up imaging at the end of the first week is recommended to define progression and overall extent of injury [6].

In adults and infants with closed anterior fontanelles, unenhanced head CT is the initial examination of choice. If CT is positive, performing an MRI to assess the extent of the injury can be

considered. Currently, there is no clear role for MRI perfusion imaging in this clinical setting.

Summary

HII is a highly variable entity that can pose significant difficulties to the diagnosis from a clinical and neuroimaging standpoint especially in newborns.

Different patterns are observed in these patients and depend mainly on brain maturity, severity and length of the injury, and type and timing of the imaging studies. A clear understanding of the pathophysiological events related to the global hypoxic–ischemic injury may help in understanding its different imaging patterns. The concept of selective vulnerability allows imagers to focus their attention in specific areas that are most likely injured. The most sensitive imaging modalities in the detection of HII in the hyperacute stage are DWI and MR spectroscopy. DWI can underestimate the extent of injury in very young children, so performing delayed imaging is recommended to assess the extent of injuries and shed light on the long-term prognosis of these patients.

Key Points

- Imaging findings in HII are highly variable and depend mainly on brain maturity, severity and duration of the injury, and timing and imaging modality used to study these patients.
- Conventional T1- and T2-weighted images are most useful at the end of the first week when DWI abnormalities have pseudo-normalized.
- DWI is useful in the first week. When used for the evaluation of the neonatal brain, it should be reviewed carefully in conjunction with ADC maps because true restriction may be masked by intrinsic T2 hyperintensity of the unmyelinated brain at this age.
- In preterm neonates, profound ischemia presents with damage to the deep gray matter and brainstem. Moderate-to-mild insults present as germinal matrix hemorrhage, intraventricular hemorrhage, and/or periventricular white matter damage (PVL).
- MRS and DWI are the most sensitive modalities for detecting HII in the acute period.

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