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Review Article

HYPOXIC-ISCHAEMIC ENCEPHALOPATHY: EARLY AND LATE MAGNETIC RESONANCE IMAGING AND CT FINDINGS

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ABSTRACT

Hypoxic ischemic encephalopathy (HIE) is a serious birth complication affecting full term infants: 40–60% of affected infants die by 2 years of age or have severe disabilities. The majority of the underlying pathologic events of HIE are a result of impaired cerebral blood flow and oxygen delivery to the brain with resulting primary and secondary energy failure. In the past, treatment options were limited to supportive medical therapy. This review discusses the findings of imaging of head of hypoxic-ischemic event .

Global hypoxia, hypotension or hypoglycaemia can damage the whole brain, usually but not always symmetrically. It is seen most often in the newborn. Two patterns are recognisable in the newborn on CT and MRI: *acute asphyxia* for more than 6 minutes results in signal changes in the thalami (not basal ganglia) and sometimes also the peri-Rolandic regions of the cerebral hemispheres; *partial asphyxia* (hypoxic ischaemic brain damage) results in periventricul ar leucomalacia in premature infants and more peripheral cortical watershed infarcts in full-term infants. In adults, patterns vary from total cerebral infarction to predominantly white matter infarction, cortical watershed or white matter terminal zone infarction, basal ganglia infarcts (especially globus pallidus), and pure cortical damage in cerebral hemisphere or cerebellum such as in severe hypoglycaemia. Severe clinical disability can occur with little or no changes on CT or MR.

Keywords: infant, CT and MRI

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is one of the most serious birth complications affecting full term infants.[1] It occurs in 1.5 to 2.5 per 1000 live births in developed countries. HIE is a brain injury that prevents adequate blood flow to the infant's brain occurring as a result of a hypoxic-ischemic event during the prenatal, intrapartum or postnatal period.[4] By the age of 2 years, up to 60% of infants with HIE will die or have severe disabilities including mental retardation, epilepsy, and cerebral palsy (CP).[4–8] The incidence of HIE has not declined even with advances in obstetric care (i.e. fetal monitoring) aimed at preventing the hypoxic-ischemic event;[9] thus much of the current neonatal research about HIE focuses on minimizing the extent of subsequent brain injury.[10] In the past, treatment options were limited to supportive medical therapy to maintain cardiopulmonary function and to manage seizure activity. Currently, several experimental treatments are available to infants with HIE and many others are being evaluated in animal models. Therefore, the purpose of this paper is to explain the key pathophysiological effects that occur after a hypoxic-ischemic event and discuss current experimental treatment modalities.

Pathophysiology of HIE:

HIE is a disorder in which clinical manifestations indicate brain dysfunction.[3] While the exact cause is not always identified,[10] antecedents include cord prolapse, uterine rupture, abruptio placenta, placenta previa, maternal hypotension, breech presentation, or shoulder dystonia. The manifestations of perinatal HIE in early postnatal life include abnormal fetal heart rate tracings, poor umbilical cord gases (pH < 7.0 or base deficit ≥ 12 mmol/L),[13] low Apgar scores,[14] presence of meconium stained fluid,[9] or the need for respiratory support within the first several minutes of postnatal life. [15] Health care providers also use the Sarnat staging criteria[16]or an adapted version to describe the severity of encephalopathy within the first several postnatal days of life in conjunction with neuroimaging to assess the severity of the insult.[15] See Table 1 for neonatal encephalopathy staging criteria.

Table 1

Sarnet Stages of Neonatal Encephalopathy

Assessment	Stage 1	Stage 2	Stage 3
Mental status	Hyperalert	Lethargic	Stuporous
Suck reflex	Weak or absent	Weak or absent	Absent
Moro reflex	Strong	Weak	Absent
Muscle tone	Normal	Hypotonia	Flaccid
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Absent
Pupils	Mydriasis	Miosis	Variable
Seizures	None	Common	Variable
EEG	Normal (awake)	Early: low-voltage theta and delta	Early: periodic pattern with isopotential phases Late: isopotential
Duration	< 24 hours	2–14 days	Hours to weeks

Adapted from (16)

The majority of the underlying pathologic events of HIE are a result of impaired cerebral blood flow[17] and oxygen delivery to the brain.[15] However, the pathophysiologic effects of the hypoxic-ischemic insult are complex and evolve over time. The unfolding of signs and symptoms makes it difficult for health care providers to determine timely appropriate treatment options.

PATHOLOGY

Hypoxic–ischemic encephalopathy (HIE) following perinatal asphyxia (i.e., severe oxygen deprivation at birth) is one of the leading causes of neonatal death and adverse neuromotor outcome in term and near-term infants worldwide. In high-income countries, the incidence of HIE has been estimated between 0.5 and 1.0 for every thousand live births, although some sources have reported an incidence as high as 8 per 1,000 live births (16, 17). In low- and middle-income countries, the incidence of HIE is higher, affecting more than 1.1 million babies annually (18–20).

The overall burden of HIE is high, in terms of quality-adjusted life years, years of life lost, and years lived with disability, not to mention a great financial cost for both society and the families involved (21, 22). With an estimated annual one million deaths worldwide, HIE is accountable for roughly 25% of all deaths in the neonatal period (18, 23).

Hypoxic–ischemic brain injury is not a single event, evoked by the actual asphyxia, but rather an

ongoing process that leads to significant neuronal cell death over hours to days after the initial insult (24, 25). Several distinct phases have been identified in this process. The primary energy failure takes place during the hypoxic–ischemic event, resulting in failure of oxidative metabolism, cytotoxic edema, and accumulation of excitotoxins (26). After resuscitation and restoration of cerebral circulation, a latent phase, lasting approximately 6 h, commences (27, 28). Subsequently, starting between 6 and 15 h after asphyxia, the brain experiences a secondary energy failure that can last for days. This phase is marked by seizures, renewed cytotoxic edema, release of excitotoxins, impaired cerebral oxidative energy metabolism, and finally, neuronal cell death (29).

Currently, the only treatment that has proven to effectively reduce hypoxic–ischemic brain injury following perinatal asphyxia is the application of therapeutic hypothermia (TH). During TH the brain temperature is lowered to 33–34°C which is maintained for 72 h (16). Since the introduction of TH, the combined adverse outcome of death and disability, such as hearing loss, cerebral palsy, and other neuromotor disorders, has been reduced from approximately 60–45% (30–32). TH has widely been implemented as the standard of care treatment for moderate to severe HIE in high-income countries. However, TH needs to be started within 6 h after birth, leaving clinicians with a narrow window for establishing the diagnosis and severity of HIE as well as transportation to a medical facility equipped for TH (33). Additional neuroprotective strategies for HIE are urgently needed to augment TH, but when hypothermia is not yet feasible, act as a first line treatment option (18, 19, 20).

A potential target for (additional) neuroprotection in patients with HIE is the inhibition of nitric oxide synthase (NOS, enzyme commission number 1.14.13.39). NOS is an enzyme catalyzing production of nitric oxide (NO) from L-arginine. After perinatal asphyxia, NO can react with the superoxide free radical to form toxic peroxynitrite, setting a pre-apoptotic pathway in motion, resulting in neuronal loss (25, 35). Nitrotyrosine, an end product of this process, has been demonstrated post mortem in neonatal brain and spinal cord tissue after severe HIE (36, 37).

Three isoforms of NOS have been identified: endothelial (eNOS), neuronal (nNOS), and inducible NOS (iNOS) (38). All isoforms are upregulated after asphyxia; both nNOS and eNOS immediately after reperfusion and iNOS from several hours onward (39). While eNOS is regarded to be critical in maintaining pulmonary blood flow, preventing pulmonary hypertension and thereby maintaining adequate oxygenation of tissues throughout the body, excessive activation of nNOS and iNOS is associated with deleterious effects on the brain (39,40). To illustrate, in mice genetically deficient of eNOS, infarct size after middle cerebral artery occlusion is larger compared with wild-type animals, due to a reduction in regional cerebral blood flow (41). By contrast, nNOS knockout mice are protected against hypoxic–ischemic brain injury, while mice lacking iNOS showed a delayed reduction in brain injury (42–47).

NEUROIMAGING: USG, CT AND MRI:

DEVELOPING BRAIN:

Well-recognized patterns of brain injury have been attributed to hypoxic–ischaemic injury and are believed to vary according to the nature and severity of the insult and the degree of maturity of the developing brain48-51. The term *partial* hypoxic–ischaemic injury is used to describe an episode or episodes of hypoxia or hypoperfusion to the developing brain, whilst *profound* hypoxic–ischaemic injury is used to describe a briefer episode of anoxia or circulatory arrest. Injuries occurring in the first and early part of the second trimester of pregnancy are expected to result in brain malformations and will not be discussed further in this section. Injuries occurring later will be discussed below.

Preterm patterns:

The so-called 'preterm' patterns of hypoxic–ischaemic injury tend to be seen in brains of about 20–35 weeks gestational age and are characterized clinically by a neonatal encephalopathy. Few survive a profound hypoxic–ischaemic injury, but if they do, the pattern of injury appears predominantly to affect the thalami with relative sparing of the other deep grey matter structures. Partial hypoxic–ischaemic injury is believed to result in the most common pattern seen in this age group, which is that of periventricular leukomalacia (PVL), germinal matrix or periventricular haemorrhage and intraventricular haemorrhage (GM/IVH), also described as periventricular haemorrhagic infarction (PVHI)50,51. In extreme cases, cystic encephalomalacia may be seen. Outcome is determined by the degree of brain injury and is also influenced by any complications and the effectiveness of any intervention, such as CSF diversion procedures for hydrocephalus. The physiological conditions necessary for the development of PVL are thought to be present from 25 to 34 weeks gestational age, the condition being most frequent in the older group, 30–33 weeks gestational age. The precise mechanisms responsible for these lesions are not fully understood, but this condition is usually considered to be a complication of prematurity and is probably multifactorial. The clinical picture is spastic diplegia or quadriplegia, often with visual impairment.

Mental retardation is usually absent or mild, except in very severe cases, as are seizures52. The simplest theory suggests that there is cerebral hypoperfusion and hypoxia causing ischaemic infarction, which in 20% may be complicated by secondary haemorrhage following reperfusion of the damaged areas. The parts of the immature brain most sensitive to insufficient cerebral perfusion or hypoxia are found in the periventricular white matter, which is therefore the most common location of PVL. Factors such as respiratory problems, sepsis, necrotizing enterocolitis, feto-maternal haemorrhage, or hypoglycaemia are associated with PVL. PVL can also be seen in mature newborns but the early stages of damage are not seen as the lesion occurs in utero and is well into the sequence of pathological development by birth at term. PVL results in infarction with oedema seen in the periventricular region. This may be seen as increased

echogenicity on US. The damaged tissue undergoes cystic degeneration 10–20 d after the insult. Small, often confluent, cysts form in the periventricular white matter; these are usually transient and subsequently collapse. The detection of these cysts is the most reliable US finding of PVL in its early development (Fig.1).

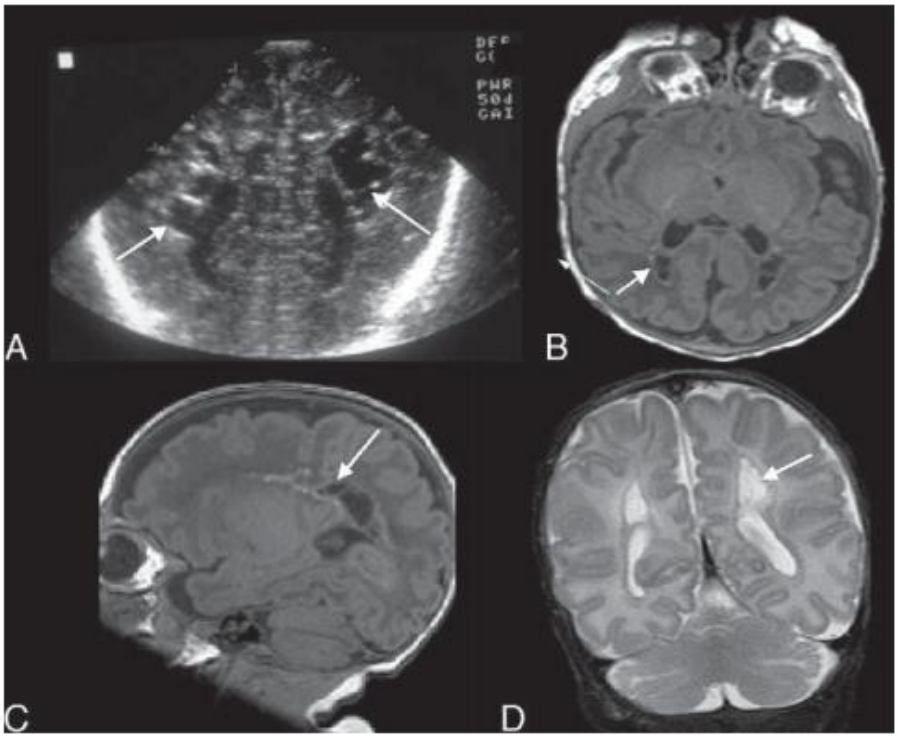

Figure 1: Early sign of periventricular leukomalacia. (A) US shows periventricular echolucencies (arrows), one of the earliest signs of periventricular leukomalacia. (B,C) On T1-weighted MRI sequences, these are seen posteriorly in the peritrigonal area and are lined by small focal regions of T1 shortening in keeping with haemorrhage (arrows).

As the cysts collapse, atrophy of the damaged brain tissue follows and this process is first detected by the demonstration of secondary ventricular dilatation; in more severe cases there is a more generalized loss of brain tissue, particularly white matter. Ventricular dilatation beyond normal limits is usually detectable by US or CT 4–8 weeks after the injury, depending on the severity of the lesions, and persists throughout life as permanent tissue loss. The features of end-stage PVL result from the decreased amount of periventricular white matter adjacent to the trigones. There is ventricular dilatation with irregular ventricular margins and the distribution is characteristically worst in the parieto-occipital regions with sparing of the frontal and temporal regions. Injury to the remaining white matter is more difficult to detect and MRI is most reliable in demonstrating these end-stage changes of PVL, 1–2 years after the injury, when the myelination process is complete or almost complete. MRI then shows abnormal signal in the remaining periventricular white matter (Fig. 2).

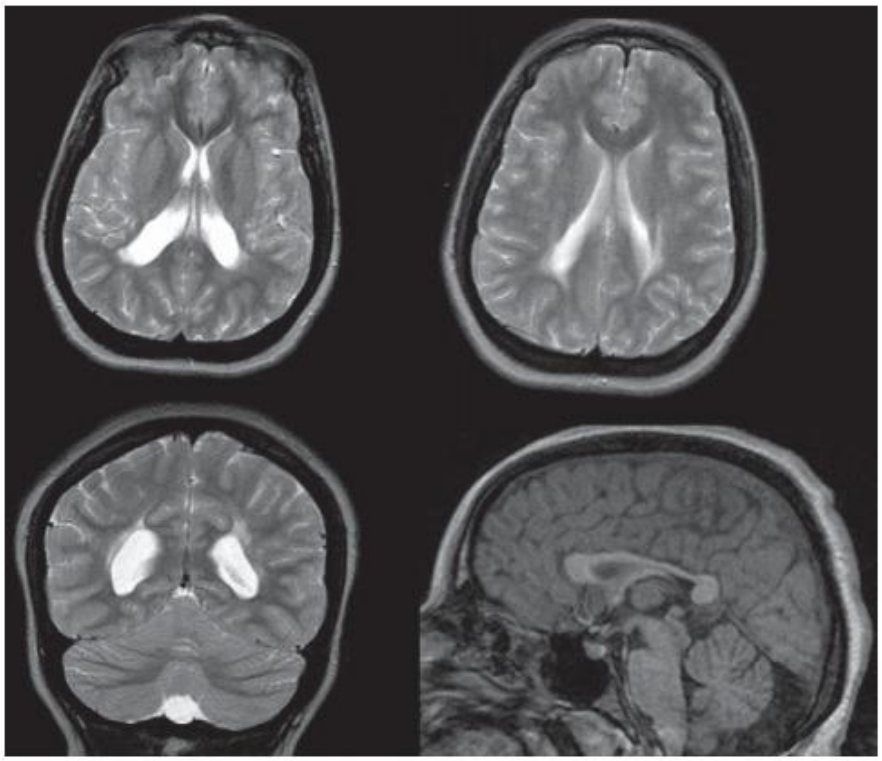

Figure 2: End-stage changes of periventricular leukomalacia. A child with spastic diplegia scanned much later in life (15 years) has the typical chronic changes of periventricular leukomalacia. There is posterior periventricular increased signal on T2-weighted images and enlargement of the ventricles posteriorly with irregular, scalloped margins, indicating white matter loss. The corpus callosum seen on the sagittal T1-weighted MRI is markedly thinned, particularly affecting the posterior body.

GM/IVH is also common in the immature brain but is possibly less significant in terms of subsequent handicap. The cause of IVH is also thought to be fluctuations in cerebral perfusion. The germinal matrix is in a process of involution after 24 weeks gestational age and its fragile vessels rupture easily. Its proximity to the lateral ventricle, from which it is separated only by ependyma, frequently results in rupture of haemorrhage into the ventricular system.

In some immature neonates with IVH, the amount of blood is excessive and it dilates the ventricle, causing congestion in the periventricular white matter, venous infarction and secondary haemorrhage. The lesions are often unilateral and anterior, and tend to occur in the group of neonates younger than 30 weeks gestational age. The findings are well seen on US which is used for grading the severity of disease. Later, resolution of the parenchymal haemorrhage results in either paraventricular cavities which may communicate with the ventricle or focal dilatations of the ventricles.

Term patterns:

The 'term' patterns of hypoxic–ischaemic injury tend to be seen in brains of about 36–42 weeks gestational age at the time of the insult. The pattern that is attributed to profound hypoxic–ischaemic injury characteristically affects the brain regions that are most metabolically active and therefore most selectively vulnerable at the time of insult. These are the posterolateral putamina, ventrolateral thalami and adjacent capsular white matter. The hippocampi, peri-Rolandic (motor and sensory) cortex and visual cortex are also often affected, and the changes are typically bilateral and symmetrical. The cerebellar vermis is also recognized as selectively vulnerable in this context. This pattern is often matched with the clinical picture of dyskinetic or dystonic cerebral palsy49-51. The injuries attributed to partial hypoxic ischaemia are seen in a parasagittal distribution, typically involving a combination of cortex and subcortical white matter, and most often across the frontoparietal regions. Whilst usually bilateral, this pattern is not uncommonly asymmetric. A characteristic region of involvement is the posterior part of the Sylvian fissures. More characteristically, the greatest injury occurs at the base of the gyri, within the depths of the sulci, resulting in focal atrophy in these areas and a pattern recognized as ulegyria (Fig. 3). As with the preterm brain, more prolonged insults are thought to result in cystic encephalomalacia (Fig. 4). The predominant involvement of the cerebral hemipheres with relative sparing of the posterior fossa structures is a pattern that favours hypoxic–ischaemic injury over other causes of global brain injury at term, such as perinatal/neonatal infection. The common clinical sequelae of this type of injury are microcephaly with severe mental retardation and spastic quadriplegia which may be asymmetric52.

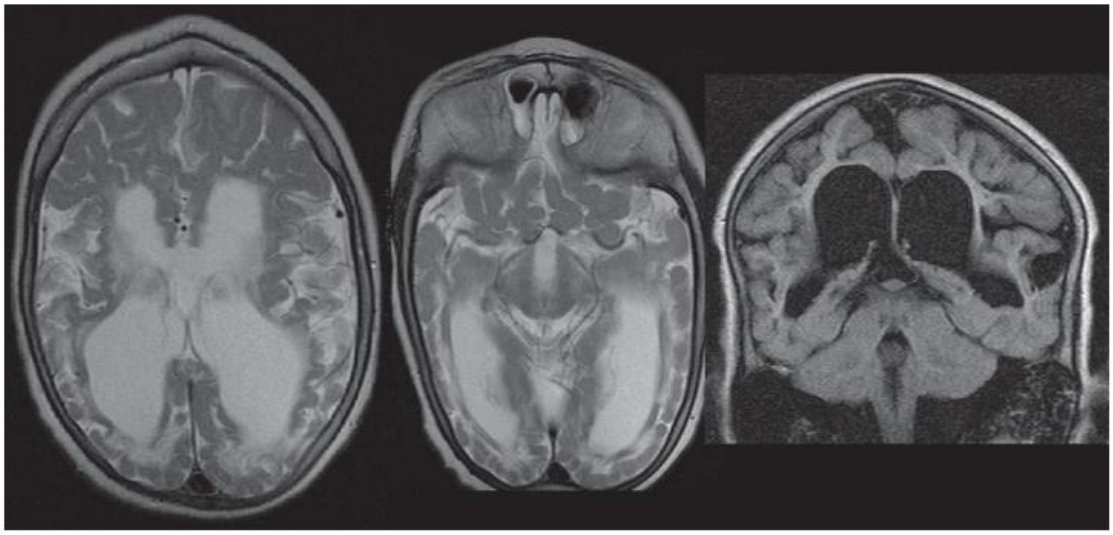

Figure 3: Hypoxic ischaemia at term, imaged in childhood. The gyri are thinner at their bases than at their apices. This is known as ulegyria and dates the hypoxic–ischaemic event to term. Note the relative preservation of the cerebellum and brainstem.

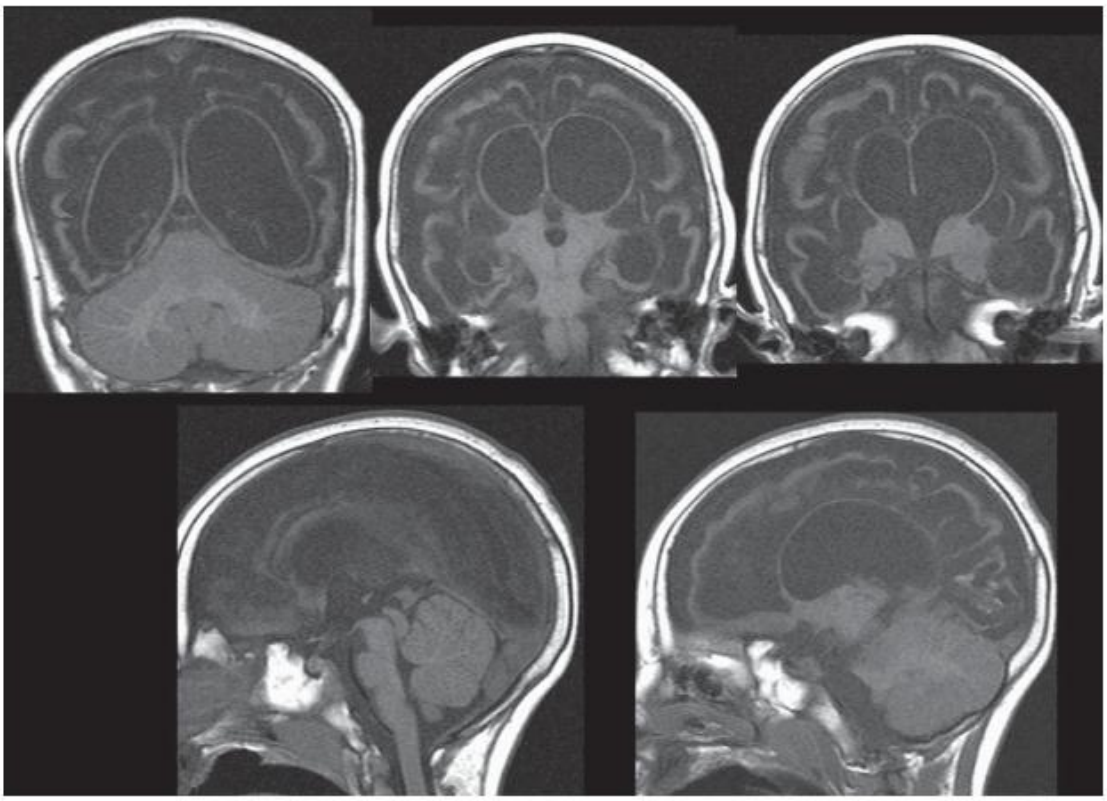

Figure 4: Prolonged hypoxic ischaemia resulting in multicystic encephalomalacia. There is cystic cavitation of most of the white matter with grossly thinned corpus callosum, leaving only a very thin rim of preserved cortical mantle.

CONCLUSION

Global hypoxia, hypotension or hypoglycaemia can damage the whole brain, usually but not always symmetrically. It is seen most often in the newborn. Two patterns are recognisable in the newborn on CT and MRI: *acute asphyxia* for more than 6 minutes results in signal changes in the thalami (not basal ganglia) and sometimes also the peri-Rolandic regions of the cerebral hemispheres; *partial asphyxia* (hypoxic ischaemic brain damage) results in periventricul ar leucomalacia in premature infants and more peripheral cortical watershed infarcts in full-term infants. In adults, patterns vary from total cerebral infarction to predominantly white matter infarction, cortical watershed or white matter terminal zone infarction, basal ganglia infarcts (especially globus pallidus), and pure cortical damage in cerebral hemisphere or cerebellum such as in severe hypoglycaemia. Severe clinical disability can occur with little or no changes on CT or MR.

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