Hypoxic-ischaemic Brain Injury in Young Infants

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Abstract

Many imaging techniques are available for the detection of hypoxic-ischaemic brain injury in young infants. This paper presents an overview of the imaging findings in hypoxic-ischaemic brain injury with an emphasis on MR imaging.

Key words: Hypoxia-ischaemia, Infants, Imaging, MR imaging, Neonates, Ultrasonography

In young infants, different types of hypoxic-ischaemic brain injury can occur.1-6 Brain injury can be localised or diffused.2-6 In localised brain injury, arterial or venous periventricular infarctions are encountered. Causes of arterial infarction in the paediatric population are coagulopathies, vasculopathies, polycythaemia, and emboli from cyanotic congenital heart disease.7 In the paediatric population, including young infants, the cause of arterial infarction is unknown in more than half of the cases.8 The infant may present with seizures, hypertonia, lethargy or motor asymmetry or the infarction may be asymptomatic, which may remain undetected until neuroimaging is performed for other reasons.7,8 Compared to adults, the prognosis in young infants with arterial infarction is generally better.7 When no underlying cause is found, the child is unlikely to have another stroke in the future and neurological prognosis, apart from the local injury, is good.7 Venous periventricular infarction is typically associated with severe germinal matrix haemorrhage in pre-term infants.7,9

Diffuse ischaemic brain injury is the result of decreased brain perfusion or hypoxaemia. This may result in diffuse or territorial ischaemic injury in full-term infants and in germinal matrix haemorrhage and/or white matter injury in pre-term infants.1,6,8,9,11-14 In full-term infants, the clinical entity is referred to as hypoxic-ischaemic encephalopathy, and has been classified into 3 grades according to Sarnat.15 In general, infants with signs of hypoxic-ischaemic encephalopathy show foetal distress prior to delivery, have abnormal Apgar scores, require resuscitation at birth, and have neurological abnormalities within the first days of life, such as feeding difficulties, irritability, abnormality of tone, seizures and decreased level of consciousness.3 In mild encephalopathy (grade 1 according to Sarnat), recovery is usually complete within 2 days.16 Children may show mild abnormalities in tone and may show tremor and/or abnormal motor development in early childhood, but usually there are no long-term sequelae.2,7,16 Infants with moderate encephalopathy (grade 2 according to Sarnat) have a 10% risk of death, and survivors have a 30% risk of disabilities.17 Surviving children may have spastic and/or dyskinetic motor impairment, generally with intellectual preservation.2,7,16 Sixty percent of infants with severe encephalopathy (grade 3 according to Sarnat) die, and many survivors, if not all, are handicapped.17 Those who do survive suffer from severe neurological abnormalities, including microcephaly, mental retardation, spastic quadriaparesis, choreoathetosis, and visual impairment.16

The clinical picture, neuroimaging findings and electroencephalography (EEG) results help to prognosticate neurological outcome in infants with hypoxic-ischaemic encephalopathy. Severe hypoxic-ischaemic encephalopathy, basal ganglia and/or widespread cortical abnormalities on neuroimaging, and severe EEG abnormalities portend a poor outcome.18,19 Fifteen to twenty per cent of all infants with hypoxic-ischaemic encephalopathy die in the neonatal period,20 and another 25% develop significant neurologic sequelae.20

Imaging Modalities

Different imaging modalities are available to detect neonatal brain injury, including cranial ultrasonography, computer tomography (CT) and magnetic resonance imaging (MR imaging).21,22 Cranial ultrasonography can be performed at the bedside, which is an advantage in unstable and/or very pre-term infants. Furthermore, this method is non-invasive and relatively low-cost. Cranial ultrasonography is particularly suitable for screening and follow-up examinations.23 It is
generally performed using the anterior fontanelle as an acoustic window. The posterior fontanelle and mastoid fontanelles can be used as acoustic windows to study the posterior fossa and brainstem. The superficial part and deep regions of the brain as well as the intracranial blood vessels can be studied with the array of available transducers. The sensitivity and reliability of cranial ultrasonography for detection of germinal matrix haemorrhage, intraventricular haemorrhage and periventricular leukomalacia are well known. Although cranial ultrasonography may not depict white matter signal abnormalities visible on MR imaging, it has better spatial resolution than MR imaging and is able to depict small cysts and striatal vasculopathy that are not apparent on MR imaging. Territorial infarction and focal white matter injury are well detected with cranial ultrasonography. Cranial ultrasonography is less sensitive to abnormalities of convexity structures and the posterior fossa. It does not give detailed information about myelination and it shows difficulty in detecting lesions of the posterior limb of the internal capsule (PLIC). There are limited data in the literature regarding comparison of the accuracy of cranial ultrasonography and MR imaging for the detection of hypoxic-ischaemic lesions in full-term infants. Duplex Doppler examination provides additional information on cerebral perfusion.

CT is not sensitive in depicting oedema and infarction in hypoxic-ischaemic brain injury because of the high water content in the newborn brain, resulting in poor contrast resolution. CT is not the modality of choice for investigating ischaemic brain injury in infants, particularly as ionising radiation is involved. On the other hand, CT affords excellent depiction of haemorrhage, such as intraventricular haemorrhage. Since cranial ultrasonography also depicts most haemorrhages, the role of CT in young infants is very limited.

MR imaging has the advantage of superbly displaying soft tissue contrast differentiation and it displays the exact extent and site of brain injury better than cranial ultrasonography. In addition, the myelination process can be assessed by MR imaging while cranial ultrasonography does not visualise myelination. However, performing MR imaging is logistically more challenging in infants than cranial ultrasonography. Consequently, MR imaging, especially serial, is not performed routinely. In imaging neonatal hypoxic-ischaemic brain injury, conventional T1- and T2-weighted pulse sequences are used most often. Due to the myelination changes associated with the maturation process of the brain, T1- and T2-relaxation times change over time in the maturing brain, leading to changing contrast between grey and white matter on T1- and T2-weighted images. During the first 6 months of life the myelination process is best visualised on T1-weighted images, whereas after 6 months T2-weighted images better reflect this process. Because of the high water content of the immature brain, fluid-attenuated inversion recovery (FLAIR) imaging is of less use in the first year after birth than in older children and adults. Only limited data are available on the value of contrast enhanced imaging in imaging hypoxic-ischaemic brain injury.

Currently, 2 useful MRI techniques are available for assessing acute hypoxic-ischaemic brain injury and used often in tertiary referral centres and large children's hospitals:

1) Diffusion-weighted imaging (DWI) makes use of the hydrogen molecule’s physical property of diffusion. Unless restricted (for instance by cell membranes and white matter fibre sheaths), diffusion occurs in all directions. DWI is sensitive in showing cytotoxic oedema. DWI may not detect brain injury if performed in the first hours after the incident, as delayed injury and late glial swelling due to delayed energy failure (also called bi-phasic energy failure) have not yet taken place. Therefore, if performed in the first 24 hours, DWI may underestimate the extent of brain injury, also when compared to MR spectroscopy. DWI is probably most sensitive 2 to 5 days after hypoxia-ischaemia. In cases without visual abnormalities on DWI, diffuse hypoxic-ischaemic brain injury cannot be excluded with certainty and a follow-up scan may be useful. In contrast to that in adults, DWI may be falsely negative in neonates due to the very long T2 values of the infant brain. It has therefore been advocated to perform apparent diffusion coefficient (ADC) measurements routinely in young infants. ADC maps are used to exclude T2 shine through as a cause for increased signal on DWI. In adults, normal brain ADC values have been published. In young infants less information is available about normal brain ADC values. ADC values measured after acute ischaemia are mostly below those of normal tissue and often remain markedly reduced for 3 to 5 days. ADC values generally return to baseline at 1 to 4 weeks. This normalisation is often referred to as ‘pseudonormalisation’. It probably reflects persistence of cytotoxic oedema, associated with decreased diffusion, and at the same time development of vasogenic oedema and cell membrane disruption, leading to increased extracellular water, associated with increased diffusion. The affected tissue is damaged and probably nonviable with persistence of high signal intensity on T2-weighted images, but with normal ADC values. This increased diffusion resulting from cell membrane disruption results in elevated ADC values. Elevated ADC values return to baseline after weeks to months. After pseudonormalisation, because of
increased diffusion due to increased extracellular water, the ADC values continue to increase and remain elevated during a longer period of months, thereafter returning to baseline.

2) MR spectroscopy (MRS) provides information on the concentrations of numerous neurochemicals. MRS is used in the evaluation of neoplasms, metabolic disease and hypoxia-ischaemia. Although MRS is one of the most sensitive methods to detect hypoxia-ischaemic brain injury, it is still not performed routinely on a large scale because of technical difficulties and lack of experience. It is not possible to routinely study the entire brain with MRS in clinical practice due to the long imaging time and technical requirements. Long echo times provide optimal evaluation and quantification of metabolites such as lactate and N-acetylaspartate (NAA). Hypoxia-ischaemia triggers anaerobic metabolism with production of lactate. Elevated lactate and reduction of NAA are seen in the first few hours after a hypoxic-ischaemic incident. If still present after 24 hours, lactate is a good indicator of permanent brain injury. However, lactate is not specific for hypoxic-ischaemic brain injury. Presence of lactate may be normal in the premature or term neonate and it decreases with maturity. As different brain regions mature differently, it is important to know the infant’s gestational age and region where the MRS spectrum was obtained. In tertiary referral centres and large children’s hospitals, DWI and MRS are used on a regular basis to investigate hypoxic-ischaemic brain injury in young infants. However, a considerable proportion of young infants with hypoxic-ischaemic brain injury are imaged in primary and secondary care centres where experience with these advanced neuroimaging techniques is limited. Consequently, cranial ultrasonography and the more conventional MR imaging techniques and pulse sequences, such as T1- and T2-weighted imaging remain the mainstay of neonatal neuroimaging today. However, detection of early hypoxic-ischaemic brain injury in young infants solely on these conventional sequences can be challenging.

Imaging Findings in Hypoxic-ischaemic Encephalopathy

Rapidly maturing and myelinating brain regions have a high metabolic demand. These metabolically active regions (brainstem, deep grey matter and peri-Rolandic region) are more susceptible to hypoxia-ischaemia than areas with a lower metabolic demand. Developing brain tissue responds to a hypoxic-ischaemic assault with anaerobic glycolysis, resulting in lactic acidosis. Oligodendrocyte progenitors are particularly susceptible to lactic acidosis. This susceptibility and the immature vascularisation of the white matter in pre-term infants explain the remarkable vulnerability of the white matter and periventricular white matter injury in these patients after moderate hypoxia-ischaemia. Injury of the periventricular white matter can be periventricular leucomalacia, both cystic and non-cystic, and a more diffuse form of white matter injury. Diffuse white matter injury is not easily detected by cranial ultrasonography but is recognised on MR imaging as signal intensity changes in the periventricular white matter and/or as small punctate lesions. In pre-term infants, white matter injury is the predominant hypoxic-ischaemic injury pattern. In a large number of infants with a gestational younger than 30 weeks, diffuse and excessive high signal intensity (DEHSI) of the white matter on T2-weighted images is seen at term equivalent age. DEHSI is commonly associated with signs suggestive of cerebral atrophy, thus it was suggested that DEHSI represents a mild form of diffuse white matter injury. Although white matter injury is the predominant hypoxic-ischaemic injury pattern in pre-term infants, injury to the basal ganglia and brain stem may be seen in these patients after profound hypoxia-ischaemia. Another frequently encountered form of brain injury in pre-term infants is germinal matrix/intraventricular haemorrhage, being the result of the metabolic high demand and high vascularity of the germinal matrix of the immature brain, often combined with haemodynamic instability and a defective coagulation in these immature patients. Due to involution of the germinal matrix with increased gestation, germinal matrix haemorrhage is unusual after 34 weeks.

Thus, the site, extent and severity of neonatal hypoxic-ischaemic brain injury depend, amongst others, on maturity and on severity of the hypoxic-ischaemic incident (profound, mild or moderate events). In (near) term infants, grey matter injury is common in profound hypoxia-ischaemia. Injury is seen in the lateral thalami, globus pallidus, posterior putamina, hippocampi, dorsal brainstem and peri-Rolandic cortex (the sensorimotor cortex), often combined with cortical and/or white matter injury (Figs. 1 and 2). In less severe cases of hypoxia-ischaemia in term infants, injury is mainly confined to the cortex and sub-cortical white matter in the intervascular boundary zones, which are the most susceptible regions in full-term infants with moderate hypoxia-ischaemia. Classically, this injury pattern has been attributed to the location of these intervascular boundary zones. In chronic repetitive hypoxia-ischaemia in (near) term infants, predominantly cortical and white matter injury (classically located in the parasagittal boundary zones) is seen. Symptoms may be discordant with the extent of the brain injury seen with imaging. Possibly, repetitive antenatal incidents prime the white matter. Thus, even after a relatively minor perinatal
incident extensive brain damage may occur.\textsuperscript{2}

Increased echogenicity in the periventricular white matter, equal or more than that of the choroid plexus, on cranial ultrasonography, is termed periventricular flare.\textsuperscript{3,7,22} In periventricular white matter injury, cranial ultrasonography can be normal in the first 2 days after the hypoxic-ischaemic incident.\textsuperscript{3,7} Thereafter it may show hyperechoic changes in the periventricular regions,\textsuperscript{3,7} which may later evolve into cystic lesions.\textsuperscript{61} Formation of cavities may typically occur 2 to 6 weeks after injury and is due to liquefaction.\textsuperscript{3,7} Cavitation is recognised as localised anechoic or hypoechoic lesions. Although serial, high quality cranial ultrasonography may also demonstrate noncystic white matter injury, it seems to be less sensitive for noncavitary white matter injury than for cystic lesions.\textsuperscript{3,7,14,16,26,55} Cranial ultrasonography demonstrates hypoxic-ischaemic injury of the deep grey matter as hyperechogenicity, mostly subtle during the first days after the incident, but more prominent several days after the hypoxic-ischaemic incident.\textsuperscript{2,7} In severe hypoxic-ischaemic brain injury, Duplex Doppler measurements of cerebral blood flow may demonstrate abnormal resistive indices. Watershed injury may be hard to detect with ultrasonography due to its location at the brain’s convexity.\textsuperscript{7}

On MR images in young infants with hypoxic-ischaemic brain injury, brain swelling, abnormal signal intensity in the brainstem, basal ganglia, thalami, and/or PLIC, and restricted diffusion can be seen (Figs. 1, 2 and 3).\textsuperscript{2,6,8,16} Other findings can be loss of the grey/white matter differentiation, white matter signal intensity changes, and cortical highlighting (high signal intensity of the cortex on T1-weighted images due to laminar necrosis).\textsuperscript{2} In cases with cortical infarctions, local loss of grey/white matter differentiation can be seen.\textsuperscript{2,7} Hypoxic-ischaemic injury to grey matter is characteristically seen as high signal on T1-weighted images and variable signal intensity on T2-weighted images. Injury to white matter is characteristically seen as low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. Conventional MR imaging may not be able to demonstrate abnormalities in the first few days after the hypoxic-ischaemic incident.\textsuperscript{62} In end-stage white matter injury, wide ventricles with irregular outline, loss of white matter, and thinning of the corpus callosum, deep sulci, delayed myelination and periventricular high signal intensity on T2-weighted images are seen.\textsuperscript{3,7} It may be difficult to detect pathology on neonatal brain MR images due to the high water content of the neonatal brain and the sometimes subtle findings of hypoxic-ischaemic lesions. The process of myelination results in signal changes on T1- and T2-weighted images which should not be mistaken for pathology.

**Current Developments**

Accumulating evidence points to an evolving intricate and complex process of brain injury after hypoxia-ischaemia with secondary energy failure as an important determinant for subsequent brain injury.\textsuperscript{20,63} Treatment options are directed to this secondary energy failure and its effects. Experimental studies revealed a therapeutic window in which neuroprotection can be initiated.\textsuperscript{20} Possible pharmacologic treatment options are directed to modulation of calcium influx, modulation of free radical formation, modulation of neurotropic factors and
neurogenesis, inhibition of apoptotic activity and reduction of inflammatory activity. Moderate hypothermia has been shown to be neuroprotective after moderate to severe hypoxia-ischaemia. Two large studies showed that infants with moderate hypoxia-ischaemic encephalopathy benefit from hypothermia either in the form of selective brain cooling or whole body cooling. Possibly combining hypothermia with pharmacologic treatment may further improve outcome in these infants. Current research also involves the possible application of stem cells.

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