Magnetic resonance imaging of preterm brain injury

S J Counsell, M A Rutherford, F M Cowan, A D Edwards

Magnetic resonance imaging (MRI) has proved to be a valuable tool for monitoring development and pathology in the preterm brain. This imaging modality is useful for assessing numerous pathologies including periventricular leukomalacia, intraventricular haemorrhage/germinal layer haemorrhage, and periventricular haemorrhagic infarction, and can help to predict outcome in these infants. MRI has also allowed the detection of posterior fossa lesions, which are not easily seen with ultrasound. Additionally, and perhaps most relevant, quantitative MR studies have shown differences between the normal appearing preterm brain at term equivalent age and term born infants, confirming that the brain develops differently in the ex utero environment. Further studies using quantifiable MR techniques will improve our understanding of the effects of the ex utero environment, including aspects of neonatal intensive care on the developing brain.

The developing brain is vulnerable to injury from many causes, resulting in significant mortality and morbidity despite recent improvements in neonatal intensive care, and at 30 months corrected age impairment can be identified in one half of all infants born at 23 weeks gestational age (GA) or less. However, even those with no identifiable disability at this age may experience learning difficulties when they enter mainstream school or have behavioural problems in adolescence.1,2

The neuropathological correlates for neurodevelopmental impairments are incompletely defined. Most of our knowledge comes from ultrasound, which shows a relation between periventricular haemorrhagic infarction (PHI) and periventricular leukomalacia (PVL) and the development of cerebral palsy. There are, however, no pathological or imaging correlates for the spectrum of neurocognitive impairments seen in the child who was born preterm.

Magnetic resonance imaging (MRI) provides an ideal and safe technique for imaging the developing brain. It is non-invasive and non-ionising and allows considerable differentiation of structures within the immature brain, showing the extensive maturation that occurs from 23 to 40 weeks gestation while these vulnerable infants are receiving intensive care. MRI shows the well recognised pathologies seen on ultrasound and in addition allows the detection of more subtle abnormalities.

Abbreviations: ADC, apparent diffusion coefficient; CSE, conventional spin echo; DEHSI, diffusion excessive high signal intensity; DWI, diffusion weighted imaging; FSE, fast spin echo; GA, gestational age; GLH, germinal layer haemorrhage; IVH, intraventricular haemorrhage; MR, magnetic resonance; MRI, magnetic resonance imaging; PHI, periventricular haemorrhagic infarction; PVL, periventricular leukomalacia; 3D, three dimensional.
The germinal matrix is visible up to around 32 weeks GA as a prominent structure along the margins of the lateral ventricles (fig 2). After this age, small residual areas of germinal matrix are visualised at the anterolateral angles of the lateral ventricles and adjacent to the head of the caudate nucleus and in the roof of the temporal horn, a site not readily visualised with ultrasound. The germinal matrix is shown as high signal intensity on T1 weighted imaging and low signal intensity on T2 weighted FSE imaging.

Myelin has been shown in numerous white matter tracts and grey matter nuclei in the preterm brain, corresponding to those sites that show myelination on histology at this age. These areas lie within the brain stem, cerebellar vermis, and the thalami. From 28 weeks GA, myelination is not visualised at any new site, until 36 weeks GA, when myelin is visualised in the corona radiata, the posterior limb of the internal capsule, the corticospinal tracts of the precentral and postcentral gyri, and the lateral geniculate bodies. We have found that T2 weighted FSE imaging is the best imaging pulse sequence to show myelin in grey matter nuclei; however, T1 weighted imaging shows myelin earlier in some white matter tracts in the preterm brain.

QUANTITATIVE MR TECHNIQUES

Recently, quantitative MR techniques have been used to assess the preterm brain, the preterm brain at term equivalent age, and the preterm brain later in adolescence. These techniques produce objective and reproducible measurements that improve our understanding of brain development and provide a more accurate correlate for neurodevelopmental outcome.

Techniques include three dimensional (3D) volumetric MR and measurements of cortical folding, which have been used to determine the increase in brain volume and cortical folding with increasing GA. Diffusion weighted imaging...
(DWI) is an MR technique which studies the Brownian motion of water in tissue and can be used to calculate apparent diffusion coefficients (ADCs), which quantify water molecular motion. Additionally anisotropy, which is a function of the directional dependence of water motion in a restricted environment, can be measured using DWI, and provides an insight into white matter structure. T1 and T2 relaxation values have also been studied in the preterm brain. MRI parameters are associated with cerebral water content, and are raised in pathology and in the immature brain.

**MRI ASSESSMENT OF CEREBRAL PATHOLOGY**

The developing brain is susceptible to injury from infective, ischaemic, and inflammatory insults. The majority of preterm infants show some evidence of brain injury on MRI in the early neonatal period. MRI has shown that there are a variety of white matter abnormalities that can be visualised in the preterm infant. It is not yet clear whether these represent a spectrum of one disorder or separate entities with different aetiological factors. These abnormalities may be related to factors such as poor nutrition, steroids, and infection, which are known to affect development of the preterm brain.

**DIFFUSE WHITE MATTER ABNORMALITY**

The majority of preterm infants at term equivalent age appear to have areas of diffuse excessive high signal intensity (DEHSI) within the cerebral white matter (fig 3). These changes are most marked in the periventricular white matter, but may be evident throughout the white matter. Assessment of these changes is difficult with visual analysis as the appearances are markedly influenced by the windowing used prior to image processing. This has led to strategies that allow a more objective measurement. DWI has shown raised ADC values in the cerebral white matter in infants with DEHSI compared to preterm infants with normal white matter, suggesting that DEHSI represents diffuse white matter disease. ADC values were comparable with those obtained from infants with obvious white matter pathology such as PVL and PHI. It is unclear what causes the increase of ADCs in DEHSI, but it may be due to vasogenic oedema, oligodendrocyte damage, or a reduced axonal diameter. DEHSI represents one of the many differences between the preterm brain at term equivalent age and the brain of the term born infant. Quantitative MR techniques may be used to further delineate these differences.

**PERIVENTRICULAR LEUKOMALACIA**

PVL is a histological diagnosis with “softening” of the white matter and focal cystic degeneration. Its incidence is 3–9% in preterm infants. Traditionally, PVL was thought to be due to ischaemia, but recent studies have suggested an infective cause. PVL is shown as periventricular regions that are hypointense on T1 weighted imaging and high signal intensity on T2 weighted imaging in the early neonatal period. These areas may become cystic and lead to dilatation of the lateral ventricles, particularly in the region of the posterior parietal white matter adjacent to the occipital horn. Additionally, areas of short T1, presumably a haemorrhagic component, have been identified in the acute/subacute stage. DWI has identified PVL as areas of high signal intensity, representing restricted diffusion, before cysts were evident on ultrasound. Additionally, Roelants-van Rijn and colleagues reported high signal intensity on DWI adjacent to cystic areas, which we have also seen in an infant at 32 weeks GA with PVL (fig 4A–C). On histology, these areas were found to be undergoing active degeneration with cytotoxic oedema, apoptosis, and macrophage infiltration. We have noted increased T1 and T2 relaxation values in the white matter adjacent to cystic areas, probably representing more diffuse white matter damage. Chronically, DWI shows low signal areas in the affected white matter. At this time ADCs are elevated, representing frank cystic lesions and areas of vasogenic oedema. By term equivalent age, the cystic lesions are often incorporated into the lateral ventricles, resulting in the characteristic squared off appearance of the posterior horns (fig 4D). Frequent associated findings are thalamic atrophy and abnormal signal intensity within the PLIC. The latter may help predict neuromotor outcome.

PVL is associated with delayed myelination, which is probably caused by extensive glial necrosis and oligodendrocyte dysfunction as a consequence of white matter injury.
Intraventricular/Germinial Layer Haemorrhage

The appearance of haemorrhage on MRI depends on the age and site of the haemorrhage, and the pulse sequence used (Table 1). Haemorrhage usually arises from a glial lesion in preterm infants, and is the most common form of intracranial neonatal haemorrhage. The incidence of IVH in preterm infants increases with decreasing birth weight. IVH often occurs in association with thrombophilic disorders, such as factor V Leiden heterozygosity, and IVH has recently been established. GLH is shown as low signal on T2weighted imaging (Figure 6) and high signal intensity on T1weighted imaging. GLH may occur at any site along the immature ventricle wall, but most commonly arises from the periventricular parenchyma, and the caudate head and the roof of the temporal horn. It can be differentially diagnosed from the germinial layer by irregular appearance, and it is slightly more hypointense on T2weighted imaging. The low signal intensity on T2weighted imaging may persist for several months because of the presence of haemosiderin. GLHs were shown in one third of preterm infants on MRI in the early neonatal period. It is thought that this lesion may damage oligodendroglial progenitors and disrupt their migration, potentially resulting in impaired myelination. A further consequence of GLH may be damage to astrocytic precursors bound for the upper layers of the cerebral cortex, and thereby impairment of cortical neuronal development. Neurological outcome in infants with IVH depends largely on the severity of the haemorrhage and the site of any parenchymal infarction.

Periventricular Haemorrhagic Infarction

Blood in the cerebral white matter is drained by the medullary veins, into the veins of the germinial matrix, and finally into the terminal veins. Periventricular haemorrhagic infarction (PHI) probably occurs as a consequence of obstruction of venous drainage and subsequent infarction of the white matter. Diminished cerebral blood flow in the periventricular white matter has been shown by positron emission tomography, and Doppler ultrasound has shown reduced blood flow velocity in the terminal vein on the affected side, suggesting impaired venous drainage. The periventricular haemorrhage is shown as a fan shaped structure, due to obstructed medullary veins, of low signal intensity on T2weighted imaging (Figure 7). Parenchymal haemorrhagic infarction results in interruption of projection and association fibres and oligodendroglial damage, which disrupts myelination. PHI and large GLHs may also affect the subplate neuronal layer, which is related to the extent of the lesion. It is possible that injury to the subplate neuronal layer may result in cognitive delays and attention deficits in this group of infants.

Table 1: Evolution of signal intensity in parenchymal haemorrhage

<table>
<thead>
<tr>
<th>Age of haemorrhage</th>
<th>T1 weighted imaging</th>
<th>T2 weighted imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 days</td>
<td>Not seen/high signal intensity</td>
<td>Low signal intensity</td>
</tr>
<tr>
<td>3–10 days</td>
<td>Not seen/high signal intensity</td>
<td>Low signal intensity (with high signal intensity periphery)</td>
</tr>
<tr>
<td>10–21 days</td>
<td>High signal intensity</td>
<td>High signal intensity</td>
</tr>
<tr>
<td>3–6 weeks</td>
<td>High signal intensity</td>
<td>High signal intensity (with low signal intensity periphery)</td>
</tr>
<tr>
<td>6 weeks – 10 months</td>
<td>Not seen/ minimal high signal intensity</td>
<td>Not seen/low signal intensity</td>
</tr>
<tr>
<td>10–22 months</td>
<td>Not seen</td>
<td>Minimal low signal intensity/ not seen</td>
</tr>
</tbody>
</table>

Figure 5  [A] Transverse T1 weighted image of an infant at 29 weeks GA showing a high signal lesion adjacent to the optic radiation on the left (arrow). (B) Transverse T2 weighted FSE image showing the lesion as low signal (arrow).

Figure 6  Transverse T2 weighted FSE image of an infant at 27 weeks GA showing bilateral germinial layer haemorrhages (arrows).
Although brain volume in preterm infants at term was similar to that of infants born at term, the surface area of the cortex and cortical folding was reduced in preterm infants. Additionally, Peterson et al. showed reduced volumes of the basal ganglia, corpus callosum, amygdala, hippocampus, and cerebellum in preterm infants at 8 years of age compared with term born controls. These findings provide objective evidence that brain development differs in preterm infants compared to infants born at term.

Quantitative MR techniques are also providing an insight into the effects of drugs; for example, 3D volumetric MRI has shown a reduction in cortical grey matter volume in preterm infants treated with dexamethasone when compared to untreated preterm infants, implying that dexamethasone impairs cortical grey matter development. Similar findings have been reported in term infants exposed to multiple doses of antenatal steroids.

**References**


