

CURRENT TOPICS

Magnetic resonance imaging in perinatal asphyxia

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Introduction

The purpose of this review article is: (i) to recall the impact of perinatal asphyxia and its consequences on child development; (ii) to establish the diagnostic benefit of magnetic resonance imaging (MRI) and to compare it with other imaging modalities; (iii) to summarise the range of imaging patterns viewed on different brain scans and to discuss their aetiology; (iv) to describe the evolution of characteristic MRI findings observed during the early postnatal period and during later childhood; and (v) to estimate the role of MRI in predicting later neurodevelopmental outcome.

Acute perinatal asphyxia refers to a condition of hypoxaemia, hypercapnia and insufficient blood perfusion of the newborn during labour and birth. It is considered to be the 'single most important perinatal cause of neurological morbidity'.¹ Perinatal asphyxia and its consequences have an incidence of 2-9%, in term neonates,² which is very much higher in premature babies, causing not only neurological impairment, but also behavioural problems and intellectual deficits.³ Depressed fetal heart rate, meconium stained amniotic fluid, low Apgar scores, low scalp and cord pH, or clinical signs of neurological depression soon after birth signify the acute clinical condition of the newborn. The predictive value of the clinical features for later neurodevelopmental outcome is, however, rather disappointing. Affected neonates present with a characteristic, although non-specific, syndrome called hypoxic-ischaemic encephalopathy (HIE). They may be initially hyperalert, or often lethargic, with diminished muscle tone and spontaneous movements. They demonstrate poor suck, apnoea, and other signs of brainstem dysfunction, or in severe cases, they are comatose, with seizures beginning within hours of birth. The death rate in term infants with HIE is around 11%, and as many as 60% of affected premature newborns die. Moreover, 20-30% of survivors suffer from mental retardation, cerebral palsy, and seizure disorders in later childhood.³

Despite major advances in obstetric and neonatal care, the prevalence of cerebral palsy has not decreased over the past decade.⁴ About 10-15% of children who later develop cerebral

palsy have intrapartum insults with symptoms of HIE during the first week of life. In an appreciable number of children with cerebral palsy in utero hypoxia-ischaemia must therefore have preceded the perinatal period, which caused neither maternal symptoms nor relevant HIE in the newborn.^{5,6} Sarnat has developed a grading system for HIE, based on neurological evaluation in the newborn period, which helps to differentiate babies with favourable outcome from those with a poor prognosis for developing neurological sequelae.⁷ Although it has been of great prognostic value for infants with mild HIE and those with severe encephalopathy, the prognosis of moderately affected infants is less certain. Moreover, many babies with HIE require intensive care and artificial ventilation during the first days of life, and are not accessible to clinical evaluation.

Importance of MRI compared with other techniques

In an attempt to improve diagnostic value and prognostic power, recent efforts have been directed towards investigatory techniques such as real-time ultrasound scans, Doppler ultrasound scans, computed tomography scans, and magnetic resonance spectroscopy.

Ultrasound scanning is an easily applicable bedside tool and has been used extensively as a screening method in preterm infants.^{8,9} Although the signs of HIE are often short-lived and end stage periventricular leucomalacia is inadequately assessed, ultrasound scanning still has some predictive value, particularly when periventricular-intraventricular haemorrhage is present.¹⁰⁻¹² However, it has low sensitivity in term babies with HIE, and correlation with spastic diplegia is not good unless cystic lesions are detected, which severely limits its prognostic value.¹³⁻¹⁵ In several studies the assessment of blood flow velocity in the anterior cerebral artery using Doppler ultrasound scanning has shown a high positive predictive value, but long term follow up has not been done.^{16,17} Some authors believe that characteristic post-ischaemic cerebral lesions can be delineated on computed tomography only beyond the age of 6 months, although the maximum extent of acute cerebral oedema and necrosis has been

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Figure 1 MRI scan of acute and chronic periventricular white matter injury. T1 (A) and T2 (B) weighted images of an asphyxiated 28 weeks' gestational age infant performed during the second week of life show hyperintensity and hypointensity, respectively (arrows), in the periventricular white matter. First echo (C) and second echo (D) from a study performed at age 19 months shows diminished periventricular white matter with irregularly enlarged ventricles and abnormal hyperintensity (arrows).

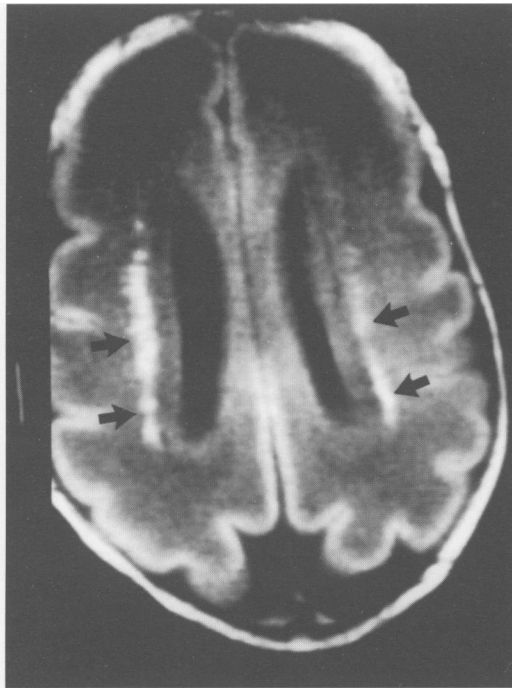


Fig 1A

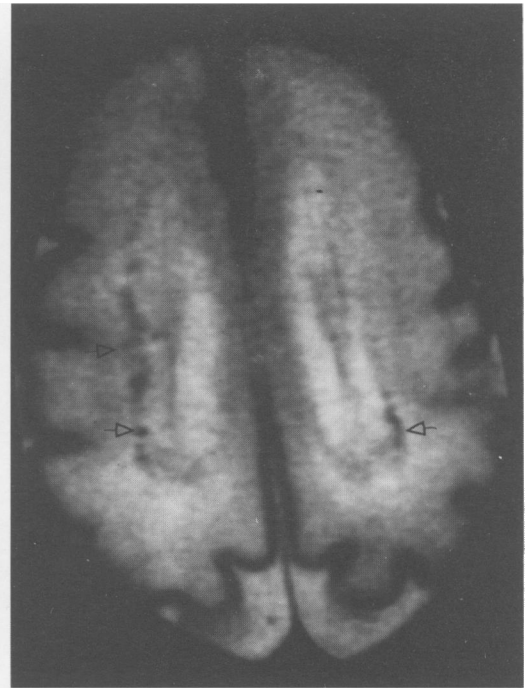


Fig 1B

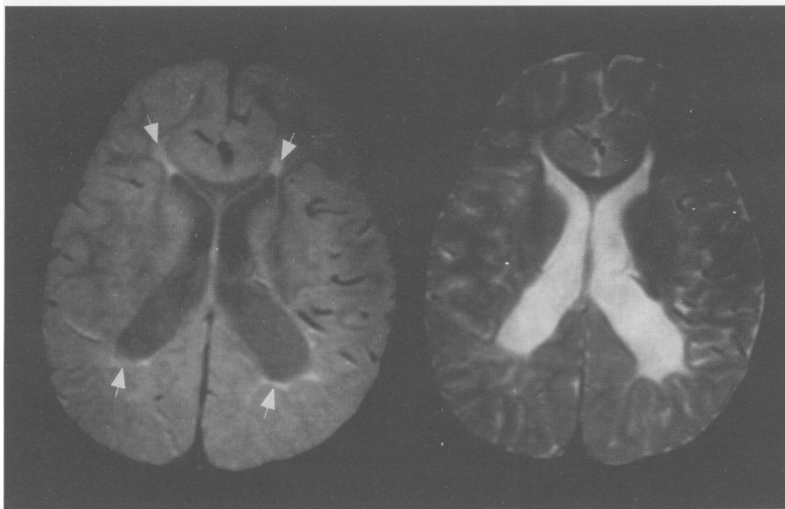


Fig 1C

Fig 1D

demonstrated between two and four days of the insult, and generalised decreased tissue density (particularly thalamic hypodensity) in early postnatal computed tomography clearly predicted an unfavourable outcome in term infants.¹⁷⁻¹⁹

Because of higher sensitivity and specificity to maturational changes, such as visualisation of myelination and changes in cerebral structures, MRI has had an enormous impact on neurological imaging.²⁰⁻²¹ Although expensive and sometimes difficult to perform in acutely ill newborns, MRI overcomes many of the shortcomings of ultrasound scanning and computed tomography.²²⁻²³ It has a higher sensitivity and has been extremely valuable in assessing the extent of hypoxic-ischaemic brain damage during the early postnatal period and later infancy.²²⁻²⁴⁻²⁶ It also is more specific, clearly differentiating fluid filled cavities,

oedema, gliosis and haemorrhage.²⁷ Moreover, it can provide better anatomical resolution, particularly in the basal ganglia, thalamus, and in the periphery of the cerebral cortex. MRI might be the only method to diagnose hypoxic brain injuries in mild to moderately affected patients, and to detect discrete lesions of the cerebellum and the brain stem. The large normal variability in the progress of myelin deposition²⁰⁻²¹⁻²⁵ sometimes makes the interpretation of delayed myelination by early neonatal MRI difficult, especially on inversion-recovery images.²⁴ However, delayed myelination, as a likely consequence of neuronal destruction, is a predictor of later longterm neurodevelopmental outcome, and thus is of considerable importance.

Retrospective studies on children with cerebral palsy, in which the magnetic resonance examination was carried out when the brain showed an adult pattern of myelination – for example, beyond 2 years of age – demonstrate abnormalities of the brain in over 90%.²¹⁻²⁹⁻³⁰ In children born prematurely a strong correlation was found between:

- (i) reduction in the amount of white matter in the centrum semiovale and in the periventricular area;
- (ii) periventricular prolongation of T2 relaxation; and
- (iii) ventricular dilatation and the severity of motor disability. Although a close relation between HIE, periventricular leucomalacia, and delayed myelination in MRI with the degree of motor impairment in premature infants could be demonstrated, the correlation with cognitive outcome seems somewhat weaker.³¹⁻³³ Lesions in basal ganglia and thalamus correlate strongly with athetotic cerebral palsy, most probably caused by asphyxia. Cerebral palsy in children born at term seems to have its origin in acute perinatal

Figure 2 MRI scan of acute and chronic boundary zone injury in term (41 week) infant. (A) and (B) At age 4 days, T2 weighted images show abnormal high signal in the cortex at the vascular boundary zones (arrows). (C) and (D) At age 3 months, the cortex is thin, the subcortical white matter too bright, and the subarachnoid spaces enlarged in the vascular boundary zones.

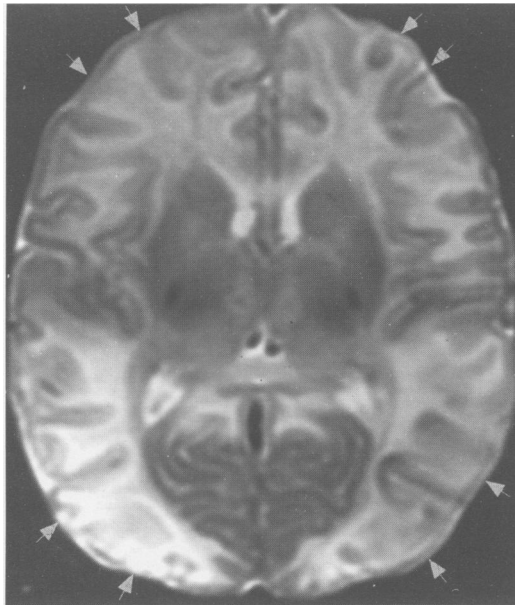


Fig 2A

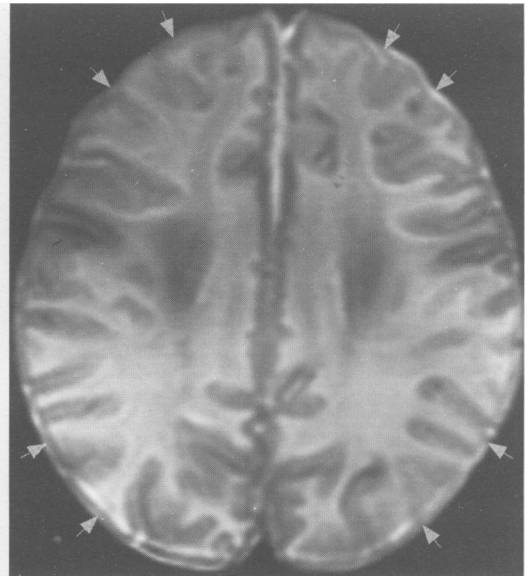


Fig 2B

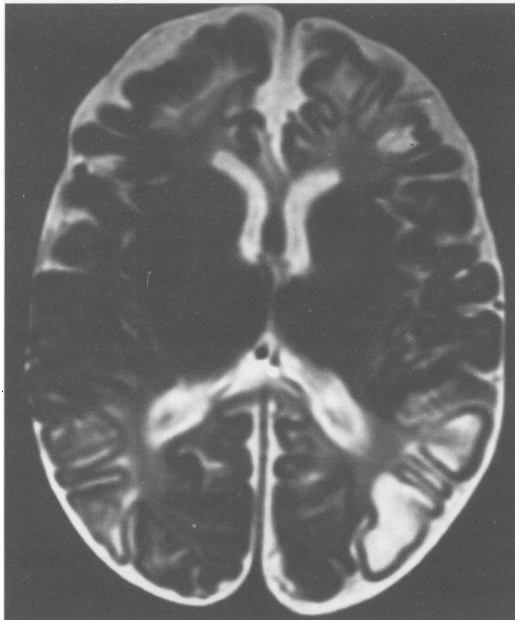


Fig 2C

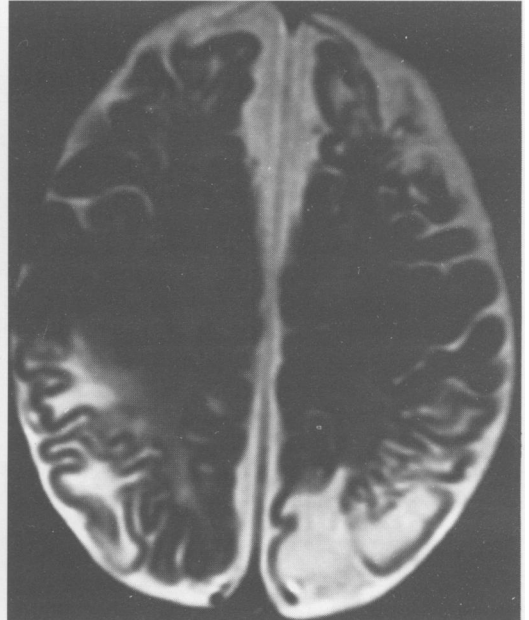


Fig 2D

Figure 3 MRI scan of chronic deep grey matter and perirolandic injury. (A) T2 weighted image at the level of the basal ganglia shows high signal (arrows) in the ventrolateral thalami and posterior putamina. (B) T2 weighted image at the high cerebral level shows high signal (arrows) in the perirolandic region.

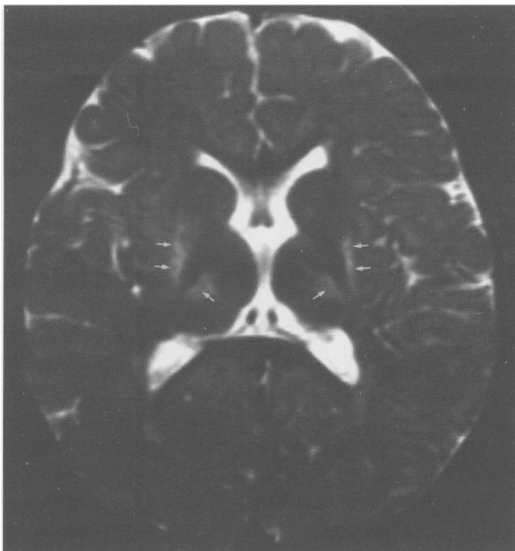


Fig 3A

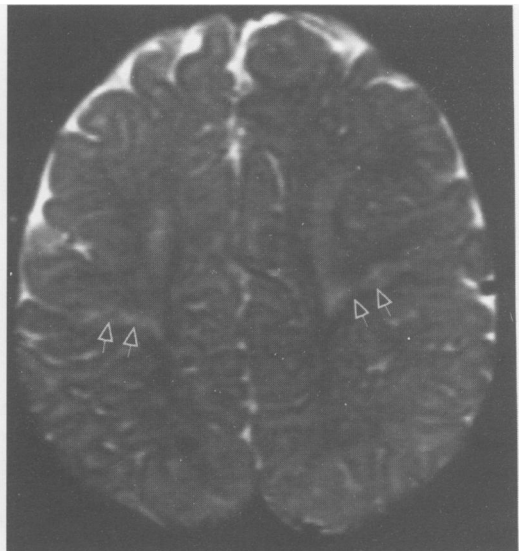


Fig 3B

Figure 4 MRI scan of acute deep grey matter and perirolandic injury in term infant, age 5 days. (A) Abnormal high signal is seen in the globi pallidi, putamina, and ventrolateral thalami and the normal high signal of the posterior limb of the internal capsule is not seen on this T1 weighted image. (B) T2 weighted image shows abnormal high signal in the lateral thalami but is otherwise nearly normal. (C) Transverse T1 weighted image at the upper cerebral level shows abnormal high signal (arrows) in the deep portions of the pre- and postcentral gyri.

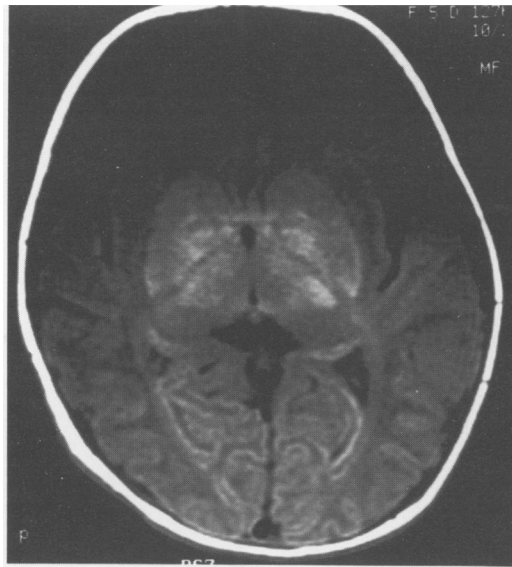


Fig 4A

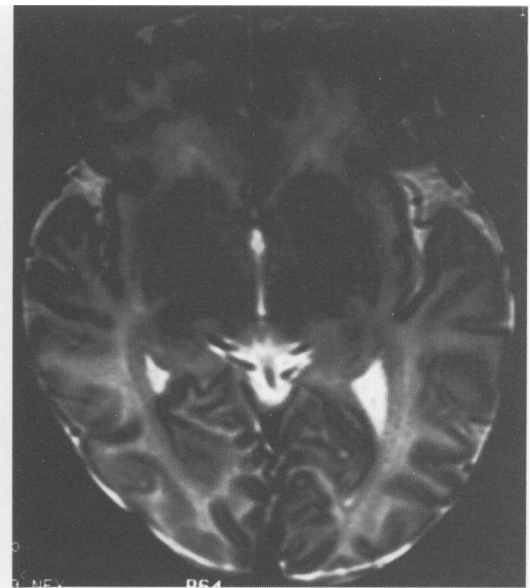


Fig 4B

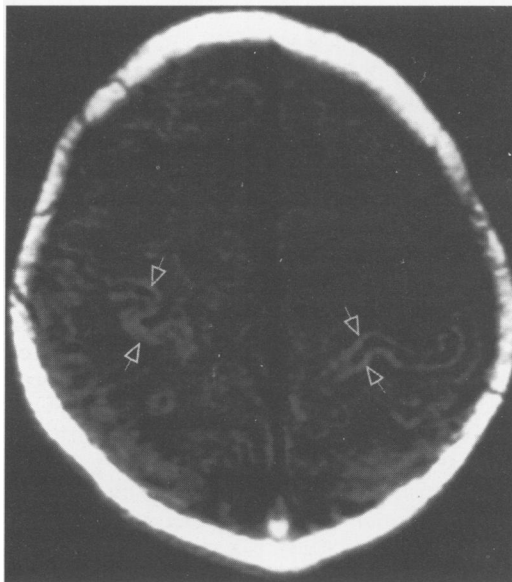


Fig 4C

asphyxia in only 15 to 25%. Moreover, the MRI scan shows a more heterogeneous pattern, ranging from cortical dysplasia to focal infarcts and atrophy, or basal ganglia lesions, depending on the timing of the asphyctic event during gestation.

Hypoxic-ischaemic brain lesions

As neurons are particularly vulnerable to oxygen and glucose deficiency, cerebral lesions are either a direct consequence of hypoxia-ischaemia or gradually develop during recovery, when excitatory amino acids, mainly glutamate, and calcium ions have an important destructive role.^{34 35} Several distinct neuropathological patterns of ischaemic brain injury have been observed, depending on the gestational age of the child and the severity of the insult:

(i) selective neuronal necrosis of the cortex,

predominantly the hippocampus, and also of deep grey matter nuclei;

(ii) leucomalacia of periventricular and subcortical white matter; and

(iii) focal or more generalised infarction.

There is a dynamic evolution of any hypoxic-ischaemic injury, and the MRI pattern develops gradually until the final stage is achieved. The clinician urgently needs early information about the severity of HIE because important decisions on continuation of intensive care measures and potential therapeutic interventions are being considered at that time. Therefore, the issue of optimal timing for MRI becomes crucial.

Patterns of injury and their aetiology

The pattern of injury that results from HIE in the neonate, as determined by MRI, seems to depend primarily on two factors: (i) the gestational age – the maturity of the brain, at the time of the injury; and (ii) the duration and severity of the hypoxic-ischaemic insult.

PARTIAL ASPHYXIA

When injury is caused primarily by mild or moderate hypoxia or hypotension, injury seems to occur in regions that have the most tenuous perfusion.²⁴ The periventricular white matter is most severely affected in infants of less than about 34 weeks' postconceptional age (fig 1).^{24 36–40} By 40 weeks, the mature intervascular boundary zones (the most peripheral zones of the areas perfused by the anterior, middle, and posterior cerebral arteries) are affected. Included in these zones are the periventricular white matter, subcortical white matter, and cerebral cortex in the boundary regions (fig 2).^{24 37 41 42} The deep grey matter structures of the cerebrum are typically spared in these patients.

The patterns observed on MRI scans suggest that the injury is caused by simple

Figure 5 MRI scan of subacute or chronic deep grey matter injury at age 8 weeks. T1 (A) and T2 (B) weighted images show loss of periventricular brain tissue. The basal nuclei are shrunken and show abnormal patchy high signal on T1 weighted image and abnormal patchy low signal on T2 weighted image (arrows).

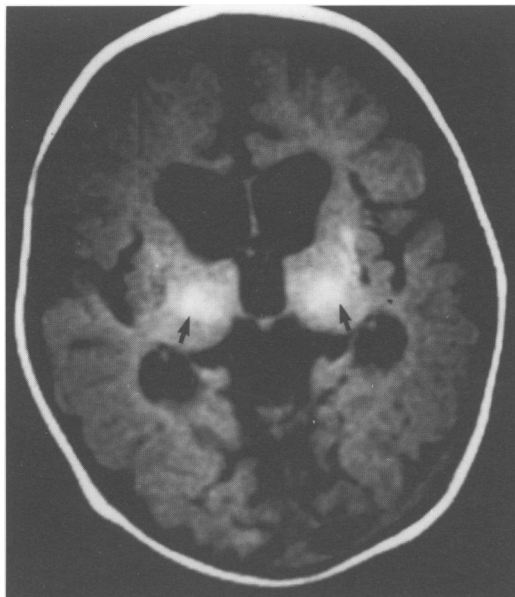


Fig 5A

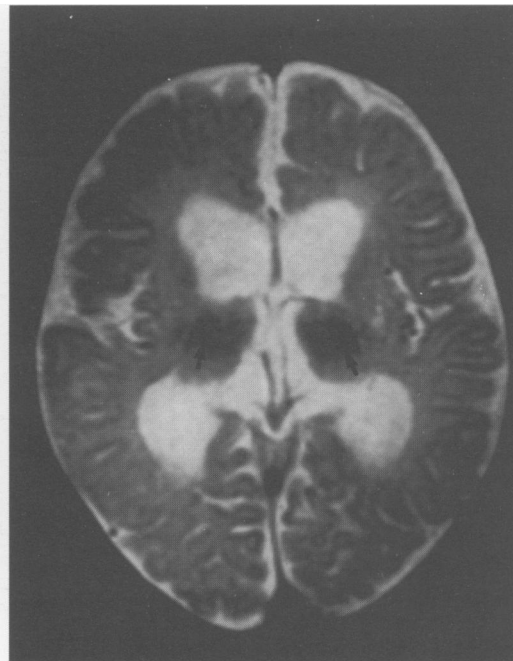


Fig 5B

hypoperfusion, perhaps as a result of impaired autoregulation. Some authors have suggested that the change in pattern of injury from exclusively periventricular (with cortical sparing) to largely cortical or subcortical is the result of maturation of the cerebral vasculature.^{36-39, 40} These postulated changes in the cerebral vascular supply during the last trimester have been disputed.⁴⁴⁻⁴⁵ Others have suggested that the periventricular injury in premature neonates is the result of oligodendrocyte development in the germinal zone during the first half of the last trimester, consequent increased metabolic demands in the periventricular zone, and, perhaps, vulnerability of oligodendrocytes to the excitatory amino acids produced by ischaemia.⁴⁶⁻⁴⁸ This controversy has a greater impact on the proposed mechanism of injury than on the observation that the region of injury varies with brain maturity.

PROFOUND ASPHYXIA

A different, more complex, pattern of injury is produced when injury is the result of a more severe event, such as cardiocirculatory arrest or profound hypotension. The MRI imaging findings in these patients correlate well with reported pathological studies.^{22, 49, 50} The pattern of injury in this group of neonates varies with postconceptional age (brain maturity) of the affected child, as it does in infants who have partial asphyxia. However, the regions of brain affected are quite different. The volume of damaged brain also seems to vary with the duration of the injury in profoundly asphyxiated neonates. An arrest of long duration (25 minutes or greater) damages nearly the entire brain; no useful patterns can be detected by imaging. Arrests of shorter duration, however, show specific patterns that vary with the state of brain maturity. Profound injuries to infants of about 26 to 32 weeks' postconceptional age result in injury primarily to the lateral

thalami. By 34 to 36 weeks, the lentiform nucleus and hippocampus are injured and, in some patients, the perirolandic cortex. By 40 weeks, the corticospinal tracts are affected from the internal capsule to the perirolandic cortex (fig 3). More severe or more prolonged events result in injury to the optic radiations.

The regions of brain injured in profound asphyxia correlate temporally and topographically with the progression of myelination and of metabolic activity within the brain at the time of the injury. The ventral lateral thalamic nuclei and pallidothalamic fibres begin to myelinate by about 25 weeks' gestational age.⁵¹ The lentiform nuclei and the pre- and postcentral gyri stain for myelin at 35 weeks and the optic radiations at 37 weeks. The posterior limb of the internal capsule and the subcortical white matter of the postcentral gyrus show evidence of myelination at 40 weeks.⁵¹ It would be expected that metabolic activity would increase as myelination proceeds. Although no studies have described localised cerebral metabolic activity in preterm infants, localised glucose metabolism has been reported in term infants using positron emission tomography (PET) measurements of 2-deoxy-2-[18F]fluoro-D-glucose.⁵² In this study term neonates showed highest metabolic activity in the thalami, basal ganglia, and the primary sensorimotor areas of the cerebral cortex (the pre- and postcentral gyri). The relation between the location of myelination and the location of brain injury in the asphyxiated neonate can be explained by another mechanism. Axons in the immature nervous system can substantially regenerate after injury.⁵³ However, some myelin components seem to inhibit axonal growth.⁵⁴ It is therefore possible that the brain is diffusely injured by profound asphyxetic events and that only those

Figure 6 MRI scan of normal newborn. (A) T1 weighted image through the level of the basal ganglia shows that the high signal (arrows) of the posterior limb of the internal capsule is the brightest on the image. This high signal merges imperceptibly with the ventrolateral thalamic and posterior putaminal high signal. (B) T2 weighted image at the level of the basal ganglia shows low signal, indicating myelination, in the ventrolateral thalami (large open arrows), dorsal putamina (large closed arrows), and posterior limb of the internal capsules (small arrows). (C) T2 weighted image at the upper cerebral level shows more pronounced low signal in the pre- and postcentral gyri, indicating the presence of myelination in those structures.

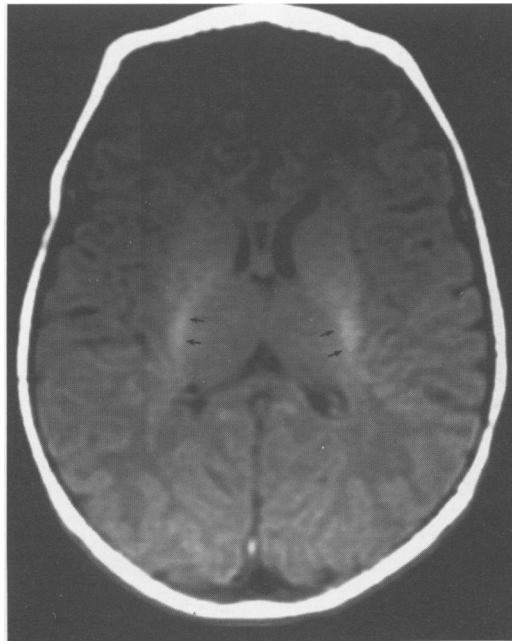


Fig 6A

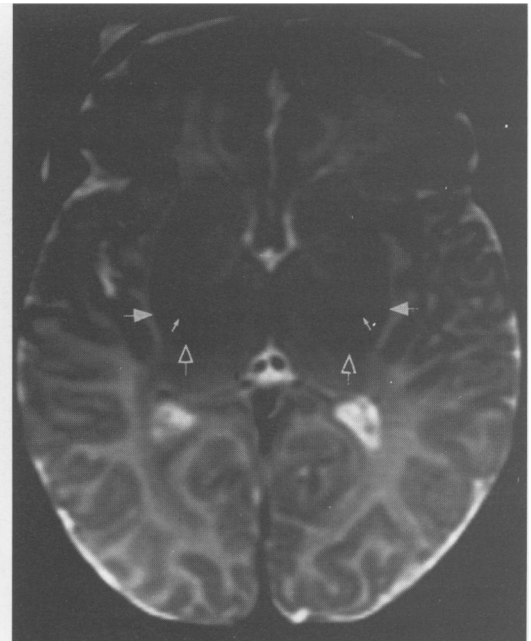


Fig 6B

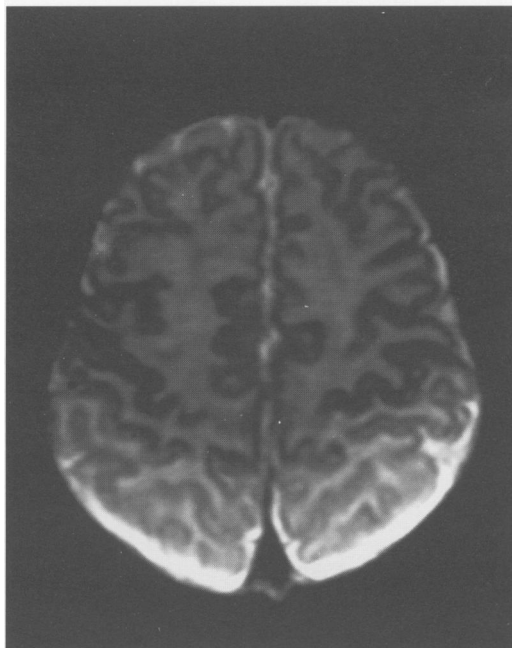


Fig 6C

regions that are myelinated are unable to regenerate.

Evolution of MRI observations

There are few published reports about the changes that occur in the MRI signal intensity of the cerebral parenchyma after hypoxic-ischaemic injury of the newborn infant. Reports of findings in term infants in all stages after asphyctic injury can be found,²²⁻²⁵ but reports of MRI findings in asphyxiated premature infants almost exclusively focus on subacute and chronic changes.^{24 55 56} Therefore, this discussion will focus primarily on the evolution of MRI findings in asphyxi-

ated term infants. MRI scans performed within the first two to three days after injury show low signal on T1 weighted images and high signal on T2 weighted images in the affected regions. In term infants with profound asphyxia signal changes are seen in the lentiform nuclei and along the corticospinal tracts; in term infants with partial asphyxia the changes are seen in the vascular boundary zones (fig 2). By four to five days, T1 shortening becomes evident in the affected regions (fig 4). This becomes quite pronounced by about seven days after the injury. It remains present for a variable time, almost always for at least four weeks and sometimes for as much as eight or 10 weeks after the injury (fig 5). T2 shortening (low signal on T2 weighted images) slowly develops during the first month and lasts for two to three months (fig 5). Notably, the location of the lentiform nuclei signal abnormalities in infants with profound neonatal asphyxia is subtly different at the age of 2 to 3 months than in the first few weeks after the injury. They are located in the lateral thalami and posterior putamina (fig 5). As the T1 and T2 shortening gradually disappear, the injured areas of brain show tissue loss with low signal intensity on T1 weighted images and high signal on T2 weighted images (fig 3).

The MRI signal abnormalities associated with asphyctic brain injury can be subtle and difficult to detect in the first few days of life. In patients with profound asphyxia injury tends to occur in those areas that are myelinating or myelinated. Unfortunately, identification of injured regions of brain is hampered by the fact that the signal characteristics of myelin, with respect to the unmyelinated brain, are similar to those of the damaged tissue. Two imaging features are helpful in distinguishing the normal from the damaged brain in these patients. The first is the appearance of the internal capsule. In the normal newborn the posterior

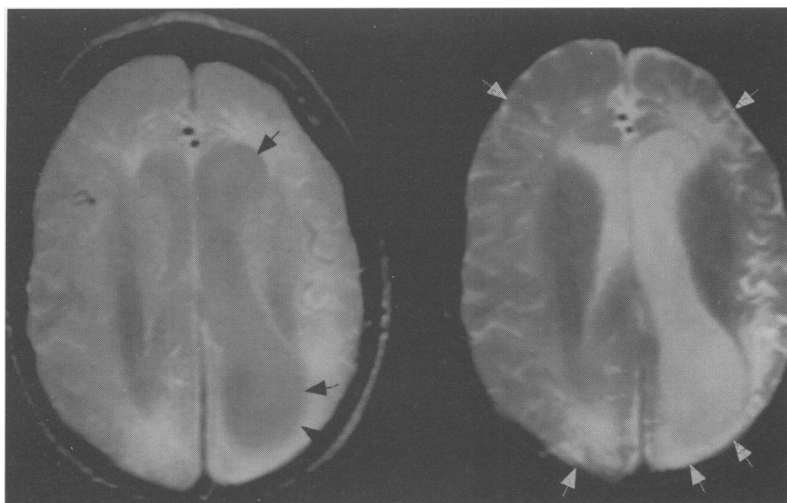


Fig 7A

Fig 7B

Figure 7 Chronic boundary zone injury. First echo (A) and second echo (B) T2 weighted images show cortical thinning and high signal of the white matter in the vascular boundary zones (white arrows) and ventricular enlargement (black arrows). Asymmetric injury is seen more commonly than symmetric injury.

limb of the internal capsule is bright on T1 weighted images; it cannot be distinguished from the myelinated ventrolateral thalamic nucleus medially, or the myelinating posterior putamen laterally (fig 6). In the asphyxiated newborn the posterior limb of the internal capsule is hypointense relative to the high signal in the thalamus and putamen (fig 4). Moreover, the globus pallidus is sometimes bright in the asphyxiated newborn. The second helpful feature involves the differentiation of the normal short T1 and T2 seen in the neonatal pre- and postcentral gyri from the short T1 and T2 of damaged gyri. In the normal newborn the altered signal (bright on T1 weighted images and dark on T2 weighted images) is seen along the length of the gyrus. In the asphyxiated newborn, the altered signal is greater in the deepest portion of the affected gyrus (fig 4), an area known to be more severely affected in asphyxia injury.⁵⁷

The MRI findings are also subtle in term neonates with partial asphyxia. The major finding on MRI in these neonates is oedema within the affected cortex. Because oedematous cortex has a higher water content than normal cortex, it has longer T1 and T2 relaxation times (darker on T1 weighted images and brighter on T2 weighted images). The damaged cortex, therefore, becomes isointense with the subjacent unmyelinated white matter. The appearance is one of apparently discontinuous cortex (fig 2). Unless the entire cerebral cortex is scrutinised for these areas of discontinuity, the damaged regions may be missed.

Although it is accepted that the T1 and T2 prolongation in acutely damaged tissue is the result of oedema, the cause or causes of the T1 and T2 shortening in the subacute phase is not firmly established.²² Some attribute it to haemorrhage,²³ but it would be unusual for parenchymal haemorrhage to remain unchanged in size and signal intensity over a period of one to two months, as is seen on MRI

scans of asphyxiated newborns. Possible causes of short T1 and T2 other than haemorrhage include the presence of lipids from myelin breakdown, T1 shortening secondary to myelin clumping (status marmoratus), and dystrophic calcification. Lipid is an unlikely source in view of the small amount of lipid present in the newborn brain and the lack of chemical shift artefact (which should, theoretically, be present when lipid protons are situated next to water protons) on those MRI studies that have been analysed. Myelin clumping, known to occur in the basal ganglia after profound asphyxia,⁵⁸ could cause accentuated T1 shortening of water protons in the region. Another possibility is that petechial haemorrhage, present in the early phases after injury, slowly undergoes dystrophic calcification as the blood products are resorbed. This process would explain the slight change in the location of abnormal signal without substantial change in the signal characteristics. Future studies may help to elucidate better the cause of the signal changes.

As the patient ages and the brain myelinates damaged areas become more difficult to identify by changes in signal intensity on T1 weighted images. Instead, regions of focal atrophy must be detected. Damaged areas are difficult to detect on T2 weighted images before adequate myelination has occurred. In particular, signal abnormalities are difficult to detect on T2 weighted images before the age of 8 to 10 months.⁴¹ As myelination progresses and the brain becomes more hypointense on T2 weighted images, areas of damage become more conspicuous, appearing as regions of T2 prolongation (figs 3 and 7). The damaged foci remain hyperintense on T2 weighted images for decades afterward.^{22 24}

Prognostic value of early MRI

Several prospective studies have tried to compare acute hypoxic-ischaemic cerebral lesions evaluated with MRI shortly after birth with later MRI patterns, stages of myelination, and neurodevelopmental outcome of the child.^{23 25 26 59} Although there is much debate about the usefulness of early MRI in a clinically unstable asphyxiated neonate, we strongly believe that MRI can provide excellent morphological information about the cerebral injury. This information allows outcome to be anticipated in most cases, based on location, extent, and severity of the principal ischaemic damage and the occurrence of secondary lesions like oedema, haemorrhage, or thrombosis, even in the acute neonatal period.^{56 59} In our experience a normal MRI obtained in the first 24–72 hours always predicts a favourable outcome even in a severely asphyxiated baby. On the other hand, extensive brain oedema with effacement of the cortical ribbon or lesions in the ventro-lateral thalamic nuclei and the dorsal striatum have a poor outcome, irrespective of birth variables, such as Apgar score or cord pH. In some patients the prognostic value can be improved by repeating the study after several weeks

to months, when delayed myelination and structural damage can be appreciated more easily.^{60 61} As myelin is produced by oligodendrocytes which are dependent on oxygen and nutrient supply, early detection of delayed myelination is possible, and important for predicting neurodevelopmental outcome, such as cerebral palsy. Yet it has to be borne in mind that MRI by itself remains a morphological method, and that either degenerative or ongoing destructive processes, or reparative brain plasticity, can only be estimated.

This work was supported by the Swiss National Foundation, grant No 32-37811.93.

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