Brain magnetic resonance imaging and outcome after hypoxic ischaemic encephalopathy

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Abstract

Objective: To correlate pattern of injury on neonatal brain magnetic resonance imaging (MRI) with outcome in infants ≥36 + 0 weeks gestation with hypoxic ischaemic encephalopathy.

Methods: Prospective cohort study. Images were blindly reviewed. Children were assessed using a variety of standardised assessments.

Results: MRI brain was performed on 88 infants. Follow up was available in 73(83%) infants. Eight of 25(32%) children with normal imaging had below normal assessment scores. Eight infants (12%) had isolated punctate white matter lesions and five of these had abnormal assessment scores. Death and cerebral palsy were seen only in children with imaging scores ≥3 on basal ganglia/thalami (BGT) score or ≥4 on watershed score. No developmental concerns were raised in 3/7(43%) infants with isolated watershed injury. Ten of 13(77%) infants with isolated BGT injury died or developed cerebral palsy. All 23 children with posterior limb of the internal capsule (PLIC) injury displayed developmental difficulties.

Conclusions: Almost one-third of infants with a normal MRI brain may be at risk of developmental problems. Punctate foci of white matter injury are common and not always benign. PLIC involvement is usually associated with neurological sequelae including isolated cognitive deficits. Worst outcomes are associated with basal ganglia injury.

Keywords
Basal ganglia, patterns of injury, PLIC, watershed

Introduction

Difficulty accurately defining both birth asphyxia and cerebral palsy has led to wide disparity in estimates of the proportion of cerebral palsy attributed to birth asphyxia [1]. However, it is widely accepted that birth asphyxia in term infants causes 10–15% of cases of cerebral palsy (CP) [1–3].

In the last 15 years, magnetic resonance (MR) techniques – including MR imaging (MRI), diffusion tensor imaging and proton MR spectroscopy – have become the techniques of choice in the study of brain injury in term infants [4,5]. MR is widely reported as the most sensitive tool and shows a good association with neurodevelopmental outcome [4,6]. MRI findings, together with clinical examination and if available electroencephalogram, assist in clinical decision making, such as withdrawal of care and referral to multidisciplinary developmental teams. A number of scoring systems have been introduced in an attempt to evaluate imaging findings and predict outcome [7,8].

The objective of this study was to correlate pattern of injury on neonatal MR brain images with long-term outcome in infants’ ≥36 + 0 weeks gestation with hypoxic ischaemic encephalopathy (HIE).

Methods

Participants

Newborns ≥36 + 0 weeks gestation admitted with HIE in the first 48 h after birth between January 2001 and December 2008 were identified. Infants born between January 2001 and July 2005 (98 infants) were identified retrospectively from intensive care admission records, ward journals and radiology records. Those admitted between July 2005 and December 2008 (147 infants) were identified prospectively. HIE was graded as grade 1, 2 or 3, according to Sarnat and Sarnat grading [9]. HIE was defined by the presence of encephalopathy with onset from birth and evidence of intrapartum or antepartum brain hypoxia and ischemia. Biochemical evidence of multi organ injury (raised liver transaminases, creatinine, lactate dehydrogenase and creatinine phosphokinase) was used to support the diagnosis [10]. Newborns with any primary cause for encephalopathy other than hypoxia-ischaemia were excluded. Placental histology was available on 56(64%) of included newborns with MR imaging [11]. All the babies had negative blood cultures. The study design and details of this population have been previously described [12].
Magnetic resonance imaging scans were performed on all the infants with HIE grade 2 or 3 and in infants with Grade 1 HIE and abnormal cranial ultrasound findings. MRI scans (GE signa 1.5 Tesla LX) were done with sagittal and axial T1 inversion recovery, (TR 1966, TE 8 and TI 750) and axial T2 sequence (TR 4520 and TE 200). Diffusion imaging was also performed (B = 0, B = 1000). S.R. (consultant paediatric radiologist) and M.D.K. (consultant paediatric neurologist) blindly reviewed brain MRI. These images were scored as described by Barkovich et al. [8] (Table 1). Some infants had injury which did not fit into the above scoring system and were classified as ‘other’ pattern of injury.

Table 1. MR brain injury scoring classification [8].

| Basal ganglia injury score                      |    |
|-----------------------------------------------|----|
| Normal or isolated focal cortical infarct      | 0  |
| Abnormal signal in thalamus                   | 1  |
| Abnormal signal in thalamus and lentiform nucleus | 2  |
| Abnormal signal in thalamus, lentiform nucleus and perirolandic cortex | 3  |
| More extensive involvement                    | 4  |

| Watershed score                              |    |
|----------------------------------------------|----|
| Normal                                       | 0  |
| Single focal infarction                      | 1  |
| Abnormal signal in anterior or posterior watershed white matter | 2  |
| Abnormal signal in anterior or posterior watershed cortex and white matter | 3  |
| Abnormal signal in both anterior and posterior watershed zones | 4  |
| More extensive cortical involvement          | 5  |

**Neurodevelopmental assessments**

All the infants were invited to attend for neurodevelopmental assessments. Children with CP were assessed using the Gross Motor Function Classification Scale (GMFCS) and manual ability classification system (MACS). Children >42 months of age without CP were assessed using the NEPSY 2 (A Developmental NEuroPSYchological Assessment), Movement Assessment Battery for Children 2 (MABC2), Behaviour Rating Inventory of Executive Function (BRIEF) and Child Behaviour Checklist (CBCL). These assessments were individually scored. Any child who obtained a score within the borderline or clinical range had all the assessment scores reviewed by a senior clinical neuropsychologist. The senior clinical neuropsychologist then decided whether the assessments represented difficulties likely to be of clinical significance.

Children <42 months age without CP were assessed using the Bayley Scales of Infant/Toddler Development 3 (BSITD3). For children assessed with BSITD3, borderline developmental delay was defined as a scaled score 5–7; composite score equivalent 55–70 and percentile 5th–16th. Significant developmental delay was defined as a scaled score 1–4; composite score equivalent 55–70 and percentile 0.1–2nd.

Details of individual assessment scores and definitions for borderline and clinical abnormalities within each assessment are outlined in Table 3.

**Patterns of injury**

Magnetic resonance imaging brain was performed on 88 study infants in the neonatal period. Age at time of scan ranged from 2 to 42 days, with a median age of 6 days and mean age of 7.4 days. About 78/88(88.6%) scans were performed within 10 days of birth. Early scans (i.e. day two or three after birth) were performed on 13(14.8%) newborns.

Abnormalities were seen on conventional (T1 and/or T2) sequences only in seven subjects. Mean and median day of imaging were 7.6 and 8 days, respectively (minimum 2 days and maximum 16 days) for these subjects. Abnormalities were seen on diffusion-weighted sequences only in two infants. Both of these subjects were imaged on day 2 after birth. Abnormalities were seen in both diffusion imaging and conventional imaging in remaining 41 infants. However, in general, abnormalities were more readily appreciated viewing diffusion-weighted sequences and may not have been fully appreciated on conventional sequences alone.

Imaging was normal in 38(43.1%) infants and abnormal in 50(56.9%). Thirteen infants (14.7%) had an isolated basal ganglia/thalami (BGT) pattern of injury, nine (10.2%) had an isolated watershed pattern of injury and a mixed pattern of BGT and watershed injury was found in 14(15.9%) infants. The posterior limb of the internal capsule (PLIC) was affected in 23(26.1%) scans (Table 2). Fourteen (15.9%) infants had MRI abnormalities that did not fit into the classical watershed or BGT patterns of injury. The results of neonatal and follow-up MRI and outcome of these infants are detailed in Supplementary Tables 1 and 2. Eight infants with injury classified as ‘other’ (Supplementary Table 1; subjects A–H), had changes that are best described as punctate hemorrhagic foci in the white matter.

**Ethics**

Ethical approval was obtained from the Ethics committee of the Rotunda Hospital. Parents of children who attended for assessments or agreed to chart review have given informed consent to the research and to publication of the results.

**Results**

From January 2001 to December 2008, 245 newborns ≥36 + 0 weeks gestation were admitted with HIE in the first 48 h after birth. Of these, 237 newborns were studied. One-hundred fifty-five infants had grade 1 encephalopathy, 61 infants had grade 2 encephalopathy and 21 infants had grade 3 encephalopathy. Eighty-eight newborns underwent MRI (18 with grade 1 HIE, 58 with grade 2 HIE and 12 with grade 3 HIE). An Apgar score of <5 at 10 min and/or continued need for resuscitation (including endotracheal or mask ventilation) at 10 min after birth and/or acidosis within 60 min of birth (defined as any occurrence of umbilical cord, arterial or capillary pH <7.10) was present in 74/88(84%) of newborns with MR brain imaging. Nineteen (22%) newborns had a documented sentinel event (1 cord prolapse, 5 significant abruption, 1 uterine rupture, 2 substantial ante-partum haemorrhages and 10 shoulder dystocia). Clinical seizures were documented in 63(72%) newborns (single seizure15 and recurrent 48).

Imaging was normal in 38(43.1%) infants and abnormal in 50(56.9%). Thirteen infants (14.7%) had an isolated basal ganglia/thalami (BGT) pattern of injury, nine (10.2%) had an isolated watershed pattern of injury and a mixed pattern of BGT and watershed injury was found in 14(15.9%) infants. The posterior limb of the internal capsule (PLIC) was affected in 23(26.1%) scans (Table 2). Fourteen (15.9%) infants had MRI abnormalities that did not fit into the classical watershed or BGT patterns of injury. The results of neonatal and follow-up MRI and outcome of these infants are detailed in Supplementary Tables 1 and 2. Eight infants with injury classified as ‘other’ (Supplementary Table 1; subjects A–H), had changes that are best described as punctate hemorrhagic foci in the white matter.
Representative images of BGT, watershed, mixed and “other” patterns of damage are shown in Supplementary Figures 2–6. Normal scans were seen in seven infants, four had isolated BGT injury, six had a mixed pattern and scans of two infants were classified as “other” pattern of injury. Isolated watershed damage was not seen in this group. Transient hypoglycaemia (glucose <1.6) was present in nine subjects. Imaging was normal in five of these subjects. One had isolated basal ganglia injury and punctate foci of injury were found on imaging the remaining three subjects.

Neurodevelopmental outcome
Outcome was not available in 15 infants due to emigration (6) and lack of contact details (7) or refusal of parents to participate in the study (2) (Table 3). Therefore, follow up is available in 73(83%) of 88 infants with neonatal MRI. Parents of eight infants declined study assessments but consented to information from phone enquiry and chart review: one child has a diagnosis of ADHD and a specific learning disorder in reading and mathematics; one child was attending specialist services with moderate learning disability. The third child was developmentally normal.

Normal MRI
Magnetic resonance imaging brain was normal in 38 infants. Outcome was available on 25/36(69%) infants with normal neonatal MRI (Supplementary Figure 1). No infant with a normal MRI died or developed CP, epilepsy or autism. The remaining eight children had scores which fell below the normal range (Table 3 and Supplementary Figure 1).

Basal ganglia/thalami pattern of injury
Thirteen infants had an isolated BGT pattern of injury. Outcome on all of these infants is known (Supplementary Figure 1). Three infants died in the neonatal period. The remaining 10 children attended for follow-up assessments. Seven (54%) children were diagnosed with CP at >24 months of age. In those without CP, one child scored at or above the normal range on all the domains using BSITD 3 at 16 months of age. The remaining two children had significant abnormalities on neurodevelopmental assessments (Table 3). No child without CP had epilepsy or autism.

Watershed pattern of injury
Nine infants had an isolated watershed pattern of injury. Outcome on 7/9(77.7%) of these infants is known (Supplementary Figure 1). One infant developed mild CP (GMFCS1 and MACS 2). Parents of three children declined study assessments but consented to phone enquiry and chart review: one child has a diagnosis of ADHD and a specific learning disorder in reading and mathematics; one child was attending specialist services with moderate learning disability. The third child was developmentally normal.

Two children <42 months assessed with BSITD 3, scored within or above the normal range. One child >42 months assessed with NEPSY, CBCL, MABC2 and BRIEF, scored within the clinical range of difficulty on the CBCL (Table 3).

Mixed pattern of injury
Fourteen infants had a mixed pattern of injury. Outcome is available for all the infants with this pattern of injury (Supplementary Figure 1). Cerebellar injury was noted only with a mixed pattern of injury and present in five infants. Cerebellar changes were seen on diffusion-weighted imaging only and cerebellar volume was normal in all the cases (Supplementary Figure 5). In total, five infants with a mixed pattern of injury died in the neonatal period, all with evidence of cerebellar injury. Three children developed CP.
Three children <42 months were assessed with BSITD3 and two showed borderline delays. Two children >42 months had abnormal NEPSY2 scores. The first child scored in the clinical range on movement ABC, CBCL and BRIEF and has epilepsy. The second child scored in the borderline range on CBCL. On parental report, the remaining child is attending specialist developmental services with a diagnosis of moderate learning disability and poor motor skills.

"Other" pattern of injury

Imaging was classified as “other” pattern of injury in 14 infants. None of these infants died in the neonatal period. All 14 children attended for follow-up assessment (Supplementary Figure 1).

Three (31.4%) infants developed CP. One child had epilepsy and abnormal scores on NEPSY2 assessment. Two children had autism. Eight of 11 children without CP, had assessment scores below the normal range. Three children scored at or above the normal range (Supplementary Figure 1 and Table 3).

Detailed injury score and outcome

Posterior limb of internal capsule involvement

Isolated PLIC injury was not seen, always being associated with lesions elsewhere. The PLIC was abnormal in 23 infants, 20 of whom had a BGT pattern of injury. All 23 infants had an abnormal outcome. Six infants (26%) died in the neonatal period. Seventeen children attended study assessments.

| MRI Pattern of Injury | Normal | Basal ganglia/thalami | Watershed | Mixed | Other | Total |
|-----------------------|--------|-----------------------|-----------|-------|-------|-------|
| **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** | **%** | **n** |
| Outcome | | | | | | | | | | |
| Death | 0 | 0 | 3 | 21 | 0 | 0 | 5 | 36 | 0 | 0 | 8 |
| Cerebral palsy | 0 | 0 | 7 | 50 | 1 | 11 | 3 | 21 | 3 | 21 | 14 |
| Epilepsy (isolated) | 0 | 0 | 0 | 0 | 0 | 0 | 1*** | 7 | 1*** | 7 | 2** |
| Diagnosed autism | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2††† | 14 | 2††† |
| Abnormal assessment | 8 | 38 | 9 | 64 | 2 | 22 | 7 | 50 | 11 | 79 | 37††† |
| Normal assessment | 13 | 62 | 1 | 7 | 2 | 22 | 1 | 7 | 3 | 21 | 20 |
| Normal | 13 | 22 | 1 | 7 | 2 | 22 | 1 | 7 | 3 | 21 | 20 |
| Total | 13 | 34 | 0 | 0 | 2 | 22 | 0 | 0 | 0 | 0 | 15 |

Assessments

| Assessments | BSITD 3 | | | NEPSY 2 | | | Movement ABC | | | Child behaviour checklist | |
|-------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| | Normal | Borderline delay | Significant delay† | Total assessed | | | Normal | Borderline | Clinical abnormality# | Total assessed | |
| | **n** | **%** | **n** | **%** | **n** | | **n** | **%** | **n** | **%** | **n** | |
| | | | | | | | | | | | | |
| BSITD 3 | | | | | | | | | | | | |
| Normal | 8 | 1 | 2 | 1 | 0 | 12 |
| Borderline delay* | 2 | 0 | 0 | 2 | 2 | 6 |
| Significant delay† | 2 | 0 | 0 | 0 | 0 | 2 |
| Total assessed | 12 | 1 | 2 | 3 | 2 | 20 |
| NEPSY 2 | | | | | | | | | | | | |
| Normal | 4 | 0 | 1 | 0 | 4 | 9 |
| Abnormal‡ | 4 | 2 | 0 | 2 | 5 | 13 |
| Total assessed | 8 | 2 | 1 | 2 | 9 | 22 |
| Movement ABC | | | | | | | | | | | | |
| Normal | 6 | 1 | 1 | 1 | 5 | 14 |
| Borderline* | 2 | 0 | 0 | 2 | 4 |
| Clinical abnormality§ | 1 | 1 | 0 | 1 | 3 |
| Total assessed | 9 | 2 | 1 | 2 | 7 | 21 |
| Child behaviour checklist | | | | | | | | | | | | |
| Normal | 3 | 0 | 0 | 0 | 4 | 7 |
| Borderline|| | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Clinical abnormality# | 5 | 2 | 1 | 1 | 3 | 12 |
| Total assessed | 8 | 2 | 1 | 2 | 7 | 20 |
| Brief | | | | | | | | | | | | |
| Normal | 1 | 0 | 1 | 0 | 1 | 3 |
| Borderline** | 3 | 0 | 0 | 0 | 1 | 4 |
| Clinical abnormality†† | 2 | 1 | 0 | 1 | 2 | 6 |
| Total assessed | 6 | 1 | 1 | 1 | 4 | 13 |

*Scaled score 5–7; Composite score equivalent 75–85; Percentile 5th–16th.
†Scaled score 1–4; Composite score equivalent 55–70; Percentile 0.1–2nd.
‡Scores >1.5 SD below mean.
*Total test percentile rank 5th–15th percentile.
††Total test percentile rank <5th percentile.
||t score 65–69.
#t score <65.
**t score 50–65.
†††t score <50.
***Both children with epilepsy had borderline delays on assessments.
| | | | | | | | | | | | |

Includes children with Cerebral Palsy.
Ten of 23 (43%) developed CP. One child developed autism. Both children <42 months assessed with BSITD 3, scored below the normal range. Four children >42 months assessed with NEPSY2 had abnormal scores. Three of the four assessed with CBCL were in the clinical or borderline range as was the child assessed with BRIEF questionnaire. Two of three children (without CP) assessed using the MABC2, scored in the normal range.

**Injury scores**

Death and CP were seen only in the children with scores ≥3 on BGT score or ≥4 on watershed (WS) score (Supplementary Table 3). Three of four infants with a BGT score of 1 or 2 and three of six infants with a WS score of 1 or 2 who attended assessments were classified as having an abnormal outcome. No child with a total score (BGT + WS score) ≥4 was classified as having a normal outcome.

**Discussion**

As expected more extensive damage and higher image injury scores were associated with poorer outcomes. However, a normal neonatal MR did not guarantee a normal neurodevelopmental outcome. One-third of infants (8 of 25) with normal MRI had clinically significant developmental delay. Only 1/13 newborns with early imaging (i.e. day 2 or 3 after birth) had a normal MRI. This child had a normal BSITD3 at 30 months of age. As the majority of the remaining scans were performed between day 5 and day 10, timing of MRI is unlikely to have greatly influenced the predictive value of a normal study. The detailed neuropsychological assessments applied in this study probably exposed subtle, yet significant cognitive difficulties which may not be detected by other assessments. This may explain why the percentage of children classified as having difficulties despite a normal MRI is higher than previous studies. Belet et al. [13] found that a normal neonatal MRI was associated with a normal outcome at 4 years of age. However, in that study, there were only four infants with a normal MRI and development was assessed using Bayley and Denver developmental tests in addition to blinded examination by a paediatric neurologist. Robertson et al. [14] in a meta-analysis of the prognostic accuracy of cerebral MR biomarkers in which outcomes were defined as favourable (normal or mild disability) or unfavourable (death or severe/moderate disability) concluded that early conventional MRI had poor discriminatory power with late MRI having a very high sensitivity (97%) but low specificity (56%). In keeping with the present study, van Kooij et al. [15] found a weaker association between a normal/mildly abnormal MRI result and normal outcome, but that study was limited as the cohort was imaged between 1993 and 1997 without diffusion-weighted imaging. In the present study, although the cohort is larger than many previous studies, the numbers are small and the developmental delays seen may be due to other genetic or environmental factors.

Focal non-cystic white matter injury is increasingly recognised in populations of term newborns with HIE [16]. In keeping with other reports [17,18], punctate haemorrhagic white matter lesions were frequently associated with later developmental problems, suggesting that this type of injury is not always benign.

Isolated watershed injury was less common than isolated BGT injury. This pattern was seen only in grade 2 encephalopathy and never with an acute sentinel event. It is possible that this study underestimates the incidence of isolated watershed injury as infants with this type of injury may present with milder symptoms [19] and therefore may not have reached criteria for imaging. In three of seven infants (42.9%) with an isolated watershed injury, no developmental concerns were raised. The finding that injury in a watershed distribution in term-born neonates is not invariably associated with adverse sequelae is in keeping with recent reports [19,20]. Three infants had problems which only became evident with time [ADHD (1), learning disability (1) and behavioural problems (1)]. The concept that these infants “grow into their deficits” has been described [18–22] with a wide range of cognitive, visual, language and behavioural difficulties being associated with more severe grades of watershed injury [23]. Our study supports these findings.

In contrast, children with an isolated BGT pattern of injury had poor outcomes. Even mild BGT injury (BGT injury scores of 1 or 2), while not associated with death/CP, was associated with abnormal outcomes. Three of four children (75%) with mild BGT injury had abnormalities detected on assessment. In contrast, three of six children (50%) with mild watershed injury (WS injury scores 1 or 2), were considered normal. This is in keeping with Perez et al. [21] who found BGT and perirolandic region scores showed the strongest correlation with the presence of a major disability. This confirms previous reports that severity of outcome appears to depend on the extent of basal ganglia involvement [21,22,24–27].

Infants with a mixed pattern of injury were more likely to die in the neonatal period. This MRI pattern probably reflects the most severely affected children. The high mortality may explain why the rate of CP, in this group was lower than that found with an isolated BGT injury. In keeping with previous studies, cerebellar injury was uncommon and associated with very poor outcomes [28]. As cerebellar injury was seen only in infants with extensive global ischemia this likely reflects the severity of insult rather than the cerebellum being an independent factor.

As described by others [22,24,28,29], involvement of the PLIC was highly associated with BGT pattern of injury and usually associated with adverse outcome. Motor difficulties predominated although sequelae were not limited to motor deficits. This is consistent with recent studies suggesting that children with a history of neonatal encephalopathy remain at increased risk of cognitive deficits even in the absence of functional motor deficits [15].

**Limitations**

The neurodevelopmental assessments applied in this study do not screen specifically for autism. Autism was reported only when children already had a formal diagnosis of autism. This study was performed prior to the introduction of therapeutic hypothermia. Therapeutic hypothermia reduces seizure burden in infants with mild and moderate injury [30].
In addition, there is a trend towards more normal scans in infants treated with therapeutic hypothermia [31]. Whether these effects alter the predictive value of MRI following HIE is unclear.

Conclusions

Almost one-third of infants with a normal MRI brain in the initial neonatal period may be at risk of developmental problems. Death/CP is seen only in the children with more extensive damage (BGT $\geq 3$ or WS scores $\geq 4$). The pattern of punctate foci of injury within the white matter is common in HIE and not always associated with a benign outcome. Involvement of the PLIC is a poor prognostic sign usually associated with neurological sequelae including isolated cognitive deficits.

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Declaration of interest

The authors report no declarations of interest.

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Supplementary material available online.
Supplementary Figures 1–6 and Tables 1–3.