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Imaging of Hypoxic Ischaemic Encephalopathy in the term neonate

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1 Introduction

In 2000 an encephalopathic neonate who had been exposed to an episode (or episodes) of hypoxia/ischaemia (HIE) would probably have been imaged with a cranial ultrasound and may have received an MRI in selected teaching hospitals. MRI would probably not have been used in neonatal units without teaching hospital paediatric MR units.

The cranial ultrasound would have allowed assessment for hydrocephalus, germinal matrix and intraventricular haemorrhages, parenchymal cysts, mass lesions and gross congenital brain malformations.

MRI for neonates was in its infancy with early case reports and case series of patterns of injury and things to look for on imaging both in HIE and in clinical mimics such as hypoglycaemia. Imaging protocols were starting to be tailored to neonates and new technology and imaging sequences (such as MR spectroscopy and diffusion weighted imaging) were being applied to imaging of the neonatal brain.

The clinical impact of HIE on subsequent developmental impairment and the anatomical substrate of cerebral palsy due to HIE was starting to be acknowledged and correlated.

Neonatal care of the neonate with HIE was evolving and improving, particularly in terms of ventilation and prevention of hypocarbia due to overventilation.

In 2020 any neonate who requires unexpected neonatal care, let alone an encephalopathic neonate, will be investigated with cranial ultrasound and MRI of the head. The cranial ultrasound will often be repeated regularly through the duration of their care on the neonatal unit. The MRI will often be performed at the local hospital and will involve the use of sequences such as DWI, susceptibility weighted imaging, diffusion tensor imaging and MR spectroscopy. The MR scanner may be on or near the neonatal unit and specific incubators may be used to transport the neonate to and from the scanner.

MRI after myelination is complete (beyond two years of age) will provide exquisite anatomical information if the child goes on to develop cerebral palsy. The report of the MR scan will often include reference to clinical and radiological mimics of HIE, reference to specific anatomical substrates for subsequent neuro-disability and information regarding prognosis. Some of the information included in the report will reference new knowledge available to the reporting radiologists regarding in utero injury to the fetus.

Providing an accurate estimation of the timing of the insult (or insults) is of increasing importance to the reporting radiologist and their hospital and earlier imaging (within the first days of life) with DWI to aid the reporter with the issue of timing and to exclude post-natal causes of brain injury and encephalopathy such as metabolic disorders, infection and/or cardio-respiratory dysfunction is required. It is now known that some pathologies thought only to affect term neonates may affect the preterm brain and also that pathology previously considered to only affect the preterm brain may affect the term neonate. The use of early MRI should now include statements from the radiologist regarding likely prognosis for the term neonate with HIE.

There has been a huge expansion in the interventions available to the treating neonatal team and the impact on outcome from interventions such as therapeutic hypothermia has seen a dramatic improvement in neurological outcome for the term infant with HIE. The interventions have also raised doubts about the applicability of previously held dogma regarding the duration and nature of HIE at term.

In the near future clearer guidelines should allow the reporting radiologist to better define the nature and timing of the insult causing HIE, to exclude mimics and to provide better prognostic information to the clinical teams, to focus interventions and reduce subsequent neuro-cognitive disability.

This commentary will review the literature in brain MR imaging of the term neonate with HIE over the last 20 years with specific reference to my published papers which have contributed to advances in the field and which are included at the end of the thesis.

2 Figures and Tables

3 Commentary on thesis

3.1 The term and preterm brain

Babies are most commonly born around 40 gestational weeks (gw) after conception and those delivered between 37 and 41 gw, are considered to be 'term' babies. Babies may be born after term (beyond 41 gw). Normally delivery is achieved by 42 gw and these babies born between 41 and 42 gw are thus considered to be 'post mature'. If pregnancy proceeds towards 42 gw then delivery is normally expedited or induced (with prostaglandin suppositories and / or oxytocin infusion) as beyond this gestation maternal and fetal outcome deteriorates as the placenta starts to involute.

Babies born before 37 gw are considered premature. Advances in neonatal care has improved survival massively, so that for example 50% of babies born at 24gw survive, although there is a high risk of poor long-term neurological outcome for this group.

A term neonate with a brain injury, from whatever cause, may develop encephalopathy, which can manifest in a variety of ways including focal seizures, lip smacking, general irritability and jitteriness or unresponsiveness. The more preterm a neonate is the more difficult the clinical assessment for encephalopathy becomes. Skilled clinical assessment to detect and characterise the seizures can be augmented by monitoring of brain electrical activity with either cerebral function monitoring (CFAM) or electro-encephalography (EEG).

3.2 Hypoxic ischaemic encephalopathy

Definitions

In cases of neonatal hypoxic ischaemic encephalopathy the fetus and /or neonate is starved of energy supply to the brain due to a combination of reduced oxygen in the blood and impaired cardiac function. The fetus / neonate demonstrates symptoms and signs of encephalopathy, which may or may not be associated with subsequent early developmental impairment manifest as motor impairment (cerebral palsy) and /or cognitive dysfunction.

Asphyxia means that there is a reduced level of oxygen being supplied to the fetal brain.

Encephalopathy is a coverall term for a state of brain dysfunction which in adults and older children can have a wide range of presentations, ranging from coma to seizures or cognitive dysfunction.

Neonates are children up to the age of 28 days following delivery.

Term neonates are children born near to full gestation of 40 weeks after conception. Paediatricians have traditionally considered a term neonate to have been born after 37 gw, reflecting physiological maturity (for instance lung function due to surfactant production). Confusingly radiologists have traditionally considered a term neonate to be one born after 36 gw. This is because the blood supply to the brain changes between 34 and 36 gw and this alteration in brain arterial blood supply affects the at-risk regions of the brain to hypoxia and hypoperfusion.

Preterm neonates are therefore defined as being born before 37 gw by paediatricians. Alternatively, they are defined as having been born before 34 gw by radiologists. Radiologists consider neonates born between 34 and 36 gw to have variable blood supply to the brain. Preterm and term neonates can be exposed to similar hypoxic / hypoperfusion insults and experience different patterns of damage with different clinical presentations.

Early developmental impairment (EDI), previously called global developmental delay, is characterised by a child's development falling below 2 standard deviations from the population mean in two or more domains (Hughes et al). EDI can be isolated, i.e., not associated with other findings like macrocephaly, dysmorphia, or associated with additional clinical features. EDI affects 1-3% of children and has many aetiologies, including genetic, metabolic, endocrine and structural brain abnormalities.

The **Gross Motor Function Classification System (GMFCS)** refers to a five-point range (levels I - V) of severity of motor impairment in CP with levels IV and V being the most severely affected persons (Palisano et al).

GMFCS

Hand function - normal, little useful function, no function

Speech and swallowing – mild dysarthria, limited speech, no swallow

Cognitive function – normal/mild, definite learning difficulties, severe

Mobility, Standing and sitting / stability – mild impairment, can sit, unable to lift head.

Societal importance with relevance to the NHS; medicolegal overview and importance of timing for the ENS

The neuro-radiologist may use imaging in the form of ultrasound, computed tomography or magnetic resonance imaging to assess the fetal / neonatal brain. My work since commencing as a paediatric neuro-radiologist in Sheffield in 2002 has focussed on trying to improve the quality of information which the radiologist is able to produce in a radiology report in such cases to assist the decision making for the clinical teams involved in care of the fetus / neonate and to assist the families to understand what has happened to their child.

Many of the most expensive settlements for clinical negligence cases against the NHS over recent years have involved birth injury, with settlements regularly in the range of £5-10 million, with some cases now settling for over £30 million. This represents a huge financial burden to the NHS with clinical negligence settlement fees now accounting for 10% of the overall NHS budget and therefore has a massive societal importance for the United Kingdom. Neonatal brain imaging is a cornerstone of the early assessment of these cases as a predictor of outcome. Neonatal brain imaging is used to assess both the nature of the insult/s, the extent of the insult/s and the timing of the insults. In 2000 for most cerebral palsy cases the imaging would be performed late, by which I mean several days or weeks after the child was born or even many years later when trying to establish the likely cause/s of the cerebral palsy. In 2020 we now try to image earlier to provide more clinical information to the clinical teams and family and to provide more information on the timing and nature of the insults.

Research questions addressed in the thesis

How can the radiological reporting of perinatal brain injury on MR imaging be improved?

a. To make improvements that address some of the barriers to radiological interpretation of MR brain imaging

    I. Image acquisition

        i. Using a dedicated neonatal 3T MR scanner designed to be located on or close to the neonatal unit so that timely high quality MR imaging became more accessible.

        ii. Improve accessibility of MR scanning for potentially unwell neonates by using a dedicated MR compatible incubator designed to settle the neonate leading to reduced movement and easier completion of imaging.

    II. Identifying the new features of hypoxic ischaemic brain injury on MR imaging to demonstrate the anatomical markers of the phenotypic expression of the brain injury more fully to the neonate exposed tp hypoxia.

    III. Identifying and differentiating mimics of hypoxic ischaemic brain injury on MR imaging to understand more fully what is attributable to HIE and what has been caused by other conditions which may complicate or mimic the condition clinically.

b. To improve understanding of the phenotypic expression of brain imaging changes identified in term HIE and to improve the prognostication required to guide clinical care decisions and medicolegal issues.

c. To reduce the requirement for, and extent of, investigation of children with early developmental impairment.

3.3 Acute profound hypoxia

The commonest causs of neonatal encephalopathy in the term infant are perinatal hypoxia. Perintal hypoxia in a term infant is commonly divided into either acute profound hypoxia (APH) or chronic partial asphyxia (CPH). In reality there can be a mixture of the two mechanisms in play before during and after delivery.

After discussing APH and CPH I will describe how imaging has been optimised to improve the quality of information available to the reporting radiologist and then the clinical team. I will then describe both the clinical and the radiological mimics of HIE in the term infant, affecting the preterm brain, in utero, at delivery and after delivery before describing the mimics of HIE occurring at and after delivery in the term brain. The impact of HIE on subsequent early development wil then be described. I will highlight the areas where research which I have led in Sheffield has had an impact on these topics.

Aetiology

In most cases of neonatal HIE the fetal and/or neonatal heart rate slows below the normal range of 110-160 bpm, to a rate often less than 60 bpm because of a catastrophic event such as acute cord compression, shoulder dystocia or uterine rupture. The fetal bradycardia may be demonstrated with auscultation, on a cardiotocograph (CTG a measure of the fetal heart rate,

which because it is non-invasive and as it is now universally available for hospital deliveries is often the biomarker of the severity of fetal hypoxia prior to delivery), fetal scalp electrode or with trans-abdominal ultrasound.

During labour it has long been established that fetal blood sampling is the best way to establish if there is fetal acidosis (Beard et al). However, this is invasive and not without risk. Transabdominal measurement of the fetal heart rate in relation to uterine contractions (cardiotocography) can provide an indirect measure of fetal acidosis (Spencer). Fetal acidosis is rare if there is good beat to beat variability (5-10 bpm) and no slowing with contractions. Fetal heart rate decelerations accompanied by fetal tachycardia and/or loss of beat-to-beat variability are early markers of fetal acidosis and late deep and/or delayed decelerations are frequently a marker of severe fetal acidosis.

Observations in primates have demonstrated that the fetus is able to withstand up to ten minutes of acute / profound hypoxic (APH) ischaemia without sustaining neurological injury and that if the insult extends beyond this duration, injury affecting the areas of the brain with the highest metabolic rates (energy demands) the deep grey nuclei ensue (Myers). The totally asphyxiated baby monkeys (rather than near totally asphyxiated babies) suggest that irreversible brain damage may start to occur from about 10 minutes after the start of bradycardia in a human fetus. The more severe the bradycardia (and thus the hypoxic ischaemic insult) then the more likely that the brain will be damaged.

Clinical discussion with reference to impact on outcome

Once brain damage commences from an acute profound asphyxia then the primate experiments suggest that over the following 15-20 minutes the degree of brain damage progresses in a now predictable way partly based on radiological assessment that the work in these thesis and other places has addressed. Beyond that time point then the baby monkey will be very unlikely to survive (Myers). These timings have been extrapolated to human fetuses / babies and are most useful when the onset of a severe (less than 60 bpm) bradycardia is clear from other data. In human fetuses and neonates the posterior putamen, anterolateral thalamus and peri-rolandic cortex are most vulnerable due to their high energy requirements compared to the rest of the brain at this stage of development in a beyond 36 gw fetus.

One must acknowledge that the severity of bradycardias is more variable, as evidenced by periods of variably deteriorating and improving fetal heart rate on CTG, in human clinical practice and that the fetus may tolerate hypoxia better that the baby monkey. Fetal health prior to the HIE resulting in alterations in resilience and possible preceding chronic partial hypoxia (CPH) is then important when estimating likely outcome. It is therefore more accurate to suggest that the variability of the onset of HIE and preceding fetal status alters the time prior to the onset of brain damaging acute profound asphyxia, but that once this brain damage commences then the fetus/neonate will only survive for a further 15-20 minutes of acute profound hypoxia. The duration of the bradycardia ends when the fetal/neonatal heart rate rises above 100 bpm.

Westgate et al demonstrated that both arterial and venous samples from the cord should be obtained and assessed to estimate the nature of an acidosis. This is now routine clinical practice in the UK for encephalopathic neonates born in hospital. The venous gas is commonly the more easily obtained of the two samples. In APH the arterial sample is often more depressed that the venous sample (say pH 6.9 arterial versus pH 7.1 venous) whilst in CPH the two samples often demonstrate more closely aligned pH values. Interpretation of the results requires the examination of pCO_2 and the base deficit of the extracellular fluid from each vessel as well as the pH to determine the contribution of metabolic and respiratory components to the acidosis (Westgate et al 1994).

Ross and Gala attempted to rationalise an approach to interpreting cord arterial blood gas results in then predicting the length of the brain damaging period of CPH (Ross and Gala). They suggested that when the metabolic acidosis became worse than 12mmol/l, then there was likely to be evidence of brain damage in human and animal studies. They also reported a reduction of buffer base during the first stage and second stage of labour and during both normal delivery and in periods of fetal distress. Their report concluded that during a period of subacute fetal compromise the base excess, a measure of blood buffering capacity, may reduce by 1mmol/l per 6-15 minutes. For instance, if a child is born with a cord arterial base excess of minus 24 mmol/m then the period of brain damaging metabolic acidosis probably started between 2 and 4 hours prior to the taking of the blood gas (presumed to be the time of delivery) being obtained. We have commenced a retrospective review attempting to use brain MR spectroscopy measurement of lactate as a surrogate marker of base excess in neonates who suffered HIE and this work has just been submitted for review.

The lactate elevation following HIE is likely to persist in brain tissue for longer than the 4 hours that Shah et al discovered when reviewing base deficit recovery in 244 neonates (Shah et al). They discovered that in all cases except nine the base deficit normalised within 4 hours of delivery regardless of whether the child had suffered from APH or CPH. The base deficit recovered at 0.11 mmol l^{-1} min^{-1} over the first 4 hours after delivery whether the infant had suffered an APH or CPH episode. The rate of recovery was similar in infants with relatively good and with poor outcome.

Frasch et al altered the rate of umbilical cord occlusions in near-term ovine fetuses from 1 minute every 5, to 1 every 3 to 1 every 2 over a one-hour period or until fetal arterial pH decreased to less than 7.00 (Frasch et al). They found that each minute of cord occlusion led to base deficit and serum lactate increases of 0.56 and 0.35 mmol/l per minute respectively. During a two-hour recovery, base deficit and lactate normalised at rates of 0.09 and 0.04 mmol/l per minute. The base deficit and lactate correlated closely.

A child's impairments after HIE may result from a combination of insults and not just an acute profound HIE, for instance if there was also neonatal hypoglycaemia, kernicterus or CPH.

Kayani et al (Kayani) reported on 33 babies exposed to placental abruption – a common cause of an APH insult to the brain – with varying periods of terminal bradycardia (90 bpm or less). Outcome was divided into good or poor. No neonatal data was presented. Outcome was assessed as good (22/33) at one year or older when there was no evidence of a developmental problem. The good outcome cases had a bradycardia lasting from 6-65 minutes. 25% good outcome cases had a bradycardia lasting longer than 33 minutes. Therefore, one needs at least 10 minutes, and possibly much longer

before a child will suffer from cerebral palsy. Poor outcome (11/33) was death or survival with cerebral palsy. Cognitive outcome was not assessed. The outcome measures were very limited when compared to the GMFCS outcome measures.

Naeye and Shaffer retrospectively reviewed the clinical, laboratory, brain imaging and placental findings in 608 pregnancies that had produced term neonates with cerebral palsy of possible antenatal hypoxic ischemic aetiology (Naeye and Shaffer). This was a poorly designed study with no prospective data collection. Exclusion criteria (e.g., congenital brain malformation or genetic disorder) resulted in just 92 cases being included. The study had numerous flaws but suggested that cerebral palsy rarely resulted from a bradycardia of 70 bpm or less that lasted less than 15 minutes.

Early radiology

Early radiology covers the imaging appearances over the first three months after delivery and can be further subdivided for individual pathologies and imaging modalities. Early CrUS will demonstrate cerebral swelling for up to a week after the insult with increased echogenicity in the basal ganglia and thalami. CT is rarely performed due to radiation dose to the newborn brain, but it can produce very useful information if it must be used. CT is often used if there is no MRI availability, if there is birth trauma or if the neonate is admitted via the emergency department. CT would demonstrate lower than normal attenuation in the putamen and thalamus for up to a week. MRI will show acute low T1, high T2 signal and restricted diffusion in the lentiform nuclei and ventral posterolateral thalami with obscuration and loss of the posterior limb of internal capsule (PLIC) with lies between the

damaged structures. There may also be high T2 signal in the globus pallidus, hippocampi and head of caudate nucleus. The perirolandic cortex may demonstrate subcortical high T2 signal, and loss of cortical grey-white differentiation acutely and then cortical highlighting extending caudally to the posterior insular cortex from about day 7-10. After about seven days there will start to appear in the mildly damaged posterior putamen and ventral postero-lateral thalamus high T1 and slightly later (by a few days) low T2 signal which may last for 2-3 months. If damage is more severe a larger part of the antero-lateral thalamus will be damaged and more of the putamen extending anteriorly.

Late / follow up radiology

CT may demonstrate focal low attenuation and volume loss in the posterior putamen, perirolandic cortex and antero-lateral thalamus but only if there has been a severe injury. If there is only a mild APH then CT will most likely be normal. On MRI there will be high T2 signal and possibly low T1 signal from about 3 months onwards. There may be free diffusion in areas of cystic change which may affect the most severely damaged regions. The more severe the injury then the more structures that will be damaged including the hippocampi, head of caudate nucleus, globus pallidus, subthalamic nucleus and anterior lobule of the cerebellar vermis. In infants with very severe injury lasting over 25 minutes then all areas of the brain may be injured with significant brainstem and white matter volume loss.

Anatomical substrate for disability with reference to the vermis and subthalamic nucleus

APH will damage the most metabolically active regions of the brain which are those which are myelinated and most functional. The normal timing of myelination includes the ventral postero-lateral thalamic nuclei and pallido-thalamic fibres at 25gw, the lentiform nuclei and pre and post central gyri at 35gw, the optic radiations at 37gw and the PLIC at 40gw (Martin and Barkovich).

The PLIC has long been a focus for reporting radiologists in acute profound asphyxia and absence of the normal high T1 signal of the PLIC at term is considered to be a marker for poor outcome (Martin and Barkovich). However, this cannot be an anatomical marker of primary injury, or all children injured by APH would have a spastic quadriplegia as the corticospinal tracts would be damaged. Rather I consider this to represent increased T1 signal in the adjacent thalami / putamen and low T1 signal in the PLIC due to oedema. Also, on T2 imaging the PLIC is normally low signal and the loss of the normal low T2 signal is probably more likely a representation of high T2 signal and oedema centred on the ventral posterolateral thalamus and the posterior putamen. Similarly, diffuse white matter high T2 signal (DEHSI) was a marker of APH but is more likely just normal white matter incomplete myelination. Despite this whit ematte rhigh T2 signal but was found to have use in prediction of outcome (Hart, Smith et al). Diffusion tensor imaging with artificial intelligence interpolation of data to estimate white matter tract volumes is starting to be employed by some centres as a marker of severity of brain injury from HIE (Salas et al).

The pattern of brain injury seen on MRI is not limited to the regions of the brain described above by Myers. The medial temporal lobes and head of caudate nucleus have also been demonstrated to be affected by APH injuries. Damage to the posterior putamen and the ventral postero-lateral thalamus should not produce a dyskinetic cerebral palsy as can easily be appreciated when reviewing the numerous adult brain imaging acquisitions which demonstrate vascular injury to the head of caudate nucleus, putamen, and thalamus. We discussed this anatomical conundrum with Alan Crossman (Professor of neuroanatomy, University of Manchester) an internationally recognised expert on basal ganglia function, who suggested other anatomical targets for injury from APH which could better explain the clinical effect of APH. We then tailored our imaging protocol to better appreciate these regions by producing coronal high resolution and high grey-white matter differentiation images to show focal injury to the subthalamic nucleus (Radon). This area of injury had not previously been described in the APH literature. Injury from APH to this nucleus far better explains the subsequent development of a dyskinetic movement disorder as injury to the putamen and antero-lateral thalamus do not frequently cause a movement disorder.

Sargent et al. demonstrated that the anterior lobule of the cerebellar vermis was another area of the brain which could be damaged following an episode of APH. We published one paper demonstrating that damage to the anterior lobule tended to be associated with more severe APH (Connolly). We have recently demonstrated that APH can produce isolated brain injury to the cerebellar vermis and clinically this can produce an ataxic cerebral palsy rather than the usual dyskinetic or spastic cerebral palsy associated with APH (Joshi). This pattern of radiological and clinical isolated injury to the vermis from APH had not previously been reported and indeed some experts did not believe in the entity of an ataxic cerebral palsy.

Imaging and prediction of outcome

There have been many attempts over the years to predict clinical outcome from the early and late MRI appearances. Weeke et al have produced a recent version but it requires the use of MR spectroscopy DWI and includes reference to many areas of the brain. It also requires evaluation of many image sequences including DWI, T1w and T2w imaging (Weeke et al). The scoring system has been shown to be reliable with high inter-rater scoring and to predict outcome well (Machie). However, I am not convinced about its capacity for widespread implementation given the complexity of the scoring system. As I will discuss later an easier to implement scoring system based on a limited number of anatomical locations and requiring abnormality in any one of the image sequences would be far more likely to be widely implemented in clinical practice.

3.4 Chronic partial hypoxia

Aetiology

Perinatal asphyxia refers to the condition characterised by hypoxaemia, hypercapnia and insufficient blood perfusion of the fetal and newborn brain. The incidence is rated at between 2 and 9 % in term neonates and is higher in premature infants. Clinically the fetal heart rate will be decreased, there may be meconium-stained amniotic fluid, low Apgar scores, low scalp and cord pH or clinical signs of neurological depression. All of these are poor predictors of neurodevelopmental outcome. Chronic partial asphyxia is often difficult to accurately time in terms of when it happened and how long the asphyxia went on for. CPH is commonly considered to be due to intermittent cord events with spasm or intermittent occlusion.

Clinical discussion with reference to impact on outcome

Neurons are especially vulnerable to hypoxia and glucose deficiency both separately and in combination. Cell injury is either due to the direct effect of hypoxia or can develop during recovery when excitatory aminoacids such as glutamate, free radicals and calcium ions have a destructive role.

Chronic partial hypoxia (CPH) induces the ‘diving reflex’ in the fetal brain. This means that the most important and most metabolically active areas of the brain are prioritised for oxygenation and blood supply, with redistribution of the fetal blood supply. The areas of the fetal brain which are protected include the cortex around the central sulcus, the brainstem, the occipital cortex, the basal ganglia and the thalami. This means that the

vascular watershed territory of the mature or term brain, the region of the brain both deep in the white matter and extending up to the cortex between the middle cerebral artery and the anterior/posterior cerebral arteries, is at risk.

Injury to this region therefore affects the white matter of the frontal lobes and parieto-occipital lobes, together with the cortex. Clinically it produces reduced intellect, spastic quadriplegia, seizures and possibly visual impairment. The children most severely affected cannot care for themselves and often have severe microcephaly.

Ikeda et al produced a CPH in 17 near term fetal lambs who then survived 72 hours after birth (Ikeda et al). The most common mechanism for inducing CPH in vivo is a partial or intermittent complete cord occlusion which produces a slowly escalating fetal hypoxia unlike the rapid onset fetal hypoxia of APH. Asphyxia in the Ikeda et al work was produced by umbilical cord occlusion lasting for approximately 60 minutes until fetal pH was < 6.9 and the base excess was > -20 mEq/l. Neuropathology changes varied hugely from case to case and ranged from extremely subtle and patchy white matter vacuolation to increased cellularity at the cerebral cortical grey / white matter junction up to extensive necrosis of grey and white matter. Even the fetuses that showed full recovery on EEG and all physiological parameters demonstrated subtle but distinct white matter lesions. Unfortunately, in the Ikeda study there was no neuro-imaging correlation with the histology, but this work does support the premise that CPH can auto-recover in utero, but that there is likely to be some neurological injury to white matter, due to the sensitivity of oligodendroglia, even if the imaging studies are normal (Rutherford et al 1998).

Early radiology

MR scans in the first few days demonstrate restricted diffusion in the deep and/or cortical watershed zones with high T2 signal and loss of cortical grey-white matter differentiation also termed discontinuous cortex. T1 signal may be low.

After four or five days high T1 signal in the cortex with underlying low T1 signal may start to develop but normally occurs after 10 days. This persists for a variable period but is normally present for at least 4 weeks and possibly up to 10 weeks (Martin and Barkovich). This cortical highlighting is the same radiologically as the described cortical laminar necrosis in adult strokes. Low T2 signal slowly develops during the first 4 weeks and persists up to 3 months. This low T2 and high T1 signal is potentially due to microhaemorrhage with secondary dystrophic calcification.

DWI may demonstrate acute restricted diffusion (high b700 and low ADC) in the deep white matter or cortex where there is cortical high T2 signal. After 5 to 7 days the areas of primary injury will pseudo-normalise on DWI, with high b700 and normal ADC. However, areas of secondary atrophy such as the corpus callosum, sensory nuclei of the thalamus and spino-thalamic tracts may start to demonstrate high T2 signal and restricted diffusion, depending on the areas of white matter and cortex which suffered the primary injury.

Late / follow up radiology

In the long term damaged white matter regions are difficult to demonstrate on T2 weighted images before myelination is complete. As white matter

matures areas of high T2 signal become more evident and are most obvious in the subcortical white matter at the deep bases of cortical sulci. There is also potentially some volume loss in these regions producing mushroom shaped gyri; with wide outer cortex and a narrow base to the gyrus with widening of the deep sulci giving an appearance known as ulegyria. There may be thinning of the corpus callosum, microcephaly and widening of the ventricles (Stivaros). The thalami may have slightly high T2 signal and volume loss.

Imaging and prediction of outcome

This is a relatively under reported and investigated subject, especially given the huge interest in evaluating MRI for APH, but it is ripe for future research as I will discuss later.

3.5 White matter injury to the term brain

Li et al and subsequently Hayman et al have demonstrated that focal non-cystic white matter injury can be demonstrated in populations of term neonates (Li et al, Hayman et al). Li looked at 48 term neonates with HIE studied with MRI at 72 hours and found that 11 had white matter lesions (high T1 and low T2 signal, with 10/11 associated with restricted diffusion). The restricted diffusion implied (when extrapolating adult stroke DWI data) that the injury occurred in the week before the imaging rather than being a late manifestation of injury occurring prior to 34gw. Li et al also demonstrated that the presence of white matter lesions was associated with reduced gestational age but not with lower birth weight. The white matter injuries were also demonstrated in neonates with milder encephalopathy

and fewer seizures. This suggests that an earlier stage of brain maturation rather than IUGR is a greater risk factor for white matter injury at term. Therefore, it would follow that those comorbidities that impede brain maturation would also be risk factors for white matter injury from HIE in the term brain. 2/11 also has strokes and 1/11 had basal ganglia injury.

Hayman et al in their later work demonstrated, in 42 near term neonates with punctate white matter lesions, that lesion load does not correlate with outcome (Hayman et al). The study excluded children with perinatal arterial ischaemic stroke (PAIS), congenital heart disease or who had neonatal surgery. The 42 cases were poorly selected and included neonates with various conditions including tuberous sclerosis and venous sinus thrombosis. 19/42 had HIE, 11/42 had a pathological genetic diagnosis, 10/42 had seizures and 1/42 had parechovirus infection. The 42 cases were selected from 2 tertiary centres over a more than ten-year period during which both centres imaged all children with HIE, all neonates with seizures, or other neurological symptoms, and all neonates with suspected white matter lesions on ultrasound. In Sheffield most neonates imaged with MRI have HIE and therefore it is not surprising that 45% of children with PWMI have HIE. There is no mention of a control group.

Hayman et al showed that the children with less than three lesions were all neurologically and developmentally normal at follow-up and that lesion load alone does not appear to be a good predictor of outcome. The worst outcome group also had a genetic disorder and over-all the study concluded that underlying cause was more important to outcome than lesion load. 5/42 had irreversible white matter lesions on follow-up MRI performed due to clinical concern at 18-24 months. DWI abnormality in the PLIC seen in 8/42 was not associated with a higher rate of motor impairment, suggesting that the restricted diffusion in the PLIC alone is a poor predictor of motor

outcome. It does not appear from this paper that white matter abnormality on ultrasound was a major predictor of PWMI.

Merhar et al demonstrated with MR that punctate white matter lesions were found in 8/20 term neonates with prenatal opioid exposure, but no punctate white matter lesions were found in 20 controls (Merhar et al). All children were imaged at week 4-8 post-delivery. Merhar et al also found 2/20 in the prenatal opioid group had septo-preoptic fusion anomaly. Therefore, a comprehensive prenatal and perinatal history with good neuro-developmental outcome data is required when considering PWML.

3.6 Optimising imaging of the neonate

Imaging modalities used in the neonate

There are three commonly available radiological technologies by which a radiologist may assist in the assessment of the neonatal brain. The three imaging modalities are cranial ultrasound (CrUS), computed tomography (CT) and magnetic resonance imaging (MRI).

Cranial ultrasound (CrUS) is the most used brain imaging technique in neonates as it is readily available at the neonatal cot side and does not utilise radiation. CrUS can therefore be used repeatedly to mark the evolution of appearances and at short notice if there is clinical deterioration. There are no confirmed side effects to using this imaging technique. Ultrasound is used for demonstrating focal brain pathology such as haemorrhage or cysts within the brain substance. CrUS can also clearly demonstrate ventricular dilatation either due to enlargement of the ventricles following accumulation of CSF within the brain (hydrocephalus) or loss of brain volume (brain atrophy). The weaknesses of the technique are the complete dependence of the image acquisition and interpretation on the skill and experience of the operator acquiring the images and the difficulty of demonstrating subtle brain parenchymal pathologies and symmetrical abnormalities.

CrUS is a useful adjunct to MRI in helping to time the insult to the brain. There should be a timeline of evolving CrUS appearances that can be established following a hypoxic brain injury.

The brain will demonstrate early brain swelling with effacement of the sulci and ventricles. There may be increased echogenicity of the brain either in the basal ganglia and thalami if there has been an acute profound asphyxia, or in the white matter of both cerebral hemispheres if there has been chronic partial asphyxia. The brain swelling will tend to start to regress about five days after the insult and there may go on to be some later brain volume loss. The regions of increased echogenicity may undergo cystic degeneration. Cysts tend not to appear after a hypoxic insult to the brain for at least ten days.

Computed Tomography (CT) is not frequently used in neonates due to its high radiation dose and its limitations in demonstrating parenchymal pathology. CT is an X-ray derived imaging modality. As with ultrasound, CT is very good at demonstrating acute haemorrhage, large focal brain parenchymal lesions and enlargement of the ventricular system of the brain. CT is also extremely useful when investigating for possible bone injury or congenital anomalies (Ref Mohan et al).

CT is actually very sensitive to perinatal brain asphyxia particularly between days two and four after the insult (Mohan et al). The CT will demonstrate acute low attenuation in either the basal ganglia and thalami with acute profound asphyxia or in the cortical mature vascular watershed territories in chronic partial asphyxia. After a week the areas of low attenuation may become high density due to cortical laminar necrosis and luxury perfusion. In the long term these regions of injury will demonstrate low attenuation and focal brain volume loss.

Magnetic Resonance Imaging (MRI) is the most modern imaging modality of the three and is commonly used for the investigation of complex neonatal brain pathology.

MRI is a complex technology which has evolved significantly over the last 25 years and involves a strong magnetic field (commonly 1.5 or 3 Tesla), energy application to the neonatal brain with radiofrequency (RF) waves and then the detection of very low energy emitted RF energy from the neonatal brain. The detection of the emitted RF energy allows localisation of the pathology and characterisation of the pathology. The neonatal brain is placed in a high-quality RF detector coil to enhance detection of the emitted energy, to optimise both spatial resolution and signal to noise ratio. Coil technology development has had a huge impact on improved MR imaging of the neonatal brain.

MRI has several advantages over both CT and CrUS as it can demonstrate subtle and symmetrical brain pathologies which may have previously not been appreciated until the child's brain had matured or myelinated completely (beyond at least two years of age). The child may also have had a neurological and cognitive developmental outcome which was difficult to predict or assess in the first few years of life. The clear superiority of MRI of the neonatal brain is mitigated by the difficulties experienced when monitoring for the safety of the neonate in the MRI scanner and the challenge of bringing the neonate to the scanner unit (which may require ambulance transport to attend the MRI scanner if they are not co-located) or building MRI scanners close to the neonatal unit.

Development of new hardware and technology to support neonatal brain MRI

A significant amount of work over the past years in Sheffield and elsewhere has focussed on the development of MRI scanners which can be housed in a neonatal unit environment. Initial work focussed on an in-house construction with a low field strength (0.2T) system (Whitby et al 2004). This scanner had the advantage of being housed in a side room on NICU itself. There was no development of monitoring equipment but rather a parent or other carer would hold the neonate in the scanner. That 'Niche' scanner had the marked disadvantage of limited sequences which could be used to image the neonatal brain. Imaging was almost entirely T1 spin echo with no FSE T2 or DWI echo planar imaging possible. The lack of monitoring meant that the neonate had to be stable and thus unwell and particularly premature infants could not be assessed before they were at least 40gw. A lot of the early literature in neonatal imaging therefore involved delayed imaging at term equivalent or later and focussed on appearances on T1 images when the pathology was often ≥ 10 days matured (Rutherford, Pennock et al). This delayed imaging was often limited by motion artefact and limited image sequences (often simply spin echo T1 and sometimes fast spin echo T2) and would have no impact on early decision-making regarding care and prognosis of the neonate.

More recent work focussed on the development of new rapid acquisition MR sequences for use in neonatal and fetal MR imaging with a higher field strength(3T) MRI scanner (Firefly) housed on a NICU which would allow complete sets of images including single shot (ss)T2, SWI, DWI, FSE T2, T1 volume images, MR spectroscopy, MRA of the Circle of Willis and MRV (Griffiths et al 2013 and Griffiths et al 2018). The Firefly scanner produced exquisite images equivalent to those which would be acquired on a main MR

unit scanner, but the scanner was housed just 5 yards from the Sheffield NICU in a small room footprint. The small scanner was developed from animal / peripheral limb MR scanners and could allow a transport table holding the monitored neonate to transfer directly from the NICU cot-side into the scanner. The environment was well received by NICU senior staff and parents. However, the costs of the scanner versus the number of potential patients to be scanned (even on a large NICU this averages approximately two patients per week in Sheffield – one of the three largest NICU in the country) meant that the developing manufacturer was unwilling to continue to fund the next stage of development. However increased use and applications would have made a scanner most cost effective.

When it becoame apparent that there were severe limitations to appplying the niche scanner to routine clinical work we started to explore ways to facilitate MR scanning of neonates in departmental clinical canners. Our work in Sheffield then evolved to develop methods of transporting neonates from the NICU to the MR scanner table with the minimum amount of disturbance of the neonate and whilst maintaining a safe ecosystem for the child (Whitby et al 2004). Despite the improved incubators and increased acceptance of the need for MR imaging of neonates, safety concerns and staffing issues, such as the need for a senior neonatal nurse and a doctor having to accompany the neonate in the incubator to the imaging department imaging is not as frequently performed as it could or should be. Finally, we have worked on a 3 Tesla MR scanner to be housed in the neonatal unit, the Firefly project, which achieved departmental standard 3T neonatal imaging within a neonatal unit (Griffiths et al 2018).

There have been three different incubators developed which have the capacity to take the neonate from the cot-side on NICU after transfer to the incubator which can then be directly placed into the MR scanner. The

incubators have improved in the quality of images produced as the coils integral to the incubators have improved. The incubators have also improved the visibility of the neonate for the accompanying advanced neonatal nurse practitioner or neonatologist and the quality of data for monitoring their well-being. I have been involved in reviewing image quality from the acquired MR scans and in the assessment of the most useful imaging protocols.

The improved neonate safety and improved image quality with greater range of MR sequences has allowed for greater clarity in the reports issued and in better and earlier prognostic information to the clinical team and to the family. The imaging interpretation of neonates with HIE has recently been made more complex due to the widespread use of therapeutic cooling. Cooling may or may not produce clinical effect in an individual neonate and the extent of the impact cannot be predicted or estimated.

Therapeutic cooling and the impact of new interventions for the term neonate with HIE

The TOBY cooling study demonstrated that therapeutic cooling (reducing core body temperature to below 32^{o}C) of the HIE neonate significantly reduced the level of damage manifested both clinically and radiologically (Azzopardi et al). Quantification of this beneficial effect is not possible with the current knowledge base though cooling has been shown to be effective in reducing the risk and the severity of permanent neurological injury following neonatal hypoxic-ischaemic encephalopathy, but it does not necessarily prevent neurological injury (Edwards et al).

Therapeutic hypothermia (cooling) is offered as a neuroprotective measure to term/near term infants with symptoms of neonatal encephalopathy after perinatal hypoxia. Treatment needs to be commenced within six hours of delivery for maximum effect. The criteria for initiating cooling in UK practice are derived from those used in the TOBY trial of therapeutic hypothermia (Azzopardi et al 2009). The target temperature for therapeutic cooling is 33.5 (33-34 degrees centrigrade) as a study has shown no benefit of cooling to 32 degrees or lower (Shankaran et al). There was also a suggestion of increased mortality with the combination of deeper and longer cooling.

The primary effect of cooling is reduction of delayed neuronal loss / apoptosis (also known as secondary neuronal injury following recovery and reperfusion – (Drury et al) following an acute profound hypoxic ischaemic insult and early initiation of cooling following an acute insult is most likely to be of benefit. Secondary energy failure is not just Wallerian degeneration but is a combination of oxidative stress, excitotoxicity (free radicals, $Fe2^{+}$, low antioxidants, high glutamate) and inflammation exacerbated by reperfusion and reoxygenation.

Although the extent of the benefit of cooling in an individual case cannot be determined it is likely to have a mitigating effect (Drury et al). In my experience therapeutic cooling has a greater benefit in terms of reducing physical disability rather than cognitive disability after HIE. In individual cases it is impossible to state the extent of benefit, if any, that the baby received from the intervention, though some authors have tried to estimate the benefit at 12.5% in an individual. This is based on the need to treat 8 for benefit in one individual (Edwards et al). Statistically this conclusion (not one that was extrapolated by the authors) is obviously flawed.

The TOBY-Xe trial (Azzopardi et al 2016) used 24 hours of adjunctive treatment with inhaled xenon alongside the standard 72 hours of therapeutic cooling showed that the treatment was feasible and deliverable. However, the study demonstrated no additional benefit, based on MRS lactate to N-acetyl aspartate performed as single voxel over the thalamus and posterior limb of internal capsule. The TOBY-Xe study also demonstrated similar mortality rates between the two groups and an increase in adverse events in the xenon with hypothermia arm of the trial.

Interpreting brain MR imaging in acute profound asphyxia after the use of therapeutic cooling

Within the spectrum of dyskinetic CP patients with GMFCS 1 and 2 outcome subtle injury may not be detected with long term traditional structural brain MRI though the use of DTI may provide information in clinical applications in the future (Salas et al). As cooling improves outcome then subtle permanent brain injury may no longer be recognised either at MR imaging either in the neonatal period or when re-imaged after 2 years of age.

Yokochi et al reported 16 children with asphyxia related dyskinetic CP who underwent MR imaging. 2 children had no abnormality on scan. Population studies of children with cerebral palsy (CP - a permanent and non-progressive disorder of movement and posture attributed to injury to or maldevelopment of the fetal or infant brain) have shown that there is commonly a 10-20% incidence of normal MRI reports amongst children with cerebral palsy. It has also been reported that there is a trend towards normality of MRI findings amongst the more mildly affected cases (Reid SM et al). In relation to normal MRI findings in CP Reid et al state “the reported proportions of normal imaging for children with dyskinetic CP were mixed,

with high rates reported from Quebec and Victoria but low rates from Sweden. There was a trend towards lower rates of normal imaging for GMFCS levels IV and V. Rollins and colleagues reported that cooled neonates who experienced an encephalopathy following HIE, discharged with normal MR scans are still at risk of learning impairment (Rollins et al). It has even been described that although significant motor delay is not probable that the risk of mild to moderate learning impairment may be as high as 50% (Cawley and Chakkarapani).

3.7 Clinical and radiological mimics of HIE in the term neonate.

When reporting imaging in an encephalopathic neonate or reporting the follow up imaging years later the radiologist must understand the clinical mimics of APH/CPH, acutely and in the long term. The other insults may have occurred in utero, at and around the time of delivery, or in the days weeks and years following.

What are the other causes of encephalopathy in neonates?

Most children who are exposed to a period of hypoxia and then go on to develop encephalopathy will not go on to have cerebral palsy. The reporting radiologist must be aware of the other clinical causes of encephalopathy in a neonate. In utero acquired pathologies such as global hypoxia and stroke may produce encephalopathy whilst a child with a genetic epilepsy syndrome and a congenital brain malformation causing seizures may present as neonates. Kernicterus, neonatal hypoglycaemia, perinatal arterial ischaemic stroke, dural venous sinus thrombosis and birth trauma with intracerebral haemorrhage, contusion or other parenchymal injury may present with encephalopathy and other specific features which may help the clinician to suspect the diagnosis. Genetic and metabolic disorders, such as non-ketotic hyperglycinaemia and maple syrup urine disease may present with neonatal encephalopathy within hours of delivery. Meningo-encephalitis, classically due to HSV type 2 or group B streptococcus, may present within hours / days of delivery and whilst there may be clinical markers of these causes of encephalopathy the radiology often has significant overlap with HIE. I will expand upon all of these pathologies in the following sections of the thesis

to describe their clinical and radiological presentations together with their impact on long term development of the child.

When do they occur and why?

When reviewing these other causes of neonatal encephalopathy, I will describe their early and late radiological appearances. It is important when reporting to understand the timing of the brain imaging appearances on MRI, the overlap of the pathology with HIE, and how to differentiate or not the impact on development. For instance, a child with HIE who has a cardiorespiratory collapse on day seven from group B Streptococcal meningitis may have brain injury due to any one of or a combination of; the complications of meningitis (such as arterial stroke, cortical vein thrombosis and cerebritis secondary to empyema), peripheral perfusion injury to the brain due to cardio-respiratory dysfunction or acute profound and/or chronic partial asphyxia.

If one images this child at four years and discovers a structural brain malformation and is informed of a genetic chromosomal microdeletion then ascribing clinical features to anyone of these pathologies may be very difficult. Very clear description of the acquired pathology may assist as may good contemporaneous information about the delivery and neonatal status. An MRI performed before the day seven collapse with DWI will allow the reporter to suggest prenatal chronic partial injury with auto-recovery in utero (if there is no restriction and some volume loss on day 5). Alternatively, no volume loss and cortical watershed restriction, with restriction in the posterior tips of the putamen on day 4 would suggest a perinatal hypoxic injury with some injury on going at the time of delivery. If imaging is repeated at day 11 and there is restriction in the watershed

territories with no cystic change and no volume loss then the reporter may confidently suggest that there was no perinatal injury and that all disability, epilepsy and brain volume loss is likely to be due to the late collapse due to meningitis. Contemporaneous CrUS imaging demonstrating the evolution of cerebral swelling and parenchymal cyst formation will provide further helpful information to the reporter.

Therefore, early MRI with DWI is the cornerstone of neonatal MRI reporting particularly if one applies a forensic eye to the timing and nature of the encephalopathy and brain injury.

In the term infant neonatal hypoglycaemia will tend to occur in the first 72 hours of life as the neonate adapts to supporting its own blood glucose level. Kernicterus will tend to occur between days four and eight as the neonatal bilirubin level escalates often in the home environment. PAIS will tend to present either in the first 48 hours of life with focal neurology and seizures, or much later as an incidental finding. Dural venous sinus thrombosis often presents in the first 72 hour of life or in the presence of post-natal infection and/or dehydration. Bacterial meningitis may present from a couple of days to several weeks after delivery. Viral encephalitis due to in utero, perinatal or post-natal acquisition has a very variable time of symptom onset. Brain injury due to birth trauma should be suspected from soon after delivery when the neonate is first assessed and examined. Punctate white matter injury is often an incidental finding, whilst metabolic disorders may present in the first hours or days of life.

When reporting an acute term neonatal HIE MR scan there is multi-parametric MR data and multi-modality imaging data together with extensive clinical information with high levels of complexity that produces a

significant barrier to accurate interpretation of the MR findings for those radiologists who do not report these studies regularly. Our work had been based at one of the UK's three largest neonatal units together with research work and interpretation of many MR scans for medico-legal work. DWI restriction, the early presence of high or later low signal on T2, the delayed evolution of signal change on T1, lactate levels on MRS, the presence of cerebral swelling and/or volume loss and the temporal evolution of CrUS changes must all be taken together with the history and other clinical features to establish the most likely timing of the insult or insults which have contributed to the acute presentation and to predict the subsequent neuro-cognitive developmental impairment.

DWI is the most useful in terms of timing as restricted diffusion should be present for a maximum of just seven days after the acute injury in the regions of primary injury. For example, we demonstrated MRS and DWI imaging appearance stogether in a case of neonatal hypoglycaemia for the first time and demonstrated that DWI had the greatest importance in predicting permanent injury and clinical outcome (Musson et al). Restricted diffusion may persist in areas of secondary Wallerian degeneration for much longer as cells in white matter pathways extending from areas of primary injury involute. For example, after a chronic partial asphyxia affecting the posterior watershed territories, there may be restricted diffusion in the splenium and posterior body of the corpus callosum and posterior thalamus with high T2 signal for a few weeks as these white matter extensions from the primary area of cortical injury involute.

3.8 In utero injury to the fetus

Acquired pathologies

Congenital CMV infection (Gabrielli et al) produces varying patterns of damage to the fetal brain depending upon the fetal age, tissue viral load, inflammatory response, placental function and extramedullary haematopoesis. Severe placental involvement and subsequent fetal brain hypoxia together with viral load were most closely correlated with poor outcome and severity of brain damage. Up to 1% of children born in the USA shed CMV in urine or saliva consistent with congenital infection. 10% of those children will have clinical features of CMV infection (Barkovich and Raybaud). The children may present clinically with jaundice, hepatosplenomegaly, microcephaly, sensorineural hearing loss, chorioretinitis or a purpuric rash. Treatment with ganciclovir may improve neurodevelopmental outcome.

Early *in utero* infection will likely lead to termination of the pregnancy due to severe brain damage. Infection at 14-16 gw will often produce cortical malformations, such as agyria or lissencephaly with periventricular calcification, ventriculomegaly, anterior temporal and germinal zone cysts and cerebellar hypoplasia. Infection at 16-20gw most often produces polymicrogyria. Late in utero infection will produce mild ventriculomegaly, with damage to the deep or peripheral white matter, and scattered white matter calcification, which may be in the periventricular white matter though more diffuse calcification may also be seen. Mild late in utero infection produces minor scattered white matter high T2 and low T1 signal on MRI or low attenuation on CT. The extent of damage depends upon a

combination of viral load, genetic predisposition, fetal well-being at the time of exposure and maternal health / immunity.

Congenital brain malformations

Neonates may present with symptoms which may be confused with HIE, but which are not due to a perinatal acquired pathology. A small cohort of children may present with symptoms due to a genetically determined epilepsy syndrome (e.g Aicardi syndrome or DiGeorge syndrome) producing seizures, encephalopathy, and neurology but without clinical or radiological evidence of HIE or other perinatal injury. Someof these children may have a congenital brain malformation such as polymicrogyria (Robin et al, Kuzniecky et al).

Neonates may present with symptoms consistent with HIE, but which are in fact due to an injury to the brain which occurred some days or weeks prior to delivery. For example, Marciano et al described five cases of feto-maternal haemorrhage (FMH) with characteristics of both acute and chronic anaemia (Marciano et al). FMH can be diagnosed by checking for the presence of fetal red blood cells with one of the Kleihauer-Betke test, flow cytometry and Rosette tests. Outcome is affected by fetal age, rate of haemorrhage and volume of haemorrhage. In this series four out of the five children were discharged by day 15 in good condition and the fifth child expired at 7 hours of life despite aggressive resuscitation and red cell transfusions. Early cranial ultrasound brain imaging in this neonate demonstrated mild to moderate frontal and basal ganglia increased echogenicity. This implies that FMH is most likely to either lead to a catastrophic (and likely not survivable) brain injury – with probable multi-organ involvement – or a milder insult without brain injury.

Neonates may also present with encephalopathy symptoms due to either congenital brain malformations or brain pathology acquired in utero several weeks prior to delivery. Congenital brain malformations may be due to one of, or a combination of, genetic, hypoxic/ischaemic, and infective aetiologies. Since the 1960's assessment of the fetal brain has been performed with antenatal ultrasound. Recent work from the MERIDIAN study has demonstrated the superiority of fetal MRI compared to ultrasound in evaluation of the fetal brain. This superiority of MRI is not just in the confidence of diagnosis of fetal brain pathology but also in the prediction of long term neurological and cognitive outcome.

The long-term outcome and effect from a congenital brain structural malformation cannot beaccurately predicted from MR imaging and one must also consider the clinical evidence. Nevertheless, more accurate diagnosis of a structural brain abnormality by in utero MRI allows the supervising clinical obstetric and midwifery team to provide far more valuable information for the family, often with direct input from paediatric neurology, neurosurgery, and neuroradiology. I was first author of the paper looking at acquired fetal pathologies affecting the fetal brain in the MERIDIAN cohort. This was one of the first papers to look at the incidence of such pathologies rather than focussing on case series or case reports of individual pathologies and I reviewed all the raw data and all of the fetal MR studies for the cases included in the paper (Connolly et al). This paper is included as one of the papers in the thesis.

3.9 Injury to the preterm brain

PVL

Prematurity and intrauterine growth retardation are both recognised to independently predispose the fetus to spastic, often diplegic, cerebral palsy (Stanley). Khwaja and Volpe described the pathogenesis of cerebral white matter injury of prematurity. The injury is characterised by loss of pre-myelinating oligodendrocytes. The physiology and anatomy of the preterm (prior to 34 gw) brain predisposes the periventricular white matter to damage. Ischaemia (including postnatal hypoxia or hypocarbia, necrotising enterocolitis, pneumothoraces, etc.) and inflammation (such as in utero infection or postnatal infection) either individually or in combination lead to activation of excitotoxicity and free radical injury in the presence of reactive oxygen and nitrogen species. The pre-myelinating oligodendrocytes have immature antioxidant enzyme systems and are also vulnerable to iron accumulation. Ischaemia and inflammation also directly trigger glutamate receptor mediated injury leading to cell death.

Prematurity in the presence of ischaemia and inflammation also predisposes to germinal matrix and intraventricular haemorrhage with possible subsequent iron accumulation. It has been demonstrated in laboratory models that IVH related blood products could have a directly damaging effect upon subependymal pre-myelinating oligodendrocytes, but this effect is not reproduced in clinical practice as evidenced by the absence of PVL in most cases of grade 2 IVH.

Miller *et al* reviewed a single-centre, small population of 12 term children with PVL demonstrated on subsequent brain CT and MR imaging (Miller et al). The children had presented variously with seizures, developmental delay, and attention-deficit-hyperactivity. When they were subsequently clinically examined by an experienced paediatric neurologist; 3/12 had normal motor examinations, three were hypotonic, three had spastic diplegia, two had spastic quadriplegia and one had fine motor difficulties. Nine had developmental delay and two had epilepsy. Four of the eight children with global developmental delay also had enlarged cerebral sulci as well as the PVL. This suggests that a child born at term with PVL on scan may have a wide range of clinical presentations not just the classic spastic diplegia.

It is known that antenatal administration of steroids to the mother and delayed delivery to 39 weeks can protect fetuses from the risk of admission following delivery to special care baby units with respiratory distress syndrome (Stutchfield et al). The incidence of PVL can also be significantly reduced with delayed delivery (Perlman).

GMH

Germinal matrix haemorrhage is the result of a complex set of stimuli and vulnerabilities affecting the germinal matrix. Very low birth weight, extreme prematurity, chorioamnionitis and perinatal stress such as hypoxia may all increase the risk to the fetus / neonate of developing a GMH. The more severe / extensive the GMH then the greater is the chance of extension of blood into the cerebral ventricles.

The Papille classification of supratentorial GMH / IVH is used as the basis for grading the severity of GMH / IVH (1-4) and therefore predicting outcome (Papille et al). The higher the grade then the worse the outcome. Grade 2 IVH is often subdivided in to type a and type b where type b has a cast of blood filling over 50% of the ventricular volume and type a does not. There is a recognised difference in predicted outcome between the grade 2 subgrades which is used in regular practice by neonatologists and radiologists who perform CrUS.

A group of children with GMH/IVH will go on to become shunt dependent and they will tend to have a worse outcome due to the problems associated with shunt failure or infection. Those children that did not require shunt insertion will have a better long-term outcome, even if they required an external ventricular drain or repeated CSF drainage in the neonatal or early infant periods. Late follow up MRI in these children may not demonstrate blood products such as haemosiderin as CSF macrophages may have mopped up and digested the blood. Alternatively, some children will have susceptibility artefact due to haemosiderin and / or calcification especially prominent in the occipital horns of the lateral ventricles or in the thalamo-caudate notch. The thalamo-caudate notch is the most common primary site of GMH.

Tam et al demonstrated that supratentorial IVH was associated with reduced cerebellar growth but could not deduce if this was due to contemporaneous cerebellar injury or due to a direct effect of IVH on cerebellar development. They did not discuss the potential role of Wallerian type reduced stimulation of cerebellar growth due to supratentorial brain injury (Tam et al).

Cerebellar haemorrhage

Haemorrhage in the cerebellum is increasingly recognised as an injury pattern demonstrated in the premature brain. It is often found in association with supratentorial germinal matrix haemorrhage and periventricular haemorrhage. Neonatal CrUS routinely now includes views of the posterior fossa to look for this pathology.

Given that the haemorrhages are often small they may easily be overlooked by the inexperienced neuro-radiologist when reviewing delayed MR and CT imaging of the brain. Blood sensitive brain imaging sequences may underestimate the presence of blood products in the cerebellum due to macrophage activity. There may be artefact from the tentorium cerebelli which masks subtle haemorrhage. The long-term volume loss and destruction of cerebellar parenchyma may be subtle even when there has been a known previous injury or encephalitis.

Most commonly in my experience injury to the premature infant's cerebellum affects the inferior-paramedian, superior and lateral aspects of the cerebellum with relative sparing of the midline structures. It is increasingly recognised from fMRI projects that different parts of the cerebellar cortex are involved in higher functional processes including language, working memory, social processing, and emotion processing (Guell et al). Therefore, future work should look to assess acute cerebellar and supratentorial brain injury and long-term motor, cognitive and psychosocial outcomes.

Limperopoulos et al studied 40 ex-preterm infants with isolated cerebellar injury using MRI. This study demonstrated that injury to the premature cerebellum was associated with secondary impairment of remote contra-lateral cerebral cortical growth and functional disabilities in survivors. There was highly significant association between early signs of autism and dorsolateral prefrontal cortical volume, gross motor scores and sensorimotor cortical volumes and finally between cognitive and expressive language scores and premotor and mid-temporal cortical volumes. They demonstrated by multivariant analysis that each unit increase in the corresponding regional cerebral volume was associated with lower odds of abnormal outcome score, adjusted for age, and contralateral cerebellar volume.

The relationship between the cerebellum and supratentorial brain is not a simple one-way process with injury to the supratentorial brain causing brain volume loss and / or haemorrhage secondarily producing reduced cerebellar volume and functionality, but rather it is a two-way process with possible supratentorial reduced volume and function related to a primary cerebellar insult. This cerebellum-cerebrum inter-relationship is ripe for further investigation in preterm infants.

3.10 Perinatal insults to the term brain

Kernicterus

Bilirubin is a breakdown product of haemoglobin. There are several conditions which can predispose the neonate to breakdown more blood cells and produce higher bilirubin levels such as blood group incompatibility with the mother, Rhesus factor disease (where the mother has Rhesus negative blood, and the baby is Rhesus positive) and an inherited enzyme deficiency such as glucose 6 phosphate dehydrogenase.

Bilirubin is transported around the body in the blood either free or bound (conjugated) to the serum protein albumin. The level of albumin in the blood, which is partly age dependent, therefore affects the proportion of bilirubin which is free or unconjugated in the blood (Le Pichon et al).

Kernicterus is due to deposition of bilirubin in the brain and is a cause of both acute neonatal encephalopathy and chronic neuro-disability because free, unconjugated bilirubin is neurotoxic.

Uptake of bilirubin into the brain may also be modified by several factors such as hypoxia and/or sepsis which damage the blood-brain barrier and facilitate uptake of bilirubin. Genetic factors, excretion and metabolic function may all also affect bilirubin uptake into the brain and/or susceptibility to neurotoxicity from brain intracellular bilirubin. Bilirubin is predominantly deposited in the subthalamic nucleus and the globus pallidus, but the brainstem nuclei of the VIIIth cranial nerve and the VIIIth nerve itself are frequently involved as well.

In the acute phase there may be clinical evidence of jaundice (yellow colouration of the sclera and skin) opisthotonus (arching of the back) and a high-pitched cry. These acute clinical features do not predict outcome. In the acute setting clinicians should attempt to reduce the serum bilirubin level as a matter of urgency with the use of phototherapy, 'bili-blankets' and, in the most severe cases, exchange transfusion.

Some reports suggest that mildly abnormal movements at 1 year of age may result without overt perinatal kernicterus if the bilirubin level is above 340 mmol/l (Soorani-Lunsing et al) but long term follow up was not provided in their cohorts.

Chronic bilirubin encephalopathy (CBE), kernicterus and bilirubin induced Neurological Dysfunction (BIND) all refer to the effect of the uptake of bilirubin to the long-term neurological outcome of the child. Predominantly the children have motor and/or audiological disabilities (Olds and Oghalai). The child with kernicterus may have any or all the classic tetrad of clinical features; sensori-neural hearing loss, failure of upwards gaze, dyskinetic cerebral palsy and bilirubin staining producing dysplasia of the dental enamel of the deciduous teeth. Children might also have subtle neuro-cognitive developmental impairment if they have only been mildly affected, whilst other affected children might have seizures, gastro-oesophageal reflux, scoliosis, and hip dysplasia. There is evidence from a systematic review that in term (rather than premature) infants BIND is associated with later development of autistic spectrum disorder.

Brain MR imaging can help to confirm the diagnosis of kernicterus if there is focal T1 and or T2 signal abnormality in the globus pallidus and/or

subthalamic nucleus. Imaging of the VIIIth cranial nerve will not demonstrate abnormality. Acute MR imaging in the first 5-7 days after the insult may demonstrate restricted diffusion in the globus pallidus. The imaging features after the first week of life may be subtle as the globus pallidus demonstrates high T2 signal in normal infants for the first year of life and in my clinical experience MR scans are often normal beyond one year of life despite clear clinical features of kernicterus.

Neonatal hypoglycaemia

The normal term infant can mount a physiological response to hypoglycaemia after delivery by mobilising alternative energy substrates from fat and carbohydrate stores until blood glucose levels are restored following establishment of feeding. Infants with an impaired ability to mount this physiological ketogenic response after delivery are at risk of potentially damaging neuro-glycopenia due to an inability to maintain an adequate supply of energy substrate for brain metabolism.

Infants at increased risk for hypoglycaemia include growth restricted infants (lack of energy substrate stores), preterm infants (lack of energy substrate stores), intrapartum hypoxic stress (depletion of energy substrate stores and possible transient secondary hyperinsulinism) and infants of diabetic mothers (hyperinsulinism).

Infants with hyperinsulinism (infants of diabetic mothers or infants with primary hyperinsulinism) are at risk of neuro-glycopenia because insulin antagonises the normal catabolic ketogenic response and actively lowers

blood glucose levels. Children can be identified to have growth restriction from their birth weight and head circumference. Normally birth weight and head circumference are roughly on the same centile. If there is intra-uterine growth retardation, then the birth weight will tend to fall across the centiles before the head circumference (OFC).

Vannucci and Vannucci described the accepted lower threshold blood glucose level of 2.6 mmol/l for infants at risk from hypoglycaemia for later reduced mental and motor developmental outcome based on the work of Lucas (Lucas, and Vannucci and Vannucci). Hussain suggested that neonates with transient hyper-insulinaemic hypoglycaemia should have their glucose maintained at above 3.5 mmol/l during management to avoid recurrent / persistent brain injury as prolonged mildly reduced blood glucose levels are thought to potentially have the same long-term adverse effect on outcome as a short-term profoundly reduced blood glucose level (Hussain et al). Therefore, clinical teams must regularly monitor the at-risk infant's blood glucose and provide early treatment, whether by increased feeds (e.g., naso gastric feeds, bottle top ups), by dextrose infusions or by glucagon injections.

Barkovich et al first described the classic paramedian occipital subcortical and cortical volume loss with subcortical high T2 signal pattern of brain damage from neuro-glycopenia and this was later updated to include other potential areas of injury including the thalamic nuclei and many other areas of the brain (Barkovich et al, Caksen et al and Burns et al). If the neonatal hypoglycaemia is associated with any cause of periventricular leukomalacia or a cardio-respiratory collapse with peripheral perfusion failure, then it may be very difficult radiologically to categorically ascribe all or even some of the injury to hypoglycaemia given the anatomical overlap in the distributions of injury from these other pathological processes.

Whipple's Triad is a collection of three criteria suggesting that a patient's symptoms result from neonatal hypoglycaemia; (1) clinical features are typical of hypoglycaemia and (2) a low plasma glucose concentration is documented concurrently using accurate and precise methods and (3) that clinical features resolve within minutes to hours after normo-glycaemia is restored unless brain injury has already occurred. Tin suggested that both Whipple's triad should be satisfied and that the pattern of brain injury revealed by diagnostic imaging is characteristic of that described in the neuropathological literature to attribute later disability to hypoglycaemia in the neonatal period (Tin). This injury may be most eloquently demonstrated with DWI images obtained within 5 days after the ictus (Musson et al). Even extensive DWI change may produce very subtle changes on follow up MRI after 2 years of age, despite significant neurodisability. Tin's suggestion followed on from previous work describing proposed diagnostic criteria for neonatal hypoglycaemic brain injury (Wang et al and Mao et al). These later proposals suggested that the blood glucose laboratory measurement should be below 2 mmol/l (rather than 2.6) and that there also should be contemporaneous clinical manifestations of symptomatic hypoglycaemia such as paroxysmal cyanosis, tremors, convulsions, apnoea, and decreased responsiveness.

Vannucci and Vannucci together with Yager et al. suggested that asphyxia and hypoglycaemia acting together (at the same time) exacerbate brain damage which individually would not be sufficient to cause brain damage i.e. reduction in overall energy supplies from many sources makes the brain more vulnerable to a specific energy depleting insult (Vannucci and Vannucci 1978, Yager et al) Their animal studies demonstrate that resistance of the animal neonatal brain during asphyxia is decreased in the presence of hypoglycaemia. Insulin dependent hypoglycaemia depletes lactate, which

may be utilised by the brain as an alternative energy metabolite to glucose, and therefore makes brain injury even more likely.

The at-risk territories for damage from hypoglycaemia and chronic partial asphyxia overlap posteriorly within the brain as the posterior vascular watershed extends from the parietal to the occipital lobes and the hypoglycaemia vulnerable regions extends supero-laterally from the medial occipital lobes towards the parietal lobes. This produces a radiological conundrum in the late follow up period. Brain MR is most likely to be able to apportion injury to one or both mechanisms (CPH and / or hypoglycaemia) in the acute phase, due to the DWI pattern and distribution of restriction, rather than at late follow up when there is gliosis and volume loss in the parieto-occipital regions.

PAIS

Perinatal arterial ischaemic stroke (PAIS) is defined as a group of heterogenous conditions (usually primarily ischaemic in nature, though secondary haemorrhage may occur) in which there is a focal disruption of cerebral blood flow secondary to cerebral arterial or venous thrombosis/embolization, between 20 weeks fetal life through to the 28th post-natal day, confirmed by neuroimaging or neuropathological studies. Arterial ischaemic stroke accounts for approximately 80% of perinatal stroke with the rest caused by parenchymal primary haemorrhage or dural venous sinus thrombosis (Ferreiro et al).

Stroke can occur *in utero* (Connolly et al 2019). The causes of PAIS are usually unknown and therefore the investigation, imaging, and treatment of

PAIS are different from the older paediatric and adult populations. Outcome is often good but around 30% of cases develop cerebral palsy, 15-20% develop epilepsy and cognitive problems may also occur. Recurrent stroke is rare (1.2% - Fullerton et al)

PAIS is estimated to affect between 1;2300 and 1;4000 live births. The neonate may be asymptomatic or only have mild symptoms that settle spontaneously in the neonatal period. Outcome can be entirely normal following PAIS and therefore it is probable that several children and adults that have experienced a PAIS episode have never received a diagnosis or that the diagnosis is made several years after delivery (Hart et al).

The exact cause of a PAIS is often unknown. The commonest explanation is of a clot forming in the ageing placenta, entering the fetal circulation, via the umbilical vein and entering the cranial circulation after passing through a patent foramen ovale. The commonest site for the embolus to lodge is the left middle cerebral artery (MCA) or its branches, which occurs in 80% of neonates with PAIS as reported by my group in our published review (Johns et al).

There are numerous associations and perhaps risk factors (maternal and fetal) for PAIS including primiparity, prolonged second stage of labour, a non-reassuring CTG trace, obstetric intervention at delivery, maternal smoking, pre-eclampsia, neonatal meningitis, IUGR and many more (Cheong and Cowan, Harteman et al, Lehman and Rivkin). Kiserud suggested that a preferential increase in the shunting of blood from the umbilical vein through the ductus venosus to the IVC and right atrium in response to fetal hypoxia thus increased the magnitude of the right to left shunt across the

foramen ovale and it was suggested that his may increase the likelihood of embolization from the placental bed (Kiserud).

Neonates may also have risk factors for PAIS such as thrombophilia, infection, coagulopathy, cardiac lesions, and trauma. Genetic disorders such as mutations affecting COL4A1 and COL4A2, subunits of type IV collagen involved in angiogenesis, are now recognised as risk factors for in utero stroke (Ferreiro et al). These mutations are particularly associated with primary haemorrhagic stroke and should be considered once a vascular abnormality such as an arteriovenous malformation (AVM) or aneurysm has been excluded. AVMs and aneurysm are extremely rare in neonates, but both must be excluded before surgery is considered and extensive genetic testing commenced. The potential of a genetic mutation should be especially considered if there is evidence of glaucoma or cataract. Haemorrhagic disease of the newborn is still prevalent in regions of the world where vitamin K is not administered as routine to neonates.

PAIS is rare following uncomplicated vaginal delivery or elective Caesarean section without labour. Freud, who first trained and worked as an obstetrician before transferring to psychoanalysis, is reported to have suggested that delivery of a healthy child required both the efforts of mother and child. Therefore, one could suggest that if the fetus cannot move and assist in the process due to a PAIS then this may predispose to a difficult delivery with maternal injury and hypoxic injury for the neonate. The literature is often interpreted as PAIS being the result of a causative hypoxic insult rather than reflecting the potential that in utero PAIS may have predisposed to the hypoxic event.

PAIS commonly presents with seizures, characteristically (94% of cases) unilateral limb motor seizures, typically within the first few days following delivery, but PAIS is often asymptomatic during the newborn period. The lack of symptoms in the neonate may reflect the distant time of the event from delivery (Hart et al 2018). PAIS is a common cause of childhood hemiplegia, but that clinical presentation may take years to be recognised (Rutherford et al 2012). Therapy is usually supportive (oxygen, fluids, anti-epileptics etc) in the neonatal period.

Imaging in the neonatal period will demonstrate restricted diffusion for 5-7 days in the affected region of the brain and possible early Wallerian degeneration in the connected white matter tracts which may last for longer as reported by Tony Hart in one of the papers from his PhD work (Hart et al). For instance, a left MCA infarct may produce Wallerian degeneration in the corpus callosal fibres connecting the affected cortex to the opposite hemisphere and may also affect the corticospinal tracts extending down to the same side cerebral peduncle and then the brainstem. There will be acute loss of grey-white matter differentiation on T1 and T2 weighted images in the affected cortex with subjacent white matter high T2 and low T1 signal. There is subsequent focal cystic encephalomalacia in the distribution of the infarcted tissue. There may be transient cortical laminar necrosis (high T1 signal and mild low T2 signal) before volume loss and marginal gliosis if the PAIS occurs after 28 gw as we have demonstrated in our group's papers based on our clinical experience (Johns et al). If the infarct occurs earlier, before glial cells have matured and thus can attempt to produce a reparative process then there will be no marginal gliosis and imaging follow-up will demonstrate a porencephalic cyst.

DVST

Cerebral dural venous sinus thrombosis (DVST) is a common cause of intraventricular haemorrhage and/or parenchymal haemorrhage at term (Wu et al). DVST can be a clinical mimic of HIE and is more likely to oocur in encephalopathic neonates who have been stressed due to HIE and possibly other causes such as hypoglycaemia and kernicterus. Reduced feeding can produce a prothrombotic tendency as can an inflammatory response. DVST can also radiologically mimic HIE due to intracranail haemorrhage and brain swelling and oedema due to venous hypertension and / or ischaemia. Straight sinus thrombosis is commonly associated with thalamic haemorrhage (often bilateral) with possible subsequent intraventricular extension. Presentation is often non-specific with lethargy, irritability, or seizures (Ferreiro et al).

If DVST is diagnosed, then a thrombophilia screen could be performed to assess for risk factors (Ramenghi et al). Thrombophilia can be transient, for instance if there is dehydration or if there is a transient protein-C deficiency in an infant of a diabetic mother (Carvalho et al, Vielhaber et al). DVST is also common in neonates with meningo-encephalitis (Hughes et al) but no cause is found in the majority of cases of neonatal DVST.

Following DVST venous pressure escalates in the vessels and parenchyma drained by the occluded vein and haemorrhagic infarction can develop in this region due to venous congestion, vasogenic oedema and increased capillary hydrostatic pressure. IVH can also ensue by direct extension of haemorrhage from the parenchyma.

Treatment options include supportive measures with rehydration, treatment of infection or other causes, treatment of seizures and treatment of iron deficiency if present. Anticoagulation is surprisingly (until one assesses the lack of significant supportive literature) more controversial amongst physicians and various treatment regimens are employed, especially varying if there is evidence of intracranial haemorrhage.

Ventricular enlargement can follow intraventricular haemorrhage, this is then followed by raised intraventricular pressure due to obstructed CSF circulation that can lead to trans-ependymal CSF flow with periventricular white matter damage especially at the anterior tips of the frontal horns and the posterior tips of the occipital horns. Clinically the neonatologist should suspect raised intraventricular / intracranial pressure when there is a head circumference which enlarges beyond the 99th centile and in the presence of sunsetting pupils. Neurodevelopmental outcome is often poor, with or without the development of hydrocephalus (Moharir et al). Recurrence rates appear to be low (Ferreiro et al).

PWMI

Punctate white matter (PWMI) lesions demonstrate high T1 and low T2 signal at neonatal brain MRI. They have traditionally been associated with injury to the preterm brain but are now reported in term brains at beyond 36 gw when they can present with DWI changes. The lesions can completely disappeara at followup MR imaging or they may manifest as areas of persistent gliosis (Logitharajah et al, Kersbergen et al, Hayman et al). In a population of 42 infants PWMI are associated with perinatal asphyxia (19/42) and genetic mutations (though cause and effect of the mutations is inconclusive). 5/42 had hypoglycaemia, with one metabolic disorder

diagnosis and one parecho-virus infection (Hayman et al). However, over half of the children in the population would have been imaged for perinatal asphyxia, thereby cause and effect cannot be attributed to the asphyxia.

Most lesions in this term (36 gw or older at delivery) group were described as appearing in clusters and are predominantly found in the parietal region (Hayman et al). 30/42 in the Hayman paper had more than 6 lesions which is a predictor of poor outcome in premature infants with PWMI. Description of lesions as being either linear or cluster in distribution is based on previous work in 112 preterm infants from the Utrecht group and the images in the paper only weakly support such a subgroup distribution of lesions (Kersbergen et al). The Kersbergen paper suggests that associated DWI rather than SWI changes may be associated with increased risk of developing CP. CP was diagnosed in 9/112 but 6/9 had new/extra lesions at a term equivalent MRI. Associated risk factors such as clotting factors and cardiac anomalies were not clearly excluded and so this evidence is weak.

Clinically they may present with seizures (24%). In those patients in the study who had a follow up MRI at 18-24 months for evaluation of clinical concerns then irreversible white matter injury was demonstrated (Hayman *et al*). However, 2/9 infants who had a follow up MRI at less than 3 months no longer had evidence of PWMI with no gliosis or white matter volume loss. The case in figure 4 in the Hayman paper where they state that there is evidence of white matter volume loss is unconvincing at best and was in a patient with coexistent DVST and where an intermediate time point MRI demonstrated ischemic brain lesions appearing at day 8 follow up MRI. Most children (32/37) had unremarkable clinical follow up. Neurodevelopmental outcome was poorest amongst those children who also had a genetic disorder.

Birth trauma

Birth trauma may mimic HIE with encephalopathy in neonates and is more likely to occur in neonates that experienced a difficult or instrumental delivery (ventouse, forceps, manual disimpaction etc). The pattern of injury will rarely if ever overlap, but a significant traumatic birth injury might produce a reduction in blood volume (subgaleal haematomas, extradural haematomes etc) sufficient to induce a peripheral perfusion injury to the brain or even a cardio-respiratory collapse with injury to the basal ganglia.

It is amazing that most or all children do not go on to suffer from a traumatic injury to the head and/or brain following vaginal or instrumental delivery, but clinically significant intracranial injury is rare. Soft tissue injury to the scalp with haematoma formation is relatively common but does not produce subsequent neuro-developmental problems. The percentage of children who suffer from fractures of the skull vault is very small as the skull can remodel with overlapping of the sutures and bone plates.

Extradural haematomas and/or subdural haematomas requiring evacuation are very rare though small subdural haematomas are present in a large proportion of neonates, with increased detection rates as neonatal MR scan quality improves (Whitby et al 2004). Small volume subarachnoid blood is relatively rarely demonstrated and of no clinical concern in isolation. Contusion and tear of the brain cortex is rare.

There is an increasingly recognised group of children injured at delivery who are born to mothers with small pelvic outlets or to obese mothers. The mothers often have labour augmented by syntocinon (synthetic oxytocin)

with the fetal head becoming wedged in the true pelvis above the ischial spines. Ventouse cap and/or forceps delivery cannot be achieved as the head is so high in the true pelvis and therefore extraction via a Caesarean section is required. The fetal head is so wedged in the bony pelvis that manual manipulation of the fetal head is required, either from above by the obstetrician, possibly with use of forceps blades, or from below with transvaginal manual pressure on the palpable head. In this group extra-axial haematomas requiring evacuation, and tears / contusions to the brain are far more common.

Further research is required to assess for imaging features which may help to predict which fetuses will struggle to descend through the birth canal and for whom early transabdominal delivery should be offered to the mothers.

3.11 Post-natal injury

Meningo-encephalitis

In older children meningo-encephalitis is a rare but potentially life-threatening condition. Bacterial meningitis can either be the result of blood born bacterial infection or direct spread from either the petro-mastoid air cells or the paranasal air sinuses. Blood born infection is more likely in the immunocompromised, those with congenital cardiac problems and those with poor nutrition. Direct spread from the local petro-mastoid air cells or paranasal air sinuses is rare (less than 1 %) but is more likely with chronic infection (De Oliveira Penido et al). Bacterial meningitis can be associated with a wide range of direct or indirect complications including hypoperfusion, hydrocephalus, abscess, cerebritis, thrombosis, infarction, ventriculitis and empyema (Hughes et al). In the long term there is an increased risk that the children will develop a shunt dependent hydrocephalus, though this is reducing with improved antibiotic regimens (Cole et al). Neuro-surgical intervention with burr hole aspiration, and or craniotomy is sometimes required.

Viral meningo-encephalitis is rare in older children in the UK and is most often due to the Herpes Simplex type 1 virus (HSV 1). Herpes zoster can also cause a meningo-encephalitis as well as rarer viruses (e.g., Japanese B virus). The outcome is poorer with any delay in initiating anti-viral therapy.

In neonates, bacterial meningitis often presents in the first few days of life, though presentation can be delayed for a few weeks. The presentation is

often non-specific with low grade pyrexia, grunting, chest infection, poor feeding and irritability. White cell count and inflammatory markers such as CRP are not necessarily raised at presentation. As the disease progresses focal seizures, increasing head circumference and focal weakness may become manifest as blood tests become increasingly abnormal. Infection is usually acquired in utero or as the fetus descends through the birth canal.

Infection is most common in those whose mother suffered from chorioamnionitis / funiculitis during the latter stages of pregnancy, those whose mothers had prolonged rupture of membranes (PROM) and/or maternal pyrexia, and those whose mothers had colonisation of the lower uro-genital tract. Foul smelling infected meconium may be present at delivery. High vaginal swab culture growth, maternal or neonatal blood cultures and placental histology / culture may all give clues to the pathogenic organism. Group B Streptococci is the commonest bacterium acquired in the neonatal period, but there are many other pathogens which can be the cause of sepsis and meningitis (e.g., Listeria, Serratia, Candida etc). The complications of neonatal bacterial meningitis are the same as those in older children. Meningitis and intraventricular haemorrhage are the commonest causes of a neonate developing a shunt dependent hydrocephalus.

Bacterial infection (for instance in older children from prior asymptomatic carriage of pneumococcus in the nasopharynx) first invades the blood stream, there follows multiplication of the bacteria in the blood stream causing symptomatic infection (sepsis). There is then spread from the blood stream to the meninges, initially without specific meningeal symptoms, but with continuing symptomatic blood stream infection. The time interval between blood stream infection and meningeal invasion varies between different organisms and within organism strains. It may be that a threshold

number of organisms for an individual must be present in the bloodstream before meningeal invasion can take place. The threshold can be determined by host immunity, concomitant viral (Influenza especially) infection and bacterial virulence.

Once meningitis becomes symptomatic clinically there can also be involvement of the petrous bone labyrinth and subsequently sensorineural deafness can ensue. The probable mechanism of hearing loss is the spread of bacteria and / or toxins and / or inflammatory mediators to the cochlea via the cochlear aqueducts (Tsuprun et al). Imaging of the petrous bones may remain normal despite the sensorineural deafness. Gentamicin may cause sensorineural deafness if blood levels are raised due to direct toxicity on the eighth cranial nerve.

In adults earlier antibiotic administration has been demonstrated to improve outcome (Aronin et al). At the time of presentation hypotension, altered mental status and seizures were independently associated with poor clinical outcome. Therefore, early antibiotic treatment following LP and blood cultures are advised for suspected bacterial meningitis, especially if there are seizures and/or altered mental status.

Neonatal viral meningo-encephalitis is extremely rare and is most commonly due to the acquisition of a Herpes Simplex type 2 (HSV 2) viral infection as the fetus passes through the birth canal of an infected mother (genital herpes). It can also be acquired after delivery.

There are three potential clinical manifestations (Anzivino et al, James and Kimberlin). 45% present with vesicular skin rash, eye keratitis /

conjunctivitis and mucous membrane involvement which has a high risk of progressing to nervous system infection. 30% present with CNS infection which may be non-specific with lethargy, poor feeding, irritability, and seizures. 2/3 also have a vesicular rash. 25% present with disseminated infection affecting multiple organs (e.g., liver, lungs, adrenals) and often there is CNS infection. A vesicular rash is not always present in this last group. Therefore, identification of a vesicular skin rash is the most valuable sign for early identification and treatment of HSV-2 before there is CNS involvement.

Early instigation of anti-viral treatment with high dose intravenous acyclovir can lead to a good outcome. The diagnosis is often confirmed following lumbar puncture and then laboratory PCR (polymerase chain reaction) assessment for HSV 2 (Anzivino et al and James & Kimberlin).

Neonatal parecho-virus and enterovirus infection can both produce diffuse white matter injury which can mimic PVL as the distribution of injury is similar. However, the branching candlestick appearance near to the trigones and frontal horns is characteristic of these increasingly diagnosed viral infections (Brownell et al, Verboon-Maciolek et al).

Metabolic disorders

Metabolic disorders are genetically acquired but may present in the vulnerable neonate. For instance, mitochondrial disorders, urea cycle disorders, nonketotic hyperglycinaemia, molybdenum co-factor deficiency and maple syrup urine disease are just a few of the more common metabolic

disorders presenting in the first days of life. The neonate is often well at delivery but then presents soon afterwards once they must metabolise their own abnormal biochemistry (rather than the maternal circulation performing this function via the placenta) or as increased metabolic demand arises as metabolites have not been provided by the mother.

Some of the metabolic disorders may be confused with HIE by the unwary or inexperienced reporting radiologist, but HIE should be easily excluded by analysis of the distribution of lesions and restricted diffusion, and interrogation of the clinical history and biochemistry. MR spectroscopy may be very useful in diagnosing some of these conditions, for example non-ketotic hyperglycinaemia has a specific extra glycine peak visible at 3.5 ppm.

Further investigation of children with normal MRI findings in CP has been suggested but the screening of such children for neuro-metabolic diagnoses (i.e., non-CP) rarely produces an alternative diagnosis. Leonard et al reported 23 cases in which dyskinetic CP cases with normal MRI scans were investigated but no new diagnoses were discovered (Leonard et al).

Cardiorespiratory impairment

Early cardiac dysfunction in the post-natal period, whether due to electrical or physical dysfunction may lead to brain injury. The injury tends to affect the deep vascular watershed territories of the cerebral hemispheres (Peyvandi et al, Kelly et al). There may be acute encephalopathy, seizures, and focal neurology. The early MRI features will be of restricted diffusion (if imaged within the first 5 days after the insult) with high T1 and low T2 signal in the centrum semi-ovale. There will be long term gliosis and white matter

volume loss. The patient may develop spastic hemiplegia or quadriplegia (depending on the degree of asymmetry of the injured brain).

Early respiratory dysfunction will tend to cause a watershed injury (Riley et al) as demonstrated in our case report of RSV bronchiolitis in a neonate. Early onset encephalopathy will be present, and the child may go on to develop cognitive disability and spasticity.

These cardio-respiratory disorders may be impossible to differentiate clinically and radiologically from chronic partial asphyxia. If a child suffers from a collapse in the postnatal period, then MRI within five days of the ictus, accompanied by DWI, will allow the reporter to better inform the clinical teams of the likely timing and cause of the brain injury.

3.12 Developmental impairment

Clinical assessment and grading

Developmental impairment in a child often prompts clinical investigation with genetic, biochemical and MR imaging. Developmental impairment may have motor, speech, behaviour, and cognitive components. Developmental impairment will also often prompt a forensic investigation to look through the entire clinical history from before birth to the time of diagnosis and the radiologist will often be asked to define when any brain injury occurred, by what mechanism and how the injury manifest on imaging has produced the clinical constellation present in each child.

Early developmental impairment (EDI) occurs when a child's developmental skills fall two standard deviations or more below the population mean in two or more developmental domains. The developmental domains are speech, fine motor, gross motor, cognition, and behaviour. 10-12% of children have a developmental impairment, and 1-3% of children have EDI. The causes of EDI include genetic, metabolic, antenatal, endocrine, and infective conditions, amongst others. Good quality clinical paediatric assessment is required to assess and classify the child's developmental impairment.

Poor birth outcome, malnutrition, chronic ill health, inadequate stimulation, and other environmental factors may impede development. Early identification and prediction of developmental impairment should promote clinical teams to commence timely interventions which may go on to prevent delay in achieving milestones and promote competencies. With HIE in the

term infant the neuroradiologist reporting the neonatal MRI may assist with early identification of expected cognitive and motor function impairment, which may then prompt specialist services with therapy and assisted devices and special education with planning for assistance and support to impact long term neuro-cognitive development positively.

Investigation

The number of recommended investigations has increased over the last 20 years, although opinion varies on whether children with EDI are investigated appropriately, and the usefulness of specific investigations. The reasons why families wish to know the aetiology include: validation, i.e. proof of a credible problem and to help explain the problem to the affected child or siblings and others, to provide prognostic information and help set realistic expectations / plans, for any potential treatment, to allows better access to educational support, to provide the opportunity for early intervention , to provide support opportunities, the “need to know” and for prenatal testing and recurrence risk.

We asked clinicians who subscribe to the email lists of the British Paediatric Neurology Association (BPNA) and British Academy of Childhood Disability (BACD) to complete an online questionnaire on their views and approach to children with EDI (Hughes et al). Our aim was to assess the degree in variation and attitude towards the investigative approach of children with EDI. The questionnaire can be viewed at: www.surveymonkey.com/s/disordereddevelopment.

107 clinicians replied. 93 (86.9%) were consultants, 6 (5.61%) were associate specialists, 3 (2.8%) staff grades, 2 (1.9%) speciality doctors, with a single ST4-8 trainee, allied health professional and nurse practitioner. All saw children with EDI as part of their work. 67 (62.6%) responders worked in a child development centre (CDC), 37 (34.6%) in paediatric neuro-disability, 21 (19.6%) in general paediatrics, 17% (15.9%) in community paediatrics, and 11 (10.3%) in paediatric neurology. The overlap in figures is explained by responders who work across more than one department. 65 (61.9%) of responders said their department had a protocol for the investigation of EDI, 36 (34.2%) did not and 4 (3.8%) did not know.

The most commonly reported additional clinical factors to increase the likelihood of a clinician requesting investigations were increasing severity of disordered development, dysmorphia, family history of illness or disordered development, microcephaly and epileptic seizure disorder. Overall, 55/89 (61.8%) of responders felt children with EDI and additional clinical features were investigated the appropriate amount, 21 (23.6%) felt these children were under investigated, and 6 (6.7%) felt they were over-investigated.

75/89 (84.3%) of responders investigated children with isolated EDI, 11 (12.4%) did not. The investigations thought to be most likely to determine the aetiology in isolated EDI were CGH microarray, audiology referral, creatinine kinase, ophthalmology referral and fragile X 33/89 (37.1%) respondents said parental wishes affected their decision on which investigations to perform in children with isolated EDI, and 41/89 (46.1%) were sometimes affected, and 14 (15.7%) were not.

31/89 (34.8%) of responders thought children with isolated EDI were investigated the right amount, 18 (20.2%) felt they were under investigated, and 34 (38/2%) over-investigated.

In Sheffield we reviewed the cost of investigating children with early developmental impairment (EDI) using both our local guidelines of the time and previous guidelines (Hart et al). Costs ranged from £380 per patient in 1997, assuming that microarray rather than karyotype was performed, to £567.28 locally for first line investigations. MRI head under general anaesthetic is charged at £932 per patient as a second line investigation in Sheffield. 3% of children have EDI, with a UK birth rate of 777 000 per annum. If first line tests were completed, then charges would vary from £8.9 to £13.2 million per year. If MRI was added for 55% of cases, then costs rise to £20.8 to £35.0 million per annum. Therefore, we suggested that a prospective study of children with EDI was required to streamline and optimise the investigative pathway for EDI with cost effectiveness analysis.

It may of course be argued that earlier and more accurate diagnosis of the cause of EDI may facilitate more individualised early treatment and reduce unnecessary, expensive, and late investigations. Early focussed treatment may improve outcome and reduce further long-term care and therapy costs.

4 Current practice for HIE imaging and reporting

When to image to assist with outcome prediction

Early imaging guidelines for imaging of neonates based their MR protocols on the available literature. The early literature was based on limited imaging sequences performed in more mature neonates in whom imaging was performed after day 10 when the neonate was clinically more stable after their perinatal insult (such as HIE) because there was not the available technology in terms of MR compatible incubators and NICU sited MR scanners. That work suggested that diagnosis should be based on T1 imaging features (high T1 signal in areas of pathological damage is presumed to appear after day 10, although adult stroke MR imaging experience advises that not all damaged brain demonstrates high T1 signal – cortical laminar necrosis – after injury) rather than the more acute pathology sensitive DWI appearances and the acute brain swelling / oedema sensitive T2 sequences. Imaging was also performed without the use of blood sensitive sequences (e.g., SWI) and without the use of biochemical / physiological sequences (e.g., MR spectroscopy).

The British Association of Perinatal Medicine (BAPM) has published a framework document for fetal and neonatal brain MRI (BAPM 2016). The guideline suggests that all neonates who have suffered from encephalopathy, and those with seizures but no encephalopathy, should have an MRI between days 5 and 14. The guideline mentions preterm infants and advises that they should be imaged at term equivalent if the CrUS was

grossly abnormal (including focal increased echo-density persisting for more than 3-4 weeks) or with unexplained abnormal neurology. All scans should be double read, but by whom is not specified.

As MR scanner and MR compatible technology has evolved the literature has expanded with more papers describing imaging features of perinatal pathology in the first 5-7 days after delivery (Weeke et al). We have reported imaging features resulting from damage from HIE in fully myelinated brains (Griffiths et al 2010, Connolly et al 2007) and clinically have been performing our imaging in neonates between days 3 and 5 after delivery for many years. This early imaging and accurate double reporting of the MR scans has produced more useful and robust early prognostic and diagnostic information.

Medicolegal impact of ENS

The NHA litigation authority (NHSLA) has recently introduced an early notification scheme whereby any child who is admitted to NICU unexpectedly has a midwifery, obstetric and neuro-radiology preliminary opinion. A neonatal opinion may also be requested. The opinions are presented to the family with the hope that either they will be reassured or that an easy path to a settlement may be adopted. If the family are reassured, then routine clinical follow up will ensue as standard. If there is evidence of brain injury and there is substandard midwifery or obstetric care, then the NHSLA and their legal advisors will attempt to mediate an early settlement avoiding expensive legal and medical expert fees.

Working in this medicolegal milieu has prompted investigation of imaging for HIE and other causes of neonatal encephalopathy with a view to improving the prognostic and diagnostic information which can be provided to clinicians and the legal system. We have focussed on imaging the neonate, improving access to high quality MRI, and thus improving the quality of the radiology reporting of these cases.

The paediatric neuroradiologist will often be asked three questions in the early notification scheme cases; what the nature of the pathology / pathologies is, what is like likely impact on long term prognosis, what was the timing of the insult / insults causing the neurological injury.

It is the question of timing which necessitates early neonatal brain MRI. DWI at about day 5 will allow the radiologist to exclude later brain injury from a late hypoglycaemia, meningitis/encephalitis, peripheral perfusion injury from RSV bronchiolitis or a hypoxic injury from a cardiorespiratory collapse.

An MRI at about day 5 with DWI will reveal pseudo-normalisation of an in utero chronic partial asphyxia with auto-recovery 3 days prior to admission to hospital far better than CrUS would be able to narrow down the time window for the insult.

New technologies

To assist the reporting radiologist with prediction of outcome following HIE using MRI various groups have utilised advanced imaging, with computer analysis to evaluate MRI.

Lally and colleagues in the MARBLE study used thalamic MR spectroscopy at days 4 to 14 to evaluate children that received therapeutic hypothermia for HIE and correlated with outcome at 18-24 months (Lally et al). Imaging had to be done at 3 Tesla (making it impractical in all acute care settings) and the MRS protocol was over 20 minutes for a single sequence so unsurprisingly over half of cases could not be evaluated. NAA concentration could be calculated from the software applied to the MRS and independently accurately predicted outcome. Single voxel MRS over the thalamus will also evaluate injury from both CPH and APH so the pattern of injury from HE may not be so easily predicted from the MRS NAA concentration.

In Sheffield and Manchester, we evaluated computer analysis (Stivaros et al) to quantify structural changes in the corpus callosum in children with APH. This used segmentation of the corpus callosum and demonstrate good correlation with focal thinning of the corpus callosum related to the transcallosal fibres extending from the cortex of the central sulcus to long term outcome

Diffusion tensor imaging (DTI) has been used extensively for research into outcome from HIE and systematic reviews have now established that in a tertiary centre FA values and evidence of restricted diffusion in the posterior limb of internal capsule, corpus callosum and hippocampus may find correlation with outcome (Salas et al, Dibble et al). Application of this technology in the acute care setting of a DGH is difficult to envisage without centralisation of imaging and data processing / review to a limited number of centres.

5 MRI Report scoring systems

Machie et al have shown that using a scoring system to grade the extent of injury from HIE on MRI in infants with mild HIE and subtle brain abnormalities was most often detected with a more complex or detailed scoring system, but that there was greater inter-rater reliability with a simpler scoring system (Machie et al). They compared the Barkovich, NICHD NRN and Weeke scoring systems in 42 newborns with moderate to severe HIE who received therapeutic hypothermia. The Weeke scoring system is the most complex using a scoring system up to 57 and uses MRS, DWI and several subtle anatomical markers and detected abnormality in 24/42 newborns whilst the simplest system from Barkovich only detected abnormality in 3/42 (Martin and Barkovich). At least two readers (not a constant number) reached agreement levels of k = 0.9 for the simplest scoring system to 1.0 for the Weeke system. There was however no correlation in this paper of reporting agreement and prediction of outcome We need to test an achievable scoring system in the UK and compare with outcome.

How I report neonatal MRI

For medicolegal reporting, when late MRI has been obtained after two years of age corrected, I use an amalgamated scoring system devised from the STN (Griffiths et al 2010) and the vermis APH (Connolly et al 2007) papers. This is my personal adapted severity scoring system for MR evidence of brain injury from APH at beyond 2 years corrected age.

I expect that axial T2 TSE/FSE, FLAIR imaging (preferably 3D), SWI or GRE T2*, T1 volume imaging and coronal T2 TSE imaging with a short ETL (8 or less) will be included in the MR scan protocol (Radon et al).

The table is a very subjective measure of the extent of brain damage and the duration of the period of damaging APH, but it has been trialled over many years and correlated with expert perinatal obstetric and neonatal case review and also with subsequent long term paediatric neurology follow-up, often with CP motor disability classification by an expert and with a GMFCS classification.

By convention, based on the Myers model, people have described a period of 10 or more minutes of non-brain damaging acute profound asphyxia before immediately and subsequently being followed by brain damaging acute profound asphyxia (Myers 1971). The brain damaging acute profound asphyxia has been subdivided in to 3 five-minute aliquots (10+0-5, 10+5-10, 10+10-15) and any brain injury beyond those 15 minutes of brain damaging asphyxia has been considered to not be survivable.

*The duration of the non-brain damaging APH can be reduced below 10 minutes in cases of shoulder dystocia

Adapted **MRI scoring system for APH in children over 2years of age**	Duration of Nonbrain damaging asphyxia* + **brain damaging acute profound asphyxia(minutes)**	Putamen	Thalamus	PCWM	**Overall impression of injury to the brain** **Including** **Hippocampi, head of caudate, STN, anterior vermis** Signal change need only be demonstrated on one image sequence
Mild	At least 10 * + **0-5**	Minor signal change	Minor signal change	Minor signal change	Some regions have signal change but no volume loss. Not all regions affected
Moderate	At least 10 * + **5-10**	Signal change with mild volume loss	50% signal change	Signal change with mild volume loss	Most regions have signal change with early volume loss in some regions
Severe	At least 10 * + **10-15**	Signal change with volume loss	Signal change throughout	Signal change with volume loss	All regions have signal change Volume loss may be severe in some regions and there may be microcephaly

Table 5.1 How I report follow up MRI for HIE in the term infant

Long term impact of HIE and how to link imaging to outcome?

HIE at term may produce neuro-cognitive disability in the neonates who suffer from APH and / or CPH. The GMFCS grading system allows the clinician to score motor impairment. Cognitive disability can be compared to expected level of function from parental and sibling attainment.

The APH scoring system for long term MRI (table 5.1) tends to produce robust correlation with outcome. The mild MRI changes group have GMFCS level 1 or 2 outcome with preserved cognition. The moderate MRI changes group have GMFCS level 2 to 4 outcome with good cognition. The severe MRI changes group have GMFCS level 4 or 5 outcome with poor cognition.

APH will tend to produce a dyskinetic choreoathetoid cerebral palsy with variable dystonia, spasticity, bulbar palsy and rarely a cognitive impairment affecting the most severely affected group only. MRI assessment tools to predict outcome from long-term follow up MRI and acute MRI have been tested by several groups with often increasingly complicated and impractical scoring algorithms and imaging protocols. The GMFCS clinical score for cerebral palsy is used but cognitive impairment is now more difficult to predict as therapeutic cooling appears to significantly improve motor outcome and imaging appearances but to overlook APH impact on cognition. The scoring system for HIE which we will evaluate will also have a simplified scoring algorithm for APH.

CPH will tend to produce a spastic quadriplegic cerebral palsy with microcephaly, seizures, and cognitive impairment. There have been few

attempts to link acute MRI findings in CPH to long-term outcome. This is even though CPH is probably more common than APH. However, the easier linking of APH to a CTG terminal bradycardia and less variable clinical features and aetiology allow easier correlation with aetiology and outcome for doctors and lawyers. In my section on future research, I will attempt to evaluate an MRI assessment tool for acute neonatal MRI to predict long term cognitive outcome in CPH and with GMFCS grading.

6 Future research

Future work and how this will be important for the NHS and medicolegal work. How can this be applied to suggestions for improved imaging and imaging interpretation?

The work that I have been involved in over the last 17 years in Sheffield has focussed on the assessment with MR imaging for the brain and spine of the fetus, neonate and child. Imaging technology development has allowed improved MR assessment of the neuro-axis. I have been involved in the assessment of new imaging techniques, MR scanners and MR compatible neonatal transport PODS which have allowed better and more complete MR imaging assessment of the neonatal brain. We have used the scan data to better assess the pathologies which go on to produce cerebral palsy and early developmental impairment.

We have investigated neonatal HIE and its mimics. We have demonstrated in utero acquired pathologies which may mimic clinically and radiologically brain injury from HIE.

We have demonstrated new anatomical substrates for subsequent clinical presentations in HIE and assessed the clinical severity of the neonatal insult and long-term neurological impairment. The ventrolateral nucleus is the region of the thalamus most often described in association with damage from APH. However, in a histo-pathological correlate study in six piglets Martin et al found that the ventral postero-lateral thalamic nucleus (a somato-sensory nucleus) is in fact the nucleus that is consistently damaged.

On axial MRI studies the antero-lateral aspect of the thalamus is the region classically involved, but the reporter should appreciate that the orientation of the thalamus is oblique not AP to the MRI axial scan plane (the AC-PC line drawn from the anterior to the posterior commissure on a sagittal image defines the axial plane for MRI imaging). The nucleus of the thalamus most often damaged by APH is the ventral postero-lateral nucleus though other nuclei including motor nuclei such as the anterolateral nucleus may be damaged in more severe APH.

I have emphasised the importance financially and in clinical resources to the NHS of these pathologies. By improving diagnosis, prognostication and then supporting early targeted interventions outcomes for these children and their families may be changed for the better.

Routine neonatal imaging with achievable imaging protocols (not just in tertiary and quaternary centres like Sheffield) should become attainable for all UK NICUs. The image protocols should then be optimised and simplified so that reliable image interpretation can be produced, probably with specialist centre secondary reporting / support.

The radiologist must also consider and exclude the HIE mimics which I have detailed previously. I would suggest the adoption of the Sheffield neonatal MRI brain request form with answers to the 18 specific questions on the request card available to the reporting radiologist. The radiologist must be able to interpret the clinical data supplied and thus inform their report. I would add that clinical details regarding therapeutic cooling including time of commencement after delivery should be available to the radiologist. Congenital brain, orbit, spine, and petrous bone malformations must be excluded. The acute findings on MRI related to kernicterus, birth trauma,

dural venous sinus thrombosis, PWMI, perinatal viral infection, in utero pathologies, acute and chronic metabolic decompensation, PAIS, neonatal hypoglycaemia cardiorespiratory insufficiency, and bacterial meningitis must be considered and hopefully excluded prior to confirming brain injury from HIE.

The Utrecht MR scoring system for neonatal HIE is too complicated for widespread application in the UK with a final score calculated out of 57 (Weeke et al). For instance, many UK neonate imaging centres do not even perform MR spectroscopy, let alone employ it as part of their routine neonatal imaging protocol despite the recent MARBLE study outcome suggesting that MRS at 3T is the best predictor of outcome following HIE (Lally et al).

Therefore, one of my next projects will focus on refining the Utrecht neonatal MR protocol to allow reliable and widespread application of brain MR to investigation of neonatal HIE in the UK.

A limited set of images are essential and should be prioritised in the imaging protocol. Axial ssFSE T2, Axial DWI, Axial FSE T2, axial GRE T2* and PRESS MRS on one side over the basal ganglia and thalamus. MRS normal ranges for NAA/Cr and lactate peak height should be obtained.

Coronal T1 volume may then be acquired. There is no requirement for FLAIR imaging. Proton density sequences can be helpful.

I suggest two simple scoring systems to be used in conjunction when reporting all scans for neonatal encephalopathy, one each for APH and CPH, which both are much simpler to use than the Utrecht scoring system.

Adapted APH scoring system for neonatal brain MRI

Signal change in the structures may be high on T2w, high on T1w or they may demonstrate restricted diffusion (high b700 with low ADC).

Signal change may be unilateral or bilateral. The more significant side of injury should be scored.

Acute profound asphyxia neonatal MRI score	Normal Score 0	Mild less than 50% Score 1	Extensive over 50% Score 2 Signal change need only be demonstrated on one image sequence
putamen	Score 0	Score 1	Score 2
thalamus	Score 0	Score 1	Score 2
PCWM	Score 0	Score 1	Score 2
Hippocampus Signal change yes or no			Can only score 0 or 1
Head of caudate Signal change yes or no			Can only score 0 or 1
Reduced NAA/Cr			Can only score 0 or 1
Elevated Lactate			Can only score 0 or 1
Total Overall score out of 10			

Table 6.1 Proposed MRI scoring system of neonatal brain MRI in APH

Adapted CPH scoring system for neonatal brain MRI

Signal change in the cortex may be represented by high T2w signal with loss of cortical grey-white matter differentiation, cortical high T1w signal (highlighting), or the cortex and subcortical white matter may demonstrate restricted diffusion (high b700 with low ADC). Cortical highlighting is often accompanied by subcortical low T1w signal. I ignore deep white matter signal change and restricted diffusion as I am uncertain if this is primary pathology, artefact, or secondary early Wallerian degeneration. The extent of cortical signal change may be measured with a chord to the brain surface / inner table of the skull. Less than 2cm is mild. More than 2cm is extensive.

Chronic partial asphyxia neonatal MRI score	Normal Score 0	Mild signal change Score 1	Extensive signal change Score 2 Signal change need only be demonstrated on one image sequence
Right frontal watershed cortex	Score 0	Score 1	Score 2
Right parietal watershed cortex	Score 0	Score 1	Score 2
Left frontal watershed cortex	Score 0	Score 1	Score 2
Left parietal watershed cortex	Score 0	Score 1	Score 2
Reduced basal ganglia NAA/Cr	Score 0	Score 1	Can only score 0 or 1
Elevated basal ganglia lactate	Score 0	Score 1	Can only score 0 or 1
Total Overall score out of 10			

Table 6.2 Proposed neonatal brain MRI scoring system for CPH

I suggest that early MR imaging by 120 hours of life (after therapeutic cooling and then rewarming has been completed) should be achieved in all encephalopathic neonates. The first advantage is that DWI and MRS data can be evaluated and that there is a narrow window for the imaging appearances of the pathology to evolve. All readers would then be able to 'get their eye in' to images produced in a smaller time window after the presumed pathology.

The DWI would also allow the radiologist to suggest that an insult had occurred prior to delivery if there was no restricted diffusion 120 hours after delivery. Neonatal hypoglycaemia, which can mimic and exacerbate HIE encephalopathy and then brain injury, is best appreciated with DWI in the five days after the insult and may be very difficult to appreciate later. I suspect anecdotally that kernicterus will have a similar diagnostic enhancement with early MRI.

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8 List of abbreviations

Apgar	The name of the author of the paper describing the neonatal level of neurological function in five domains which can all score 0-2 with a total score out of 10.
BIND	Bilirubin induced neurological dysfunction
bpm	Beats per minute
CBE	Chronic bilirubin encephalopathy
CFAM	Cerebral function monitoring
CMV	Cytomegalovirus
CNS	Central nervous system
CP	Cerebral palsy
CSF	Cerebrospinal fluid – the fluid that surrounds the brain and spinal cord and that lies within the brain in the ventricular system
CT	Computed tomography
CTG	Cardiotocograph – a measure of the fetal heart rate
CrUS	Cranial ultrasound
DVST	Dural venous sinus thrombosis
EDH	Extra dural haematoma

EEG	Electroencephalography – a formal measure of brain electrical activity
FHR	Fetal heart rate
GMH	Germinal matrix haemorrhage
gw	Gestational weeks – age of the fetus
HIE	Hypoxic ischaemic encephalopathy
HSV	Herpes Simplex virus
IVH	Intra-ventricular haemorrhage
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
NHSLA	National Health Service Litigation Authority
NICU	Neonatal Intensive Care Unit
OFC	Occipito-frontal head circumference – a measure of head size
PAIS	Perinatal Arterial Ischaemic Stroke
PCR	Polymerase chain reaction
SAH	Sub-arachnoid haemorrhage
SDH	Sub-dural haemorrhage
US	Ultrasound

9 Papers for inclusion in thesis

9.1 Initial experience of an investigational 3T MR scanner designed for use on neonatal wards

Griffiths PD, Jarvis D, Armstrong L, Connolly DJA, Bayliss P, Cook J, Hart AR, Pilling E, Williams T and Paley MNJ

European Radiology (2018) 28: 4438-4446

The Firefly project was a collaboration between Harvard Medical School, General Electric and the University of Sheffield. The plan was to produce a small field MR scanner with a small footprint which could be easily housed adjacent to or in a neonatal unit. Safety as always would be of premium importance, and we were focussed on a system which would be accepted by the neonatal clinical nursing and medical teams.

Image quality was to be judged compared to a standard 3 Tesla MR system and all imaging sequences which might be required for assessment of an encephalopathic neonate would be optimised for clinical application. The sequences included T1, T2, T2*, FLAIR, DWI, SWI, MR spectroscopy (PRESS), time of flight MR angiography and time of flight MR venography.

Introduction

Magnetic resonance (MR) imaging has revolutionised the assessment of the brain in clinical practice, and it is the most accurate method of detecting most brain pathologies in most age groups. In addition, the ability of MR imaging to produce high spatial and high contrast resolution images without exposure to ionising radiation has ensured rapid clinical uptake. One group that has not benefited from MR imaging as much as others is neonates, in whom MR imaging of the brain is fundamentally difficult on several levels. There is inherently poor contrast resolution in the neonatal brain due to its pre-myelinated state and obtaining high quality MR images in a non-sedated/non-anaesthetised baby is challenging because of movement.

A further and substantial problem is ensuring safe transfer of the baby from the neonatal intensive care (NICU) or special care baby units (SCBU) to the MR scanner. Many neonates who may benefit from MR imaging of their brain have unstable cardiovascular and respiratory function and transfer to the MR scanners (usually in a different part of the hospital or at a different hospital) introduces extra risk. The decision to perform a clinical procedure, including a diagnostic test, should be considered based on a risk/benefit analysis and, for neonates, the decision is often not to perform MR imaging. In such cases, trans-fontanelle cranial ultrasound scanning (CrUS) is often performed as it can be done on the NICU/SCBU and has been used to good effect over many years. MR imaging is being used increasingly in a targeted fashion with clinicians evaluating the risk/benefit equation on an individual basis. These factors are well illustrated in a short educational video made at Sheffield Teaching Hospital by the Welcome Trust.[1] It has been a long-term aim of our group to improve access to MR imaging of the brain in neonates and in this paper we describe our initial experience of using a physically small, but high field MR scanner installed on the neonatal ward.

Methods

The Firefly 3T MR scanner

'Firefly' is a prototype, high field (3T) MR system built by GE Healthcare, Milwaukee and is light enough at just 500 kg to be sited on normal, non-reinforced office floors, in an area of approximately 6 x 6m (including scan control and equipment rooms) is designed to have the full capability of a current clinical MR system but customised to scan neonatal brains. The 3T static magnet is a closed loop cryogenic system with a low helium volume (30L), which maintains the magnet at 4.2 Kelvin. The 5 Gauss (0.5mT) fringe field of the static magnetic field is contained within the scanner room (dimensions 2.0m x 1.3m) and has a field uniformity of 15 ppm within a 15cm diameter sphere at iso-centre. The maximum gradient strength of the system is 70mT/m and dB/dt is kept below the FDA guidelines of 300mT/m/ms by strict software and hardware control. The RF power of the transmitter is set at 4Kw to allow maximum SAR levels in the range of 2W/Kg for babies weighing up to 6kg. The internal clear magnet bore is 28.0cm, the gradient bore is 21.8cm and the internal diameter of the quadrature transmit-receive RF coil is 17.9cm. The magnet, gradients and RF systems are linked to a standard GE 'front-end' running software at release level DV25.0. The installed system is shown in figure 1a and the site plan in figure 1b.

Ethical approval

Firefly currently has neither FDA approval nor CE marking so its use in this first stage of our programme is governed by the Medicines and Healthcare products Regulatory Agency (MHRA), which is an executive agency of the Department of Health of the United Kingdom. The MHRA specified that the system could not be used for primary diagnostic purposes at this stage and that the manufacturer (GE Healthcare) should be the sponsor of the study

and obtain ethics approval. Approval was provided by a specialist paediatric Research Ethics Committee, which allowed the researchers to approach

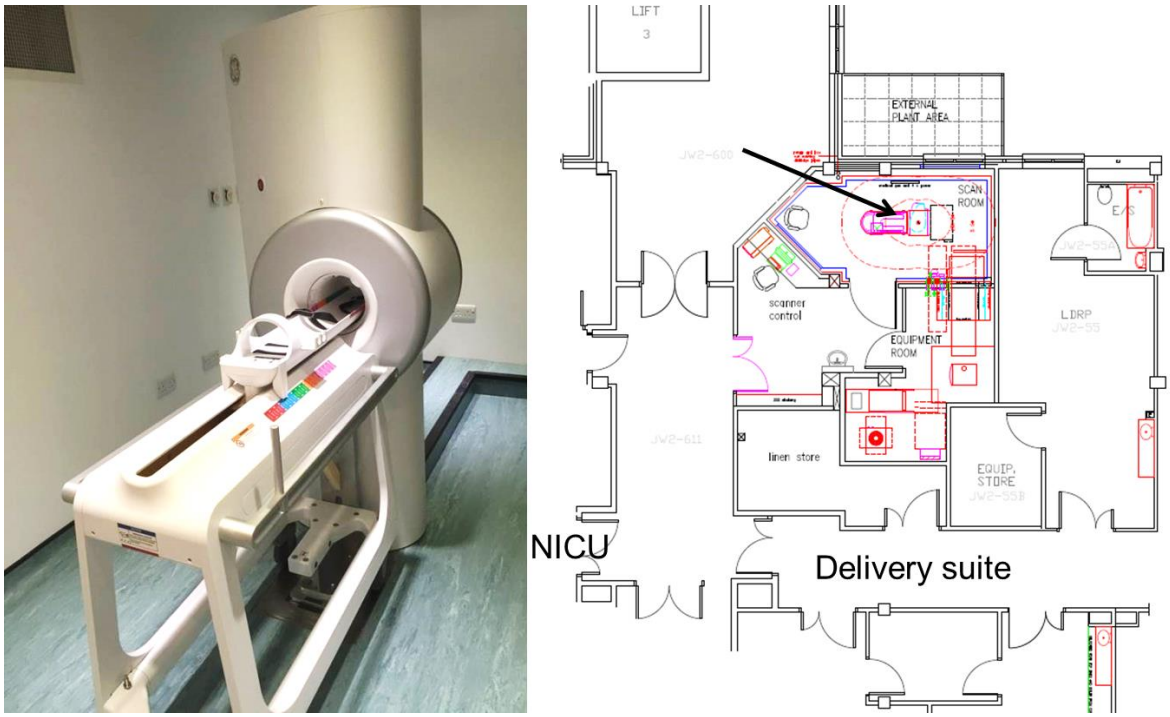


Figure 9.1.1. The Firefly 3T MR system installed at Sheffield Teaching Hospital and a plan of the MR suite showing the proximity to the neonatal intensive care unit and delivery suite. The scanner control, scan room and equipment room occupy a floor space of 6.0m x 6.5m.

families of two groups of neonates with a view to recruitment into the study as a volunteer: Group 1. Completely normal babies born at or close to term whose parents agreed to have an MR study before the baby went home.

Group 2. Premature babies that were about to go home at term-corrected age and had had clinical neuroimaging studies performed at an earlier date

All parents provided written, informed consent after reading the approved information sheet and had the opportunity to ask questions, with a target to scan between 50 and 60 babies in total.

Safety issues and patient handling

Safety considerations are paramount when designing and using an MR system for neonates. The pre-checks and preparation for the MR scan were carried out by one of two specialist research nurses associated with study (PB, JC). The scan events were scheduled to be within one hour of the baby being fed and the safety checks commenced by confirming that the head of the baby would fit into the scanner before going to the scan room, hence saving unnecessary exposure. This was done by attempting to place a soft template with the same diameter as the coil around the neonate's head before bringing them to the scan room in order to ensure that they would fit into the relatively small bore. None of the recruited babies were excluded on the basis of head size and there were no scan failures because of head size.

There are no specific safety concerns about exposing a neonate to a 3T static magnetic field,[2] although the strong field gradient at the entry to this magnet (39.8 T/m) requires a strict protocol to prevent ferromagnetic materials from entering the scan room. Parents completed MR safety screening forms for their baby and themselves, as one parent was allowed to accompany their baby in the scan room. Any monitoring device or other equipment not compatible with MR scanning was removed, and the baby changed from their usual clothing into a Velcro-fastened vest provided by the researchers to ensure there were no metal fastenings. Screening for metal prior to scanning was completed on arrival at the MR unit by the radiographer (DJ). The radiographer also ensured all ferromagnetic personal items were removed from each adult and further visual inspection of the baby was supplemented by the use of a hand-held metal detector.

Each baby's temperature was monitored and recorded in order to ensure the thermoregulation of the baby was not compromised during transfer and scanning. Temperature was first measured whilst the baby was still on the ward using a handheld electronic thermometer (Filac 3000, Covidien,

Mansfield, MA). A disposable temperature probe was then attached to the baby's axilla using DuoDerm Extra Thin, hydrocolloid dressing before transfer to the scanner suite. On arrival, temperature was recorded again using the handheld thermometer but once the baby was on the scanner the probe was connected to an MR-compatible monitoring system with a free-standing monitor in the scan room and a tabletop slave monitor in the control room (Invivo Expression MR400, Philips Healthcare, Eindhoven, Netherlands). Temperature was monitored continuously during scanning along with heart rate and blood oxygen level of the baby. The final temperature was recorded on return to the ward. A further issue for close consideration is the acoustic noise created by the scanner, which can have equivalent continuous sound levels of around 102 db(A) for some of the sequences we planned to use. As such, noise reduction of at least 22dB was required, in order to comply with IEC 60601-2-33 standards. This was achieved by using a combination of earplugs and ear protectors. Mack's® mouldable earplugs (McKeon Products, Inc. Warren, MI) gave a noise reduction rating of 22 dB (manufacturer's data) and the additional use of MiniMuffs® (Natus Medical Inc. Pleasanton, CA) provide an extra 7 dB noise reduction (manufacturer's data). These were applied just before entrance to the scan room.

Babies were transferred from the ward to the MR suite in their standard-care cot by the specialist research nurse accompanied by the parent(s). The baby was placed in a disposable sling, which swaddled them closely in order to minimise motion, help maintain body temperature and provided a secure method of transfer into the cradle of the scanner. The scan cradle is built into the scan table, which is detached from the scanner and brought into the control room. The scan table holding the baby was then taken into the scan room and manually docked with the scanner. A slide system with dual rulers on the bed and scan cradle were used to position the baby's head at the iso-centre of the scanner without the need for electrical drives for the table or positioning lasers. The whole transfer process is shown in figure 2. In the

event of an emergency or subject distress, the bed can be rapidly detached from the scanner and brought into the scan control room, where appropriate care can be provided.

MR methods

Exposure to the magnetic field was limited to one hour, including time allowed for acclimatisation to the scan room, monitoring at the start and end of scanning, positioning of the baby in the scanner, and pacifying when necessary during the scan. MR scanning commenced only when the specialist

Figure 9.1.2. Preparation of a baby for MR scanning on Firefly illustrated by a 'mock' case using a mannequin and research staff (see text for full details). The baby is changed into clothes with no ferro-magnetic components on the ward and an axillary temperature probe is attached (2a). After transfer to the atrium in the MR suite the baby is re-checked for absence of ferro-magnetic items and ear plugs, ear defenders and a vital signs monitor are applied (2b). The baby is placed in a transport sling (2c) and transferred on to the scan cradle of the tabletop, which has been detached from the MR scanner (2d). The table and baby are pushed into the scanner room (2e), the table is docked with scanner and the cradle manually slid into the bore of the MR scanner (2f).

research nurse was satisfied that the baby was settled and the initial monitoring adequate. The research nurse stayed with the baby during scanning in order to monitor the baby visually and stop the scan if there was

any concern. Approximately 40 minutes of image acquisition time was available during an uneventful scan event. We wished to optimise a full range of imaging sequences on Firefly which paralleled our current clinical MR imaging protocol on a 1.5T scanner as shown in table 1. We also wanted to develop MR arteriography and venography sequences that would be used in relevant cases.

Development of the MR protocol involved refining and trialling a single sequence before focusing on the next sequence. To begin with the imaging parameters for the T2 weighted imaging were modified until optimal contrast, resolution and scan time were achieved for both ultrafast single shot fast spin echo (ssFSE) and T2 FSE imaging. The best sequences were acquired in all subsequent cases. Long TE single voxel proton spectroscopy and T1-volume imaging sequences were added and trialled in cases 6-11, with diffusion weighted imaging and susceptibility weighted imaging (gradient echo T2* and sensitivity-weighted imaging) added in cases 9-13. Cases 13-18 were used to evaluate and refine MR arteriography and venography sequences. All sequences were acquired in cases 20-49 with further fine-tunings being made to the sequences for full optimisation. The last five cases were scanned with a protocol provided by the sponsor of the research study in order to provide the data suitable for application for CE marking.

In accordance with Ethics Committee approval, all of the images were reviewed soon after the study by one or both of the two experienced paediatric neuroradiologists involved in the study (DJAC, PDG). This first review was made in order to report any unexpected intracranial findings to the neonatologist caring for the baby. Two to three weeks later the images were formally reviewed by both reporters by consensus in order to assess the quality of the imaging and recommend any changes to the sequence parameters for future scanning. The neuroradiology reporters were asked to rate the overall quality of the imaging dataset as either i) fully evaluable.

Routine Brain Imaging								**Sequences for vascular imaging**	
	T2 ssFSE	FSPGR T1 Volume	Propeller DWI	GE	T2 FSE	SWAN	Single voxel Spectroscopy	MRA	MRV
Repetition Time (TR)	908 (min)	10	6262	600	7000	57.5	1500	21	35
Time to Echo (TE)	140	Minimum Full	60	15	124	23	144	3.4	5
Flip Angle	90	8	110	15	142	25	90	20	10
Bandwidth(KHz)	31.25	15.6	50	15.6	15.6	31.3		27.8	21
PREP TIME	-	900	-	-	-	-	-	-	-
Echo Train Length		-	20	-	16	5	-	-	-
NEX	0.55	0.75	2	2	2	0.7		1	0.63
Slice Thickness/ Slice Gap (mm)	3/0	1.0/0	4/0	3.0/ 0.3	3/0	3/0	15	1/0	2.4/0
Field of View (cm)	16x14 .4	18x12. 6	16x16	16x12	16x14.4	16x11. 2	1.5x1.5	20x14	20x13
Freq/ Phase Matrix	256/192	256/ 192	128/128	156/ 192	256/192	256/192		384/224	320/ 192
b Value	-	-	1000	-	-	-	-	-	-
Scan Time (Secs)	29	264	192	180	231	173	140	240	364
Additional		ZIP512 ZIP2			Flow comp.	Flow comp. ZIP 2		Flow comp. ZIP 2	ZIP 2

Table 9.1.1. Summary of optimised MR sequence data used in the present study.

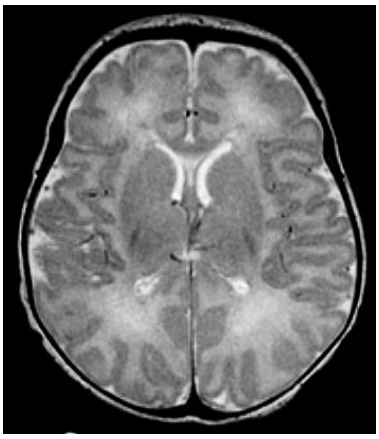
(each sequence is of diagnostic quality), ii) partially evaluable (some sequences degraded but a clinical report would have been possible) or iii) Not evaluable i.e. a clinical report could not have been made. The assessors were also asked to compare a number of aspects of image quality against the current reference standard at our institution, namely MR imaging at 1.5T. 'Poor' was used if the quality measures were worse than the current clinical standard, 'Average' if comparable and 'Good' if better than current 1.5T images.

Results

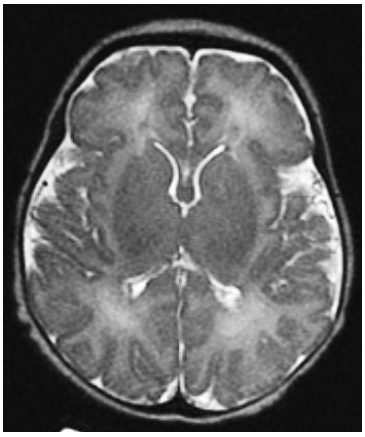
54 families provided consent for their baby to come into the study but in one case consent was withdrawn before the MR study was performed. In another case, we attempted to scan a baby but no diagnostic images were obtained because of equipment failure, therefore 52 babies had successful MR imaging. Approximately 60% of the babies scanned were born at term, defined as more than 37 gestational weeks (gw) and approximately 40% were born before 37gw. The median corrected gestational age at the time of the MR study was 39gw (interquartile range 36-40gw, full range 34-43gw), median weight was 2.8kg (interquartile range 2.4-3.4kg, full range 1.3-4.5kg) and median head circumference 34.0cm (interquartile range 32.6-35.8cm, full range 28.3-39.0cm). There was one reportable adverse event – a term baby in whom a baseline bradycardia was detected during scanning but on investigation this had also been noted before MR imaging and so it was not thought to be attributable to the procedure. The ECG was normal and the baby went home the same day and the neonatologist judged that no follow up was required.

The MR imaging studies from Firefly were considered to be evaluable in 52/52 (100%) of the babies scanned, of which 22/52 (42%) were fully evaluable and 30/52 (58%) were partially evaluable. Examples of MR images are shown in figures 9.1.3 and 9.1.4.

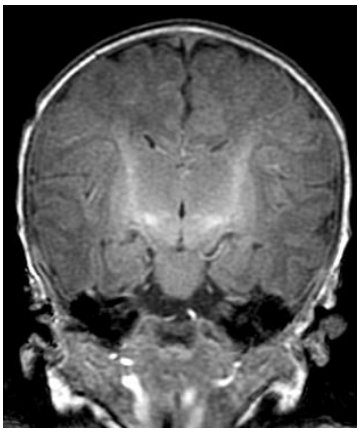
Axial FSE T2,



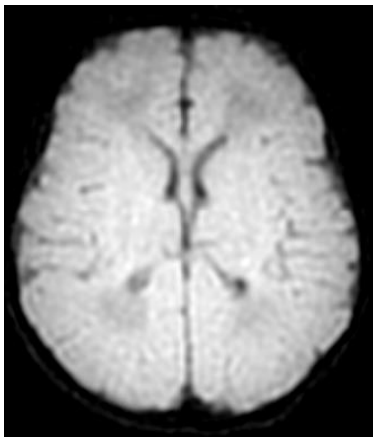
Axial ssFSE T2,



Cor T1 volume



Axial b 700 DWI,



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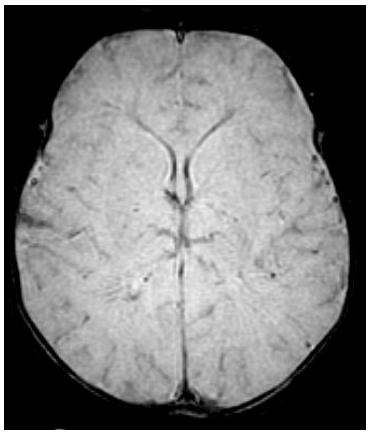
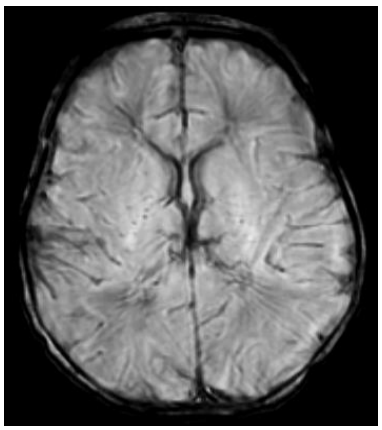


Axial SWI



Single voxel PRESS MR spectroscopy centred over the basal ganglia

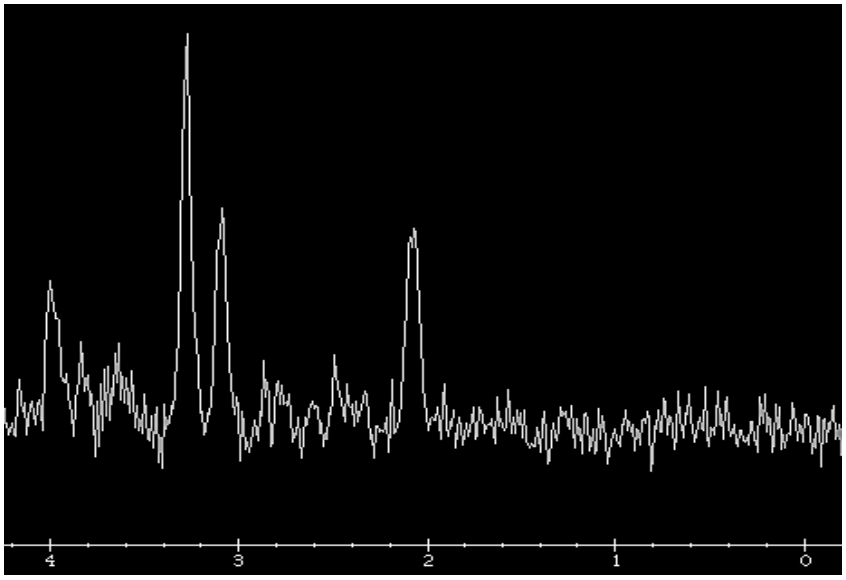
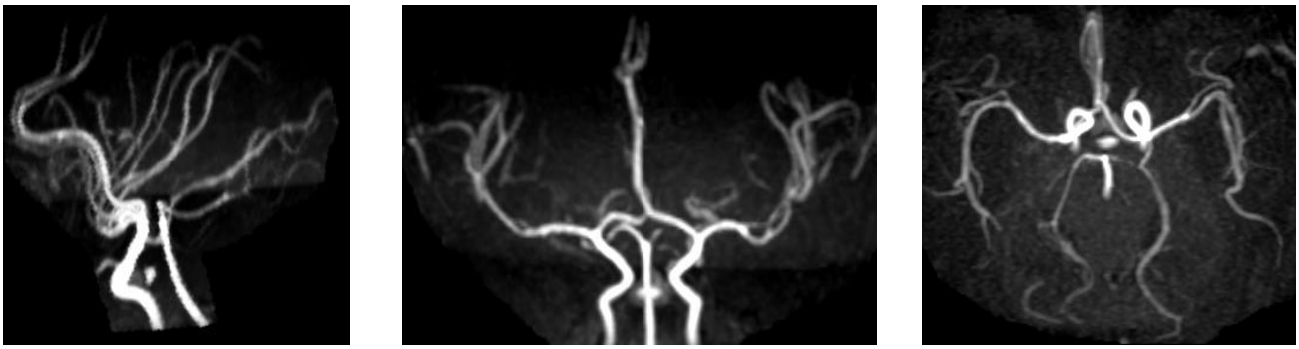


Figure 9.1.3. Representative images from a normal baby born at Term showing the range of routine sequences acquired in cases 20-49 in this study

MR Arteriography



MRV

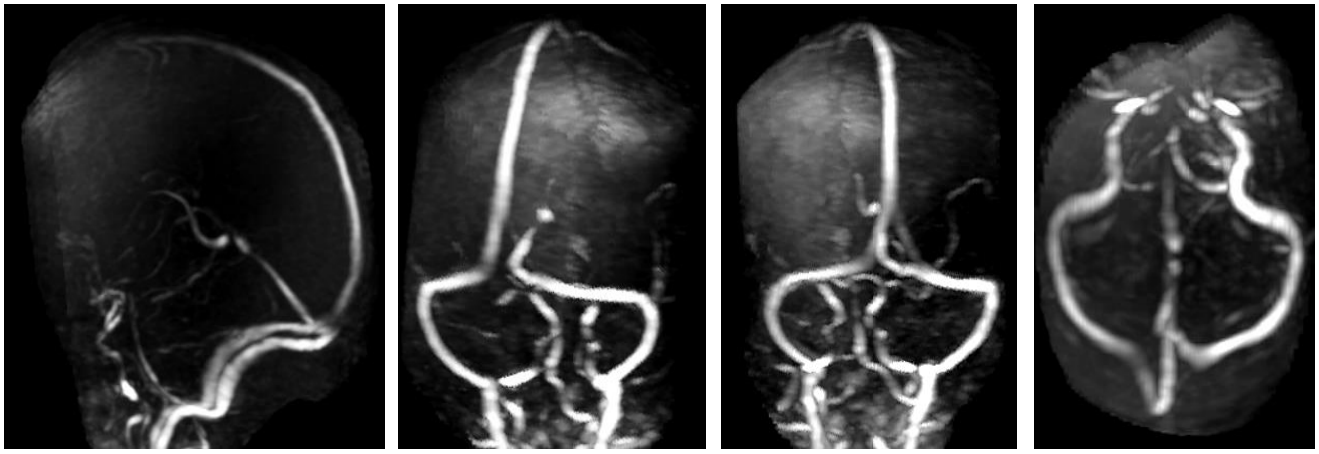


Figure 9.1.4. Representative images from a normal baby born at Term showing MR arteriography and MR venography images sequences optimised in cases 13-18 in this study.

The assessors judged the overall image quality to be at least comparable to the quality on the clinical 1.5T scanner in 47/52 (90%) of cases and better than 1.5T in 34/52 (65%). Similar results were found for image contrast, signal to noise ratio, tissue contrast and homogeneity. The worst results were for artefacts, which were thought to be worse than on 1.5T in 13/52 (25%) of cases (table 9.1.2)

	Poor	Average	Good	Percentage of cases 'Average' or 'Good'
Overall image quality	5	13	34	90%
Image contrast	4	8	40	92%
Presence of artefacts	13	20	19	75%
Signal to noise ratio (SNR)	7	7	38	87%
Tissue contrast	2	9	41	96%
Fat/water homogeneity	0	22	30	100%

Table 9.1.2. Imaging quality assessments made by the paediatric neuroradiology experts.

Two babies had unexpected intracranial findings on their MR examinations that required discussion and clinical input from the neonatology staff:

Case A (figure 9.1.5)**.** A boy born at 37gw (weight 2.59kg and head circumference 34.0cm) and scanned on day 1 with no clinical concerns. Haemosiderin staining of the ependyma was shown in both occipital horns and in both caudate-thalamic notches consistent with earlier haemorrhage. Clinical review was made the day after the MR examination after the findings had been discussed and the baby was allowed home with no need for further follow up.

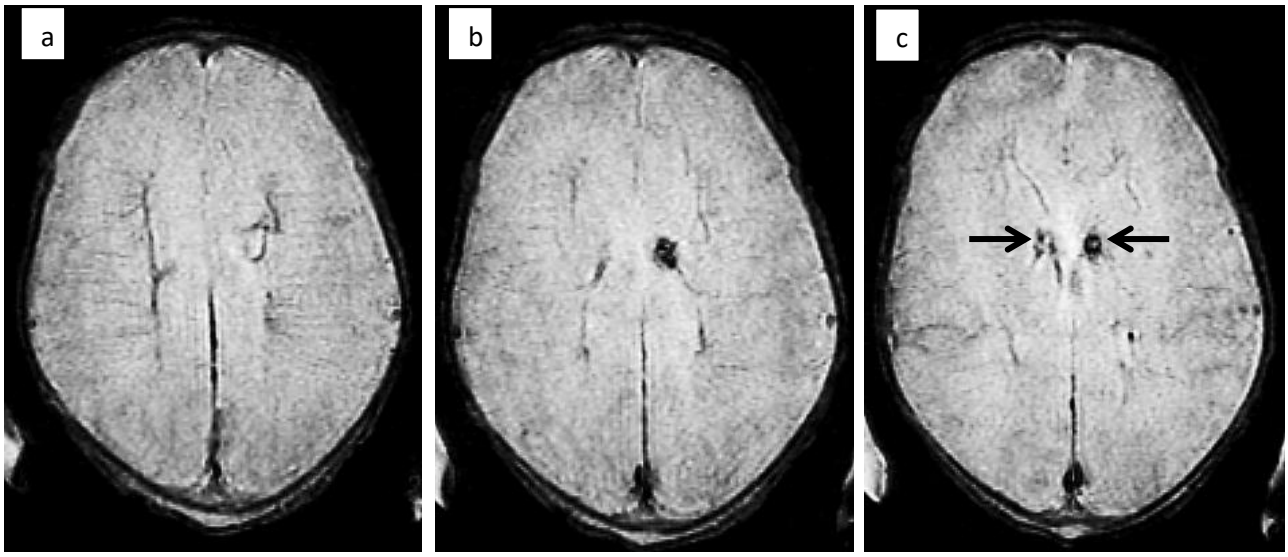


Figure 9.1.5. Representative axial gradient echo T2* images from case A described in the text showing small areas of haemosiderin staining in the caudate-thalamic notches bilaterally consistent with previous haemorrhage into the remnants of the germinal matrix (arrowed – 5c).

Case B (figure 9.1.6). A boy born at 37w and scanned on FIREFLY on day 2. His weight was 2.7kg and his head circumference was 34.0cm. There was a small volume of intra-ventricular haemorrhage in both occipital horns and a developmental venous anomaly in right frontal lobe. Clinical review was made the following day after the findings had been discussed and the baby was allowed home with no need for further follow up.

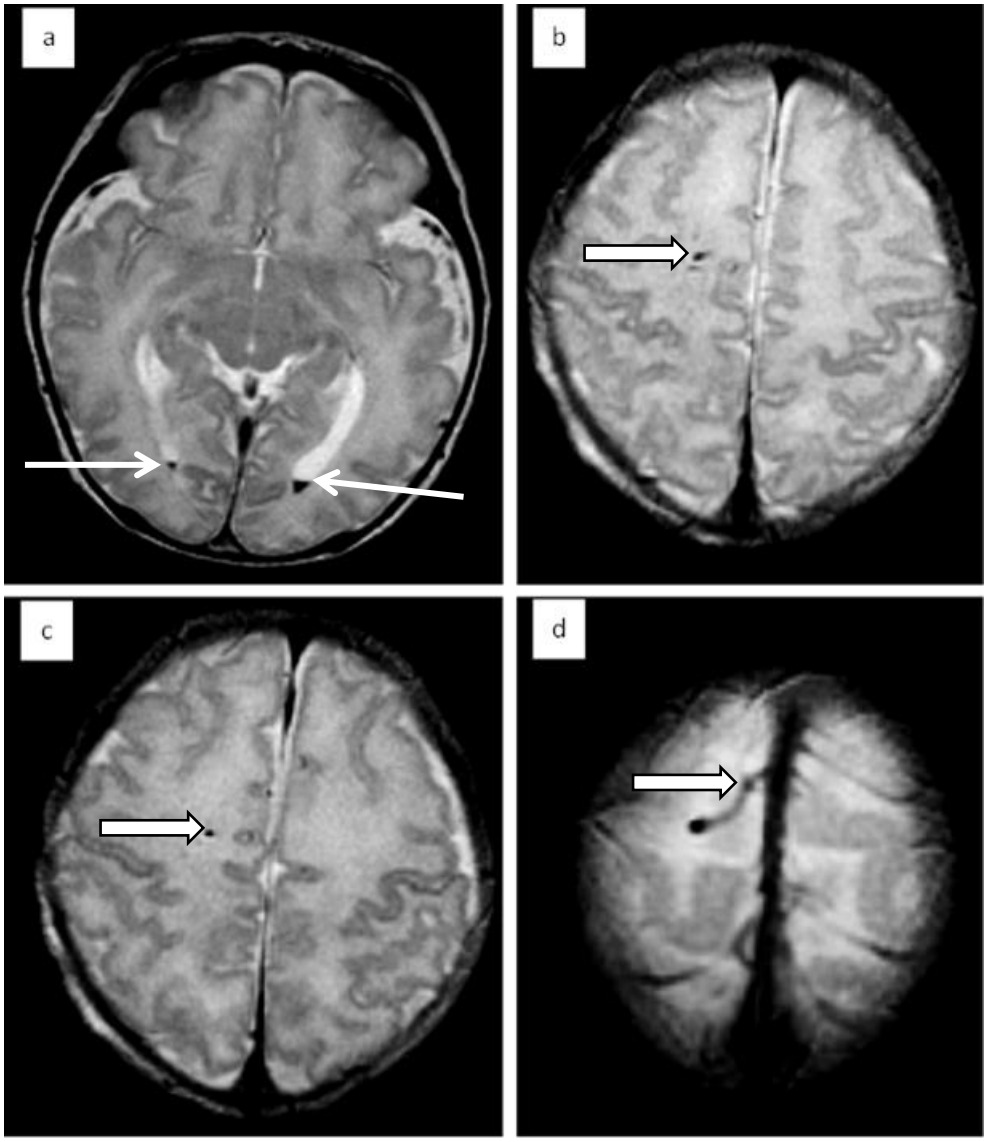


Figure 9.1.6. Representative axial FSE T2* images from case B described in the text showing a small volume of intraventricular blood in the gravity dependant parts of the occipital horns of the lateral ventricles (arrowed - 6a) and a tubular structure running through the right frontal lobe and terminating in the superior sagittal sinus (blockarrows – 6b-6d) in keeping with a developmental venous anomaly.

Discussion

The work reported in this paper is the first part of a wider study designed to improve access to MR scanning facilities for newborn babies and subsequently attempt to quantify the diagnostic and clinical impact of making MR more widely available. We have taken the approach of installing a high-field MR scanner on the neonatal unit at our Institution in order to reduce the risks of transferring babies to MR imaging facilities. This is not the only possible approach and another method is the use of an MR-compatible transport incubator, which reduces the number of times the baby has to be handled during transportation and provides a controlled physical environment during scanning. If a baby is transferred from the ward to the MR scanner without a transport incubator he/she must be handled four times, twice of the ward (in and out of the cot/incubator) and twice in MR scan room (on and off the scanner). The MR compatible transport incubator has a built in MR receiver coil so the baby goes into the scanner in the incubator reducing the number of handling events to two, both of which occur on the ward where neonatal staff are available if there is clinical deterioration during handling. Our group was involved in the early prototype trials of one such system that is commercially available[3] and we have designed and built our own MR-compatible incubator,[4] which we use for clinical purposes at present.

Although the use of MR-compatible incubators works well, we maintain that an MR scanner on the neonatal unit is a fundamentally safer approach. It is generally not practicable to install whole body MR scanners on the neonatal unit in most hospitals because of the space required and the floor loading constraints due to the heavy weight (in the order of 12 tonnes) of whole-body MR scanners. The hospitals that have created that type of facility have done so mainly because they have designed new departments with the

express intention of accommodating a whole-body MR scanner. Other centres have approached the problem by developing MR services optimised to meet the needs of imaging neonates on standard clinical MR scanners (1.5T and 3T) by using tailored equipment and/or care measures.[5,6]

There have also been several other attempts to construct small foot-print systems for neonatal imaging. Our group previously reported experience of using a 0.2T permanent magnet system, which had CE marking for neonatal imaging.[7] There have also been more recent developments using low field MR systems for neonatal scanning (0.023T),[8] and the FDA has recently approved the first commercially available small, 1.0T neonatal MR system designed to accommodate the needs of the neonate.[9] In spite of those developments, we came to the conclusion based on our experience of neonatal imaging at 0.2T that the highly detailed requirements for neonatal brain imaging (e.g. spectroscopy, diffusion imaging, MR angiography) require MR imaging at 1.5T or higher field strength. Considerable steps forward have been made by Tkach and colleagues who successfully developed a small-footprint 1.5T system which they sited on a neonatal unit and have successfully imaged several anatomical areas[10.] They have subsequently reported their experience of 492 premature neonates.[11] In this paper, we have demonstrated that a physically small, 3T MR scanner is a feasible option for imaging the neonatal brain and its smaller size/ low weight allows placement above ground level and on the neonatal unit without the need for additional major structural alterations. This is because for safety reasons neonatal units should not be housed at ground level so that the risk of theft of babies is reduced. We believe that the theoretical improvements in signal to noise ratio provided by imaging at 3T offer the best potential imaging for the neonatal brain because of the requirements of high-quality multi-sequence imaging and spectroscopy in as short a time as possible. It should be noted that the FDA guidelines confirm that MR devices with main static magnetic fields of ≤4.0T should be classified as a 'non-significant risk' for

neonates.[12] There are disadvantages of scanning at 3T, however, such as increased SAR, increased acoustic noise and more artefacts arising from for example susceptibility effects and field homogeneity problems. The problem with artefacts is compounded by the small size of the Firefly scanner and the clinical raters considered MR artefacts to be a concern in 25% of cases (although all cases were considered reportable). This issue will require further work in future studies.

The safety of the babies taking part in this study was of paramount importance and a close collaboration between the MR imaging and neonatal unit staff was vital. The neonatal staff involved in the transfer and scanning, coupled with the location of the MR scanner allowed good access, rapid assessment and transfer of babies back to the wards. The involvement of neonatologists in the study facilitated specialist medical care and intervention if required. This was not required in any of the 52 babies scanned in this study, although a consultant opinion was sought in three cases (one baby with a bradycardia and two babies with unexpected intra-cranial findings). The increased acoustic noise associated with using Firefly was successfully managed by the use of two types of ear protection. In addition, one of the major factors that influence image quality in neonatal imaging is movement of the baby and we have taken a feed and swaddle approach which appears highly beneficial for settling the babies. 1 in 52 scans stopped early due to movement but the study was partially evaluable. Close physiological monitoring of the babies did not reveal any adverse effects leading to problems with desaturation or thermoregulation. Thermoregulation is particularly important because of two competing factors. The scan room is kept at 22-24°C but the increased radiofrequency strength at 3T can potentially cause heating, particularly in a neonate whose ability to adapt to changes in external temperature are limited. Our results showed no problems with temperature control and support the findings of

Cawley et al. who measured the core temperatures of neonates during scanning at 3T and found no significant effects.[13]

At the planning stage of this study, we were prepared to take image quality that was 'no worse' than that obtained on our routine clinical scanning on a whole body 1.5T system as an acceptable outcome. This equivalence approach is justified by the extra advantages in terms of safety by having the Firefly scanner close to the neonatal units. Our results show that the quality was at least equivalent to 1.5T in the majority of cases (90%) and were judged to be better than the 1.5T images in nearly two thirds of cases. We also have the full range of MR sequences that we would expect to be used in the clinical environment all of which produced high quality images. The next stage is to see if this can be reproduced in babies that have or are expected to have acute brain pathology. At the time of writing this report an application for CE approval has been submitted. If approval is granted, then we will start to perform clinical cases on Firefly rather than on our whole body 1.5T in both premature and term babies that are fundamentally stable as we do not have the capacity to handle ventilated babies at the present time. We will judge whether the sequences developed so far allow Firefly to demonstrate pathology or if further refinements are necessary.

In conclusion, we have described a new class of high field MR scanner that has been designed specifically for imaging neonates and is small enough to be sited on neonatal units. Our initial assessments of safety and technical performance are favourable, and the next stage is to move on to evaluate diagnostic performance and diagnostic/clinical impact.

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9.2 Involvement of the anterior lobe of the cerebellar vermis in perinatal profound hypoxia.

Connolly DJA, Widjaja E, Griffiths PD.

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The Vancouver group had previously reported the focal loss of volume and mild gliosis that affects the anterior lobule of the cerebellar vermis in some children who have suffered an acute profound perinatal asphyxia at beyond 36gw (Sargent et al). This focal injury to the vermis we considered to be most likely to have occurred in the more severe cases of brain injury from acute profound HIE.

We needed to develop an MR head scoring system to decide upon the severity of brain injury at follow up MR imaging beyond 2 years of age when myelination is complete. The scoring system was based upon a combination of the number of regions of the brain that were involved, extent of signal change in a structure and degree of volume loss in the brain structure. The regions of the brain assessed included the classical triad of the posterior putamen, antero-lateral thalamus and the Rolandic (paracentral) cortex and underlying white matter. The medial temporal lobes (hippocampi) and head of caudate nucleus were also observed as it was already acknowledged that these other regions of the brain could also be injured during acute profound HIE.

We scored the brain insult as mild, moderate or severe and then demonstrated that it was more likely that there would be involvement of the vermis if there was more severe brain injury.

Abstract

Background and Purpose. We report abnormal high T2 signal in the anterior lobe of the cerebellar vermis, which we believe was the result of profound hypoxic ischemic encephalopathy in the perinatal period in term infants. We tested the hypothesis that this sign was associated with other signs of significant perinatal hypoxic damage.

Methods. 30 patients with clinically and radiologically confirmed perinatal profound hypoxia close to term were included in the study. The cranial MR images were reviewed by two pediatric neuroradiologists and were scored for the presence and severity of hypoxia / ischaemia in the regions classically affected by profound hypoxia. The presence or absence of high T2 signal in the vermis and other sites was correlated with the extent of damage in classically affected regions.

Results. 18/30 patients had high T2 signal in the vermis. The presence of vermian damage correlated positively with radiological evidence of severe hypoxic damage and extremely poor (0 or 1) one-minute Apgar scores.

Conclusion. High T2 signal in the anterior lobe of the vermis probably represents gliosis secondary to hypoxia/ischaemia and is related to the severity of damage in the term infant.

Introduction

Perinatal hypoxic/ ischemic encephalopathy (HIE) in the term infant is a catastrophic clinical event and may have considerable long-term patient care implications. The regions of the brain damaged by HIE depend on several factors, but most importantly the degree and duration of the hypoxia and the maturity of the brain at the time of the insult. Short periods of very severe HIE in children born at or close to term has been termed 'profound hypoxia' in the past. This produces a highly characteristic pattern of gliosis in the posterior putamen, ventrolateral thalamus, paracentral white matter and hippocampus (1). Another region of selective vulnerability, the anterior lobe of the cerebellar vermis (ALV) is recognised and in this paper we describe the frequency and associations of that finding (1a).

Materials and Methods

Thirty consecutive patients were included in this study who had been referred to our institution for MR examinations to investigate possible HIE in the perinatal period. No patients were excluded from these consecutive referrals but patients with severe HIE who failed to survive the first nine months of life could not be included in this study population. All patients had Apgar scores of 6 or less one minute after birth (range 0-6, median 1). Cord pH measurements had been made in 18/30 and all were 7.1 or lower (15 below 7.0). Heart rate measurements were available in 22/30. The heart rate was not recordable in eight patients, less than 100 beats per minute in thirteen patients and more than 100 beats per minute in one patient. All these children had long-term static neurological deficits, either hemiplegia or quadriplegia, and twenty children had dyskinesia. All patients were born between 37-42 weeks gestation as calculated from last menstrual period and fetal ultrasound imaging data and birth weights ranged from 2.3kg to 4.2kg. None of the patients included in this group had a documented evidence of hyper-bilirubinaemia or hypoglycaemia.

MR imaging showed patterns of damage distribution consistent with textbook descriptions of profound hypoxia and no patients had any suggestion of developmental brain pathology (1). All patients had an MR imaging at 1.5T (Eclipse or Infinion, Phillips Medical Systems) and ages at the time of scanning ranged from 1 to 24 years. Imaging consisted of axial and coronal fast spin echo T2W, axial and sagittal spin echo T1 images and fast spin echo FLAIR images in either the axial or sagittal plane.

Two experienced pediatric neuroradiologists (DJAC, PDG) reviewed the hard copy images and a consensus opinion was attained without knowledge of the clinical information at the time of image review. The posterior putamen,

ventrolateral thalamus and paracentral white matter changes were graded 0 to 3 (0 for no change, 1 for signal change but no volume loss, 2 for early volume loss and signal change and 3 for significant volume loss). A total score of these abnormalities was recorded. The presence of abnormal signal other regions was noted (e.g. hippocampus or caudate) as well as the condition of the ALV.

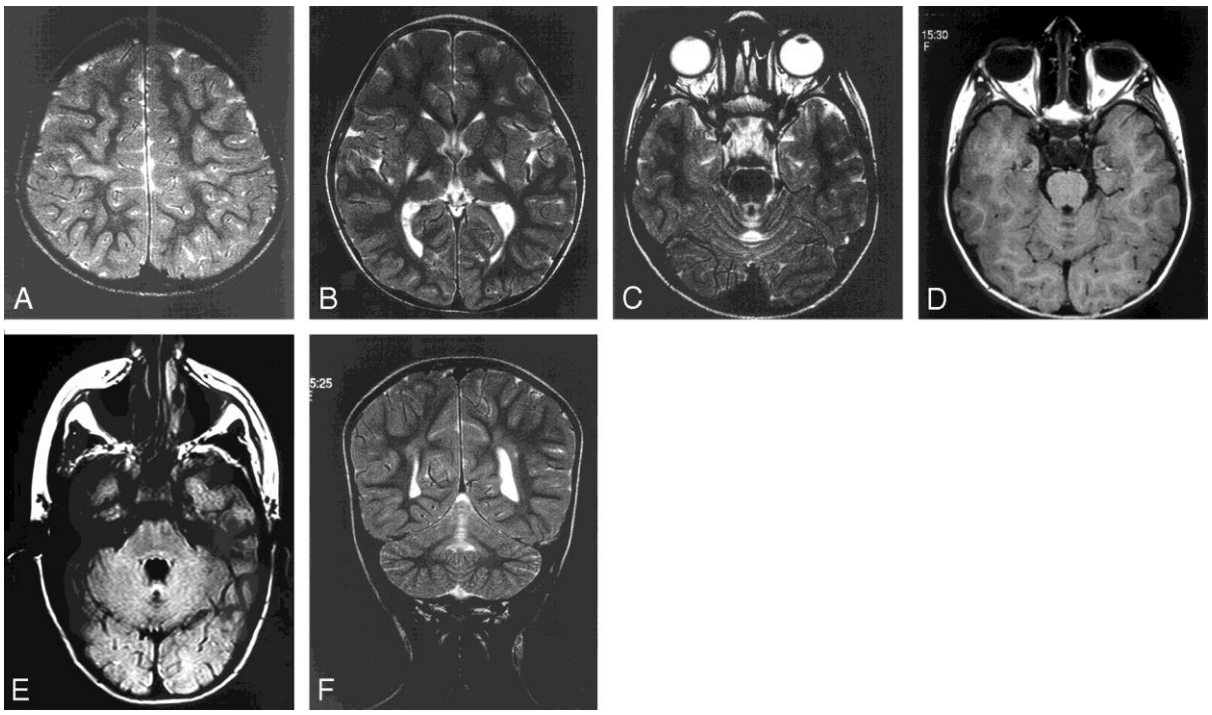

Figure 9.2.1 Five y.o. girl with athetoid spastic quadriplegia.**a)** Axial T2. Mild signal change in the perirolandic white matter.**b)** Axial T2. Typical signal change in the posterior putamen and the ventrolateral thalamus bilaterally.**c)** Axial T2. Typical signal change in the anterior lobe of the vermis.**d)** Axial T1. Low T1 signal change in the vermis.**e)** Axial FLAIR. High T2 signal and cystic change.**f)** Coronal T2. Anterior lobe of vermis high T2 signal change.

The clinical information recorded included gestational age and birth weight, 1- and 5-minute Apgar scores, lowest recordable heart rate in the perinatal period (normally a cardiotocograph or scalp electrode reading) or at birth, age at MRI and clinical symptoms. The Apgar score at one minute was categorised into those with a score of 0 or 1 (clinically severe) and those with a score of 2 to 6 (clinically moderate). The total score of putamen, thalamus and paracentral white matter abnormality was also categorised into those with a combined score of 6 or more (radiologically severe) and those with a score of 5 or less

*(*radiologically moderate*).* Chi-square analysis was performed between ALV signal change and one-minute Apgar, ALV signal change versus low and high total scores of putamen, thalamic and paracentral white matter, ALV and hippocampal signal change, and hippocampal signal change and total score.

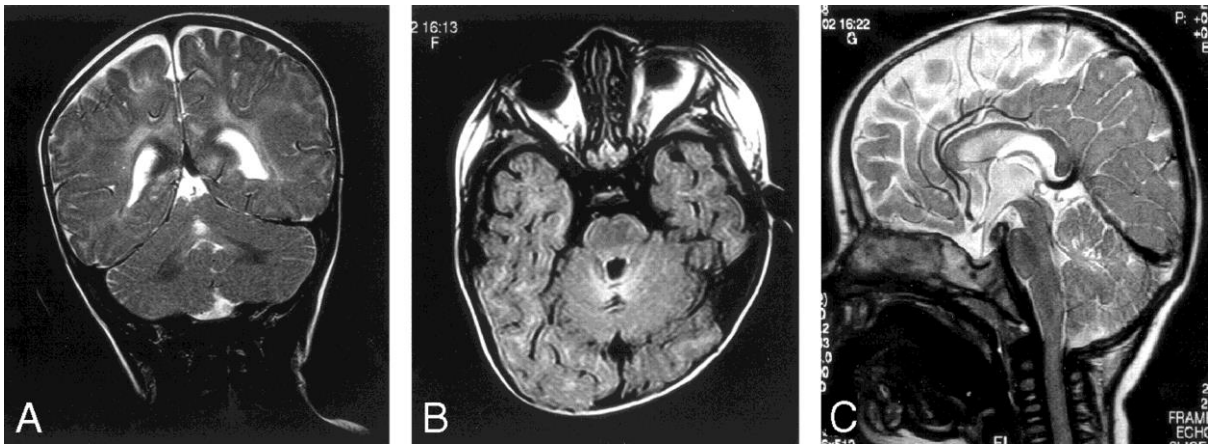

Figure 9.2.2 Images of ALV signal change and volume loss a) coronal T2, b) axial FLAIR, c) sagittal T2

Results

In the 30 patients 97% had putaminal, 90% thalamic and 87% paracentral white matter changes (Table 9.2.1). 18/30 (60%) patients demonstrated high T2 signal in the superior vermis.

The total score of changes in the posterior putamen (0-3), ventrolateral thalamus (0-3) and paracentral white matter (0-3) was scored out of nine with 15 patients scoring 5/9 or less and 15 scoring 6/9 or more. Those with high ALV T2 signal are more likely to have a high total score ($p= 0.02$). There was no association between high total score and hippocampal or caudate abnormality ($p>0.05$) or vermian and hippocampal abnormality ($p>0.05$).

Case	Age yrs	Apgar 1 min	Apgar 5 min	Heart rate bpm	putamen	thalamus	PCWM	Total score	vermis	others
1	4	6	6	>100	2	2	1	5	0	0
2	2	1	3	80	3	3	2	8	1	Hippocampus, caudate
3	3	0	2	70	2	3	2	7	1	0
4	15	0	1	unrecordable	1	3	2	6	1	0
5	4	1	7	60	3	3	3	9	1	Hippocampus
6	1	1	2	60	2	1	1	4	1	Hippocampus
7	1	1	5	<20	3	2	2	7	1	Hippocampus
8	14	1	2	Unrecordable	2	2	2	6	1	Hippocampus
9	6	0	3	Unrecordable	2	1	1	4	0	0
10	7	6	9		2	1	2	5	0	0
11	5	2			1	3	2	6	1	Caudate
12	5	3	5		1	2	1	4	1	hippocampus
13	5	0	4	Unrecordable	3	3	2	8	1	0
14	12	1	6		1	0	3	4	0	0
15	3	1	5	40-60	2	2	1	5	1	hippocampus
16	24	1	5		2	2	0	4	1	0
17	1	3	5		3	0	2	5	0	Caudate
18	5	1	0		3	3	3	9	1	0
19	1	0	0	Unrecordable	2	2	1	5	0	0
20	2			Unrecordable	2	2	0	4	1	Hippocampus
21	2	2	3	770	2	3	2	7	0	0
22	2	5	6	80	3	3	3	9	1	0
23	1	1	1	60-80	2	2	2	6	1	hippocampus
24	4	4	8	70	0	0	2	2	0	Caudate
25	2	4	6	60	2	1	3	6	0	Caudate
26	22	0	2	Unrecordable	1	2	0	3	1	0
27	15	6	7	Unrecordable	2	2	1	5	0	0
28	4	6	8		2	2	2	6	1	hippocampus
29	7	1	4	60	2	2	0	4	0	0
30	5	2	7	<80	3	2	3	8	0	0

*Total score of the abnormalities seen in putamen, thalamus and paracentral white matter (PCWM) **bpm – beats per minute

Table 9.2.1 Individual case data for assessment of brain injury from acute profound asphyxia including vermian injury

17 of 30 infants had clinically severe HIE (1-minute Apgar of 0 or 1). There was a significant (p = 0.020) association between low Apgar score (0 or 1) at 1-minute and the presence of ALV high T2 signal. There was however, no significant association between the 5-minute Apgar and high signal in the ALV (p>0.05). One-minute Apgar and total score were shown to have no direct association (p>0.05).

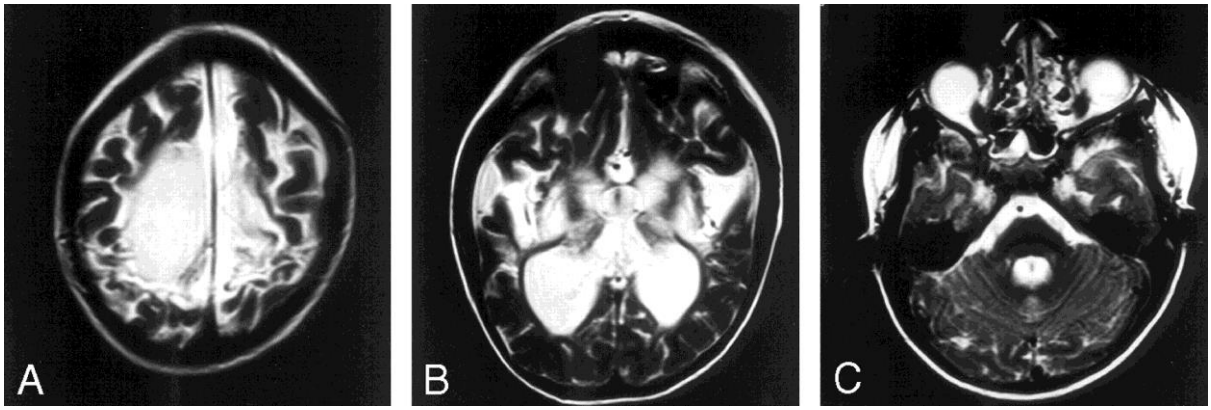

Figure 9.2.3 Seven y.o. boy with severe spastic quadriplegia **a)** Axial T2. Severe signal change and volume loss in the perirolandic white matter. **b)** Axial T2. Severe putaminal and thalamic volume loss and high T2 signal bilaterally. **c)** Axial T2. Mild vermian high T2 signal change.

Discussion

Cerebral palsy defines a group of neurological conditions involving motor disorders with neurological signs resulting from brain damage that is static and has occurred in early life (2). Patients with underlying metabolic disorders, hydrocephalus, brain tumours and various other disorders by convention are excluded from the cerebral palsies. HIE in the perinatal period contributes a significant proportion of the total number of cases and three 'text-book' clinical and radiological patterns are recognised. Hypoxia/ischaemia severe enough to cause brain damage before the 35th week of gestation usually produces 'periventricular leukomalacia' with the white matter immediately next to the ventricles being most affected. As the fetus matures, the pattern of involvement changes due to alterations in the site of the vascular watershed zones (1). For example, a 40-week fetus exposed to a long period of low-grade hypoxia will cause damage to the parasagittal white matter. In contrast, a 40-week fetus exposed to acute severe hypoxia will damage areas of the brain that are most metabolically active, including the putamen, thalamus and paracentral white matter.

MR imaging has long been identified as the method that provides important information related to the timing and severity of HIE, with altering patterns of structural involvement depending on the age of the patient (3). Posterior putamen and ventrolateral thalamic gliosis is associated with extra-pyramidal symptoms in cerebral palsy (4) (figures 1b and 3b). Paracentral lobule high T2 signal change and volume loss is another site of involvement typical of HIE in a term infant (figures 1a and 3a). The reason for the specific selection of these foci for damage in HIE is uncertain but some authors consider that they may be selected as they are areas of active myelination in the term infant (5). The reason why the vermis is selectively injured in profound HIE may differ from the above active myelination (5a). The vermis is rich in Purkinje cells, a group of

cells some of which may be deficient in aldolase C and EAAT4. Aldolase C is a fructose-bisphosphonate aldolase family enzyme expressed specifically in the hippocampus and Purkinje cells of the brain and is a key enzyme in the 4th step of glycolysis and is therefore crucial in ATP synthesis. Excitatory amino acid transporter 4 is expressed specifically in the cerebellum and has high affinity for excitatory amino acids such as L-aspartate and L-glutamate leading to chloride ion conduction. EAA4 is involved in regulation of membrane potential. Aldolase C and EAAT4 deficiency means that these cells are unlikely to survive intense synaptic input after the restoration of blood flow.

Recent studies have assessed the use of new MR techniques such as diffusion weighted imaging and MR spectroscopy in the investigation of patients with HIE. Diffusion weighted imaging has been shown to demonstrate abnormalities in the thalami and internal capsule in the first day of HIBI, when conventional MR imaging is normal (Barkovich 2001). Diffusion weighted imaging however, underestimated the extent of the long-term injury (Robertson 1999; Barkovich 2001). Delayed neuronal and oligodendroglial cell death due to apoptosis in areas with lower metabolic demand may explain the reason that diffusion weighted imaging underestimates the extent of injury (Robertson 1999). Diffusion weighted images obtained between the second and fourth day of life reflects the extent of injury more reliably. By the seventh day, diffusion MR is less sensitive to perinatal brain injury compared to conventional MR because of transient pseudonormalization of diffusion images (McKinstry 2002).

Barkovich *et al* used single voxel MR spectroscopy centred on the basal ganglia or watershed vascular region in asphyxiated term neonates to predict developmental status at 12 months (8). High lactate (lactate/choline ratio) correlated with poor neuromotor outcome. Kuenzle *et al* have demonstrated an association between changes seen in the first week post-delivery of significant brain injury on MRI (including diffuse brain injury and basal ganglia/thalamic

signal changes) with poor developmental outcome (9). However, a normal CT or MRI performed in the first few weeks of life did not preclude later neurological dysfunction (10). The optimal timing and technique for an MRI to assess for HIE is therefore uncertain. An MRI in the first few days of life allows clinicians to provide families with information on prognosis. An MRI after two years of age when myelination is complete will allow more complete assessment of HIE related brain damage.

We have described ALV high T2 signal for HIE in the term infant. ALV high T2 signal is most easily seen on coronal image. In more severe cases there may be volume loss. This sign may assist in the correct diagnosis of HIE birth injury and should not be interpreted as showing second pathology. It should be appreciated that spurious high signal change can sometimes be seen in the cerebellum on T2 weighted images if there is loss of brain volume and CSF is partial volumed into the voxel. We are confident that this is not the case in our patients because the high signal is also seen on proton density and FLAIR images. It is most likely that the T2 prolongation is due to gliosis as in the other regions of the brain affected by profound HIE.

In adults, injury to the vermis normally results in truncal ataxia. A larger study than this would be required to assess if this radiological sign is associated with specific symptoms and signs that can be attributed to injury to the vermis in patients who often have significant neurological deficits. However, it should be noted that the extensive involvement of the other regions of the brain might make attributing functional implications of ALV damage difficult or impossible.

Levene *et al* stated that severity of encephalopathy in HIE could be graded retrospectively on the basis of a set of clinical signs (11, 12). MR changes of HIE in the pediatric population have been shown to correlate with neurological

outcome (13). There is an association in our study of ALV high T2 signal with both lower one-minute Apgar scores and with a higher overall score for radiological evidence of HIE. The ALV high T2 signal sign may therefore be an independent predictor of HIE associated with significant neurological disability. We must accept that the classification of putaminal, thalamic and white matter HIE signal and volume changes into mild, moderate and severe may appear arbitrary but this was completed as a consensus opinion by two experienced neuroradiologists blinded to the clinical outcome data. The correlation of a high overall score for MRI change of HIE and vermian high T2 signal marks this as a potentially important marker of significant neurological disability.

Conclusion.

The ventrolateral thalamus, posterior putamen and paracentral white matter (perirolandic gyrus) are known areas of brain injury manifest as loss of volume and high T2 signal in term infants with profound HIE in the perinatal period.

We have described ALV high T2 signal as a sign of profound HIE in the term infant. ALV high T2 signal is associated with radiological and clinical indicators of severe HIE in term infants.

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9.3 Anatomic localisation of dyskinesia in children with 'profound' perinatal hypoxic-ischemic injury.

Griffiths PD, Radon M, Crossland AR and Connolly DJ.

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The classic triad of damage seen in acute profound HIE involves injury with signal change and possibly volume loss affecting the posterior putamen, the antero-lateral thalamus and the cortex and underlying white matter of the Rolandic region. The Rolandic cortex is the motor cortex of the brain and therefore focal injury would be expected to induce a spastic motor injury.

The posterior putamen is often injured in adult stroke cases and does not induce a dyskinetic (choreo-athetoid) motor disorder. An insult to the antero-lateral thalamus would be expected to produce a sensory deficit.

The question to be answered was which bit of the brain if injured would produce a choreo-athetoid cerebral palsy as is commonly seen in acute profound asphyxia. Discussion with Alan Crossman in Manchester led to the suggestion that the sub-thalamic nucleus (a tiny structure often not identified on brain MR) would be a suitable anatomical substrate to produce the clinical features if damaged in an acute profound HIE.

We therefore reviewed a cohort of children injured by perinatal acute profound HIE and compared their clinical outcome features to the areas of brain involved.

Two conclusions could be drawn from this work. Firstly, if coronal T2 imaging was optimised to increase signal-to-noise and to reduce voxel size then in a significant proportion of these cases high T2 signal could be identified in the subthalamic nuclei. Secondly, if there was significant injury to the Rolandic cortex then there would be a spastic rather than a dyskinetic cerebral palsy induced despite subthalamic nucleus involvement. It was deduced that this was due to the insufficient motor cortex signal for movement and therefore disorganised movement was not evident.

Abstract

Objective. Dyskinetic cerebral palsy is a common feature of perinatal hypoxic-ischemic brain damage in the context of 'acute profound' injury. This frequently produces damage to the basal ganglia and thalamus, but it is difficult to explain how dyskinesias arise from that injury based on current understanding of functional neuroanatomy. Specifically, focal destructive lesions in those locations rarely produce dyskinesia. In this paper we have made a detailed assessment of the extent of brain injury in children with dyskinetic and spastic cerebral palsy arising from acute profound hypoxic ischemic injury in order to explain why some children develop movement disorders whilst others do not.

Methods. MR imaging was used to study 40 consecutive children referred to our centre with cerebral palsy confirmed to be the result of acute profound hypoxic/ischemic injury. All children received the same high-resolution MR imaging protocol using the same 1.5T scanner. Two pediatric neuroradiologists reviewed the imaging independently.

Results. Of the 40 children with confirmed acute profound hypoxic/ischemic injury 20 had dyskinetic cerebral palsy and 20 had spastic cerebral palsy. Children with dyskinetic cerebal palsy had a higher prevalence of injury to the subthalmic nucleus, as manifest by increased T2 signal. Children with spastic cerebral palsy had more severe gliosis and loss of volume of white matter in the vicinity of the paracentral lobule. Injury to the putamen or caudate nuclei were not significant predictors for dyskinetic cerebal palsy.

Conclusion. We believe that injury to the subthalamic nucleus following hypoxic ischemic injury is central to the development of clinically apparent dyskinesia. We propose that in cases with subthalamic injury but without dyskinesia severe injury to descending cortical efferent pathways prevents the manifestation of

the dyskinesia. We discuss this hypothesis in terms of the known functional anatomy of the basal ganglia.

Introduction

Children who have suffered relatively short periods of severe hypoxic/ischemic brain damage (HIBD) and subsequently develop cerebral palsy (CP) often have similar distributions of brain damage. These were first described in pathology studies[1] and more recently in magnetic resonance (MR) imaging studies of children who have survived the initial damaging event. There appears to be a predilection for the 'central' structures of the forebrain including the putamen and thalamus, often with highly specific patterns of injury, namely the posterior tips of the putamen and the lateral aspects of the thalami.[2] Other parts of the brain that may be injured with high frequency include the paracentral white matter (PCWM), optic radiations, hippocampus and cerebellar vermis.[3] Many clinicians who work with patients with cerebral palsy consider the injury to the putamen and thalami to be the anatomical substrate of the hallmark clinical sequelae of 'acute profound' HIBD – dyskinetic CP, often accompanied by preservation of intellectual capacity.

On closer review, however, there are several problems with that theory. Firstly, many children with the typical putaminal and thalamic injury do not have dyskinetic CP, instead they develop spastic cerebral palsy. Secondly, the part of the thalamus that is most frequently involved is not thought to have a motor function. It is the ventral posterolateral nucleus, a primary somatosensory relay nucleus, that is injured in HIBD rather than the anterior region of the lateral thalamus which has a major role in motor function.[4] It is, therefore, difficult to explain how injury at this site could produce dyskinesia.

There is no doubt that the putamen has a central role in planning volitional movement. Generalized, inflammatory lesions of the putamen can produce movement disorders e.g., Sydenham's chorea. Discrete destructive lesions in

the putamen, however, rarely produce dyskinesia although a few case reports in human patients exist in the published literature.

The purpose of this study was to make a detailed review of the MR imaging in children who survived 'acute profound' HIBD and to correlate those findings with the type of CP that resulted. In the light of the information given above we have looked for evidence of damage at other sites of the basal ganglia not usually thought of as being primarily involved in HIBD, specifically substantia nigra, caudate nucleus, globus pallidus and subthalamic nucleus (STN). By doing this we hope to add to the understanding of the pathophysiology of movement disorders in these people.

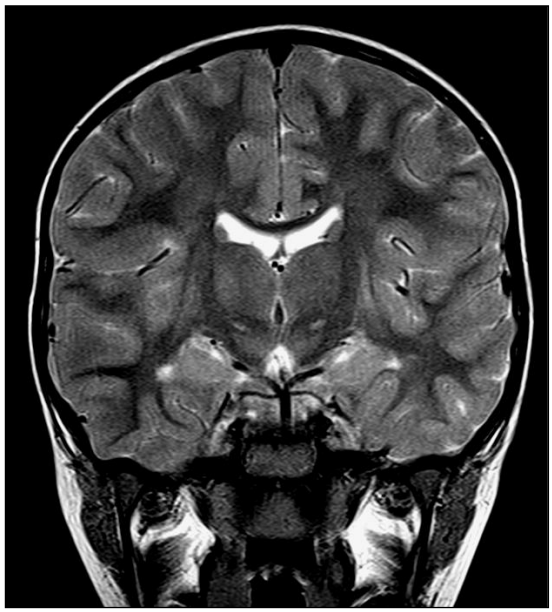
Methods

Subjects

This was a prospective study in which a high-resolution MR clinical protocol was put in place to allow for a subsequent detailed review of anatomical injury. The study consists of 40 consecutive children referred for MR imaging at Sheffield Children's Hospital. All had confirmed CP resulting from acute profound HIBD around the time of birth as defined by expert obstetricians, neonatologists and pediatric neurologists. Their summary details are shown in table 1.

MR acquisition and analysis

All children were examined on the same 1.5T superconducting system (Infinion, Philips Medical Systems) under general anaesthesia with identical imaging protocols over a four-year period in line with the existing radiological protocols at our institution. The imaging protocol consisted of a high resolution, multi-planar, multisequence protocol. The assessments used in this study were made primarily on the axial and coronal fast spin echo T2-weighted (TR 3169ms, TE 100ms, echo train length 8, two acquisitions, slice thickness 4mm, field of view 240mm matrix size 352x512) and on axial fast spin echo 'T2' FLAIR images (TR 10000ms, TI 2200ms, TE 109.6ms, echo train length 8, slice thickness 4mm, field of view 210mm, matrix size 192x256). Two experienced pediatric neuroradiologists (DJC, PDG) reviewed the images on the manufacturer proprietary workstations independently and without knowledge of the clinical information. A sample case showing the location of the STN on coronal T2-weighted imaging and an associated line diagram is presented in figure 9.3.1.



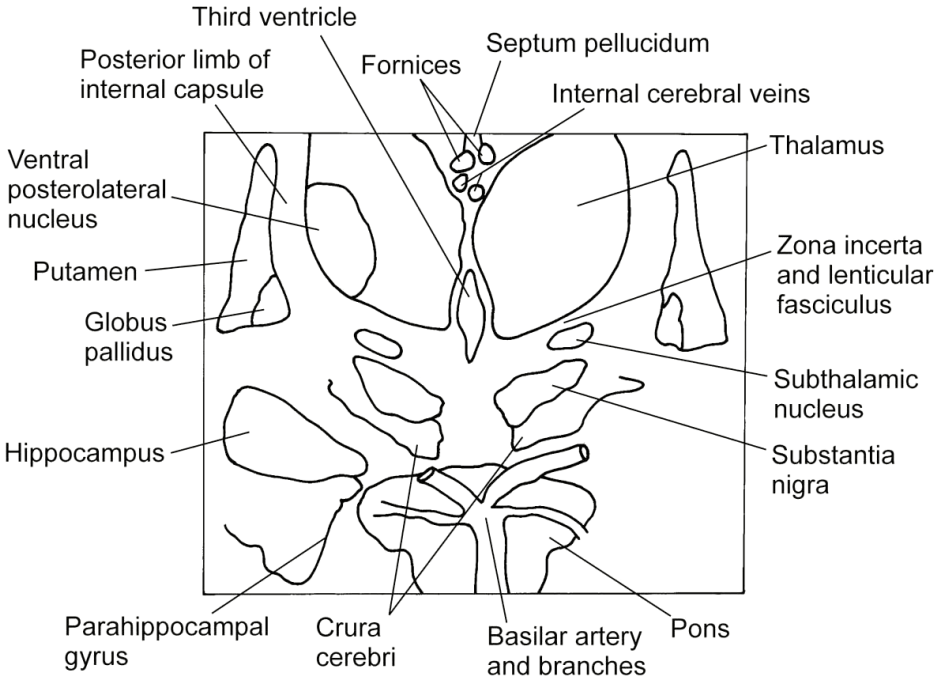
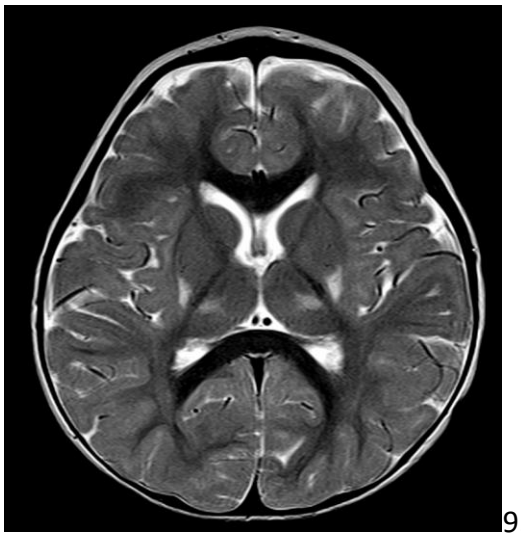


Figure 9.3.1. Location of the subthalamic nucleus. The normal subthalamic nucleus is not seen on T2-weighted images at 1.5T because of its small size and signal characteristics close to the surrounding white matter structures. Figure 1a is a coronal T2-weighted image from a child with dyskinetic CP arising from hypoxic ischaemic injury in which the subthalamic nucleus is shown because of gliosis within the nucleus. 1b is a line diagram detailing the regional anatomy of the diencephalon.

A four-point scoring system (0 to 3) was used for assessing the severity of involvement for the putamen, thalamus and the paracentral white matter as used in a previous study[3] with some modifications outlined here. Zero implied no radiological evidence of damage to that brain region on any MR sequence. A score of 1 for the putamen implied the typical text-book appearance of involvement of the posterior tip of the putamen, 2 described involvement of the posterior half of the nucleus whilst 3 described involvement of all of the putamen. Scoring of the thalamus now concentrated on the extent of signal change rather than volume loss. A score of 1 for the thalamus implied the typical text-book appearance of involvement of the ventral postero-lateral nucleus only, 2 described involvement of the central 50% of the thalamus whilst 3 described involvement of all of the structure. The PCWM was graded as 1 if there was minor signal change on T2 sequences but no volume loss. A score of two was given if there was both signal change and some volume loss confined to the PCWM and 3 if there was severe volume loss and/or white matter change extending out of the PCWM. Representative examples of the scoring system are shown in figure 2. The scoring was completed separately for both sides of the brain. A total score was then calculated for brain damage with a range from a minimum of 0 to a maximum of 18.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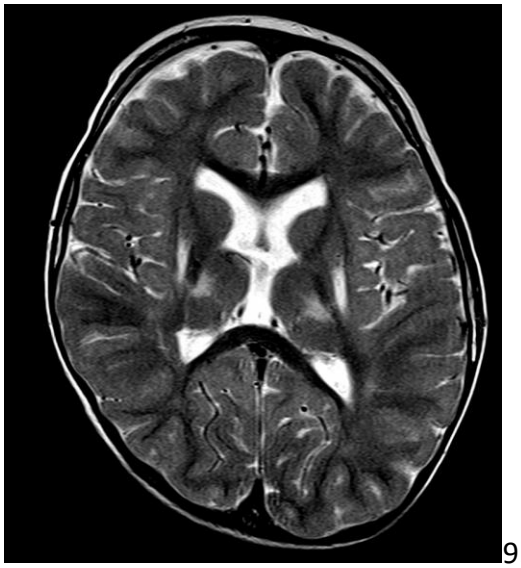
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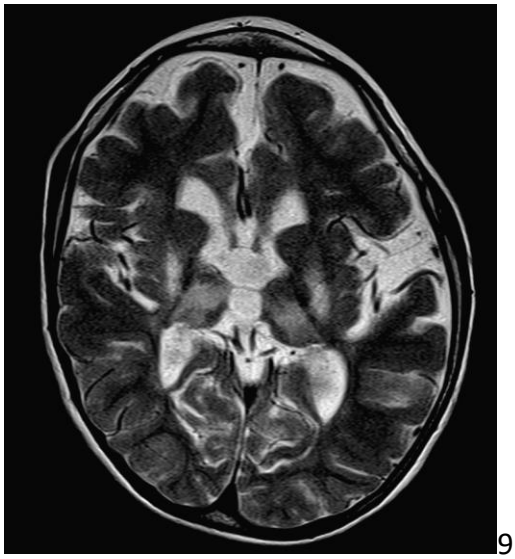
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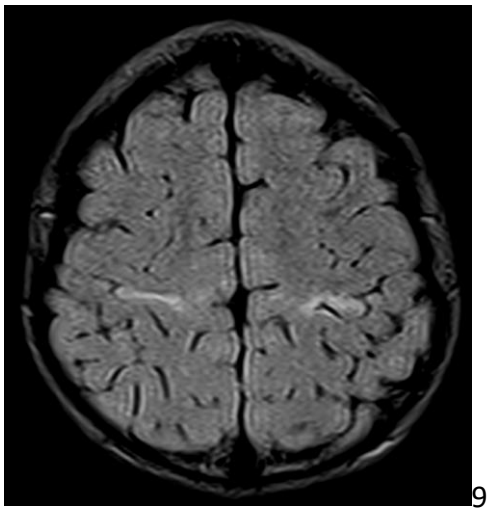
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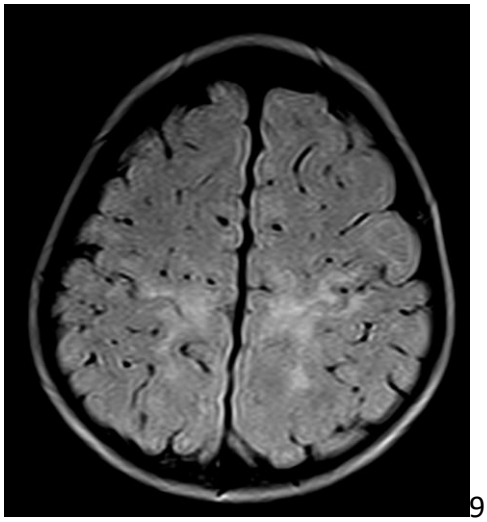

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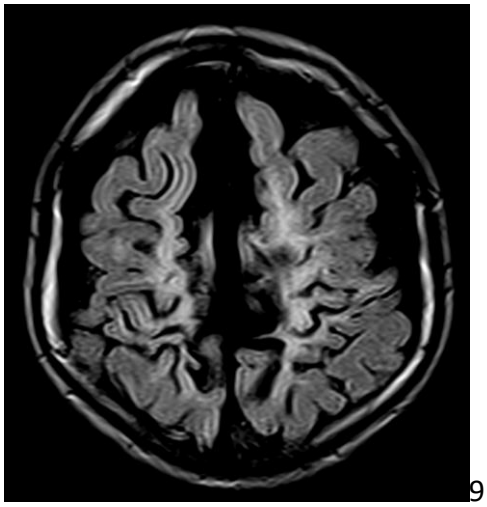

9.3.2f

Figure 9.3.2. Classification of severity of involvement used in this paper for the putamen and thalamus on T2-weighted images (3a-3c) and for the paracentral white matter on FLAIR images (3d-3f). Figure 3a shows grade 1 changes in the putamen and thalamus, 3b grade 2 changes in putamen and thalamus and 3c grade 3 changes in both structures. 3d shows grade 1 changes in the paracentral white matter, 3e grade 2 and 3f grade 3.

Changes in other regions of the basal ganglia were looked for and recorded as present or not present (caudate nucleus, substantia nigra, globus pallidus, STN). When there was disagreement over involvement of the basal ganglia structures the two neuroradiologists met in order to produce a consensus opinion.

Statistical analysis

MRI data and patient characteristics were compared between patients with dyskinetic and spastic CP using the Student *t*-test for normally distributed variables such as gestational age and birth weight and the Wilcoxon rank-sum test for categorical data including putamen, thalamus and PCWM injury scores. Fisher's exact test was used to compare the two groups regarding presence of STN, caudate and globus pallidus injuries. Multivariable logisitic regression was applied in minimize confounding with the backward step-wise method to identify the independent predictors for differentiating the two CP groups with the likelihood ratio chi-square test to assess significance and the odds ratio and 95% confidence interval (CI) to measure the strength of association. Variables with $P < .20$ from the univariate analysis were entered into the multivariable model. Predicted probabilities of dyskinetic CP were derived by maximum likelihood estimation such that 100% minus these values would indicate the probability of spastic CP based on combinations of the significant predictors.[5] Two-tailed values of $P < .05$ were considered statistically significant. Statistical analysis was performed with SPSS 16.0 software (SPSS Inc, Chicago, IL).

Results

20/40 (50%) of the children studied had spastic CP. 20 had dyskinetic CP. Comparison of patient characteristics and MR data indicate several differences between children with dyskinetic CP compared to those with spastic CP (Table 9.3.1).

Table 9.3.1. Summary Details and Comparison of Dyskinetic and Spastic CP Groups

Variable	Dyskinetic CP (N = 20)	Spastic CP (N = 20)	*P* value
Age at time of MRI, yrs	4.8 ± 3.7	6.0 ± 3.9	.35
Gestational age, wks	40.0 ± 1.3	39.1 ± 2.0	.12
Birth weight, kg	3.3 ± 0.5	3.3 ± 0.6	.78
Apgar score 5-minute	3 (1 – 7)	4 (0 – 6)	.27
Cord blood pH at birth	6.92 ± 0.15	6.83 ± 0.20	.18
Head circumference (centile)	53.5 ± 26.0	35.4 ± 20.5	.02*
Age at onset of seizures (hrs)	3 (1 – 14)	3.5 (1 – 18)	.17
Putamen injury score (0-3)			
Left	2 (1 – 3)	1.5 (0 – 3)	.72
Right	1 (0 – 2)	1 (0 – 3)	.78
Thalamus injury score (0-3)			
Left	1 (1 – 3)	1.5 (0 – 3)	.84
Right	1 (1 – 3)	1 (0 – 3)	.64
PCWM severity score (0-3)			
Left	1 (0 – 2)	2 (1 – 3)	.01*
Right	1 (0 – 2)	2 (0 – 3)	.07
Total injury score (0-18)	8.0 (4 – 14)	9.5 (4 – 18)	.38
STN injury, no. (%)	15 (75)	6 (30)	.01*
Caudate injury, no. (%)	2 (10)	8 (40)	.06
Globus pallidus injury, no. (%)	2 (10)	6 (30)	.24

Plus-minus data are mean ± SD with groups compared by the Student *t*-test. All scores and age at onset of seizures are expressed as median with ranges in parentheses and compared by the Wilcoxon rank-sum test. Proportion of patients in each group with STN, caudate, and GP injuries were evaluated by Fisher's exact test.

*Statistically significant, $P < .05$.

Significantly larger head circumference (*P* = .02), lower PCWM left side scores (*P* = .01) and a higher prevalence of STN injury (*P* = .01) were observed in the dyskinetic group. These associations were confirmed by multivariable logistic regression analysis (Table 9.3.2).

Table 9.3.2. Results of Multivariable Stepwise Logistic Regression Analysis

Predictor Variable	**LRT**	***P* value**	**Odds Ratio***	**95% CI**
PCWM left (0 – 3)	8.2	.004	0.2	0.1 – 0.7
STN injury	11.1	.001	18.6	2.4 – 141.0
Head circumference†	6.7	.010	3.0	1.2 – 7.3

* Odds ratios and 95% CIs are with respect to dyskinetic CP, and can be reciprocated to estimate the odds of spastic CP.

† Based on centiles (10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}) for head circumference with 10^{th} as the reference category.

LRT = likelihood ratio test; CI = confidence interval. Cox and Snell model R^2 = 63%, indicating good fit to the data.

The final model containing head circumference (*P* = .01), presence of STN injury (*P* = .004), and PCWM score on left (*P* = .004) provided a good fit to the data (R^2 = 0.63). Logistic regression indicated that children with STN injuries are 18 times more likely to have dyskinesia as compared to spasticity, independent of birth weight, Apgar scores, cord pH, hours to onset of seizures, as well as head circumference and presence of caudate or GP injuries. Furthermore, for each increase in centile for head circumference, the odds of dyskinetic CP compared to spastic CP are 3 times higher. With each increasing score in PCWM on the left side, the odds of dyskinetic CP decreases by 80% (95% CI: 30-90%). Maximum likelihood estimation was applied to determine the probability of dyskinetic CP for combinations of the three highly significant predictors (Table 9.3.3).

Table 9.3.3. Multivariable Algorithm for Differentiating Dyskinetic and Spastic CP*

	STN Injury				**No STN Injury**			
	PCWM Injury Score - Left				**PCWM Injury Score - Left**			
HC (centile)	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
10th	93	70	30	8	40	11	2	1
25th	97	87	55	19	66	26	6	2
50th	98	95	78	50	85	51	16	4
75th	99	98	90	66	94	75	35	9
90th	99	99	97	85	98	90	62	23

* Values represent percent probability of dyskinetic cerebral palsy according to the combination of the three predictors in the logistic regression model. Children with dyskinetic CP have larger head circumference (HC), more commonly have STN injury compared to spastic CP, and have lower left side PCWM scores. Probability of spastic CP can be determined by taking 100 minus the value in the table. If there is STN signal change with normal 50th C HC then even with severe PCWM volume loss, then 50% chance of dyskinesia

But 95% chance of dyskinesia with minor PCWM injury

If there is no evidence of STN injury with normal 50th C HC then severe PCWM injury gives 4% chance of dyskinesia

but 51% chance of dyskinesia with minor PCWM injury

Microcephaly increases the chance of spasticity

Increased head C increases the chance of dyskinesia

For example, a child with a head circumference at the 75th centile with an STN injury and PCWM on the left of grade 2 (i.e. moderately severe signal change and some volume loss) is estimated to have dyskinesia with 90% (10% probability of spastic CP), whereas with no STN injury the estimated probability of dyskinesia is 35% (65% probability of spastic CP). Figure 3 illustrates the relationship for children with a 75th centile head circumference between PCWM severity grade and the presence or absence of an STN injury in predicting dyskinetic CP. The probability of spastic CP for each combination is easily 100% minus the height of each bar (i.e., the complementary probability). Clearly, for

any given PCWM grade, the probability of dyskinetic CP is higher in children who have an STN injury.

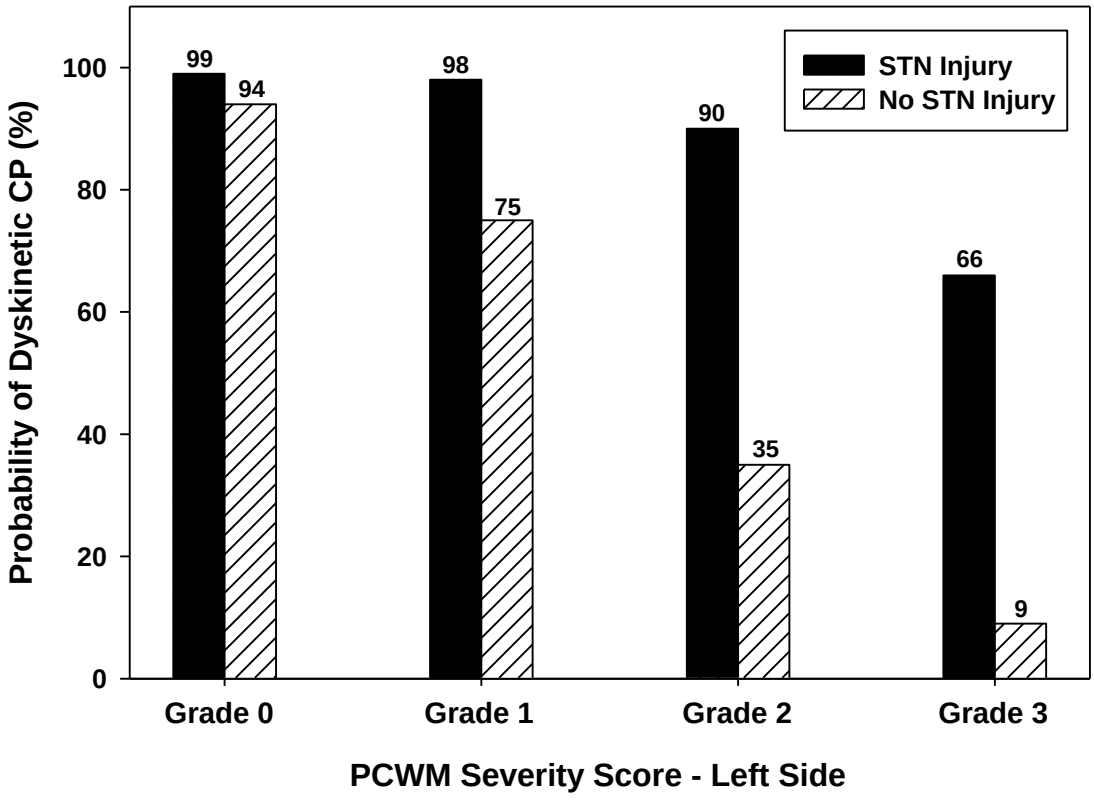

Figure 9.3.3. Probability of a child having dyskinetic CP plotted as a function of STN and PCWM injury. Data from children with head circumference at the 75th centile.

Discussion

The effects of hypoxia/ischemia on the fetal/neonatal brain are dependent on many factors such as severity, duration, amount of reserve and gestational maturity. If HIBD occurs at, or close to, term most textbooks describe two primary patterns of injury with discrete clinical sequelae. If the hypoxia/ischaemia event is severe but lasts for a short period of time

(10 to 25 minutes is the often-quoted range) the pattern of damage is usually 'central'. This results in damage to the basal ganglia and thalamus, although other areas are often damaged (e.g. PCWM, optic radiations, hippocampus). The typical clinical description of a child with that type of injury includes dyskinetic cerebral palsy with relatively well-preserved intellect. In contrast, a lower level of hypoxia/ischemia lasting for a longer period of time produces a 'peripheral' pattern of damage. This is best described as involving the vascular watershed territories of the cerebral hemispheres producing damage to grey and white matter structures in a 'parasagittal' distribution. Children with this damage will typically have spastic quadriplegic cerebral palsy, often with significant intellectual impairment.

The primary evidence for the two models of HIBD comes from carefully controlled animal experiments[6] and extrapolation to humans is difficult because the precise mechanism of injury is rarely known with certainty. One of the most difficult problems occurs when a baby is delivered in a poor condition after a short-lived emergency towards the end of pregnancy. Is it ever possible to say that the resulting HIBD was due solely to the events in the last minutes before birth? Was the fetus suffering from a protracted low-grade hypoxic/ischaemic event in the hours before birth that became significantly worse during delivery? Overlapping 'chronic partial' and 'acute profound' HIBD is often advanced as a possible cause when imaging and clinical features are not congruent, e.g. when a child has basal ganglia and thalamic damage on MR imaging but suffers from spastic CP. The simplest finding from the results of our study underlines the increasing recognition that spastic CP is a common

outcome in cases of acute profound hypoxia/ischaemia, not just those children exposed to prolonged partial hypoxia/ischemia.

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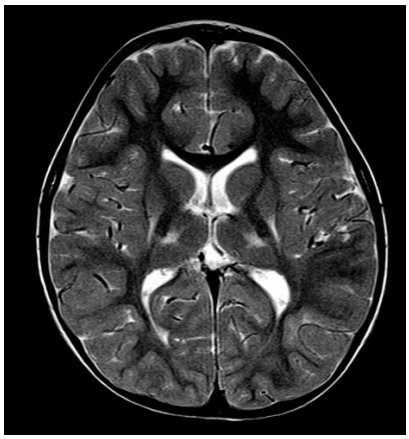

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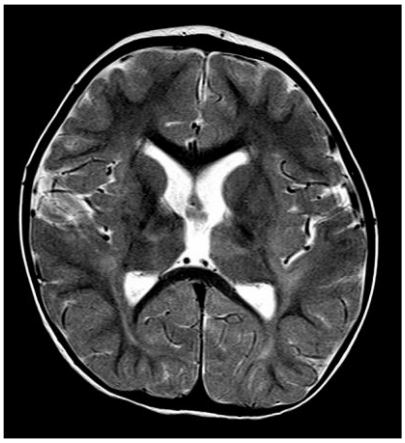

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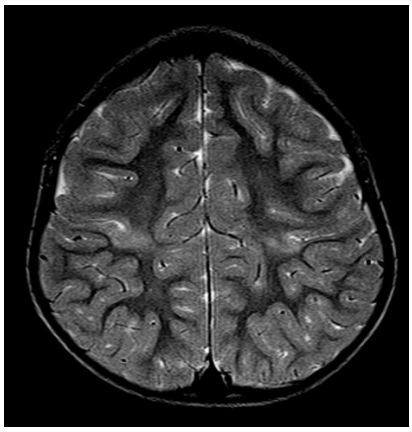

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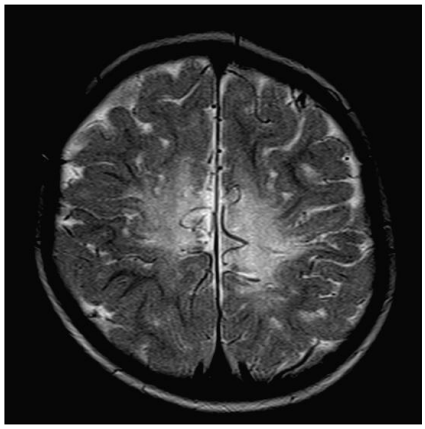

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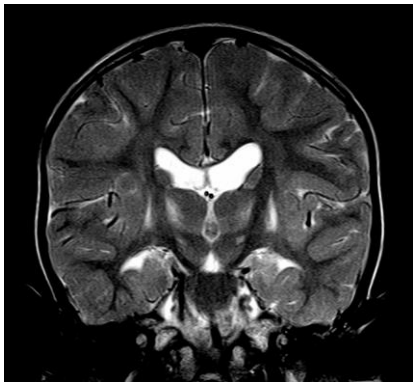

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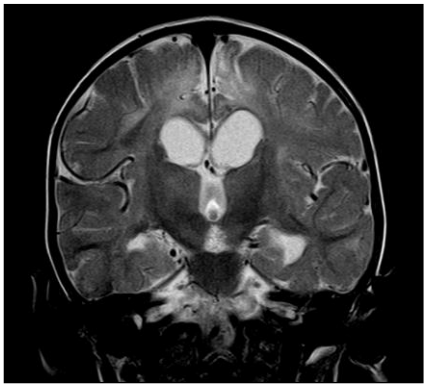

Figure 9.3.4. Typical appearances of HIBD changes in children with acute profound HIBD. Figures 4a-4d axial T2 images showing mild involvement of the putamen, thalamus and paracentral white matter in a child with dyskinetic CP (4a, 4c) and spastic CP (4b, 4d). Figure 4e-4f coronal T2-weighted images show involvement of the STN in a child with dyskinetic CP (4e), but no signal abnormality in the region of the STN in a child with spastic CP (4f)

To understand why acute profound HIBD produces dyskinetic CP in some children and spastic CP in others we need to review the anatomy and functional connectivity of the basal ganglia and motor cortex in normality and in cases of movement disorders. Original theories about the function of the basal ganglia came from observational studies in humans *post mortem* but this has been refined in recent years by detailed studies of animal models of movement disorders.[7,8] Here, we shall concentrate on the basal ganglia and its role in controlling voluntary movement and not direct our attention to the conscious mechanisms that instigate voluntary movement.

When voluntary movement is undertaken, two neuronal activities are generated within the basal ganglia using anatomically discrete pathways. One promotes the primary movement whilst the other attempts to provide the stability in other muscle groups required for the primary movement to act efficiently, which is usually a combination of stimulation and inhibition of different muscle groups. Both the primary 'direct pathway' and the associated 'indirect pathway' of movement programming originate in the putamen (caudate nucleus to a lesser extent), albeit from different neuronal subtypes. The direct pathway projects to the medial globus pallidus (GP_m), and the indirect pathway to the lateral globus pallidus (Gp_l). [9] This is shown schematically in figure 5 (modified from references 7 and 10). Some disorders selectively affect the activity of these pathways preferentially and this results in different types of clinical symptomatology. Abnormalities that reduce the activity of the direct pathway are expected to produce hypokinesia, whilst reducing the activity of the indirect pathway should produce hyperkinetic syndromes such as chorea or dystonia.

Early, untreated Parkinson's disease provides a good example of a hypokinetic syndrome and there is good evidence that the lack of dopamine caused by neuronal degeneration in the substantia nigra, pars compacta causes reduced

activity of the neurons of the direct pathway.[11] In contrast, the striatal degeneration associated with Huntington's disease, initially affects the neurons of the indirect pathway and causes chorea.[12] It should be appreciated that the two neuronal subtypes in the putamen are closely intermingled and focal lesions (either infarctions in humans or destructive lesions in animal models) do not affect one particular subtype specifically. This may explain why focal lesions of the putamen rarely produce movement disorders of any type. By implication, it is unlikely that the focal putaminal damage seen in profound HIBD is responsible for the dyskinesia associated with the cerebral palsy. Likewise, the site of predilection for damage in the thalamus is a sensory region and should not produce dyskinesia, for the reasons given in the introduction.

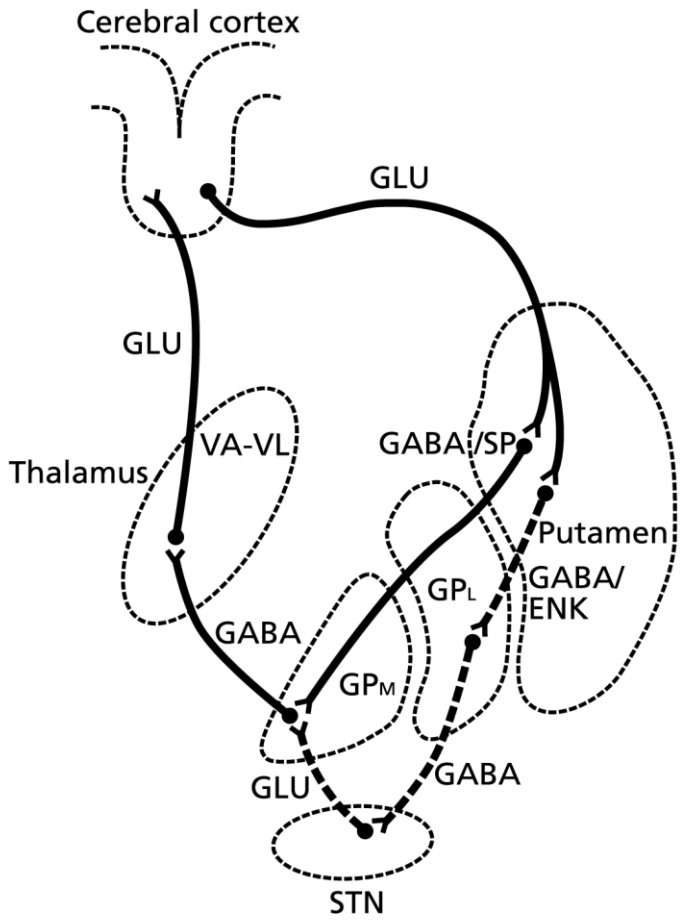

Figure 9.3.5. Line diagram to show the direct and indirect pathways from the putamen to the thalamus and hence to the motor cortex. Dashed lines indicate the neurons of the indirect pathway traveling via the subthalamic nucleus (modified from references 6 and 9). Anatomical abbreviations used – VA-VL, ventral anterior and ventral lateral nuclei of the thalamus; STN, subthalamic nucleus; GP_m, medial globus pallidus; GP_l, lateral globus pallidus. Neurotransmitter abbreviations – GABA, gamma amino butyric acid; GLU, glutamate; ENK, enkephalin; SP, Substance-P.

The indirect pathway from the GP_l first projects to a small diencephalic nucleus, the STN, using GABA as the neurotransmitter. The STN neurons then project to the GP_m using glutamatergic neurons. It has been shown that the indirect pathway has faster neuronal transmission rates when compared with the highly somatotopic direct pathway and this feature is responsible for the fast suppression of unwanted movements.[13] It has been known for a long time that injury to the STN and its associated tracts can produce hyperkinetic syndromes. In this situation, reduced activity in the STN leads to under-suppression of

unwanted movements, hence dyskinesia. The purported underlying mechanism is interruption of the excitatory glutamate-mediated projection from the STN to the GP_m which, subsequently, is expressed via altered function of the thalamocortical and corticospinal pathways.

In one series of adults with hemichorea following stroke, radiological evidence of STN damage was reported in 30%, and globus pallidus damage in 7%.[14] That series also reported a high frequency of striatal and cortical injuries which are not classical sites associated with dyskinesia. However, those patients with radiologically apparent STN damage had the worst prognosis. In infants, a similar pattern of radiologically detectable STN damage has been shown in kernicterus.[15] Pathologically, kernicterus results from deposition of bilirubin in the globus pallidus and STN and produces a clinical syndrome of dyskinetic cerebral palsy. To summarize the clinical observations and work from animal models, it is difficult to support focal injuries to the putamen as the anatomical substrate for dyskinesia. If a focal injury is to cause a dyskinesia it is much more likely to be in, or close to, the STN.

The normal STN is difficult/impossible to visualize directly on MR imaging on standard scanners operating at 1.5T (as in our cases) because of the small size of the nucleus and the lack of contrast between the nucleus and surrounding structures. MR imaging of adults at 3.0T does allow direct visualization[17] as a small biconvex hypointense structure on T2-weighted images. This is presumably due to the susceptibility effects of high iron content in the STN as is also seen in the adjacent red nucleus and substantia nigra. Our cases were not imaged at 3.0T but we predict that even if they were, the STN in normal brains would not be visualized directly because the pediatric brain is virtually devoid of iron at all sites as there is an age-dependent accumulation.[18] As shown in this study, the STN can be seen directly on T2-weighted MR at 1.5T when there is gliosis produced by ischemic injury. It should be noted that not

all children with dyskinetic CP showed radiologically apparent STN abnormality. Possible explanations include the small size of the STN, and that an injury may not be sufficiently great to be visualized. Although, all the cases in this series were imaged using the same protocol, it has been our experience that high-resolution sequences are required. In particular, injury to the STN is more apparent on relatively short echo-train length (ETL) sequences (8 echos) than on longer ETL sequences.

Previous reviews of MR findings in HIBD have linked dyskinetic symptoms to less severe patterns of injury.[19] Our study has provided support for that theory as children with spastic CP tended to have more severe signal changes and volume loss on MR imaging, particularly in the PCWM. We have also shown that injury to the STN as a common finding in dyskinetic CP (15/20) and uncommon in spastic CP (6/20). In 3/6 children with spastic CP and abnormal STN there was also severe damage to the PCWM and the dominance of spasticity in the clinical symptomatology may be explained by the injury to PCWM. It is likely damage to the descending corticospinal tracts masks the aberrant neuronal output from the injured basal ganglia and dyskinesia cannot be manifest clinically for that reason. None of the children with dyskinetic CP had severe volume loss or signal change in the PCWM suggesting that some function in the corticospinal tracts is necessary for dyskinesia to be clinically apparent.

The injury commonly seen in the ventral postero-lateral thalamus is a somatosensory relay nucleus and should not have a major role on motor function, however we have demonstrated that more severe forms of HIBD tend to involve the thalamus more generally. It is possible that this could have further deleterious effect on motor function if the damage extends anteriorly into the ventral lateral and ventral anterior thalamic nuclei through abnormal projections to the primary motor cortex and supplementary motor cortex respectively.

In summary, we found that spastic CP is a frequent outcome of acute profound HIBD in some children as well as the more extensively reported cases of dyskinetic CP. In this paper we have attempted to explore why some children have spastic CP whilst others have dyskinetic CP by making detailed anatomical studies by way of MR imaging. The main finding was frequent injury to the STN in children with dyskinetic CP, a finding that was uncommon in children with spastic CP. Those children with STN damage and spastic CP always had severely damaged PCWM. We have explained those findings on the basis of the known connectivity and function of the basal ganglia and have generated a new hypothesis. Specifically, dyskinetic CP arises from abnormal activity of the indirect putamen/GP pathway (by way of injury to the STN) and requires a functioning corticospinal pathway to manifest the movement disorder.

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9.4 Isolated superior cerebellar vermis injury: a consequence of hypoxic ischemic injury

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Ataxic cerebral palsy due to isolated injury to the anterior lobule of the cerebellar vermis was described in the medical literature for the first time in this paper.

Sargent et al first described the focal injury to the anterior lobule of the cerebellar vermis seen in children who had suffered neonatal acute profound hypoxia at term (Sargent et al). We had previously described a series of term neonates with acute profound hypoxic injury in whom the more severely injured were more likely to also demonstrate injury to the superior vermis (Connolly, Widjaja and Griffiths).

Many paediatric neurology experts suggest that ataxic cerebral palsy does not exist as a separate clinical entity, and indeed the original descriptions of cerebral palsy did not include an ataxic subtype. However, since that time the papers describing injury to the vermis and now isolated injury to the vermis have been published. Therefore, we suggest that, though rare, isolated ataxic cerebral palsy does exist. However, these two cases demonstrate no evidence of injury to the STN, ventral postero-lateral thalamus or posterior putamen, but did demonstrate focal injury to the anterior lobule of the cerebellar vermis.

The lack of correlation between focal brain injury as demonstrated pathologically and with brain MR imaging is perhaps best appreciated by the dyskinetic cerebral palsy described and witnessed frequently after acute profound hypoxia at term. The classic regions of the brain affected are the posterior putamen, antero-lateral thalamus and paracentral white matter. Damage to these regions does not explain the subsequent movement disorder. We demonstrated for the first time that injury to the subthalamic nucleus in acute profound asphyxia and described how this focal injury does explain the subsequent movement disorder (Griffiths, Radon, Crossman et al).

Abstract

Hypoxic ischemic insult (HII) in early childhood can have a varied clinical presentation depending on the timing and severity of the insult and magnetic resonance imaging (MRI) plays a key role in identifying injury patterns. Dyskinetic cerebral palsy is commonly associated with injury to the basal ganglia and thalamus. We report two cases presenting in early childhood with signs and symptoms of dyskinetic cerebral palsy attributed to focal damage to the superior cerebellar vermis secondary to a hypoxic insult in the perinatal period in term infants.

Keywords

Dyskinetic cerebral palsy, Hypoxic ischemic insult, Superior cerebellar vermis, Magnetic resonance imaging

INTRODUCTION

Cerebral palsy is a group of permanent disorders of development of movement and posture causing activity limitation that is attributable to a non-progressive disturbance that occurred in a developing fetus or an infant brain. Motor disorders of cerebral palsy are often accompanied by disturbance of sensation, perception, cognition, communication, behaviour, epilepsy, recurrent chest infections and secondary musculoskeletal problems. Hypoxic ischaemic injury (HII) to the brain in the peri-natal period is one of the causes of cerebral palsy and its clinical presentation depends upon the timing and severity of injury sustained. There are well described manifestations of HII; both periventricular white matter injury and acute profound injury may occur in the preterm (less than 34 weeks gestation) brain and both parasagittal watershed injury and acute profound injury in term neonates. There are rare exceptions which are acknowledged to occur such as white matter injury due to HII in a term infant (1).

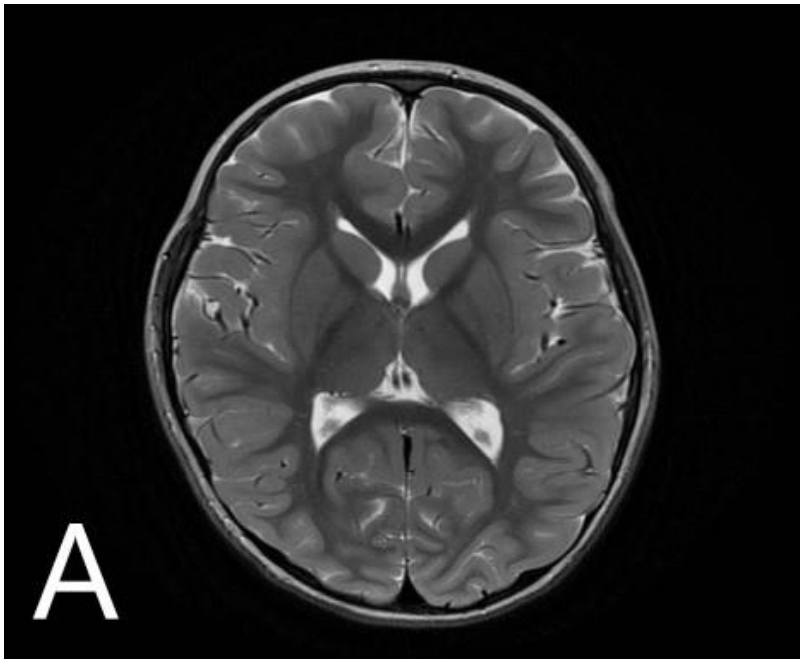
We describe 2 children with dyskinetic cerebral palsy who were found to have an isolated injury to the superior cerebellar vermis (SCV). Clinical history revealed these children had sustained a period of hypoxia in the peri-natal period.

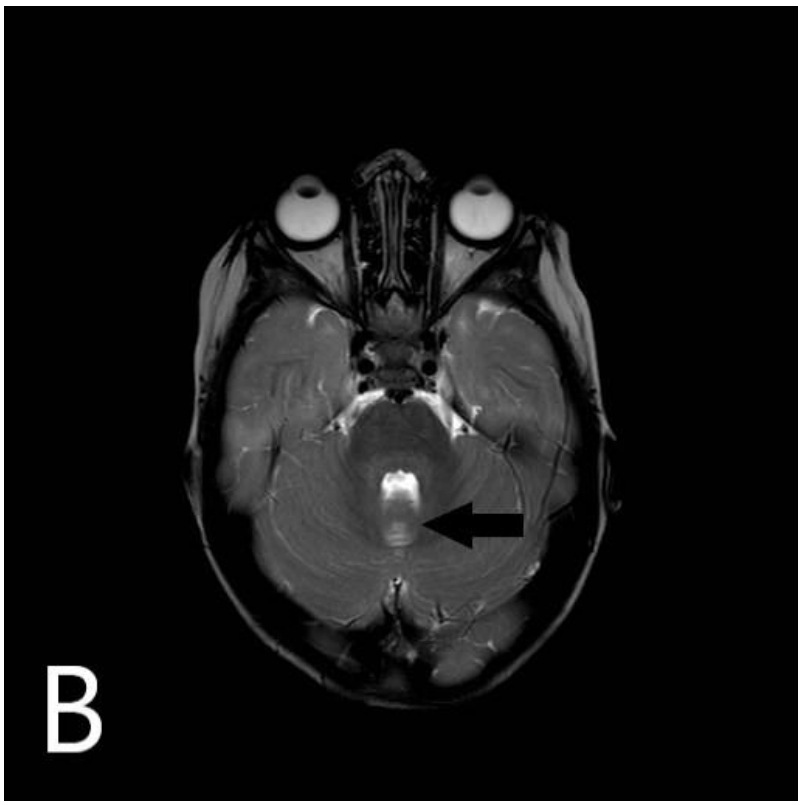
Case 1

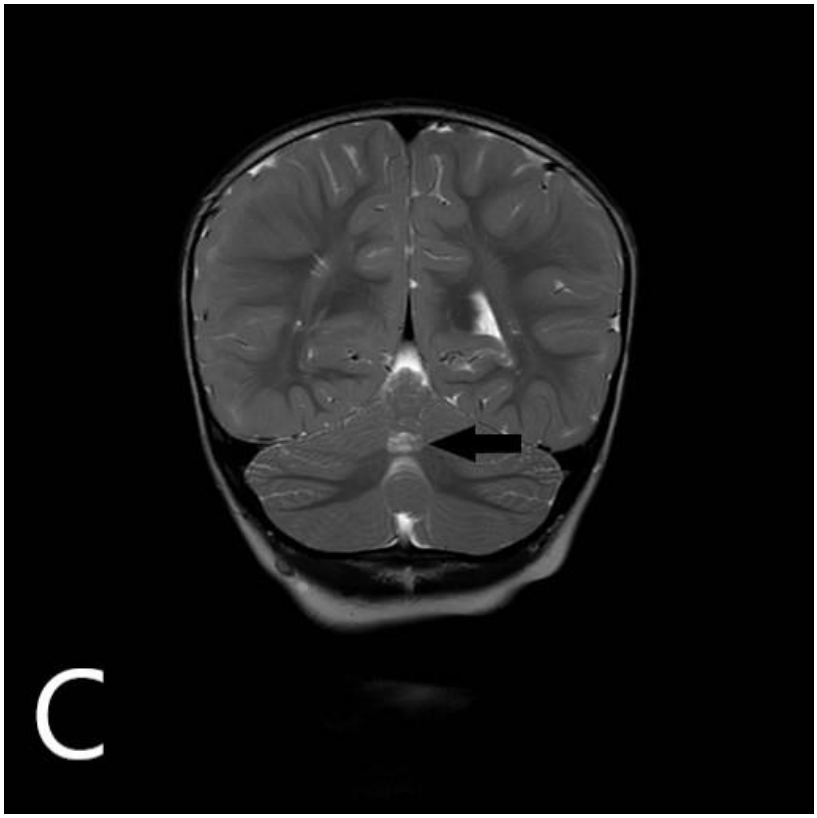
Following an uneventful pregnancy, a female was born at full term by emergency caesarean section due to reduced fetal movements. Apgar scores were 1, 5 and 6 at 1, 5 and 10 minutes respectively and the umbilical cord arterial pH was 7.11. There were features of neonatal encephalopathy with neonatal seizures. Extensive neurometabolic investigations and infection screens were negative. At 2 years of age, she presented with a developmental impairment, bulbar dysfunction and axial hypotonia with dyskinetic movements. She was diagnosed with dyskinetic cerebral palsy (DCP). She was diagnosed to have a developmental co-ordination disorder by her Paediatrician at 5 years of

age. At 5 years of age, she was reviewed by Paediatric Neurologist, who diagnosed her to have ataxia.

She continues to make slow progress and has independent mobility with difficulty in fine motor skills due to her ataxia. She can self-feed herself orally but needs her food to be cut.







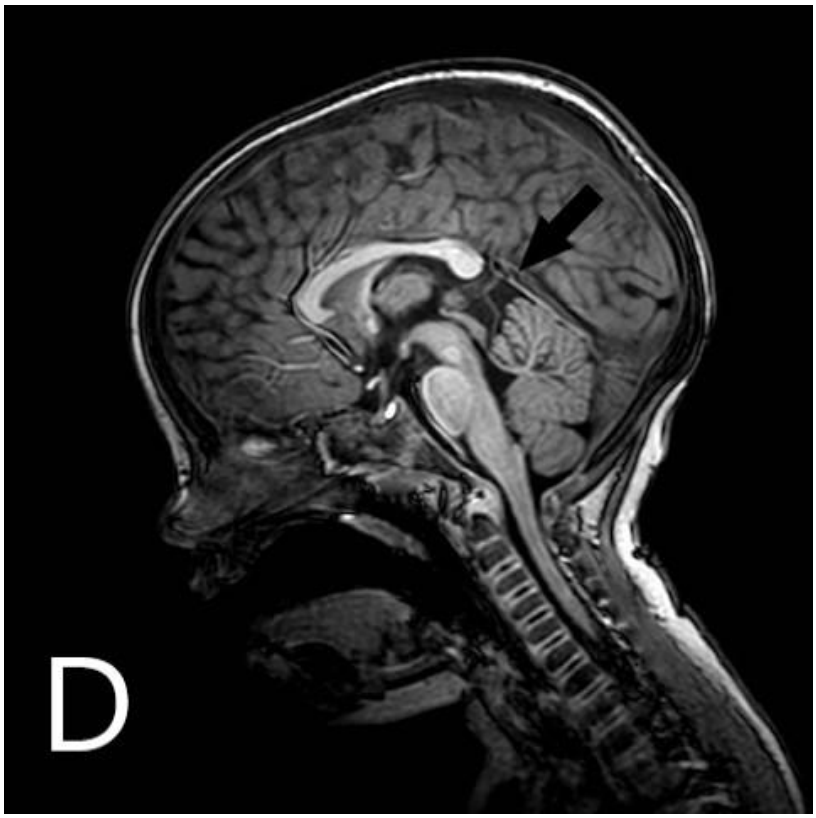
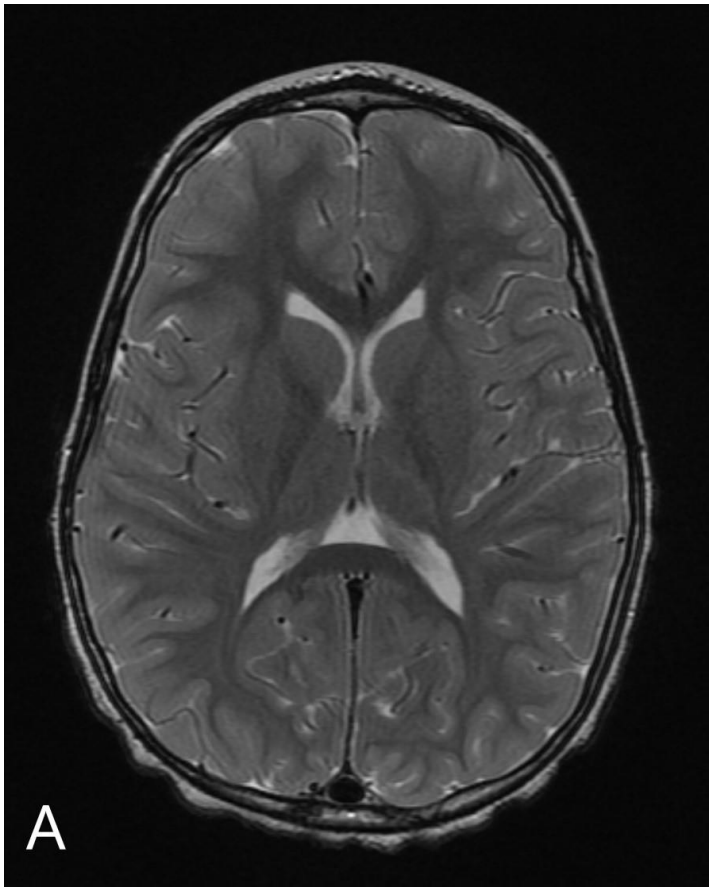


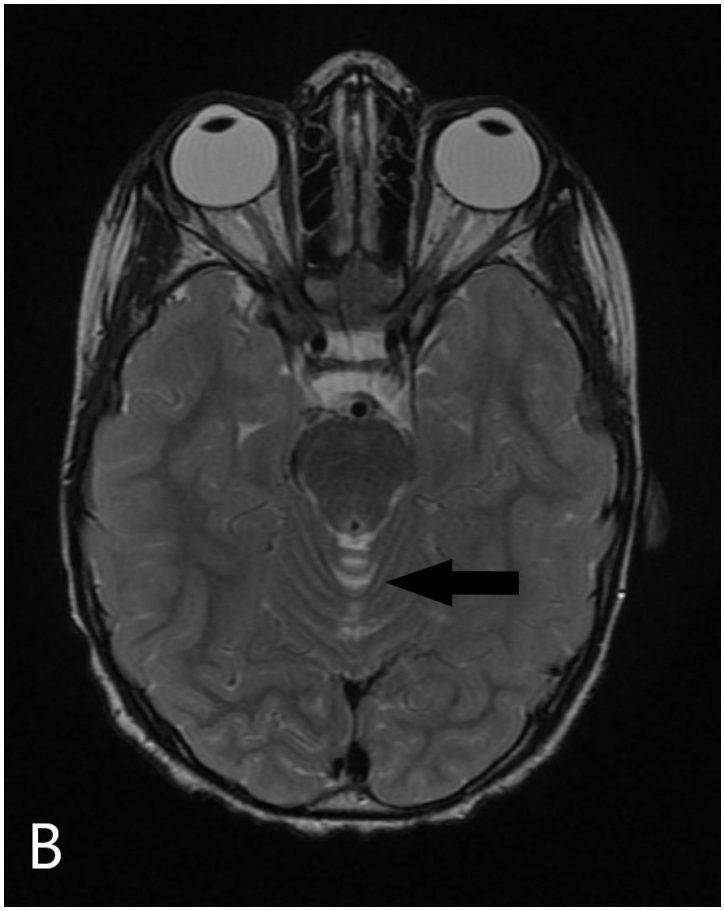
Figure 9.4.1. Selected images of Child 1. *A* axial T2 image through normal basal ganglia. *B* and *C* axial and coronal T2 images through the superior cerebellar demonstrates increased T2 signal in the superior vermis. *D* Sagittal T1 in the midline demonstrating loss of volume of the superior vermis.

Case 2

Following an uneventful pregnancy, a female was born by normal delivery at full term for reduced fetal movements. Apgar scores were 1, 3 and 8 at 1, 5 and 10 minutes respectively. There were features of neonatal encephalopathy and all neurometabolic investigations and infection screens were negative. At 3 years of age she was referred with developmental impairment, bulbar dysfunction, axial hypotonia with ataxia and dyskinetic movements. She was diagnosed with DCP. She is under regular review by a Paediatric Neurologist and at 6 years of age continues to make slow progress with independent mobility and is orally fed.

Subsequent MRI brain imaging in both children demonstrated focal damage to the superior cerebellar vermis, with normal imaging of the remaining neural-axis (Figures 9.4.1 and 9.4.2).

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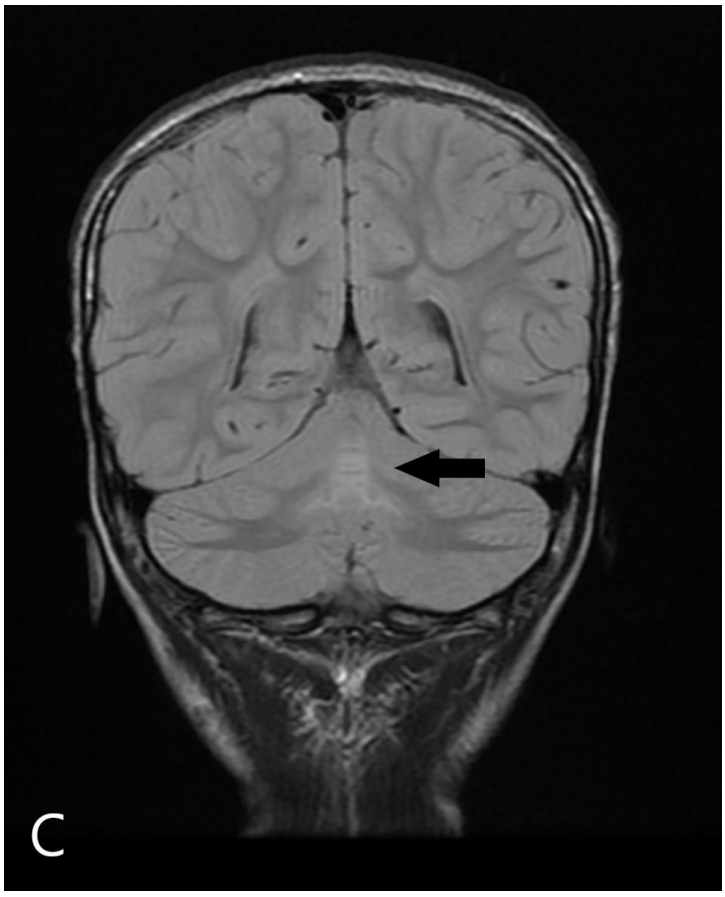
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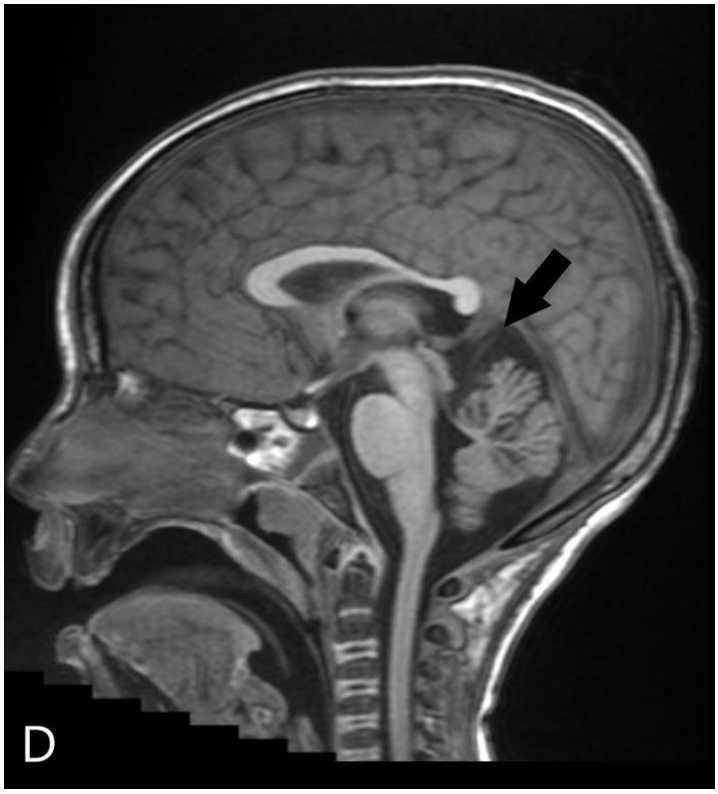

Figure 9.4.2. Selected images of Child 2. *A* axial T2 image through normal basal ganglia. B axial T2 image through the superior cerebellar demonstrates increased T2 signal in the superior vermis. *C* Coronal T2-FLAIR image through the vermis demonstrating increased signal in the vermis. *D* Sagittal T1 in the midline demonstrating loss of volume of the superior vermis.

DISCUSSION

Cerebral palsy is the most common cause of physical disability in children occurring in 2 to 3 per 1000 live births (2) and is characterised by a non-progressive motor impairment (3), secondary to an insult that has occurred in early life. Patients with cerebral palsy have an increased association with other conditions including visual and hearing impairment and epilepsy (4). In full term neonates, there are two types of HII: acute profound injury and chronic partial injury.

Neuro-imaging has played a vital role in the management of cerebral palsy by identifying patterns of brain insult attributed to different gestational age (with associated varied brain maturation) duration of insult and severity of insult sustained (5) along with other structural abnormalities and is recommended in all cases of cerebral palsy of unknown origin (6).

The pattern of subsequent disabilities in children has also been helpful in inferring causation in babies who have suffered neonatal encephalopathy. There are two clinical paradigms of survivors. In chronic partial hypoxic injury, the fetus suffers a more prolonged but a less severe episode of hypoxia due to the perfusion failure in the brain and the watershed area or the parasagittal cortex are damaged. The clinical features in such cases commonly include a spastic quadriplegic cerebral palsy with acquired microcephaly. In acute profound hypoxic injury, the fetus suffers a total or a near total hypoxia over a brief period. In this case the damage affects the most metabolically active parts of the brain called the basal ganglia and the thalami. The characteristic clinical features in these children is of a dyskinetic type of cerebral palsy with an impaired motor development with oromotor difficulties which our children had.

Dyskinetic cerebral palsy (DCP) is the second most common form of cerebral palsy (7) and is often associated with lesions involving the basal ganglia or the thalamus secondary to an acute profound hypoxic ischaemic insult, commonly in the term infant (8). Studies have shown the lentiform nuclei is the most frequent area to sustain damage (9). Anatomical studies have suggested the

subthalamic nucleus as a site of focal damage associated with later dyskinesia (10).

The underlying process leading to cerebral palsy can be multi-factorial including congenital brain malformations, toxins and in utero infection (11). HII can be indicated as the cause in a small proportion of cases.

There are three well recognised distinct patterns that can occur; insult before 28 weeks of gestation leading to hydranencephaly and porencephaly. An insult between 28 and 36 weeks of gestation is often associated with germinal matrix hemorrhage (GMH) and periventricular leukomalacia (PVL). HII affecting the term baby and can vary in its impact upon the brain depending on the severity and length of insult. An acute severe insult can result in damage to the basal ganglia (posterior putamen, subthalamic nucleus, head of caudate nucleus, hippocampus) thalamus and peri-rolandic cortex and subcortical white matter. This is in contrast to damage to the parasagittal white matter in the setting of a chronic but low-grade hypoxic/hypoperfusion insult. The changing patterns of damage and different gestational ages relates to the varying distribution of the blood supply and vascular watershed territories in the maturing fetal brain (12).

A hypoxic insult will often lead to a generalised brain insult but there are cases of focal brain damage that have been attributed to a hypoxic insult that do not follow the conventional pattern of injury as described above. The reasons for focal brain damage in HII remain unclear but may be related to areas of active myelination at the time of insult (13) areas of greatest metabolic demand or occur in cells that are enzyme deficient. For example, damage to the anterior lobule of the cerebellar vermis is well recognised in acute profound hypoxic injury (14, 15).

Our cases are unique demonstrating isolated damage to the superior cerebellar vermis. It is possible that other abnormalities may have been demonstrated if these patients underwent neuro-imaging in the neonatal period, however subsequent MRI brain studies revealed no sequelae of hypoxic insult in the remaining brain. MRI imaging in cases of HII is highly recommended due to its'

sensitivity to identify areas of damage although in some cases MRI can be normal.

The cerebellar vermis develops separately from the cerebellar hemispheres and why it is specifically targeted in some cases of hypoxic insult remains unclear. The Purkinje cells of the vermis may be deficient in certain proteins, including aldolase C, and therefore may not be able to recover from a sudden hypoxic insult, potentially leading to focal areas of damage (16).

We have described two cases of isolated superior cerebellar vermis volume loss with associated signal change, present on both T2-weighted and FLAIR sequences and these findings can be attributed to a hypoxic insult in the term infant occurring in the perinatal period. In both cases, the pregnancy was otherwise uneventful but there were features of neonatal encephalopathy and low Apgars with no other identifiable cause for damage to the vermis and subsequent cerebral palsy. Clinically these children both presented with hypotonia, developmental impairment, bulbar dysfunction and dyskinesia and ataxia.

CONCLUSION

Isolated volume loss and signal change in the superior cerebellar vermis can be a sequela of HII in the term infant and present with signs and symptoms consistent with dyskinetic cerebral palsy, an association that has not been previously described.

We certify that there are no actual or potential conflict of interest in relation to this article.

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9.5 A review of fetal brain pathology acquired in utero

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Many of the pathologies which have been ascribed to the perinatal period may also happen in utero. They may therefore be confused with a cause of perinatal encephalopathy and must be considered when reporting neonatal brain MRI studies. The MERIDIAN acquired pathology paper was the first to attempt to describe the range of common acquired in utero pathologies and their relative prevalence in clinical practice.

Fetal stroke was the most common acquired pathology of the MERIDIAN cohort found in 3.5% of cases. The majority of strokes were haemorrhagic. There were also cases of brain hypoxic injury demonstrated in utero. This paper supports the premise that neonatal brain MRI should be performed in the first 5 days after delivery so that DWI imaging and standard brain imaging may be used to assess if a hypoxic brain injury occurred at a time point distantly preceding delivery

We discussed the difference and indeed the overlap between developmental and acquired fetal brain pathology. A true congenital pathology will often be due to a genetic disorder. A disruption is impaired development due to an acquired pathology affecting a structure at an immature stage with the end result being a secondary malformation. An example of this is congenital CMV (cytomegalovirus) infection producing polymicrogyria (PMG).

Introduction

In utero magnetic resonance (iuMR) imaging is used increasingly to assist prenatal diagnosis of fetal brain abnormalities. The diagnostic and clinical value is now supported by systematic reviews, meta-analyses and a formally powered prospective study – 'Magnetic resonance imaging to enhance the diagnosis of fetal brain developmental brain abnormalities in utero' the MERIDIAN study (1-6). The results of the MERIDIAN study demonstrate improvements in diagnostic accuracy of at least 22% compared with brain abnormalities recognised on ultrasound. Positive effects on diagnostic confidence, prognostication and clinical management in anatomical sub-groups have also been reported (7-9). The purpose of iuMR in this situation is not only to confirm that the fetal brain is abnormal but to produce a definitive or differential diagnosis in order to provide highest quality information regarding the significance of the findings to the parents. One established step in medical image analysis is to distinguish between 'Developmental' and 'Acquired' pathology although, as we explain later, this may be too simplistic for fetal brain pathology.

In this review, we outline the many of the fetal brain abnormalities that can either be confidently classified as 'acquired' or there is a strong probability that they are 'acquired' after the first trimester of pregnancy. We will present an analysis of the cases from the MERIDIAN cohort that fit our definitions of acquired pathologies and provide a pictorial review of the typical imaging appearances, as well as to provide prevalence data on acquired brain pathology.

General review of acquired pathology of the fetal brain

The factors responsible for acquired fetal brain damage are usually a result of stroke (haemorrhagic or ischemic), generalised hypoxic/ischemic injury (including reperfusion injury), infection, toxic or metabolic abnormalities or intracranial mass lesions.

Fetal stroke is defined as brain injury resulting from ischemic, thrombotic or haemorrhagic causes (focal or multifocal) between 14gw and the onset of

labour (10). Generalised hypoxic-ischaemic injury to the fetal brain is not usually included in this definition of fetal stroke and is discussed separately. The prevalence of fetal stroke is not known. There is a low detection rate *in utero* and the diagnosis is often not suspected until post-natal imaging has been performed and raised the possibility of an *in-utero* event. Also, many cases of fetal stroke remain undiagnosed, particularly if there are no (or minor) clinical sequelae, as may occur following *in utero* germinal matrix and/or intraventricular haemorrhage. Ozuduman et al. reviewed 47 cases of fetal stroke from the pre-2004 published literature and added seven cases from their own institution. 49/54 (91%) of those fetuses had haemorrhagic stroke on pre-natal imaging and 5/54 (9%) had ischemic stroke. The difference in the rates of haemorrhagic and ischemic fetal stroke may result from a detection bias as intracranial haemorrhage is relatively easy to detect on USS, unlike ischaemic stroke. iuMR imaging is likely to have improved diagnostic accuracy for ischemic stroke but was used only in the later cases in the review. Another important finding was the number of fetuses thought to have intra-ventricular haemorrhage as the only intracranial abnormality on pre-natal imaging (n=15) but were shown to have brain involvement on outcome reference data (8/15 – 53%). The recognition of brain injury is important for prognostication, although the brain injury may have occurred after the pre-natal imaging was performed in some cases. The authors could not attribute an aetiology for the fetal stroke in 50% of cases and the explanation was often speculative in the others, although they made useful lists of pathologies found in association with fetal stroke and classified them into maternal (e.g. diabetic ketoacidosis, thrombocytopenia, drug use), pregnancy-related (e.g. placental abruption, thrombosis, complication of multiple gestation) and fetal causes (e.g. pyruvate carboxylase deficiency, thrombocytopenia, coagulopathies, transplacental infections). Prognosis after fetal stroke was poor in their experience, with 51% resulting in fetal or neonatal death and over 50% of survivors were neurologically impaired. Examples are shown in figures 9.5.1-9.5.4.

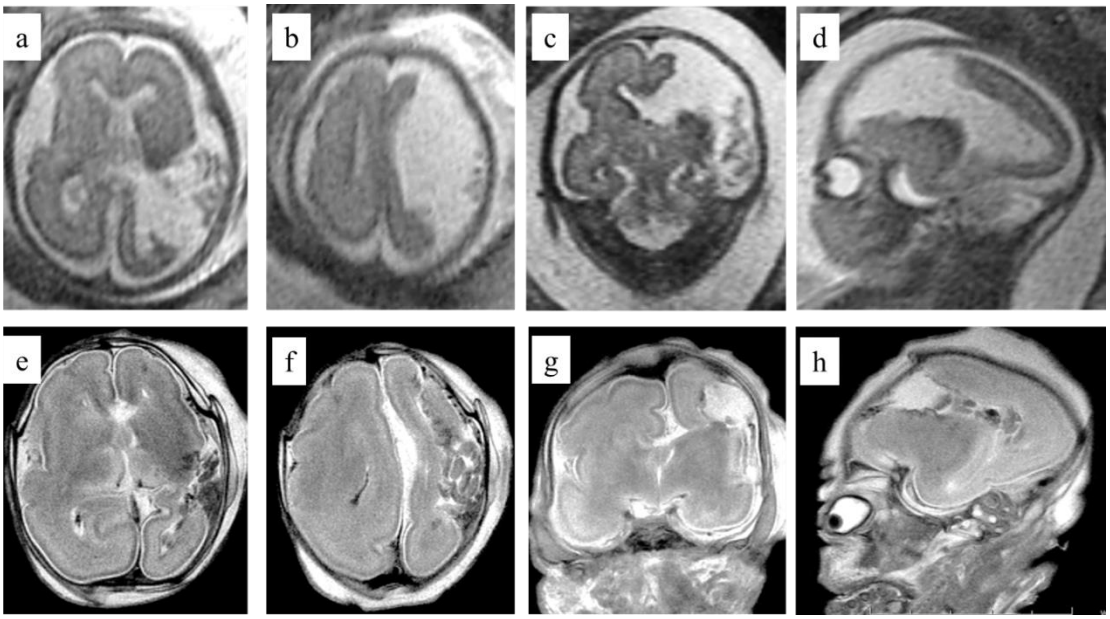

Figure 9.5.1. Ischemic stroke. Axial (1a and 1b), Coronal (1c) and parasagittal (1d) T2-weighted images of a 23gw fetus in utero with an arterial infarction of the left cerebral hemisphere involving the posterior division of the middle cerebral artery. There is no definite evidence of haemorrhage on the in-utero MR images but the equivalent T2-weighted images post-mortem MR images (1e-1h) show haemorrhagic transformation.

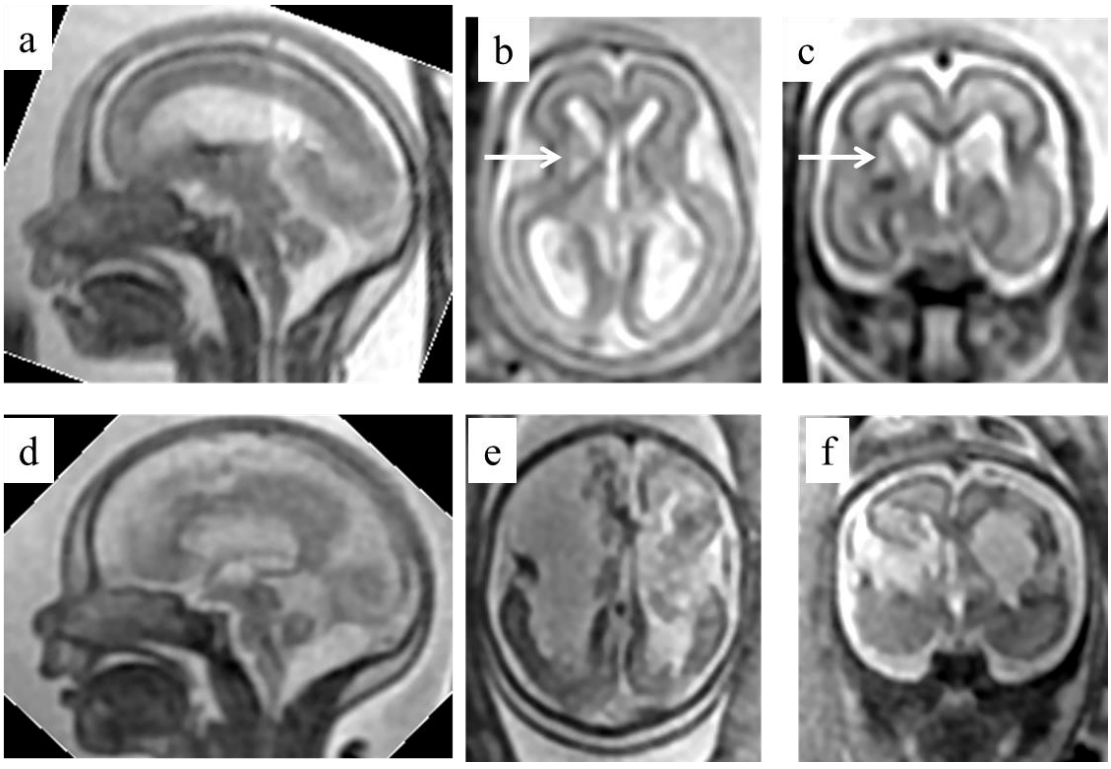

Figure 9.5.2. Recurrent, multifocal stroke. Sagittal (2a), axial (2b) and coronal (2c) T2-weighted images of a 21gw fetus investigated for ventriculomegaly diagnosed on ultrasonography. Mild ventriculomegaly was confirmed and there was abnormal signal in the right basal ganglia consistent with infarction (arrowed on 2b and 2c). Repeat imaging at 26gw (2d-2f) showed progressive ventriculomegaly and multiple areas of infarction some associated with haemorrhage. A subsequent diagnosis of a COL4A1-related disorder was made.

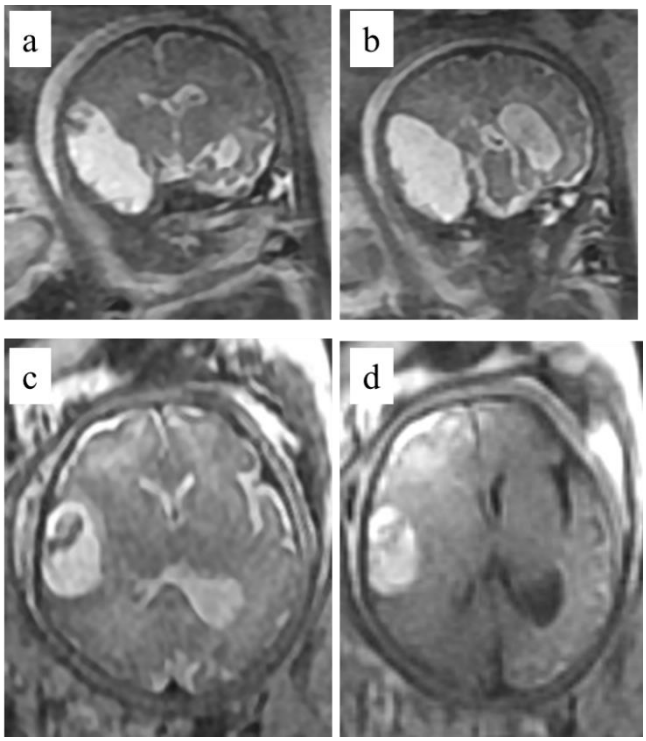

Figure 9.5.3. Haemorrhagic stroke. Coronal (3a and 3b) T2-weighted images of a 35gw fetus shows a large area of focal cystic encephalomalacia centres on the right temporal lobe and extending into the frontal lobe. The cavity has irregular margins and evidence of subacute haematoma (3c and 3d). There is mass effect with effacement of the ipsilateral lateral ventricle, midline shift and contra-lateral ventriculomegaly, probably secondary to hydrocephalus. A subsequent diagnosis of feto-maternal alloimmune thrombocytopenia was made.

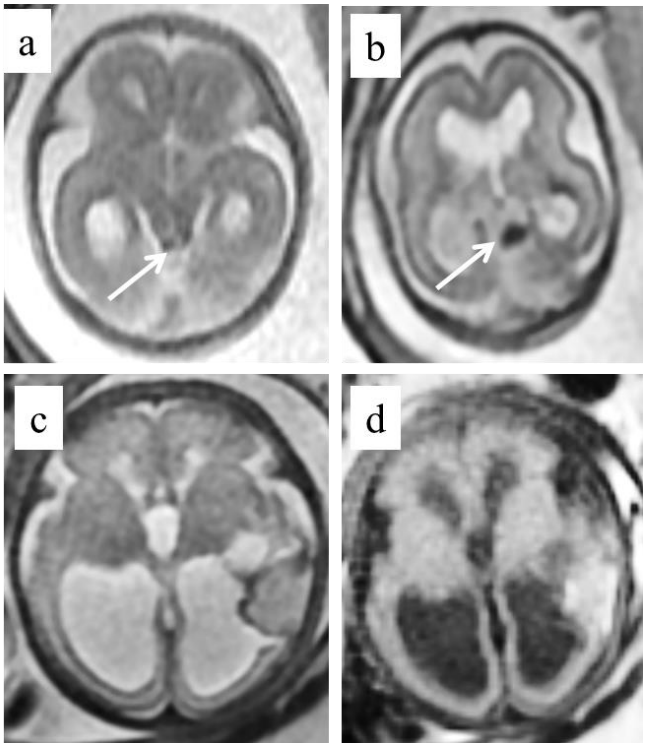

Figure 9.5.4. Recurrent, multifocal haemorrhagic stroke. A fetus was shown to have mild ventriculomegaly on ultrasonography at 21gw. Axial T2-weighted images at 22gw fetus (4a and 4b) confirm ventriculomegaly and show a low signal mass related to the tectal plate and extending into the pineal cistern (arrowed on 4a and 4b). This was thought to represent hemosiderin related to either earlier haemorrhage or a cavernoma. The fetus had a further iuMR study at 30gw because of increasing ventriculomegaly. Axial T2-weighted (4c) and FLAIR (4d) confirm severe ventriculomegaly and show a new intra-parenchymal haematoma in the left temporal lobe. No specific cause was discovered.

Ischemic stroke may be thrombotic or embolic and the fetus is potentially susceptible to emboli not only arising from its own circulation but from the vascular compartment of the placenta or as a complication of a multi-fetal pregnancy. The latter is most likely to occur in cases of monochorionic twinning complicated by death of one twin and emboli from the demised twin may pass to the surviving twin because of the vascular anastomoses in the single placenta. Thrombosis in the placental/umbilical vascular bed can occur for many reasons but is frequently associated with chorioamnionitis, resulting in an increased risk of fetal stroke. It should also be noted that certain genetic predisposition syndromes (e.g. COL4A1) may exacerbate the effect of a vascular insult (11). Although fetal stroke is clearly an acquired lesion, if it occurs at a sensitive point of brain development it may produce lesions that are typically

described as ‘Developmental’. One such mechanism is the ‘fetal brain disruption sequence’ which may be the consequence of several forms of vascular injury to the fetal brain (emboli, haemorrhage, vaso-constriction and DIC) and is linked to the development of abnormalities such as septo-optic dysplasia and schizencephaly (12-13). Reports of ‘reparative polymicrogyria’ are also appearing in the literature following ischemic stroke in the survivors of co-twin demise in mono-chorionic pregnancies (14-15).

Discussion of haemorrhagic stroke in pediatric or adult practice would include ruptured intracranial vascular abnormalities, particularly aneurysms and pial arteriovenous malformations (AVM). Both of those have relatively high prevalence in the general population and AVM are usually considered to be congenital lesions. Comstock and Kirk reported 25 000 fetal US studies in 1991 and only four vascular abnormalities were found, three vein of Galen aneurysmal malformations (VGAM) and a lesion described as an ‘AVM’ in the paper but on review it was probably an arterio-venous fistula (16). VGAM and fistulae are more likely to injure the fetal brain by ischemic, rather than haemorrhagic, mechanisms (see below). Convincing reports of the ante-natal detection of fetal haemorrhagic stroke arising as a result of a ruptured pial AVM (or aneurysm) are exceptionally rare (17).

<u>Generalised hypoxic-ischaemic injury of the fetal brain</u>

There are a number of reasons why all parts of the fetal brain may not receive sufficient blood and/or oxygen including maternal causes (e.g. prolonged hypotension), placental causes (e.g. abruption), abnormalities of the fetus *per se* (e.g. cardiac) or as complication of a multi-fetal pregnancy. The resulting brain injury will depend on such factors as severity, duration and maturity of the fetus but it is most likely to produce bilateral and symmetrical injury. One possible outcome in the third trimester fetus is periventricular leukomalacia (often with germinal matrix haemorrhage) but it should be appreciated that

periventricular leukomalacia is an end result of injury from many aetiologies, such as infection and inflammation, and is not specific for hypoxic/ ischemic injury. More extensive brain injury in the form of global encephalomalacia with micrencephaly/ microcephaly may result from pathology such as VGAM, which are rare arteriovenous malformations of the choroidal system that develop in the embryonic stage. Generalised encephalomalacia may occur in fetuses with VGAM secondary to high flow 'steal' phenomenon or intracranial venous hypertension. In a recent iuMR study of 83 fetuses with antenatally detected VGAM showed that 16% had encephalomalacia, which was often severe (18). The authors describe the middle cerebral artery 'pseudofeeders' sign (enlarged branches arising as a result of impaired cerebral blood flow) as a predictor of encephalomalacia at birth, as seen in figure 9.5.6. Co-twin demise in monochorionic twin pregnancies can also cause generalised encephalomalacia in the surviving twin, probably arising from adverse global haemodynamic effects as well as fetal stroke as discussed above.

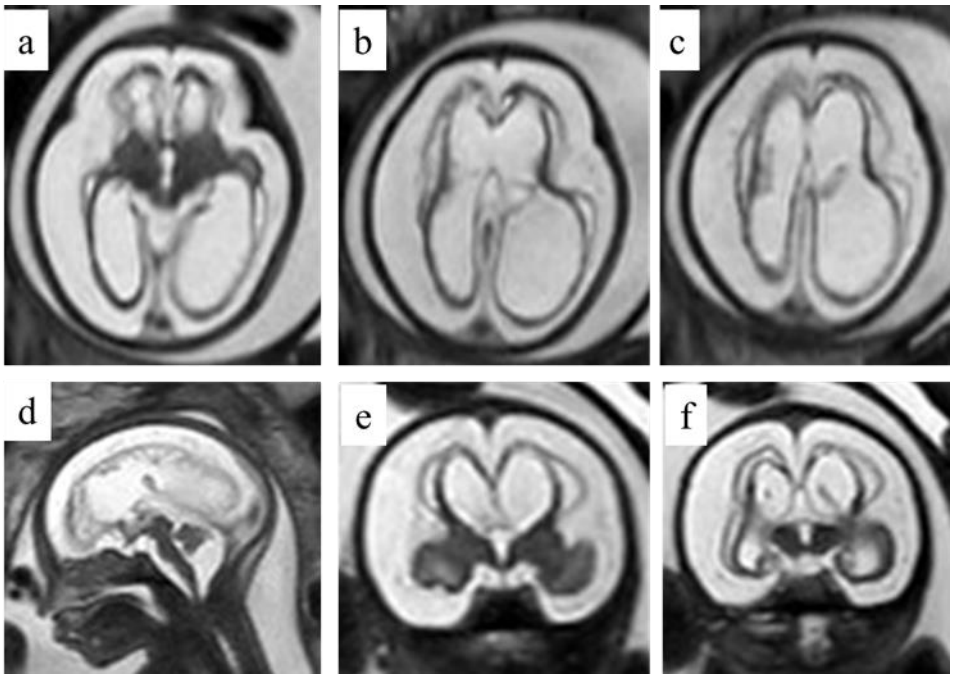

Figure 9.5.5. A fetus with established encephalomalacia of the cerebral hemispheres. Axial (5a-5c) sagittal (5d) and coronal (5e and 5f) T2-weighted images performed at 29gw show micro-encephaly, severe ventriculomegaly and extensive destruction of the cerebral hemispheres. This occurred in a fetus with Rhesus isoimmunisation (courtesy of Mr Umber Agarwal, Liverpool Women's NHS Foundation Trust).

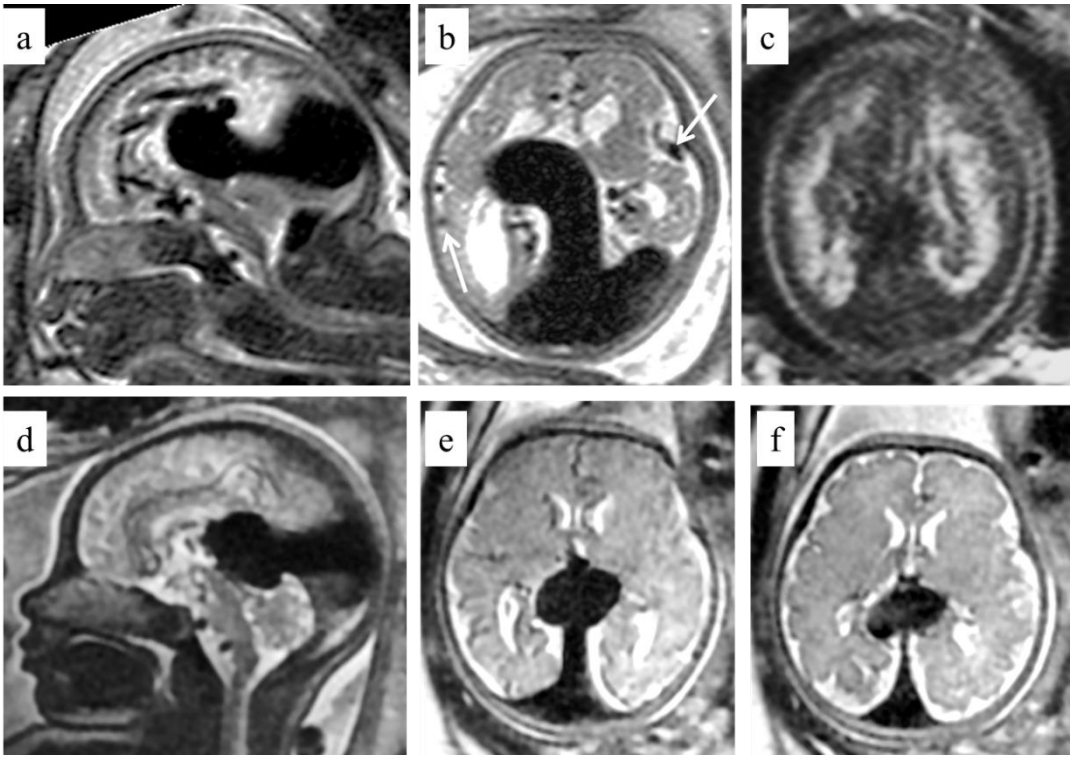

Figure 9.5.6. Two fetuses with vein of Galen aneurysmal malformations. The first fetus (6a-6c) imaged at x gw (ESS) shows a large vein of Galen aneurysmal malformation with extensive loss of volume from the cerebral hemispheres on sagittal (6a) and axial (6b) T2-weighted images and abnormal high signal on T1-weighted images (6c), probably indicating micro-hemorrhage or micro-calcification. Comparison is made with another fetus with a vein of Galen aneurysmal malformation imaged at 34gw in which there is no loss of volume or encephalomalacia (6d-6f). Note the enlarged branches of the middle cerebral artery in the fetus with encephalomalacia (arrowed on 6b) described as the 'pseudofeeder' sign resulting from of impaired cerebral blood flow that are not present in the other fetus - see the text for details.

Infections of the fetal brain

The fetus is relatively protected from micro-organisms whilst *in utero* but infection can occur by agents crossing the placenta or ascending the maternal genito-urinary system, particularly if the amniotic membranes are ruptured. The acronym 'TORCHES' is often used to describe the commonest infective agents that cause trans-placental infection (**T**oxoplasmosis, **O**ther, **R**ubella, **C**ytomegalovirus (CMV), **HE**rpes, **S**yphilis). The number of agents in the 'Other' category continues to increase and the aide memoire has been lengthened to

'CHEAP TORCHES', to include **C**hicken Pox (Varicella-Zoster virus), **H**epatitis B, C, D and E, **E**nteroviruses, **A**IDS (HIV), **P**arvovirus B19. The most recent addition of Zika virus to this list may challenge the creators of the acronyms.

CMV infection is the most frequently implicated agent to cause congenital infections in many countries but fetal infections from HIV and Zika present challenges on a global scale. One feature of transplacental infections of the fetus is the relationship between the stage at which the fetus was infected and the effect on the fetus. Significant infections occurring in the first trimester often result in death of the fetus and spontaneous abortion/stillbirth. If CMV infection is acquired in the early second trimester the virus appears to have a predilection for infecting the rapidly dividing cells in the germinal matrix (ventricular zone). As a result, normal neuro-glial proliferation, migration and/or organisation of the cerebral cortex can be severely affected. The range of imaging findings have been explained in relation to the timing of the infection e.g. second trimester infections at the time of neuronal/glial proliferation may produce microcephaly and/or micrencephaly, whereas agyria/lissencephaly is more likely to result from a failure of migration, and polymicrogyria results from abnormal cortical organisation (19-20). Fetuses infected with CMV in the third trimester tend to have gliotic reactions in the white matter and multifocal periventricular calcifications. Although it is important to consider infection with CMV when a fetus is demonstrated to have microcephaly and a cortical formation abnormality it should be appreciated that similar appearances can result from genetic disorders such as those affecting the rapamycin signalling pathway (P13K-AKT3-mTOR pathway) (21-22).

Leruez-Ville and Ville described USS findings that may provide a clue to CMV infection under the headings of 'severe USS brain abnormalities' 'mild USS brain abnormalities' and 'extra-cerebral USS abnormalities' (23). Many of those are non-specific and, in our experiences, the referral information from USS in cases ultimately shown to have CMV infection typically have some combination of

‘microcephaly’, ‘ventriculomegaly’, ‘enlarged extra-axial spaces’ or ‘germinal cysts’ on USS. Picone et al. studied 38 fetuses with proven congenital CMV infection and concluded that iuMR should be performed whenever the USS examination was not completely normal or extra-cerebral manifestations of the infection were reported (23). Doneda and colleagues also studied 38 fetuses with confirmed CMV infection and reported added diagnostic value for iuMR in 18/38 (47%) cases (20). The sensitivity of USS in ante-natal diagnosis should be considered as low as 35% whilst the addition of iuMR is thought to produce negative predictive values close to 90%.

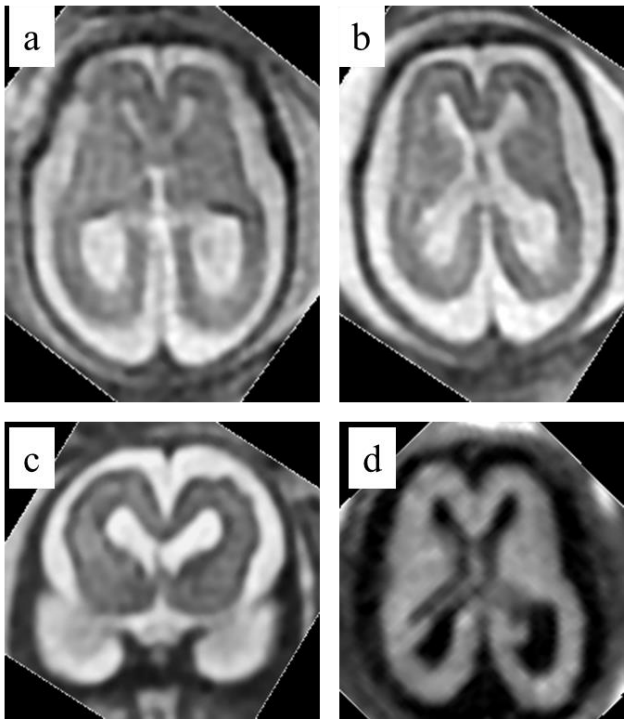

Figure 9.5.7. A fetus with confirmed transplacental infection with cytomegalovirus. Axial (7a and 7b) and coronal (7c) T2-weighted images of a 23gw fetus with mild ventriculomegaly on ultrasound. Fetal ascites had been recognised at 20gw. Mild ventriculomegaly is confirmed on iuMR but there is also micro-encephaly, poor visualisation of the sylvian fissures and uneven cortical plates in the frontal regions. Patchy abnormal signal intensity is present on axial diffusion weighted imaging (7d).

There is less information about the iuMR imaging of fetuses infected by Toxoplasma gondii although the pathology and USS literature are helpful (25). Here, too, the gestational age at infection appears to correlate with

morphology; toxoplasmosis acquired in the second trimester tends to cause microcephaly, likely by damaging the developing cerebral hemispheres and leading to more severe neurological impairment. Chorioretinitis is also common. Infection in the third trimester tends to produce dystrophic brain calcifications (denser than CMV and often parenchymal) and a non-communicating hydrocephalus, the latter secondary to a generalised destructive process of the ependyma with obstruction to CSF flow usually in the cerebral aqueduct. Brain destruction can also occur as a result of vascular thrombosis.

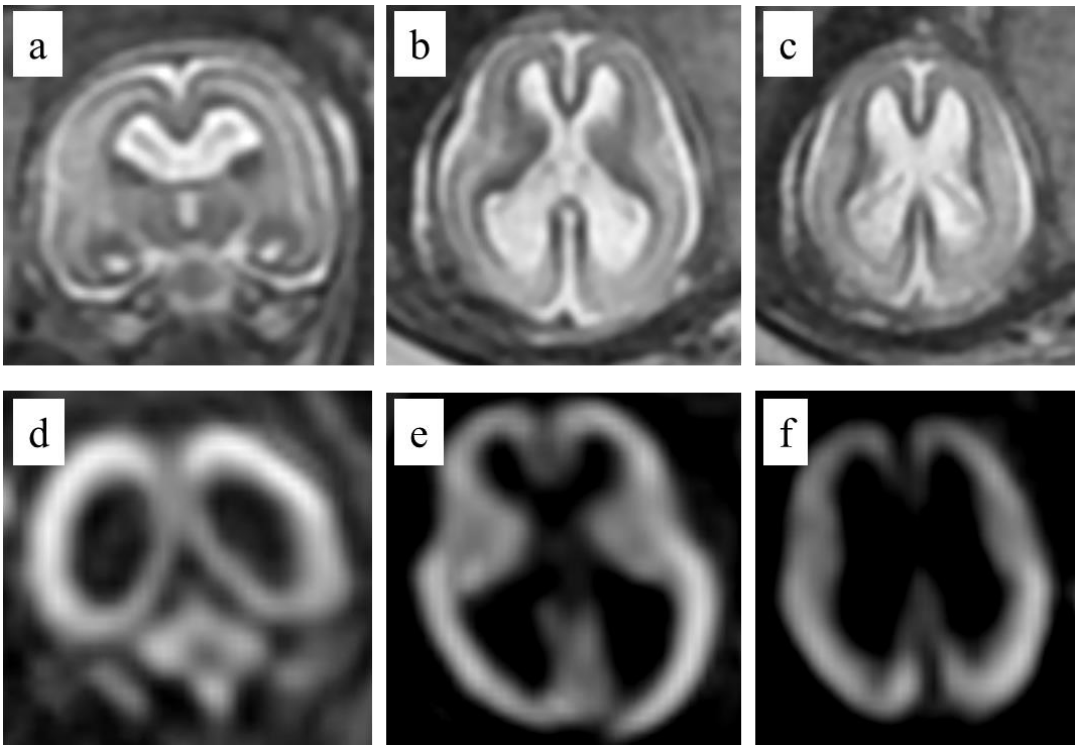

Figure 9.5.8. A fetus with confirmed transplacental infection with toxoplasmosis. The pregnancy was complicated by premature rupture of the membranes at 16gw and an absent septum pellucidum was recognised on ultrasonography at 20gw. iuMR was performed at 20gw and coronal confirms a disrupted septum pellucidum (8a), ventriculomegaly, effaced external CSF spaces and a relatively large head consistent with hydrocephalus. There is abnormal high signal on axial in the posterior portions of the cerebral hemispheres (8b and 8c) which also show restricted diffusion (8d-8f). Extensive encephalomalacia was shown on autopsy and infection with toxoplasmosis was confirmed.

Ascending infections are often bacterial and may result in direct infection of the fetus. Inflammation may also result in fetal brain injury in utero. Pre-labour

rupture of the amniotic membranes leads to an ascending infection, involving the chorionic palate and/or umbilical vessels (chorioamnionitis) and the fetal brain may be injured “at a distance” by the release of cytokines and other inflammatory agents. Fetuses in the second and early third trimester are at particular risk by this mechanism, possibly because of the lack of protective agents in the immature brain. Fetuses that survive this process often develop periventricular leukomalacia.

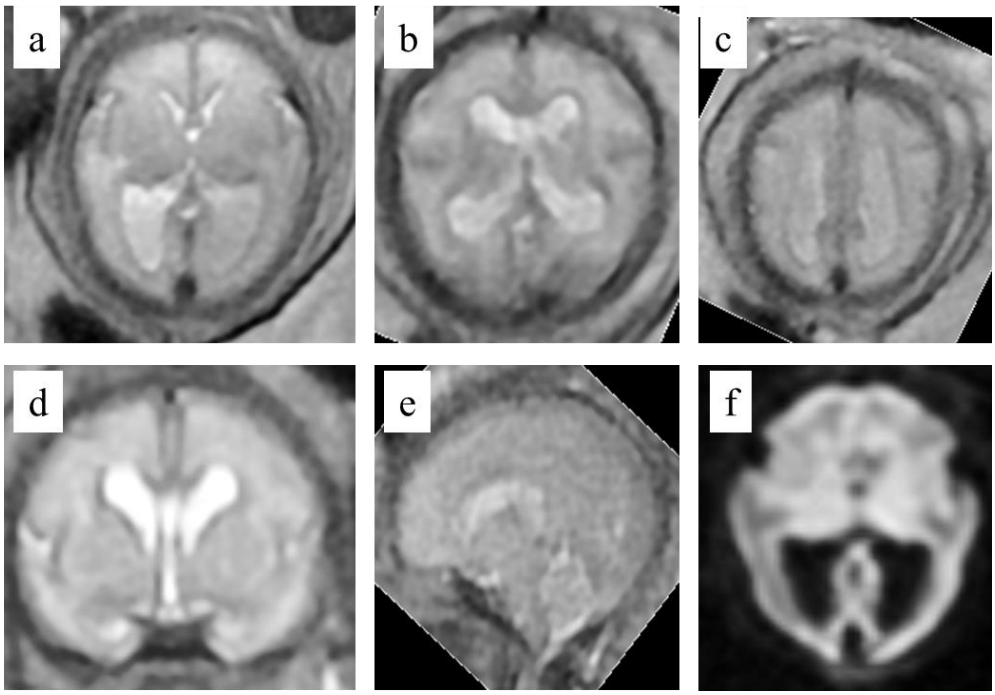

Figure 9.5.9. A fetus with brain injury presumed secondary to chorioamnionitis. The pregnancy was complicated by premature rupture of the membranes at 28gw followed by reduced fetal movements and iuMR imaging at 29gw. Axial (9a-9c), coronal (9d) and sagittal (9e) T2-weighted images shows generalised brain swelling and restricted diffusion (9f). Cardiac activity was present at the time of imaging but the fetus was stillborn the following day. A presumptive diagnosis of inflammatory brain injury secondary to chorioamnionitis was made.

Toxic and Metabolic disorders

Numerous chemicals and medications are teratogenic, including several that appear to have a predilection for the developing central nervous system. Leading examples include aminopterin, phenytoin, many chemotherapeutic agents, retinoic acid (vitamin A) and alcohol.

Di Mauro and Garone described the wide range of possible inheritable metabolic disorders and described those involving glycogenesis and mitochondrial defects of the fetus in detail (26). Mendelian or maternally inherited disease may be present in a fetus but not have a morphologic manifestation; many metabolic disorders do not produce brain injury until after birth (in infancy, childhood, or even adulthood). Reasons why a fetus may be involved but not be affected *in utero* are numerous, e.g. a genetic defect may produce a mutated 'mature' enzyme which has a fetal counterpart that is not involved or the mother is able to metabolise an abnormal gene product or the build-up of a toxic intermediate compound made by the fetus. Defects of the mitochondrial respiratory chain are amongst the most important inheritable metabolic disorders in terms of brain involvement and impaired oxidative metabolism in the child or adult metabolically active areas. In contrast, fetal tissues rely more on anaerobic glycolysis for ATP production rather than oxidative mechanisms, hence providing a measure of protection (27). A normal iuMR study in these situations should never be used to exclude a metabolic disorder in a fetus; there may be non-specific finding on iuMR that may raise suspicion (e.g. germinolytic cysts).

Intracranial mass lesions

Intracranial mass lesions cover a wide range of potential pathologies including neoplastic and non-neoplastic entities. Intracranial neoplastic lesions diagnosed *in utero* are exceptionally rare and their prevalence is difficult to quantify with certainty. Intracranial tumours are reported to have been found in 0.34/million new-borns and account for approximately 1% of pediatric CNS tumours but intracranial tumours may result in fetal demise, and therefore the true incidence may be underestimated (28). One paper, reporting the ante-natal imaging findings of 27 fetuses with histologically confirmed intracranial tumours (24 with iuMR imaging), pooled the experience of 11 collaborating centres over 14 years (29). Germ cell tumours were by far the commonest

neoplastic lesion, accounting for 15/27 cases (56%) of which 13 were teratomas. There were 4/27 (15%) glial-based tumours and small numbers of craniopharyngiomas, hamartomas, choroid plexus papillomas, haemangioblastomas, and a single undifferentiated tumour. 26/27 neoplasms originated from the supratentorial compartment (one case of

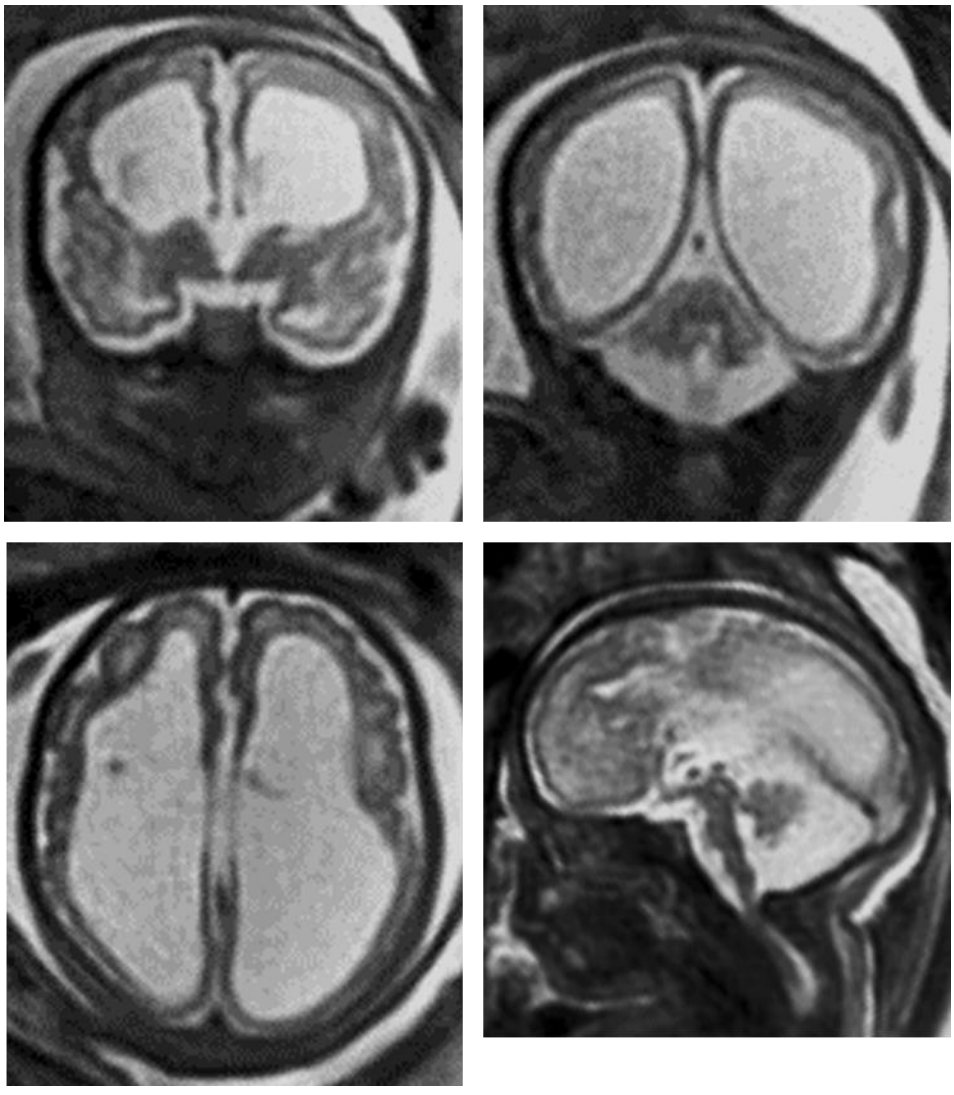

Figure 9.5.10. A fetus with pyruvate dehydrogenase deficiency had iuMR imaging performed at 34gw. Coronal (10a and 10b), axial (10c) and sagittal (10d) T2-weighted images show absence of the corpus callosum, severe ventriculomegaly, a thin parenchymal mantle with simplified gyral pattern and cerebellar hypoplasia. The enzyme deficiency was confirmed postnatally.

haemangioblastoma was infratentorial) and most were very large at the time of diagnosis. Although teratomas were more often partially cystic, it appears difficult to provide a reliable histological diagnosis from iuMR imaging based on morphology. 23 pregnancies were terminated after ante-natal diagnosis of a tumour, there were two neonatal deaths, and two children were alive at the time of reporting the case series (30).

Non-neoplastic intracranial mass lesions include arachnoid cysts, and we have included extra-axial haematoma in this group for the analysis described below. Another recently described entity that appears to be specific to the fetus is dural venous sinus ectasia with thrombosis (DVSET). This is shown on imaging as an enlargement of the venous confluence, posterior portion of the superior sagittal sinus and transverse sinuses, containing clot often of different ages but with no fistulae present. Haemorrhagic or ischaemic brain complications with this entity are rare although mass effect can be significant (31). The aetiology is uncertain but many authorities regard DVSET as self-limiting and good neurological outcome can be expected in most cases.

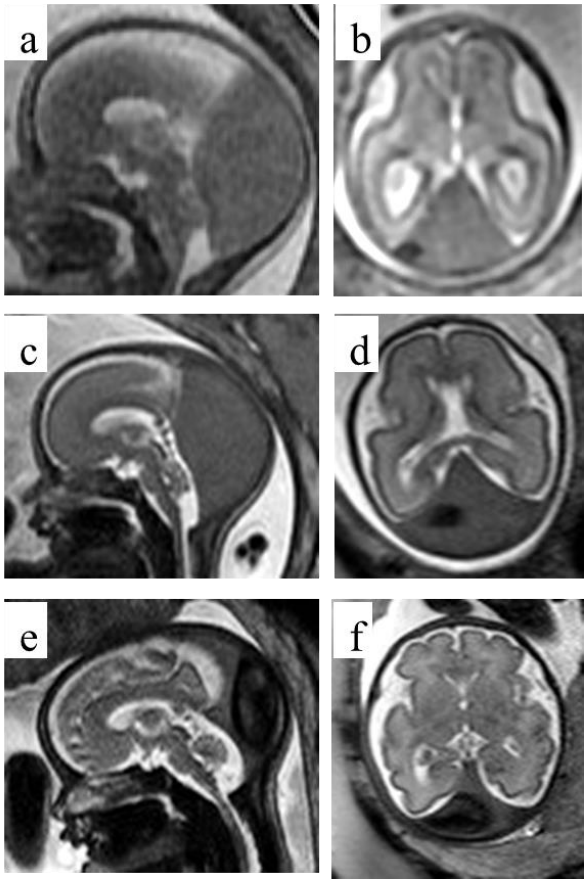

Figure 9.5.11. A fetus with a non-neoplastic intracranial mass lesion. The initial iuMR imaging study was performed at 21gw (11a and 11b) Shows an extra-axial mass lesion centred on the venous confluence and extending to involve the posterior portion of the superior sagittal sinus and transverse sinuses. The mass contains thrombus at different stages of evolution. There is significant mass effect with anterior displacement and compression of the cerebellum and brainstem. A diagnosis of dural venous sinus ectasia with thrombosis was made. A repeat study at 26gw (11c and 11d) shows greater involvement of the transverse sinuses but reduced compression of the brain, with CSF visible between the cerebellum and the mass. Imaging at 31 weeks (11e and 11f) shows further, but incomplete, resolution.

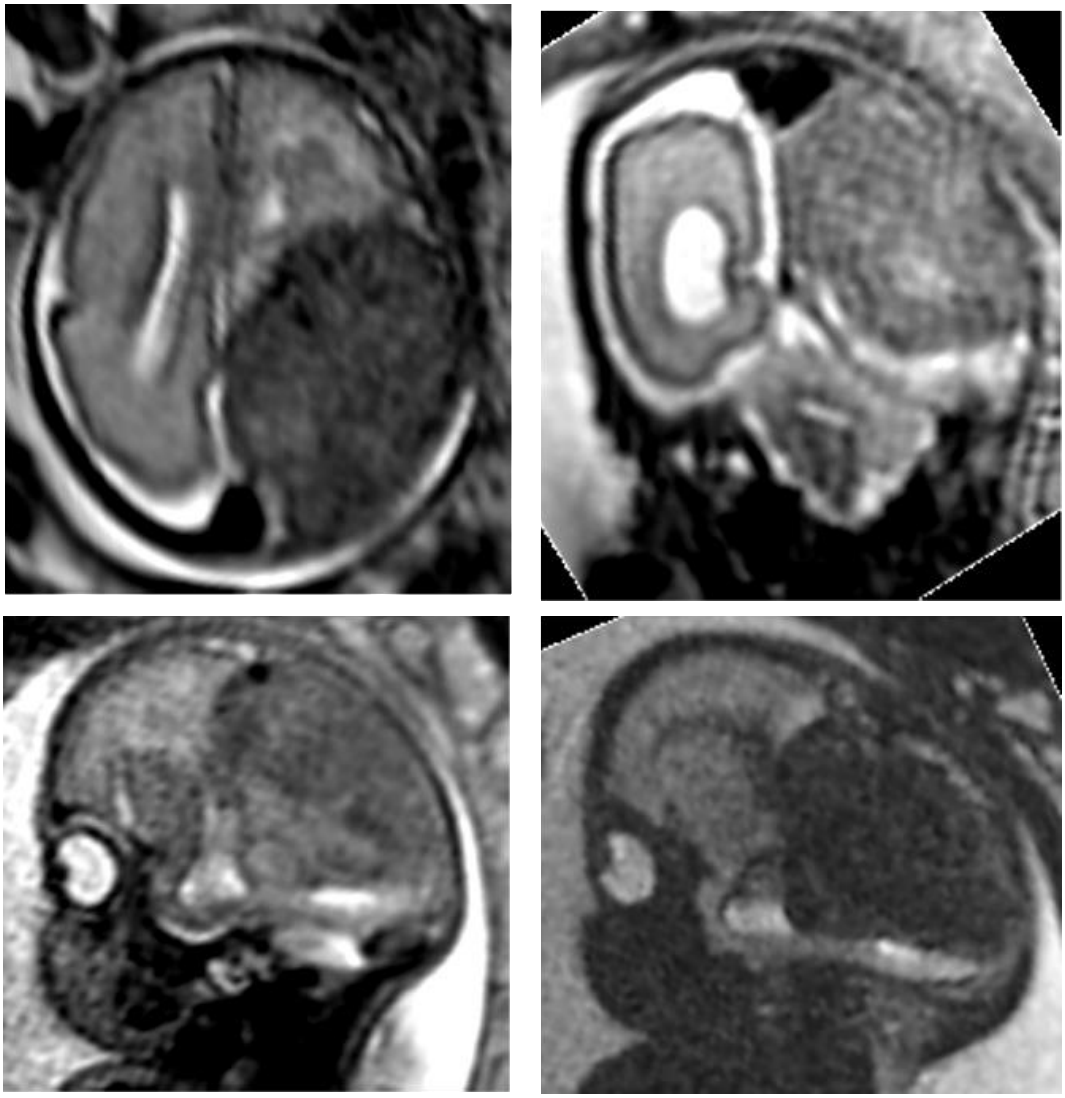

Figure 9.5.12. Intracranial vascular tumour demonstrated on iuMR imaging in a 26gw fetus from a twin pregnancy (the other twin was normal). Sagittal (12a), coronal (12b) and axial (12c) T2-weighted images show a large mass lesion in the posterior part left cerebral hemisphere. The mass is hyper-vascular with multiple flow voids from large vessels anteriorly and the superior sagittal sinus is dilated due to arteriovenous shunting. Sagittal echo-planar image (12d) shows marked hypo-intensity in the mass due to the internal haemorrhage and vascularity. Histological studies were not performed.

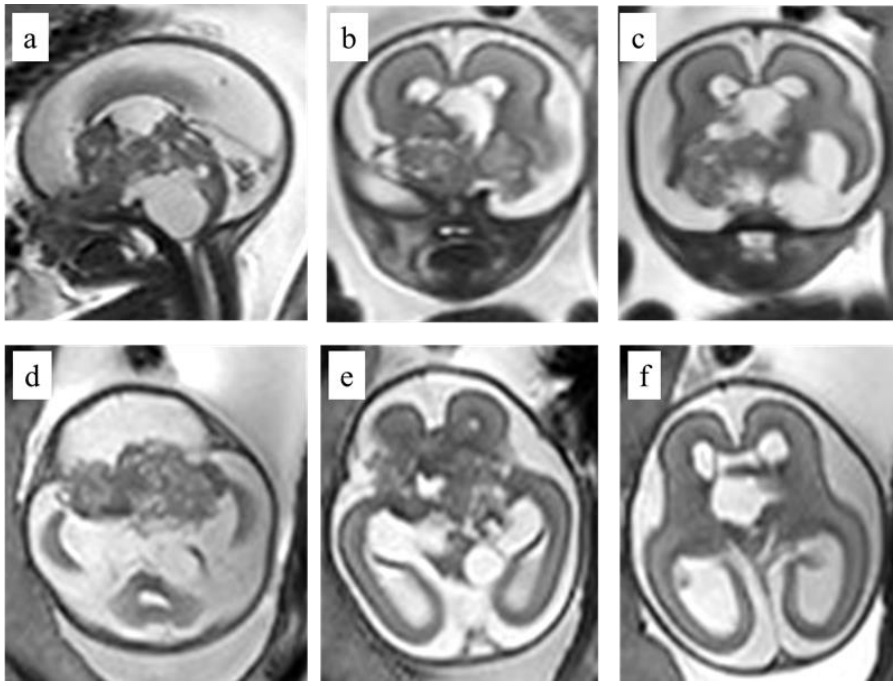

Figure 9.5.13. Intracranial mass lesion, probably neoplastic. Sagittal (12a), coronal (12b and 12c) and axial (12d-12f) T2-weighted images of a 23gw fetus with a large extra-axial mass lesion, which has solid and cystic components. There was documented increase in size and mass effect over two weeks. Histological diagnosis was not achieved but radiologically the mass was most likely to be a teratoma.

Prevalence of acquired fetal brain pathology in the MERIDIAN cohort

Full details of the MERIDAN study are reported elsewhere but are summarised here (6). A pregnant woman aged 16 years, or more, was potentially eligible for recruitment if the fetus had any brain abnormality detected at USS at ≥18gw by a formally trained fetal medicine consultant. The group consisted of 570 fetuses with brain abnormalities undergoing iuMR imaging within 2 weeks of the USS, and an outcome reference diagnosis was available. There were 369 fetuses imaged between 18-23gw and 201 fetuses ≥ 24gw. Retrospective review of the MERIDIAN cohort, leads us to suspect that 38/570 cases (6.7%) are best classified as acquired fetal brain pathology on the basis of the iuMR imaging and confirmed on outcome reference data (table 1). In 28/38 (74%) the same pathology was shown on USS, but the acquired pathology was not suspected on USS in the remaining 10 fetuses (26%). A further 7/570 (1.2%) fetuses had acquired pathology diagnosed on USS but excluded on iuMR imaging and outcome reference data (those cases involving suspected tumours, calcification,

haemorrhage and DVSET). Stroke was the suspected underlying cause of the acquired pathology in 20/38 (53%) of cases, most of which were haemorrhagic (14/38, and occurred in 20/570 (3.5%) in the MERIDIAN cohort. Generalised hypoxia/ischaemia was suspected in 9/38 (24%) based on the distribution of damage. Intra-cranial mass lesions accounted for 7/38 (18%) and all were non-neoplastic, extra-axial masses. Both infective cases (2/38 – 5%) resulted from confirmed transplacental CMV infection. Please note that the cases shown in the figures for this paper were not all from the MERIDIAN study.

Conclusions.

We have shown that acquired lesions are comparatively rare causes of fetal intracranial pathology and accounted for less than 7% of cases in one recent, large study. The distinction between 'developmental' and 'acquired' fetal brain pathology can be difficult in some cases and is often considered too simplistic by many researchers. Another approach is to distinguish between a malformation, a consequence of a malformation, a disruption, and acquired pathology. Malformations result from an alteration of the primary developmental programme, which is non-progressive after it has first manifest, whilst a malformation consequence occurs when a malformation results in additional pathology, either further malformations or destructive pathologies. These pathologies have been reviewed in earlier publications regarding failed commissuration and posterior fossa abnormalities.

A disruption is impaired development of a structure damaged in an immature stage with the end result being a 'secondary' malformation. Finally, an acquired lesion is due to damage to a previously normal structure. Unfortunately, this approach is not straightforward and practically it is often difficult to distinguish between these mechanisms with confidence. However, both cases of CMV infection found in the MERIDIAN cohort were accompanied by obvious cortical formation abnormalities and could be classified as a disruption in the more detailed classification although the etiology is an obvious acquired pathology. In addition, the unilateral cerebellar hypoplasia cases that we have classified as acquired pathology (stroke) in this paper could also be considered as disruptions. Fetal stroke appears to be the most common acquired pathology (3.5% of MERIDIAN cases, 20/570) and of those the majority are haemorrhagic.

Teaching points

The fetal brain can be damaged *in utero* from a wide range of acquired pathologies that are well demonstrated on iuMR imaging.

Acquired pathology can damage structure that have otherwise formed properly or interfere with the formation process of a structure that is not yet mature

In the authors experience, fetal stroke is the commonest acquired fetal brain pathology

Fetal stroke is frequently hemorrhagic

Transplacental CMV infection often disrupts normal development of the cerebral hemispheres

Intracranial mass lesions are rare in the fetus and may be neoplastic or non-neoplastic

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Case#:gw at iuMR	Diagnosis on iuMR and confirmed on Outcome Reference Data	Mostly likely category of acquired pathology
26:	Unilateral hypoplasia of cerebellar hemisphere and cerebellar vermis	Stroke (ischaemic)
27:	Diffuse supratentorial white matter abnormality with volume loss	Generalised hypoxia/ischaemia
37	Posterior fossa arachnoid cyst with displaced but normal cerebellum	Intracranial mass lesion (extra-axial)
43	Subdural collections	Intracranial mass lesion (extra-axial haemorrhage)
94	Focal cortical injury	Stroke (ischaemic)
97	Dural ectasia and thrombosis, displaced but normal brain	Intracranial mass lesion (extra-axial)
142	Periventricular leukomalacia	Generalised hypoxia/ischaemia
144	Unilateral hypoplasia of cerebellar hemisphere with haemorrhage	Stroke (haemorrhagic)
201	Intra-ventricular haemorrhage	Stroke (haemorrhagic)
227	Unilateral hypoplasia of cerebellar hemisphere	Stroke (ischaemic)
297	Intraventricular and choroid plexus haemorrhage	Stroke (haemorrhagic)

321	Generalised cerebral and cerebellar volume loss and abnormal signal	Generalised hypoxia/ischaemia
397	Generalised cerebral and cerebellar volume loss and abnormal signal	Generalised hypoxia/ischaemia
404	Germinal matrix haemorrhage	Stroke (haemorrhagic)
484	Unilateral hypoplasia of cerebellar hemisphere	Stroke (ischaemic)
410	Microcephaly, generalised malformation of cerebrum	Infection (confirmed congenital CMV infection)
425	Periventricular leukomalacia, germinal matrix and intraventricular haemorrhage	Stroke (haemorrhagic)
432	Germinal matrix haemorrhage	Stroke (haemorrhagic)
433	Generalised encephalomalacia and haemorrhage in germinal matrix	Generalised hypoxia/ischaemia
495	Germinal matrix haemorrhage	Stroke (haemorrhagic)
505	Bilateral cerebral encephalomalacia and vein of Galen malformation	Generalised hypoxia/ischaemia
509	Generalised encephalomalacia and haemorrhage in germinal matrix	Generalised hypoxia/ischaemia
583	Unilateral hypoplasia of cerebellar hemisphere and Blake's pouch cyst	Stroke (ischaemic)
617	Intraventricular haemorrhage	Stroke (haemorrhagic)

635	Intraventricular haemorrhage	Stroke (haemorrhagic)
734	Generalised encephalomalacia and haemorrhage in germinal matrix	Generalised hypoxia/ischaemia
753	Intraventricular and choroid plexus haemorrhage	Stroke (haemorrhagic)
754	Extradural haematoma	Intracranial mass lesion (extra-axial haemorrhage)
776	Dural ectasia and thrombosis, displaced but normal brain	Intracranial mass lesion (extra-axial)
884	Generalised encephalomalacia	Generalised hypoxia/ischaemia
897	Dural ectasia and thrombosis, displaced but normal brain	Intracranial mass lesion (extra-axial)
940	Unilateral temporal lobe haematoma and focal encephalomalcia	Stroke (haemorrhagic)
966	Lobar and intraventricular haemorrhage	Stroke (haemorrhagic)
1022	Brainstem, unilateral temporal lobe haematoma with intraventricular haemorrhage	Stroke (haemorrhagic)
1048	Microcephaly, generalised malformation of cerebrum	Infection (confirmed congenital CMV infection)
1054	Intraventricular haemorrhage	Stroke (haemorrhagic)
1071	Dural ectasia and thrombosis, displaced but normal brain	Intracranial mass lesion (extra-axial)

1102	Unilateral hypoplasia of cerebellar hemisphere and cerebellar vermis	Stroke (ischaemic)

Table 9.5.1 MERIDIAN case numbers with diagnosis on iuMR

9.6 Watershed stroke – an unexpected complication of respiratory syncytial virus bronchiolitis: a case report

Riley G, Rittey CD, Connolly DJA and Mordekar SR

European Journal of Medical Case reports (2017) 1; 36-39

A watershed injury to the brain affects the vascular boundary zone between the mature middle cerebral arteries and the anterior/posterior cerebral arteries. This vascular watershed territory only appears after 34-36gw when the major cerebral arteries mature and take on the configuration commonly seen in adults.

Watershed injuries can be induced by a combination of hypotension and hypoxia producing hypoperfusion. For instance, this can be produced in adults who suffer a cardiac arrest and have inadequate cardio-pulmonary resuscitation.

In neonates it was known that a respiratory syncytial virus (RSV) chest infection producing bronchiolitis could induce significant cardiorespiratory dysfunction requiring urgent admission to hospital and supportive care. It had not previously been reported that this cardiorespiratory dysfunction could be so severe that it might induce a hypoperfusion injury to the brain injuring the watershed territories and radiologically mimicking a chronic partial asphyxia. Radiologically and clinically a post-natal cardiorespiratory collapse may produce MRI and clinical features indistinguishable from a perinatal CPH. A post-natal collapse and CPH can produce additive injury to the brain and can only be

discriminated by the radiologist if an MRI is performed before the second insult.

Abstract

We report a case of watershed stroke in a young child, occurring as an unexpected complication of severe respiratory syncytial virus (RSV) bronchiolitis. RSV is a common childhood pathogen, with many reported extrapulmonary manifestations. Neurological involvement was once believed to be temporary or reversible; diffusion-weighted MRI proved that seizures in our patient were a consequence of more significant peripheral perfusion failure and stroke. It is important to distinguish the reversible effects of RSV from those alternative pathological sequelae necessitating changes in clinical management and re-prognostication.

Keywords

watershed stroke • peripheral perfusion failure • seizure • respiratory syncytial virus

Introduction

Watershed infarction (WSI) is a type of stroke attributed to perfusion failure at the periphery of adjacent non-anastomosing arterial territories in the brain. Various pathophysiological origins have been alluded to – such as systemic hypotension, arterial stenosis/occlusion and microemboli.[1-3] In the newborn, after 36 weeks gestational age, it is generally thought to arise from severe systemic hypotensive episodes ± hypoxaemia.[4] WSI can be a devastating event, as profound neurological disability and even death may ensue. Such sequelae could be curtailed in the young child with promising new neuroprotective techniques if introduced early.[5]

The Paediatrician and the Paediatric Radiologist should be alert to watershed stroke and to the gamut of childhood conditions having a described causal association. To our knowledge, no such association has been reported with respiratory syncytial virus (RSV) infection.

We bring to your attention a case of peripheral perfusion failure and watershed stroke as an unexpected complication of severe RSV-positive bronchiolar infection in a young child.

Case Summary

The child is a boy born pre-term at 28 weeks' gestation by emergency caesarean section for maternal pre-eclampsia, weighing 937grams and with a head circumference of 26.5cm (50th centile). Following 2 months intensive care treatment for surfactant-deficiency pulmonary disease, he was discharged home with continuous low flow oxygen therapy. Other conditions of prematurity included patent ductus arteriosus and foramen ovale, osteopaenia with long bone fractures and gastro-oesophageal reflux. Neurological examination and cranial ultrasound were unremarkable.

At 3 months of age, he was re-admitted to the paediatric intensive care unit (PICU) with acute bronchiolitis, diagnosed clinically and on chest radiograph – and subsequently confirmed on nasal washings as RSV-positive. He required

endotracheal intubation and ventilation for 48 hours, during which time he developed pneumothoraces that were successfully drained. Inotropic support was not required. On PICU day 3, he developed acute symptomatic focal seizures with secondary generalisation with corresponding electro-encephalogram (EEG) changes. Seizures were treated effectively with intravenous phenobarbital and midazolam. He was treated prophylactically on intravenous Cefotaxime and Acyclovir. Lumbar puncture showed normal microscopy, protein, glucose, and lactate. CSF virology was negative for herpes simplex virus and RSV. On day 22, the patient was discharged home without regular antiepileptic medications. Brain magnetic resonance imaging (MRI) was performed 12 hours post-onset, which demonstrated restricted diffusion in keeping with acute watershed territory infarction [figure 9.6.1].

Clinical examination at 8 months chronological age (5 months corrected gestational age) demonstrated good head control on ventral suspension, appropriate use of both hands with hand-to-mouth co-ordination, and good visual tracking. He was fully orally fed. On examination, his head circumference was 39 cm (9^{th} centile), with normal tone and reflexes with no focal neurological signs.

Clinical examination at 13 months chronological age (10 months corrected) demonstrated sitting unsupported, as well as weight-bearing and standing with support. He had achieved hand to hand transfer of objects but no pincer grasp. As far as vocalisation is concerned, he used both vowel and consonant babble. He blew raspberries, recognised his name but had no single words. On examination, his head circumference was 41.9 cm (<0.4^{th}centile). His weight and height were below the 0.4^{th} centile. His tone and reflexes were normal with no focal neurological signs.

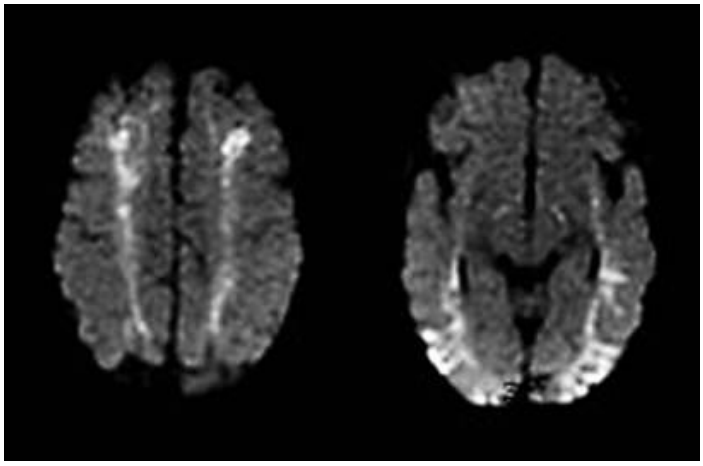
Figure 9.6.1a 

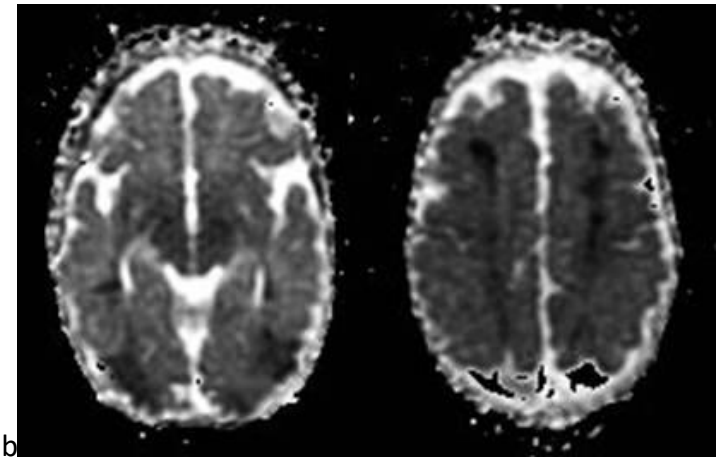
Figure 9.6.1b 

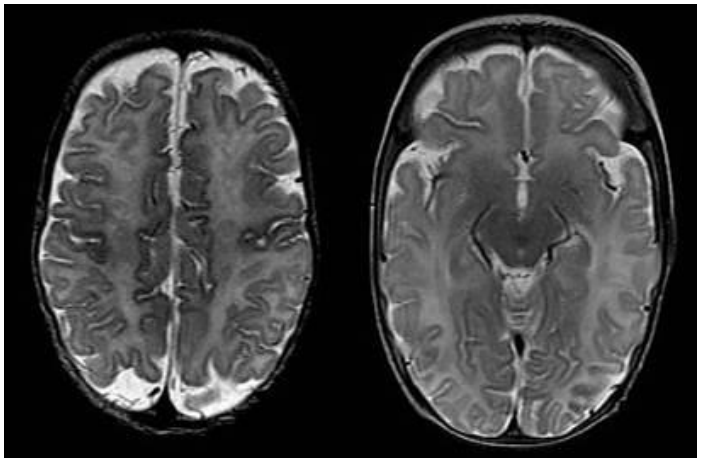
Figure 9.6.1c 

Figure 9.6.1 Representative images from the case described above. a. axial b700, b. axial ADC, c axial FSE T2

Discussion

Our patient was admitted to PICU with severe RSV-positive bronchiolitis and episodes of respiratory decompensation requiring ventilatory support; and subsequently developed acute symptomatic seizures after three days. However, throughout the PICU stay blood pressure was stable. CSF examination was normal with no evidence of RSV encephalitis. While seizures – among other acute neurological symptoms and signs – have been reported as temporary or reversible manifestations of RSV;[6-9] to our knowledge there are no such reports implicating WSI and stroke.

RSV is a common pathogen in childhood respiratory infections, and extrapulmonary manifestations are becoming increasingly recognised as reasons for acute deterioration. Around 3% of all babies with bronchiolitis develop more serious symptoms, such as difficulty breathing, that require hospital admission. This is more common in premature babies and in those born with a heart or lung condition. Our case had several risk factors.

Neurological manifestations were reported in 39% (n = 121) of RSV-positive bronchiolitis patients on a PICU. These included seizures, central apnoeas, lethargy, feeding/swallowing difficulties, muscle tone abnormalities, as well as elevated cerebrospinal fluid protein levels.[7] However, in our case, CSF protein was normal. Similar manifestations were found in 1.2% (n = 964) of ward-based patients – with milder bronchiolitis.[8]

RSV-related seizures have been described as both generalised tonic–clonic and focal seizures with altered consciousness and focal motor features or eye deviation, as well as status epilepticus.[7-8] Encephalopathy was felt to be the cause of seizures in 1.8% (n=487) in a tertiary centre study.[9] Hyponatraemia is commonly associated with RSV and possibly accounts for some seizures.[6,10] Focal temporal lobe 'slowing' was seen on electroencephalogram in one case.[8] Generally, neuroimaging has proven non-contributory.

In our case, MR Neuroimaging appearances were characteristic of acute bilaterally symmetric cortical watershed infarction (WSI) [figure 1]. WSI occurs

at border-zones between the territories supplied by 2 (or 3) non-anastomosing arterial systems – cortical WSI between ACA, MCA and PCA; and internal WSI between deep and superficial MCA or between superficial MCA and superficial ACA. Susceptibility of the border-zone areas is thought to result from their situation at the 'peripheral field' where perfusion pressure is lowest. Peripheral perfusion failure (ischaemia) is the critical physiological process most likely secondary to precipitous drops in systemic arterial blood pressure rather than hypoxia.[1] Micro-embolic disease has also been implicated in the aetiology of WSI.[2-3]

The pathogenesis of WSI in the case of severe RSV infection is uncertain; the general process is probably due to respiratory failure with asphyxia and/or periods of central apnoea, resulting in reduced blood oxygenation (hypoxaemia). With prolonged hypoxaemia, cardiac hypoxia occurs, leading to diminished cardiac output and ultimately to brain hypoperfusion. Local brain tissue hypoxaemia is probably contributory rather than the primary underlying cause for stroke. RSV encephalitis is an unlikely cause in our case. And while conditions of prematurity pre-existed, these were shown to be stable or improving. Embolic phenomena are unlikely in this age-group.

It is important to distinguish extrapulmonary organ dysfunction/decompensation as a temporary or reversible manifestation of RSV infection, from structural pathological sequelae necessitating changes in clinical management. The acute treatment is largely supportive, generally requiring escalation of care to the intensive care unit setting. Promising new neuroprotective strategies designed to limit the extent of brain injury caused by hypoxia-ischemia are under investigation. Many of these treatment strategies, including hypothermia and administration of excitatory amino acid antagonists, have a limited window of effectiveness (in some cases as little as 6 hours), making early stroke detection critically important.[5]

The prognosis for children with watershed infarct is variable in the long term. Severe motor impairment is uncommon, simulating an early normal outcome

prompting discharge from follow-up when reviewed at 12-18 months. However, suboptimal head growth, behavioural problems and delay in language are common. Several studies have now, however, shown that these children may 'grow into their deficits' and it is this group in particular that require more long-term follow-up well into childhood. As our child is currently only 13 months old and is clinically progressing quite well despite the progressive microcephaly, a repeat MRI brain scan has occurred so far. Specific cognitive functions continue to develop throughout childhood. As it is impossible to examine a function that has not yet developed, short term follow-up does not exclude further cognitive decline and behavioural difficulties especially at secondary school age.

Our case will be closely monitored in Neurology clinic, and follow-up MR imaging will be considered at 3 years of age based on clinical need.

Conclusion

RSV has many reported extrapulmonary manifestations. Neurological involvement, previously believed to be temporary or reversible, could be more significant due to peripheral perfusion failure and stroke. Watershed stroke should be considered a potential complication of severe RSV-positive bronchiolitis.

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9.7 Perinatal Arterial Ischemic Stroke in term babies

Hart AR, Connolly DJA and Singh R

Paediatrics and Child Health (2018) 28: 417-423

Perinatal arterial ischaemic stroke (PAIS) was reviewed in this paper that described the incidence, mechanism of action, anatomy, risk factors and clinical presentation. The acute and chronic imaging features on CT and MRI were described and presented with suggestions for acute management and prognosis.

EEG and MRI in the neonatal period were useful for prognostication and yet should be interpreted with caution as there are examples of neonates with restricted diffusion in the cerebral cortex, basal ganglia and cerebral peduncles, but in whom outcome is much better than predicted. This may reflect Wallerian degeneration in some of the deep structures following acute infarction to the cortex mimicking true primary PAIS of the deep structures.

Cerebral plasticity may allow the developing brain to ascribe a new region of the cerebral cortex the functional role that would have been performed by the infarcted brain. The capacity for plasticity reduces with the age of the patient at the time of the infarct.

Abstract

Perinatal arterial ischaemic stroke (PAIS) affects between 1:2300 and 1:4000 births, so most paediatricians will see cases during their working life. The exact cause of PAIS in an individual usually is unknown, and discussion may occur about whether prothrombotic investigations, aspirin or anticoagulation are needed. The causes, investigation and treatment of PAIS are completely different from stroke in the older paediatric and adult group. Outcome tends to be good, although cerebral palsy may be seen in up to 30% of cases, epilepsy in 15-25% and cognitive problems may also occur. Fortunately, EEG and MRI can help identify those children with PAIS at the highest risk of neuro-developmental difficulties. This paper reviews what we know about the potential mechanisms causing PAIS, what investigations are necessary, and the likely outcome for the child.

INTRODUCTION

Most trainees and consultants who care for neonates will see several children with a perinatal arterial ischaemic stroke (PAIS) during their career. The presentation of the child with PAIS can generate questions such as:

why?

was it caused by a difficult delivery?

do we need to do prothrombotic investigations in the baby or mother?

is anticoagulation or aspirin necessary?

what is the child's prognosis?

The investigation and management of perinatal arterial ischaemic stroke are very different from strokes affecting older children or adults. This review discusses the presentation, investigations, management and prognosis of PAIS.

DEFINITION

Perinatal arterial ischaemic stroke (PAIS) is defined as *"a group of heterogeneous conditions in which there is a focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through to the 28th postnatal day, confirmed by neuroimaging or neuropathologic studies".*

Haemorrhage may occur secondarily into an area of infarction, but we usually reserve the term "perinatal stroke" to refer to lesions that are primarily ischaemic.

INCIDENCE

The incidence of PAIS is difficult to establish, and previous figures tend to be derived from neuropathological data. The most common estimations are between 1 in 2300 and 1 in 4000 births, so a reasonable sized neonatal intensive care unit will see a handful of cases each year. This estimation relies on both the child having symptoms and being diagnosed correctly: paediatricians and neurologists will be familiar with children who present later in life with focal epilepsy or signs of unilateral cerebral palsy whose imaging reveals evidence of PAIS and where the child was asymptomatic or had mild symptoms that settled spontaneously in the neonatal period. Similarly, outcome following PAIS can be entirely normal, and it is possible that a number of children and adults that have suffered from PAIS, had normal outcome, and never received a diagnosis. Therefore, this estimation of incidence should be taken to be a minimum.

MECHANISM OF ACTION

The exact cause of PAIS is often unknown. Traditionally, PAIS has been explained as being caused by a blood clot forming within the ageing placenta, entering the fetal circulation, embolising across the patent foramen ovale, to the left ventricle, into the ascending aorta to one of the main three branches of the thoracic aorta and then up either the vertebral arteries or more commonly entering the common and then internal carotid arteries, before involving the intracranial vasculature, where it blocks one or more of the main arterial branches (see figures 1 and 2 for a revision of the neuroanatomy of the cerebral arterial branches and the brain supplied). The most common site for PAIS to occur is the middle cerebral artery, with the left side affected in approximately 67%, right 26%, and bilateral involvement in 7%.

Determining whether this hypothesis is correct is problematic because of its low incidence, our inability to identify which foetuses will develop PAIS, the difficulty in establishing when the stroke occurred, the delay between the event occurring and symptom onset and diagnosis with the possible transition from the fetal to the neonatal circulation and cardiac configuration, and the problems in generating animal models of PAIS.

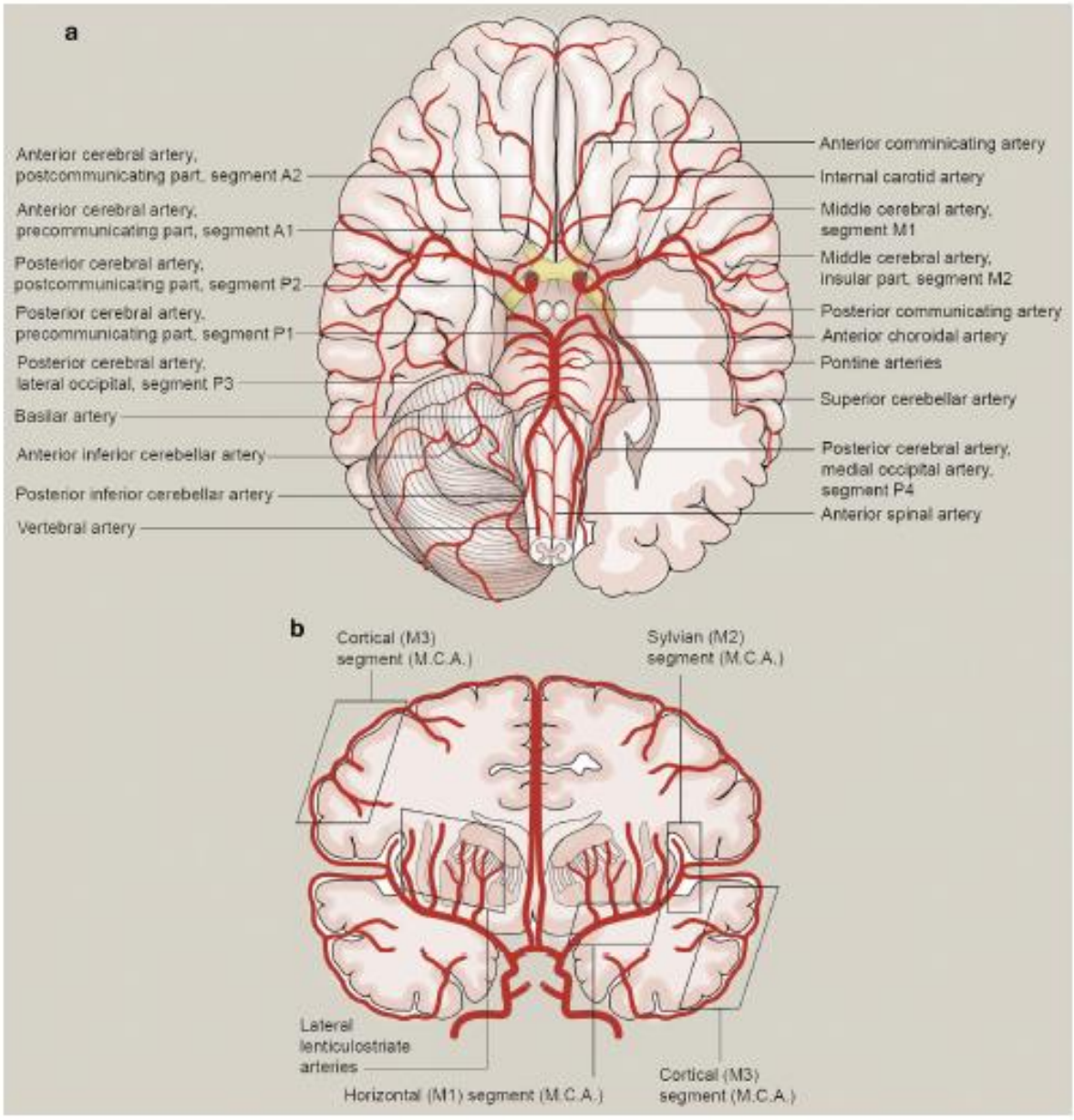

Figure 1 (a) and (b) the main blood vessels supplying the brain in the axial and coronal plane respectively.

Figure 9.7.1. Arterial blood supply to the brain

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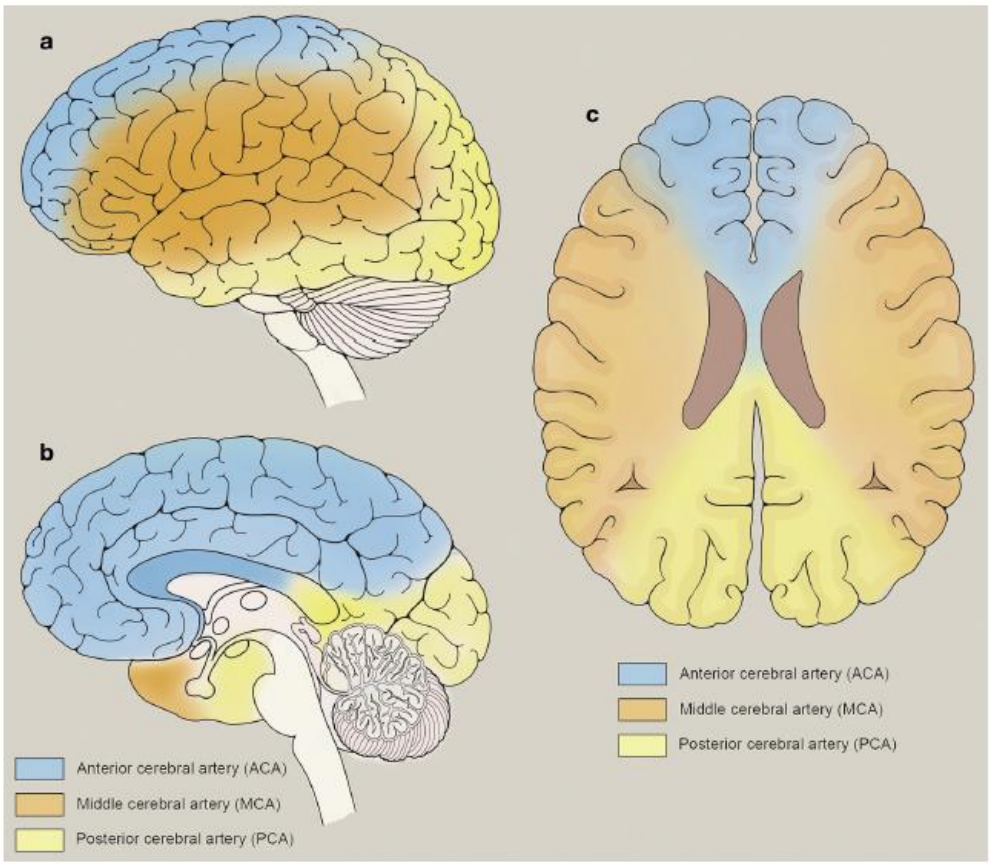

Figure 2 Diagrams showing: the vascular territories supplied by the anterior, middle and posterior cerebral arteries in (**a**) and (**b**) the sagittal plane and (**c**) the axial plane.

Figure 9.7.2 Arterial vascular territories of the brain

Original image produced for this publication

A number of risk factors have been suggested for PAIS (table 9.7.1). These factors are associations and should not be taken to be the "cause of PAIS": there are many neonates with similar risk factors who do not develop PAIS, and some without any who do. Generally speaking, the more risk factors present, the greater the risk of PAIS occurring. Martinez-Biarge et al (2016) showed 64% of controls without PAIS had no risk related to labour, compared to 15% of babies with PAIS. The presence of 1 risk factor was associated with an increased risk of PAIS with an odds ratio of 5.63, and 2 or more risk factors were associated with an odds ratio for PAIS of 19.14. Of particular mention is the role of instrumental delivery: the risk of PAIS developing following spontaneous

vaginal delivery or elective caesarean section is much lower than for instrumental delivery or emergency caesarean section.

Maternal risk factors	Pregnancy / labour risk factors	Fetal / neonatal risk factors
Nulliparity	PIH	Male sex
Family history of seizures or other neurological disease	Gestational diabetes	Small for gestational age
Maternal past history of autoimmune disease or gynaecological problems	Chronic poor placental perfusion with added acute abnormality	Apgar score ≤3 at 1 minute and <7 at 5 minutes of age
Cocaine use	Abnormal placental vessels or umbilical cord insertion, or length of umbilical cord or vessels	Neonatal hypoglycaemia <2.0
Twins	Olighydramnios	Early onset sepsis or meningitis
	Pre-eclampsia	Congenital heart disease
	Maternal pyrexia over 38°C	Need for ECMO
	Chorioamnionits	
	Prolonged second stage of labour	
	Meconium stained liquor	
	Fetal bradycardia or decelerations	
	Prolonged rupture of membranes	
	Tight nuchal cord	
	Ventouse delivery	
	Emergency caesarean section, particularly after failed instrumental delivery	
	Umbilical arterial pH <7.10	

Table 9.7.1: Suggested risk factors for PAIS in the literature, often from case control studies

The role of thrombophilia as a risk factor for PAIS is debatable. Pregnancy is naturally associated with hyper-coagulability in mothers and babies, and the fetus has a high haemoglobin and packed cell volume. This may be exacerbated

by neonatal dehydration as feeding is being established. But should prothrombotic factors be sought in the mother and baby? Günther et al noted in 2000 that 68.1% (62 out of 91) neonates with PAIS had at least 1 prothrombotic risk factor compares to 24.2% of the control group, which gave an odds ratio of 6.7. They noted:

22.0% had raised lipoprotein (a) compared to 5.5% controls (OR 4.84)

18.7% had Factor V 1691GA compared to 5.5% controls (OR 3.95)

4.4% had prothrombin 20210GA compared to 2.2% controls (OR 2.04)

16.5% had MTHFR TT677 genotype compared to 10.9% of controls OR1.59

and 6.6% had protein c deficiency.

Kocaman studied older children with presumed PAIS and looked at prothrombotic risk factors, finding the most commonly detected prothrombotic factors were:

51% had MTHFR mutations

Factor V Leiden was noted in 20% of cases

Increased lipoprotein (a) in 11%.

More recently, in 2017, Curtis et al showed there were no differences in pro-thrombophilia markers in children with PAIS. This is supported by outcome studies: strokes rarely reoccur in the children that have had PAIS, and the recurrence risks for future pregnancies in the same mothers is also low. It is the also the author's experience that haematologists may decline to look for prothrombotic agents, stating that the results are hard to interpret in the neonatal period and that the results do not change patient management given the low recurrence risk. Our view is that routine analysis of prothrombotic agents is not necessary following straight-forward PAIS, but should be

considered in more complex cases, such as where multiple arterial territories are involved, there are emboli or thrombi in other regions or the body, where the stroke occurs distant from birth towards the end of the neonatal period, or where a strong family history exists.

Where strokes and / or haemorrhages are extensive, particularly if there is a family history of early onset stroke, kidney or retinal disease, or cataracts, the COL4A1 (OMIM 120130) gene should be studied. This is a gene coding for collagen within the basement membranes, including of blood vessels, and is inherited in an autosomal dominant manner, leading to early onset stroke, renal and retinal vessel abnormalities and cataracts.

CLINICAL PRESENTATION

The most typical clinical presentation is in a child who did not require resuscitation at birth and presents between day 1 to 5 of life with focal seizures, usually clonic. There may have been parental concern before this presentation, such as with jitteriness, poor feeding, crying / irritability, or sleepiness, but children with PAIS are not typically encephalopathic. Case reports do describe large PAIS associated with raised intracranial pressure and coning, but these are exceptional cases and most neurological examinations in babies with PAIS are normal. The patency of the sutures and fontanelles in the neonatal skull allows for brain swelling not possible to survive without surgical intervention in the adult/fused cranium.

Prior to the diagnosis being made, it is usual to consider and treat for other aetiologies of neonatal seizures, such as sepsis / meningo-encephalitis, inborn errors of metabolism or congenital structural brain abnormalities, but investigations for and treatments of these diagnoses can be stopped when PAIS is diagnosed, and infection ruled out. It may be worth exploring placental histology to look for abnormalities like fetal thrombotic vasculopathy, but most

neonates are well at birth and do not need resuscitation, so the placenta may have been disposed of by the time the PAIS becomes manifest. Echocardiography may be considered in the early post ictal phase.

NEUROIMAGING

Cranial ultrasound is available quickly on most neonatal units. Cowan et al demonstrated in 2005 that cranial ultrasound in experienced hands shows abnormalities in up to 68% of neonates with PAIS, and the diagnostic rate increases to 84% if the neonates is imaged after day 4. Neonates with PAIS and normal cranial ultrasound imaging (CrUS) tended to have small infarcts, or strokes affecting the posterior cerebral artery territories. Unfortunately, not everyone has such a wealth of cranial ultrasound experience available in their unit, and other studies have suggested only 30% of neonates with PAIS have abnormalities on CrUS. Either way, when the child is acutely unwell cranial ultrasound imaging should be performed to look for evidence for stroke and to rule out other differential diagnoses, such as intraventricular haemorrhage or structural brain abnormalities. CrUS should not replace Magnetic Resonance Imaging (MRI) of the brain, which has better diagnostic rates and shows the extent of the stroke more clearly.

MRI of the brain involves using different MRI sequences (e.g. T1, T2, Proton density (PD), gradient echo T2*, SWI and DWI), each of which have their own benefits, in analysing the appearances of the brain in different planes. The standard T2-weighted imaging will usually show abnormalities in the distribution of the PAIS, including high signal in the white matter, cortex and the basal ganglia / thalami. A loss of grey / white matter differentiation may also be seen in the cortex and/or basal ganglia (figure 3). Diffusion weighted MRI (DWI) looks at the ability of extracellular water molecules to diffuse within tissues. In areas of infarction, the extracellular water molecule diffusion is reduced (or restricted), which is easily highlighted as brightness on b700 DWI

images and as dark regions on the corresponding “apparent diffusion coefficient” or “ADC” maps, shown in figure 3. DWI changes are evident early on and may be easier to see than on conventional MRI but then begin to normalise (disappear) on the ADC map 5-7 days after the ictus. T2 images are useful to detect PAIS but may over-estimate the area of the brain affected by the stroke. Areas of restricted diffusion (high b700 DWI and low ADC value) are more likely to represent the true/permanent infarct.

MRI can visualise blood vessels within the brain utilising standard T2 and PD imaging, and also with Magnetic Resonance Angiography (MRA) and Magnetic Resonance Venography (MRV). MRA and MRV can be performed with techniques which depend on the flow of blood (time-of-flight and phase contrast) or with the use of gadolinium (the MRI contrast agent). The flow dependent sequences can be prone to artefact, especially in neonates due to slower flow rates than in other children, and correlation with standard imaging is required. It is not necessary to perform MRA and/or MRV in all cases of neonatal PAIS. In the vast majority of cases angiographic imaging will be normal. The radiologist should review the imaging and suggest when angiographic sequences may be helpful. It may be worth discussing the use of MRA or MRV with your neuroradiologists in complex cases with unusual symptoms, extensive stroke, or where the PAIS occurs towards the end of the neonatal period and distant from delivery.

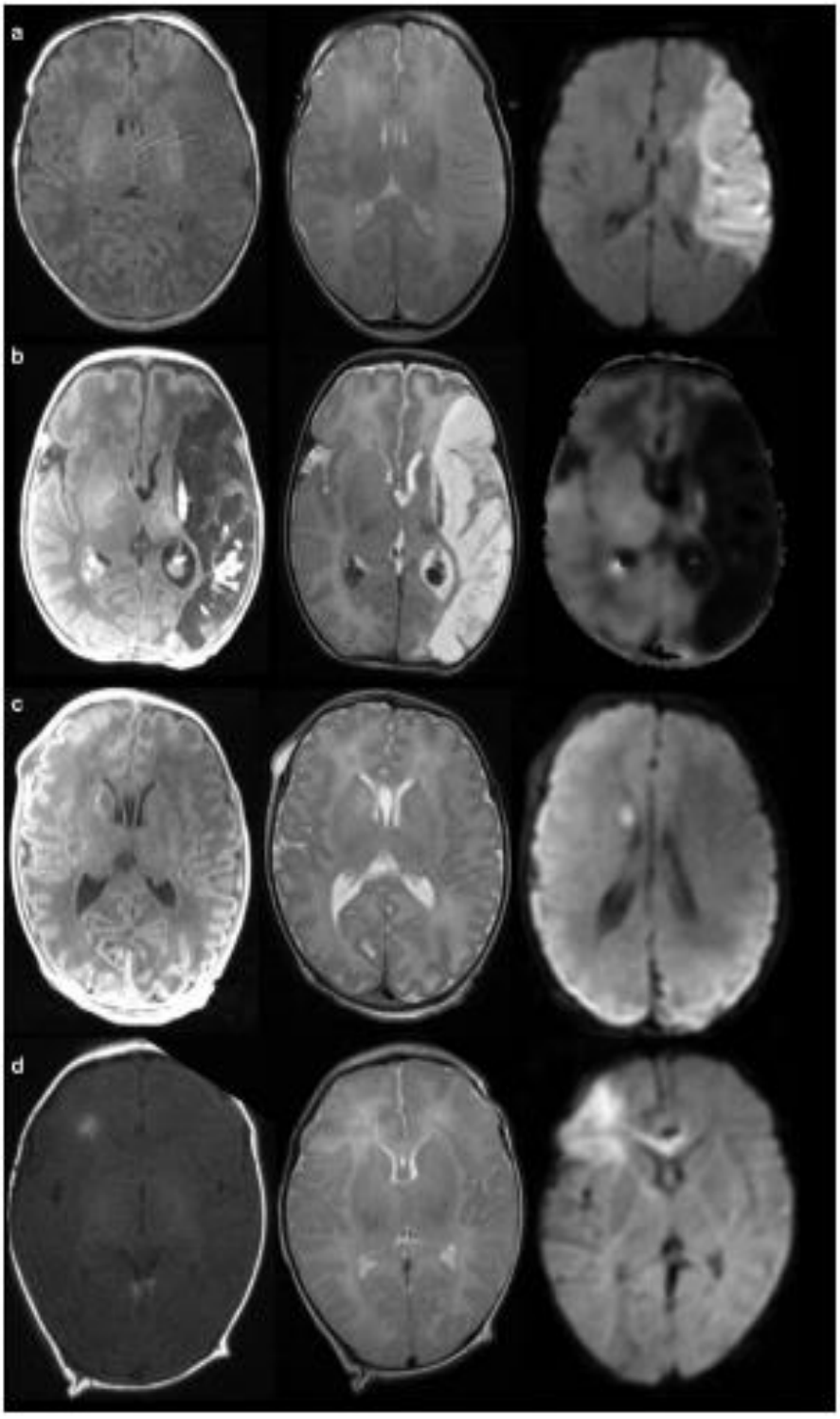

Figure 9.7.3 Magnetic resonance imaging in the axial plane of Perinatal Arterial Ischaemic Stroke (PAIS) in the middle cerebral artery territorie. Left column T1-weighted, middle column T2-weighted, and right column diffusion weighted sequences. Row a – PAIS affecting the territory of the main branch of the left middle cerebral artery. Images show loss of grey white matter differentiation on T1w and T2w sequences with restricted diffusion on DWI. Row b – imaging performed outside the neonatal period demonstrates maturation of the PAIS from row a. Row c – imaging demonstrates a right head of caudate nucleus acute infarct with restricted diffusion

Row d – imaging demonstrates a right anterior cortical MCA PAIS with mild haemorrhagic transformation as demonstrated by the high T1w signal

ACUTE MANAGEMENT

The management of a neonate with PAIS is supportive. Often antibiotics and antivirals will have been started, which can be stopped when the diagnosis is confirmed, and infection has been ruled out. Anti-epileptic drugs may be started if the seizures are frequent or prolonged. They should be withdrawn quickly once seizures have settled, as these will be "acute symptomatic" and will usually resolve quickly. Prolonged courses over weeks or months can cause significant side-effects and should be avoided. EEG may be required for neonates with frequent or prolonged seizures, and can provide useful prognostic information, as discussed later. There is no role in neonates for thrombolysis, thrombectomy, aspirin or anti-coagulation, unless an aetiology has been found, such as congenital cardiac disease, or the history is complex, thrombosis / stroke extensive, or it occurs towards the end of the neonatal period and distant from the delivery.

Referrals to outpatient physiotherapy and a neurodevelopmental clinic should be made to ensure early diagnosis of developmental impairment or unilateral (hemiplegic) spastic cerebral palsy (CP).

PROGNOSIS

A general overview of the outcomes of children following PAIS is provided by Chabrier et al (2016), who followed children up to 7 years. They found:

Cerebral palsy

32% of children had cerebral palsy, but these were at the milder end of the spectrum on the Gross Motor Function Classification Scale. A similar proportion of children had mild functional limitations with fine motor skills

Other studies support this finding but noted that 94.7% of children with unilateral PAIS and 66.7% of bilateral PAIS walked independently. Not all of these had a normal gait: 79.6% and 70.0% of children with unilateral and bilateral PAIS respectively walked with a normal gait. The side of the stroke or presence of comorbidities did not affect these results.

Epilepsy

Around 15-25% of children with PAIS develop epilepsy, and around 5% develop epileptic spasms.

Cognitive / language and schooling

Developmental scores were in the normal range for most children following PAIS

Language scores were reduced with 49% having impaired language abilities aged 7 years. Both expressive and receptive communication skills were affected.

Most children attended mainstream school, although additional education support was required in around 28%. 8.8% of children with PAIS may need special school education.

An interesting observation is that developmental quotients or estimations of cognitive abilities can be normal early on, but full stage intelligence quotients (IQ) lower by school age. This may be mediated through attentional, concentration and executive functioning problems. Bosenbark et al (2017) noted that children with PAIS showed lower abilities on formal testing of these skills, and the deficits were worse with a larger stroke and in the presence of co-morbid epilepsy.

This general overview of the development of these children is useful, but are there tools to predict outcome in an individual child? Fortunately, yes. Mercuri et al (1999) showed that EEG can be used to identify children at high risk. A child with a normal background EEG, with or without epileptiform abnormalities, is likely to have a good outcome. The presence of an abnormal EEG background with epileptiform abnormalities is associated with cerebral palsy. Interestingly, no marker of antenatal / perinatal risk factors nor the neonatal neurological examination helped predict outcome.

Neonatal MRI also has a role in prognostication. Mercuri et al describe their experience of MRI and studied three areas of the brain: the cortex / white matter, the basal ganglia and the thalami, and the internal capsule. Involvement of any two of these areas was not associated with the developmental of CP, but the risk of CP was high where all three areas were affected. It should be remembered that the thalami are supplied by the posterior circulation, whilst the basal ganglia (caudate, putamen and Globus pallidus) are supplied by the anterior circulation. This reflects what is intuitive: the more extensive the stroke, the higher the risk of neuro-developmental abnormalities. Clinicians should use the data cautiously: it is still possible for a child with two of these areas affected on the MRI to develop neurological abnormalities, including unilateral CP. Good quality neuro-developmental follow-up is mandatory for children with PAIS.

CONCLUSIONS

Most paediatricians will see perinatal arterial ischaemic stroke in the course of their career, and the neonatal period is a common time of life to have stroke because of the hyper-coagulable state of the pregnant woman and fetus. Although various risk factors are known for PAIS, the exact cause and timing is not. It most commonly presents within the first days of birth with focal clonic seizures, although pre-existing sleepiness, feeding difficulties or jitteriness may have been noted. Cranial ultrasound may be useful in experienced hands, but MRI is required to confirm the diagnosis and look at the extent of the stroke. Few investigations or treatments are needed once the diagnosis is made. Pro-thrombotic investigations are not required as a matter of routine for simple, unilateral PAIS and should be reserved for unusual strokes, where thrombosis affects other parts of the body, or there is a strong family history. No anti-coagulation or aspirin is needed in simple PAIS, but may be considered on special cases, such as congenital heart disease. Anti-epileptic drugs should be used to treat recurrent or prolonged acute symptomatic seizures and should be stopped before discharge.

Outcome is generally good. Around 30% of children with PAIS develop cerebral palsy, usually unilateral (hemiplegic) unless the stroke is bilateral. Nearly all will walk independently with normal gait. Children typically do well cognitively, with developmental scores in the normal range, although a surprising number need additional educational support in the classroom. There is a suggestion that developmental ability and IQ falls as a child gets older, which may be related to problems with attention, concentration and executive function skills as the demands put on a child in the educational environment increase. Alternatively, social factors may be important to this late fall in IQ. The risk of epilepsy is around 20%, and children with this comorbidity are more likely to experience cognitive, attentional and other learning difficulties. Generally

speaking, the larger the stroke, the more likely a child is to have cognitive / educational difficulties and epilepsy.

FURTHER READING

Mechanism and Risk factors for PAIS

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Martinez-Biarge M, Cheong JLY, Diez-Sebastian J et al. Risk factors for neonatal arterial ischemic stroke: the importance of the intrapartum period. J Pediatr. 2016;173:62-68

Li C, Miao JK, Xu Y et al. Prenatal, perinatal and neonatal risk factors for perinatal arterial ischaemic stroke: a systematic review and meta-analysis. 2017. Eur J Neurol;24(8):1006-1015

The role of prothrombotic factors

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Curtis C, Mineyko A, Massicotte P et al. Thrombophilia risk is not increased in children after perinatal stroke. Blood. 2017;129(20):2793-2800

Outcome following PAIS

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Imaging in PAIS

Cowan F, Mercuri E, Groenendaal F et al. Does cranial ultrasound imaging identify arterial cerebral infarction in term neonates? Arch Dis Child Fetal Neonatal Ed. 2005;90(3):F252-6

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9.8 Aetiological investigation in early developmental impairment – are they worth it?

Hart AR, Sharma R, Atherton M, Alabed S, Simpson S, Barfield S, Cohen J, McGlashan N, Ravi A, Parker M and Connolly DJA

Archives of Disease in Childhood (2017) 102: 1004-1013

Tony Hart, Paul Griffiths, Ruth Batty and I have published several papers on the investigation of children with early developmental impairment (EDI). We have looked at the use of MR spectroscopy in the investigation of all children with EDI (Batty et al). We have investigated the wide range of diagnostic algorithms utilised in the UK for the assessment of children with EDI (Hughes et al).

In this paper we have then used the information that we had gathered from previous studies and gone on to review the cost effectiveness of those investigational algorithms (Hart, Sharma et al). This led to the development of an investigational algorithm for children with EDI that should significantly reduce the investigational cost burden to the NHS, with far fewer numbers of children requiring MRI under general anaesthesia and also far fewer biochemical tests. There is a suggestion from the genetics fraternity that a full genome investigation will be all that is mandated. However, it is evident that clinically, biochemically and anatomically (radiologically) a genetic abnormality may produce a wide range of outcomes in a given individual.

I also believe that high quality early imaging investigation can not only predict outcome in acquired pathologies such as HIE which may go on to produce EDI and/or cerebral palsy, but in future may be used to initiate early targeted interventions in order to improve outcome.

ABSTRACT

Objective: To study the frequency a diagnosis is made in children with early developmental impairment (EDI), and the contribution made to diagnosis by specific investigations.

Design: Retrospective case note review

Setting: Community, neurodisability and neurology department at a UK tertiary centre

Participants: Children referred to determine the degree and cause of EDI in whom a cause was not evident on initial history and examination. Participants were divided into two groups: EDI and no additional features (EDI-) and EDI with additional features (EDI+).

Main outcome measures: The frequency a cause was found for the child's EDI, and which tests were diagnostic.

Results: 699 participants, 68.8% male, median age at investigation 2 years 8 months (range 3 months – 11 years 5 months). 61 (8.7%) of participants had no investigations, and children with EDI- were less likely to be investigated (χ^2=12.5, p<0.05). A diagnosis was made in 166 children (23.7%) and was more frequent in EDI+ (EDI- 9.9%, EDI+ 27.3%, χ^2 19.0; p<0.05). Full blood count, zinc, porphyrin, renal or liver function, bone profile, biotinidase, creatinine kinase, or lead level revealed no diagnoses. The following investigations found causes for EDI: MRI (23.1%), microarray (11.5%), Fragile X (0.9%), plasma amino acids (1.2%), urine organic acids (0.9%) and thyroid function tests (0.5%).

Conclusions: The majority of "screening" investigations for EDI are not diagnostic, highlighting an area of potential cost saving for the NHS. We propose a new, streamlined guideline for the investigation of EDI based on our data.

INTRODUCTION

Early developmental impairment (EDI) occurs when a child's developmental skills fall two standard deviations or more below the population mean in two or more developmental domains.(1, 2) 10-12% of children have a developmental impairment,(3, 4) and 1-3% of children have EDI.(1, 3) The causes of EDI include genetic, metabolic, antenatal, endocrine and infective conditions, amongst others. The number of recommended investigations has increased over the last 20 years,(1, 3, 5-16) although opinion varies on whether children with EDI are investigated appropriately, and the usefulness of specific investigations.(17) This work aims to determine the frequency an aetiology was found for EDI, and the contribution of individual investigations.

METHODS

Patient identification

Children with EDI referred to community paediatrics, neuro-disability or neurology services at Sheffield Children's Hospital between January 2010 and December 2015 were identified by searching the clinic letter database. Children were included if the referral was to assess the level of developmental impairment or determine cause. Children were not included if they were referred for another reason, such as epilepsy management, or if the cause was obvious on initial assessment (such as trisomy 21).

Clinical phenotype and investigation results

Clinical features were noted and two groups established: EDI without additional features (EDI-) and EDI with additional features (EDI+). Subgroups of additional features were formed if the feature was thought clinically relevant and affected at least 5 participants.

Four paediatricians reviewed the results of all investigation the participants had to determine the cause of their EDI. Results were categorised as:

normal;

abnormal but non-diagnostic (for example just outside the reference range);

diagnostic.

Where doubt existed about the categorisation of the investigation, the first author was the final arbiter. Two neuroradiologists reviewed participants' neuroimaging and categorised them as:

"normal";

"specific abnormalities that explained the participant's EDI or pointed towards a diagnosis";

"specific or non-specific abnormalities that did not suggest an aetiology" as per previous methodology (Griffiths 2011).

A Consultant Paediatric Neuroradiologist was the final arbiter on categorisation.

A diagnosis was considered to be an investigation result explaining the cause of a child's EDI, allowing parents to comprehend the problem and the child to access educational support, as per Makela et al.(18) Non-aetiological findings were considered diagnostic, such as "cortical brain malformation", based on Makela's findings, as were test results pointing towards a diagnosis proven on another investigation.

Statistical analysis

We report the frequency participants received the investigations recommended in our hospital guideline (supplementary table one), the frequency each test was diagnostic, and differences in the frequency of diagnostic investigations between EDI- and EDI+ groups using a chi squared test calculated on an online chi squared generator. $p<0.05$ was assumed to be statistically significant. The hospital clinical governance department approved this work and no ethical approval was required.

RESULTS

Participant characteristics

715 participants were referred for assessment and aetiological investigation of EDI. 16 participants were excluded because a diagnosis was obvious at first assessment or insufficient clinical details were available. 481/699 (68.8%) participants were male, 218 (31.2%) were female. Median age at time of assessment was 2 years 8 months, (range 3months to 11years 5 months). A cause was found in 166 (23.7%) participants (table 9.8.1).

Participants	Diagnosis reached?	Investigations (%)																
		Result	***FBC***	***ZPP***	***U&E***	***LFT***	***Bone profile***	***TFT***	***Biotinidase***	***CK***	***Lead level***	***Plasma amino acids***	***Urine organic acids***	***Urine GAGs***	***Karyotype***	***Microarray***	***Fragile X***	***MRI brain***
All participants (n=699)	166 (23.7%)	Number receiving test	529/699 (75.2%)	278/699 (39.8%)	512/699 (73.2%)	491/699 (70.2%)	429/699 (61.4%)	469/699 (67.1%)	227/699 (32.5%)	388/699 (55.5%)	40/699 (5.7%)	413/699 (59/1%)	318/699 (45.4%)	217/699 (31.0%)	96/699 (13.7%)	442/699 (62.2%)	113/699 (16.2%)	368/699 (55.0%)
		Normal	444/529 (83.9%)	205/278 (73.7%)	477/512 (93.2%)	434/491 (88.4%)	412/429 (96.0%)	431/469 (91.9%)	216/227 (95.2%)	340/388 (87.6%)	40/40 (100%)	392/413 (94.9%)	286/318 (90.0%)	200/217 (92.2%)	94/96 (97.9%)	342/442 (77.4%)	112/113 (99.1%)	208/368 (56.5%)
		Abnormal: non-diagnostic	82/529 (15.5%)	73/278 (26.3%)	35/512 (6.8%)	57/491 (11.6%)	17/429 (4.0%)	35/469 (7.5%)	11/227 (4.8%)	48/388 (12.4%)	0/40 (0%)	16/413 (3.9%)	29/318 (9.1%)	17/217 (7.8%)	0/96 (0%)	49/442 (11.1%)	0/113 (0%)	75/385 (20.4%)
		Abnormal: diagnostic	0/529 (0%)	0/278 (0%)	0/512 (0%)	0/491 (0%)	0/429 (0%)	3/469 (0.5%) [1]	0/227 (0%)	0/388 (0%)	0/40 (0%)	5/413 (1.2%)	3/318 (0.9%)	0/217 (0%)	2/96 (2.1%)	51/442 (11.5%)	1/113 (0.9%)	85/368 (23.1%)
EDI without additional features (n=142)	14 (9.9%)	Number receiving test	99/142 (68.7%)	66/142 (46.5%)	91/142 (64.1%)	87/142 (61.3%)	79/142 (55.6%)	91/142 (64.1%)	44/142 (31.0%)	80/142 (56.3%)	5/142 (3.5%)	75/142 (52.8%)	53/142 (37.3%)	38/142 (26.8%)	9/142 (6.3%)	79/142 (55.6%)	24/142 (16.9%)	30/142 (21.1%)
		Normal	86/99 (86.9%)	52/66 (78.8%)	90/91 (98.9%)	81/87 (93.1)	75/79 (94.9%)	86/91 (94.5%)	44/44 (100%)	73/80 (91.3%)	5/5 (100%)	71/75 (94.7%)	50/53 (94.3%)	31/38 (81.6%)	9/9 (100%)	60/79 (75.9%)	23/24 (95.8%)	20/30 (66.7%)
		Abnormal: non-diagnostic	13/99 (13.1%)	14/66 (21.2%)	1/91 (1.1%)	6/87 (6.9%)	4/79 (5.1%)	5/91 (5.5%)	0/44 (0%)	7/80 (8.7%)	0/5 (0%)	4/75 (5.3%)	3/53 (5.7%)	7/38 (18.4%)	0/9 (0%)	10/79 (12.7%)	0/24 (0%)	6/30 (20.0%)
		Abnormal: diagnostic	0/99 (0%)	0/66 (0%)	0/91 (0%)	0/87 (0%)	0/79 (0%)	0/91 (0%)	0/44 (0%)	0/80 (0%)	0/5 (0%)	0/75 (0%)	0/53 (0%)	2/38 (0%)	0/9 (0%)	9/79 (11.4%)	1/24 (4.2%)	4/30 (13.3%)
All participants with EDI and additional	152 (27.3%)	Number receiving test	428/557 (76.8%)	212/557 (38.1%)	421/557 (75.6%)	404/557 (72.5%)	350/557 (62.8%)	378/557 (67.9%)	183/557 (32.9%)	308/557 (55.3%)	35/557 (6.3%)	338/557 (60.7%)	265/557 (47.6%)	179/557 (32.1%)	86/557 (15.4%)	363/557 (65.2)	89/557 (16.0%)	338/557 (60.7%)

features (557)		Normal	358/428 (83.6%)	153/212 (72.2%)	387/421 (91.9%)	353/404 (87.4%)	337/350 (96.3%)	345/378 (91.3%)	172/183 (94.0%)	267/308 (86.7%)	35/35 (100%)	321/338 (94.9%)	236/265 (89.1%)	169/179 (94.4%)	84/86 (97.7%)	282/363 (77.7%)	89/89 (0%)	188/338 (55.6%)
		Abnormal: non-diagnostic	69/428 (16.1%)	59/212 (27.8%)	34/421 (8.1%)	51/404 (12.6%)	13/350 (3.7%)	30/378 (7.9%)	11/183 (6.0%)	41/308 (13.3%)	35/35 (100%)	12/338 (3.6%)	26/265 (9.8%)	10/179 (5.6%)	0/86 (0%)	39/363 (10.7%)	0/89 (0%)	69/338 (20.4%)
		Abnormal: diagnostic	0/428 (0%)	0/212 (0%)	0/421 (0%)	0/404 (0%)	0/350 (0%)	3/378 (0.8%)	0/183 (0%)	0/338 (0%)	0/35 (0%)	5/338 (1.5%)	3/265 (1.1%)	0/179 (0%)	2/86 (2.3%)	42/363 (11.6%)	0/89 (0%)	81/338 (24.0%)

Table 9.8.1: The frequency a diagnosis was achieved in participants, and the frequency investigations on our guidelines were normal, abnormal non-diagnostic, and diagnostic.

[1] **Thyroid function**: a) boy presented at 1yr 10mo as a placid baby with EDI most obvious in motor skills and with hypotonia. Autoimmune hypothyroidism diagnose and he improved with treatment although subsequently developed ASD; b) ex-preterm (29w) girl investigated at 4yr 7mo years to a mother with learning difficulties, had general developmental impairment, especially in speech skills who improved on treatment but had attention and behavioural difficulties; c) girl investigated at 5yr 6mo for EDI, nystagmus with a history of maternal illicit drug use in pregnancy – showed improvement on treatment, but not to normal abilities. Dual diagnosis is being investigated.

[2] **Plasma amino acids**: a) boy investigated at 4yr 1mo with EDI and seizures whose brother had similar phenotype diagnosed with homocystinura; b) 4 month old boy with EDI, microcephaly, hypertonia, and poor visual function with low serum and CSF serine, diagnosed with serine deficiency; c) girl investigated at 2yr 11mo with EDI, brittle hair, eczema, and dysmorphia diagnosed with ethylmalonic aciduria; d) boy investigated at 4yr 7mo with EDI and faltering growth diagnosed with lysinuric protein intolerance; e) boy investigated at 10mo with EDI, visual impairment and Hypotonia noted to have low serum and CSF serine, diagnosed as serine deficiency.

[3] **Urine organic acids:** Ex-premature girl investigated at 8mo for EDI, acquired microcephaly, and faltering growth with raised lactate and glutamate, subsequently diagnosed with pyruvate dehydrogenase deficiency; see case c) and d) in the plasma amino acid results

Investigation and diagnosis rates

61/699 (8.7%) participants had no investigations: 23/142 (16.2%) participants with EDI- and 38/557 (4.1%) with EDI+ (χ^2=12.5, p<0.05). The local guideline was followed in entirety in 45 (6.4%) participants. A diagnosis was made in 14/142 (9.9%) children with EDI-, and 152/557 (27.3%) with EDI+ (χ^2 19.0; p<0.05). The proportion of diagnoses for each additional feature in table 9.8.2.

Participants	**Number of participants in whom a cause was found (%)**	**Investigations** **Number of participants receiving investigation / Number of diagnostic tests (%)**						
		TFT	*Plasma amino acids*	*Urine organic acids*	*Karyotype*	*Microarray*	*Fragile X*	*MRI brain*
All participants with EDI and additional features (n=557)	152 (27.3%)	378 (67.9%) 3/378 (0.8%)	338 (60.7%) 5/338 (1.5%)	265 (47.6%) 3/265 (1.1%)	86 (15.4%) 2/86 (2.3%)	363 (65.2) 42/363 (11.6%)	89 (16.0%) 0/89 (0%)	338 (60.7%) 82 (24.3%)
Additional features and a family history of EDI / LD or neurological disease like seizures (n=115)	26 (22.6%)	82 (71.3%) 1/82 (1.2%)	75 (65.2%) 1/75 (1.3%)	50 (43.5%) 0/50 (0%)	13 (11.3%) 0/13 (0%)	81 (70.4%) 10/81 (12.3%)	19 (16.5%) 0/19 (0%)	67 (58.3%) 10 (14.9%)
Consanguity admitted by family (n=26)	7 (26.9%)	20 (76.9%) 0/20 (0%)	17 (65.4%) 0/17 (0%)	15 (57.7%) 0/15 (0%)	4 (15.4%) 0/4 (0%)	16 (61.5%) 2/16 (12.5%)	2 (7.7%) 0/2 (0%)	16 (61.5%) 5 (31.3%)
Dysmorphia (n=132)	38 (28.8%)	95 (72.0%) 0/95 (0%)	89 (67.4%) 2 (2.2%)	68 (51.5%) 1 (1.5%)	14 (10.6%) 0/14 (0%)	110 (83.3%) 13 (11.8%)	20 (15.2%) 0/20 (0%)	91 (68.9%) 19 (20.9%)
Macrocephaly (n=33)	8 (24.2%)	22 (66.7%) 0 (0%)	20 (60.6%) 0 (0%)	15 (45.5%) (0%)	3 (9.1%) 0 (0%)	23 (69.7%) 4 (12.1%)	5 (15.2%) 0 (0%)	25 (75.8%) 4 (16.0%)
Microcephaly (n=162)	46 (28.4%)	110 (67.9%) 1 (0.6%)	106 (65.4%) 2 (1.2%)	85 (52.5%) 1 (0.6%)	27 (16.7%) 1 (0.6%)	112 (69.1%) 15 (9.3%)	27 (16.7%) 0 (0%)	100 (61.7%) 24 (24.0%)

Hypertonia / upper motor neurone findings (spasticity, dystonia, brisk reflexes) (n=82)	40 (48.8%)	56 (68.3%) 0/56 (0%)	57 (69.5%) 1/57 (1.8%)	51 (62.2%) 0/51 (0%)	10 (12.2%) 0/10 (0%)	60 (73.2%) 4/60 (6.7%)	3 (3.7) 0/3 (0%)	79 (96.3%) 31 (39.2%)
Hypotonia (n=84)	27 (32.1%)	57 (67.9%) 1/57 (1.8%)	54 (64.3%) 1/54 (1.9%)	47 (55.6%) 0/47 (0%)	10 (11.9%) 0/10 (0%)	56 (66.7%) 5/56 (8.9%)	8 (9.5%) 0/8 (0%)	65 (77.4%) 18 (27.7%)
Gait abnormalities, tremor, cerebellar signs or other movement disorders (n=49)	17 (34.7%)	37 (75.5%) 0/37 (0%)	28 (57.1%) 0/28 (0%)	24 (49.0%) 0/24 (0%)	11 (22.4%) 0/11 (0%)	26 (53.1%) 3/26 (11.5%)	4 (8.2%) 0/4 (0%)	39 (79.6%) 11 (28.2%)
Epilepsy (n=29)	17 (58.6%)	17 (58.6%) 0/17 (0%)	22 (75.9%) 1/22 (4.5%)	16 (55.2%) 0/16 (0%)	4 (13.8%) 0/4 (0%)	17 (58.6%) 2/17 (11.8%)	1 (3.4%) 0/1 (0%)	27 (93.1%) 10 (37.0%)
Ophthalmological signs (n=96)	43 (44.8%)	64 (66.7%) 1/64 (1.6%)	59 (61.5%) 2/59 (3.4%)	46 (47.9%) 0/46 (0%)	15 (15.6%) 0/15 (0%)	64 (66.7%) 7/64 (10.9%)	9 (9.4%) 0/9 (0%)	78 (81.3%) 28 (35.9%)
Hearing difficulties (n=27)	7 (25.9%)	17 (63.0%) 0/17 (0%)	18 (66.7%) 0/18 (0%)	15 (55.6%) 0/15 (0%)	2 (7.4%) 0/2 (0%)	18 (66.7%) 2/18 (11.1%)	2 (7.4%) 0/2 (0%)	22 (81.5%) 4 (18.2%)
Cardiac disorder, including congenital cardiac lesions (n=24)	8 (33.3%)	14 (58.3%) 0/14 (0%)	13 (54.2%) 0/13 (0%)	11 (45.8%) 0/11(0%)	2 (8.3%) 0/2 (0%)	20 (83.3%) 6/20 (30.0%)	1 (4.2%) 0/1 (0%)	13 (54.2%) 1 (7.7%)
Airway problem / tracheostomy / sleep apnoea (n=14)	6 (42.9%)	7 (50.0%) 0/7 (0%)	11 (78.6%) 0/11 (0%)	9 (64.3%) 0/9 (0%)	3 (21.4%) 1/3 (33.3%)	9 (64.3%) 2 (22.2%)	1 (7.1%) 0/1 (0%)	11 (78.6%) 3 (27.3%)
Feeding / swallowing difficulties (n=28)	9 (32.1%)	18 (64.3%) 0/18 (0%)	17 (60.7%) 0/17 (0%)	16 (57.1%) 0/16 (0%)	1 (3.6%) 0/1 (0%)	20 (71.4%) 2/10 (10.0%)	2 (7.1%) 0/2 (0%)	23 (82.1%) 7 (30.4%)
Hepatomegaly, abnormal liver function tests, splenomegaly or other features suggestive of inborn error of metabolism (n=12)	3 (25.0%)	9 (75.0%) 0/9 (0%)	12 (100%) 0/12 (0%)	10 (83.3%) 0/10 (0%)	3 (33.3%) 0/3 (0%)	7 (58.3%) 1/7 (14.3%)	2 (16.7%) 0/2 (0%)	12 (100%) 0 (0%)
Kidney, urinary tract abnormalities (n=17)	6 (35.3%)	9 (52.9%) 0/9 (0%)	12 (70.6%) 0/12 (0%)	9 (52.9%) 0/9 (0%)	5 (29.4%) 0/5 (0%)	11 (64.7%) 2/11 (18.2%)	1 (5.9%) 0/1 (0%)	12 (70.6%) 3 (25.0%)
Poor growth / failure to thrive / short stature (n=61)	22 (36.1%)	46 (75.4%)	39 (63.9%)	31 (50.8%)	12 (19.7%)	44 (72.1%)	10 (16.4%)	39 (63.9%)

		0/46 (0%)	1/39 (2.6%)	2 (6.5%)	0/12 (0%)	5/44 (11.4%)	0 (0%)	14 (35.9%)
Obesity (n=17)	2 (11.8%)	12 (70.6%) 0/12 (0%)	9 (52.9%) 0/9 (0%)	7 (41.2%) 0/7 (0%)	1 (5.9%) 0/1 (0%)	9 (52.9%) 1 (11.1%)	1 (5.9%) 0/1 (0%)	7 (41.2%) 0 (0%)
Skeletal / rheumatological disorder (n=16)	9 (56.3%)	9 (56.3%) 0/9 (0%)	9 (56.3%) 0/9 (0%)	6 (37.5%) 0/6 (0%)	3 (18.8%) 0/3 (0%)	12 (75.0%) 3/12 (25.0%)	2 (12.5%) 0/2 (0%)	14 (87.5%) 6 (42.9%)
Features suggestive of ASD (n=99)	13 (13.1%)	62 (62.6%) 0/62 (0%)	54 (54.5%) 0/54 (0%)	44 (44.4%) 0/44 (0%)	19 (19.2%) 1/19 (5.3%)	55 (55.6%) 4/55 (7.3%)	26 (26.3%) 0/26 (0%)	42 (42.4%) 4 (9.5%)
Concerns about attention (n=14)	2 (14.3%)	9 (64.3%) 0/9 (0%)	5 (35.7%) 0/5 (0%)	2 (14.3%) 0/2 (0%)	3 (21.4%) 0/3 (0%)	8 (57.1%) 1/8 (12.5%)	3 (21.4%) 0/3 (0%)	8 (57.1%) 1 (12.5%)
Antenatal concerns e.g. hydrops, alcohol or drug use (n=24)	10 (41.7%)	15 (62.5%) 1/15 (6.7%)	12 (50.0%) 0/12 (0%)	8 (33.3%) 0/8 (0%)	4 (16.7%) 0/4 (0%)	17 (70.8%) 2/17 (11.8%)	4 (16.7%) 0/4 (0%)	16 (66.7%) 5 (31.3%)
Ex-preterm (but not felt to explain EDI) (n=59)	13 (22.0%)	39 (66.1%) 1/39 (2.6%)	34 (57.6%) 0/34 (0%)	22 (37.3%) 1/22 (4.5%)	11 (18.6%) 0/11 (0%)	33 (55.9%) 2 (6.1%)	5 (8.5%) 0 (0%)	28 (47.5%) 5 (17.8%)

Table 9.8.2: The frequency thyroid function, plasm amino acids, urine organic acids, microarray, karyotype, and MR imaging were positive subgroups of additional features

Table 9.8.3Local guidelines for investigations in children with early developmental impairment and costs over time frame of study

Blood samples

Full blood count £3

Zinc protoporphyrin £13.79

Renal function £12

Liver function £12

Thyroid function £12

Bone profile (calcium and phosphate) £12

Plasma amino acids £80

Biotinidase £52

Creatine kinase (boys only) £12

Lead level £15

Chromosome (pre 2012) or microarray (post 2012) £350

Fragile X if suspected by family history £80

Urine samples

Organic acids £89

Glycosaminoglycans (if older than three months) £104

Other recommendations (not studied in this article)

Audiology referral

Ophthalmology referral – not mandatory, to consider if concerns

Total cost £ = £669.28

Results of specific investigations

The proportion of participants who received each investigation on our guideline is shown in table 1. None of the following tests revealed a diagnosis: full blood count, zinc porphyrin, renal or liver function, bone profile, biotinidase, creatinine kinase, or lead level.

During our study period karyotype was replaced by CGH microarray screening. 430/669 (64.3%) participants had a microarray only, 84 (12.0%)

had karyotype analysis only, 12 (1.7%) had both microarray and karyotype analysis. Of the 442 participants who had microarray testing, 51 (11.5%) were diagnostic, and 49 (11.1%) were a non-diagnostic abnormal result, such as polymorphisms or results of uncertain significance (supplementary table 2). Participants with EDI+ were more likely to receive microarray testing (65.2% versus 55.6%, χ^2 4.4; $p<0.05$) but diagnostic rates were similar between groups (EDI- 11.4%, EDI+ 11.6% (χ^2 0.0; $p=0.96$). Table 9.8.4 demonstrates the proportion of diagnostic microarrays for each additional feature. Participants with dysmorphia had similar diagnostic rates to participants with EDI+ but no dysmorphia (11.8% versus 11.5%, χ^2 0.2; $p=0.66$). Fragile X was requested in 113/699 (16.2%) participants, 32 of whom had a family history of learning / developmental difficulties. Fragile X was abnormal in one case: a 2.8-year-old boy with EDI who had no family history or additional features. A number of genetic diagnoses were made following genetic review or specific gene analysis (table 9.8.4).

Diagnostic microarray results
Chromosome 1p36,13 deletion (3 cases)
Chromosome 1q21 deletion
Chromosome 1q21 duplication
Chromosome 2p25 deletion
Chromosome 2p16 deletion
Chromosome 2q deletion
Chromosome 4q33 deletion
Chromosome 5q23 deletion (two cases)
Chromosome 5q from q34 to q35
Chromosome 5 microdeletion
Chromosome 7q11 deletion
Chromosome 7q35 deletion
Chromosome 7p22 duplication
Chromosome 10 duplication with breakpoints within q22.3 and q23.31
Chromosome 11 deletion with breakpoints q14.1 and q22.1
Chromosome 11p15 duplication
Chromosome 12 duplication with breakpoints q14.1 and q15
Chromosome 13q12 deletion
Chromosome 15q11 deletion (four cases)
Chromosome 15q13 deletion (four cases)
Chromosome 15q11 deletion
Chromosome 15 microduplication (three cases)
Chromosome 16p11 duplication (three cases)
Chromosome 16p13 duplication

Chromosome 17q21 deletion Chromosome 17 duplication with breakpoints q11.1 and q12 Chromosome 17q12 duplication Deletion of short arm of chromosome 18 Chromosome 18q22 deletion Chromosome 22q11 duplication Chromosome 22q13 deletion Chromosome 22q13 deletion Chromosome Xq26 deletion Chromosome Xq24 deletion including UBE2a gene Chromosome 22q11 duplication Duplication long arm X chromosome including PLP1 gene Duplication of X chromosome Xq28 (2 cases)
Single gene or clinical diagnoses
Bardet Biedl Syndrome - 5 cases Neurofibramotisis type 1 - 3 cases SLC2A1 (GLUT1) mutation - 2 cases Rett Syndrome - 1 case Angelman syndrome - 1 case Kabuki syndrome - 2 cases (1 genetic, 1 clinical) Cornelia de Lange syndrome - 1 case Kleefstra syndrome - 1 case Creatine transport deficiency - 1 case RYR1 mutation – 1 case

ASPM microcephaly mutation - 1 case
UBE2A mutation - 1 case
PHGDH mutation - 1 case
CASK1 mutation - 1 case
COL4A1 mutation - 1 case
SLC9A6 mutation - 1 case
NRXN1 mutation - 1 case
PLP1 (Pelizaeus-Merzbacher disease) - 1 case
DGUOK (mitochondrial depletion) mutation - 1 case
SLC7A7 mutation (lysinuric protein intolerance) - 1 case
PDHA1 mutation (pyruvate dehydrogenase deficiency) - 1 case
SLC6A8 mutation (creatine transport deficiency) - 1 case
ETHE1 mutation (ethylmalonic aciduria) - 1 case
Tetrasomy 18p - 1 case
Sotos syndrome (clinical diagnosis) - 1 case
Odho symdrome (clinical diagnosis) - 1 case
Atypical ataxia telangiectasia (clinical diagnosis, gene negative) - 1 case
Fetal alcohol syndrome - 1 case

Table 9.8.4: Summary of genetic diagnoses made

Thyroid function was diagnostic in 3 participants, all of whom had additional features (table 9.8.1). Plasma amino acid screens were diagnostic in 5 participants, and urine organic acids were diagnostic in three patients, two of whom had abnormal plasma amino acids. Clinicians ordered a variety of other investigations (table 9.8.5) and they revealed a diagnosis in 5 participants.

Investigation	Number of participants (% of total)	Comments
Blood investigations		
Clotting	5	Abnormal in one patient, but already known to be abnormal prior to referral for investigation of EDI
Folate	8	Not diagnostic in any participant
C Reactive Protein	1	Not diagnostic in any participant
Erythrocyte sedimentary rate	4	Not diagnostic in any participant
Glucose	58	No abnormalities
Lactate	178	Persistently abnormal in one boy investigated at 1.4 years of age with dysmorphia, pulmonary stenosis, squint and hypertonia; MRS showed lactate peak although respiratory chain enzymes normal and no genetic diagnosis of mitochondrial disease made.
Acylcarnitine screen	100	Not diagnostic in any participant
Magnesium	3	Not diagnostic in any participant
Ammonia	67	Not diagnostic in any participant
Homocysteine	11	Not diagnostic in any participant
Uric acid	103	Not diagnostic in any participant
Lipid / cholesterols	40	Not diagnostic in any participant
White cell enzymes	45	Not diagnostic in any participant

Very long chain fatty acids	60	Not diagnostic in any participant
Transferrin isoelectric focussing	46	Not diagnostic in any participant
Galactossemia screen	15	Not diagnostic in any participant
Copper	21	Not diagnostic in any participant
Caeruloplasmin	20	Not diagnostic in any participant
Free T3	9	Not diagnostic in any participant
Cortisol	12	Not diagnostic in any participant
Vitamin A	7	Not diagnostic in any participant
Vitamin B12	10	Not diagnostic in any participant
Vitamin D	193	Low levels were not felt to be the aetiological cause of EDI in any participant
Vitamin E	9	Not diagnostic in any participant
Coeliac screen	40	Not diagnostic in any participant
Amylase	5	Not diagnostic in any participant
Parathyroid hormone	48	Not diagnostic in any participant
Immunoglobulins	42	Not diagnostic in any participant
LDH	3	Not diagnostic in any participant
Alpha fetoprotein	5	Not diagnostic in any participant
ANA	4	Not diagnostic in any participant
Rheumatoid factor	2	Not diagnostic in any participant

Congenital infection screen	34	Not diagnostic in any participant
Urine investigations		
Urine amino acids	150	Not diagnostic in any participant
Urine creatinine	13	Not diagnostic in any participant
Oligosaccharides	12	Not diagnostic in any participant
Purine / pyrimidine studies	30	Often done after a marginally low uric acid, normal in all participants
Cerebrospinal fluid tests		
CSF glucose lactate	58	Lactate raised in one boy investigated at 1.4 years of age with dysmorphia, pulmonary stenosis, squint and hypertonia; MRS showed lactate peak although respiratory chain enzymes normal and no genetic diagnosis of mitochondrial disease made. Glucose low in two patients: a boy investigated at 1.7years with EDI, Hypotonia, seizures and paroxysmal upgaze when fasted; a girl investigated at 1.9years with EDI, left hemiplegia and seizures. Both confirmed to have mutations in Glut 1 deficiency syndrome gene
CSF amino acids	19	Diagnostic in two cases: a boy, investigated at 4 months of age for developmental impairment, poor visual function, evolving dystonia and microcephaly diagnosed with serine deficiency; a boy investigated at 0.8 years for developmental impairment, poor visual function and microcephaly whose plasma amino acids revealed low serine, ultimately diagnosed with serine deficiency

CSF neuro-transmitters	32	Not diagnostic in any participant
CSF viral studies	18	Not diagnostic in any participant
Other		
Skeletal survey	2	Not diagnostic in any participant
Muscle biopsy	9	Not diagnostic in any participant
Fibroblast culture	2	Sent for variety of tests - Not diagnostic in any participant

Table 9.8.5: Number of participants receiving additional investigations

Neuroimaging

MR imaging was performed in 368/699 (55%) participants. Children with EDI+ were more likely to receive neuroimaging compared to EDI- (additional features 60.7% versus 21.1% for no additional features, χ^2 71.0; p<0.05). MRI was diagnostic in 86 (23.3%) participants: 82/338 (24.3%) participants with EDI+ and 4/30 (13.3%) EDI- (χ^2 1.8; p=0.18). Table 9.8.6 shows the distribution of abnormalities found on MR imaging.

MR abnormalities	**All participants**	**EDI and no additional features**	**EDI and additional features**
Specific abnormalities likely to explain EDI or point towards a diagnosis			

Hypoxic ischaemic injury: Periventricular leukomalacia Central (predominately basal ganglia) Peripheral (predominately watershed areas)	25	1	24
Toxic metabolic	18	0	17
Brain malformation	37	2	35
Phakomatoses / tumours	3	1	2
Previous infection	0	0	0
Hydrocephalus	3	0	3
Totals	85	4	81
Specific or non-specific abnormalities not likely to explain EDI			
Posterior fossa abnormalities, such as Chiari malformation	6	1	5
Cavum septum pellucidum	2	0	2

Under-opercularisation of the Sylvian fissure	0	0	0
Reduced volume of white matter / grey matter	20	2	18
Delayed myelination	12	0	12
Non-specific white matter abnormality or focal gliosis	30	2	28
Arachnoid cyst	2	0	2
Optic nerve hypoplasia without evidence of septic optic dysplasia	0	0	0
Subdural collection / effusion	0	0	0
Non-specific MRS abnormalities	1	1	1
Total	75	6	69

Table 9.8.6: MRI abnormalities seen in our cohort

DISCUSSION

Why investigate for the cause of EDI?

The reasons why families wish to know the aetiology include:(18)

Validation, i.e. proof of a credible problem and to help explain the problem to the affected child or siblings and others

To provide prognostic information and help set realistic expectations / plans

For any potential treatment

To allows better access to educational support

To provide the opportunity for early intervention

To provide support opportunities

The “need to know”

For prenatal testing and recurrence risk

Not all diagnoses are equally effective at enabling access to educational support, despite children having similar levels of disability. Descriptive diagnoses could be equally, if not more, effective as aetiological diagnoses.

Investigating the cause of EDI

There is little agreement on the best way to investigate a child with EDI, with wide variation in opinion existing between UK paediatricians.(17) Over the years, the number of recommended investigations for EDI has increased,(1, 3, 5-16) although the evidence base for this is lacking.

A cause for EDI was found in 23.7% of our participants, and many of the first line investigations in our guideline were of no value in determining an aetiology.

Biotinidase levels are a recent addition to published guidelines,(3, 12) and the features of biotinidase deficiency include seizures, hypotonia, laryngeal stridor, tachypnoea, apnoea, alopecia, skin rash, hearing loss, optic atrophy or conjunctivitis, ataxia, fungal infection and recurrent myelopathy(19-23) Additional clues include abnormal organic acid results or hyperammonaemia.(19) It is not clear that biotindiase deficiency presents with EDI-.(24) Recommendations that 3500 children need to be tested to diagnose one case, and the suggestion that this is cost effective,(25) are not based on high quality evidence. Furthermore, the incidence of biotinidase deficiency on newborn screening suggests pick up rates would be much lower.(19) Our view is that serum biotinidase should not be a first line investigation, and only performed in children with suggestive features.

High blood lead levels are associated with learning / developmental and mental health issues that can persist into adulthood,(26, 27) and low levels of blood lead (5-10µg/dl) are associated with reading and writing difficulties.(28) However, it is unlikely that a modern child would have moderate or severe EDI because of extremely high lead levels alone, particularly since the proportion of children with high lead levels has fallen markedly to 0.8% in the US.(29, 30) Therefore, routine lead levels appear to be unnecessary.

Creatinine kinase is recommended in boys with EDI to facilitate early diagnosis of Duchenne Muscular Dystrophy (DMD),(3, 12) ensure treatment with steroids and / or newer drugs, and for entry into research studies. No child in our study had DMD, and a CK was not indicated routinely in the 101 girls who had it. Nevertheless, a CK is cheap and there remain good reasons to perform it routinely in boys.

Investigations likely to determine the cause of EDI

The investigations that revealed a diagnosis in our cohort were:

thyroid function

plasma amino acids

urine organic acids

microarray / karyotype

Fragile X

MR imaging.

Congenital hypothyroidism is usually diagnosed on newborn screening in the UK, unless it arises from pituitary failure. Autoimmune hypothyroidism will also be missed, as noted in our cohort. The cost of each test is low (£12). Given 469 participants were tested and 3 were positive for this diagnosis, two of whom showed improvement on treatment, the cost per diagnosis in our cohort was £1876, which appears cost effective given the subsequent impact on treatment and outcome.

Plasma amino acids were diagnostic in 1.2% of our participants, all of whom had EDI+. Organic acids were abnormal in 0.9%, two of whom had abnormal plasma amino acids. Other metabolic investigations were performed in our cohort, outside of the guideline, but were rarely diagnostic. The diagnosis rates in previous studies vary, reflecting the cohort's characteristics, the investigations performed, whether newborn screening was available, and whether adults in mental institutions born before newborn screening were included. Because our participants with a positive result had EDI+, we do not recommend metabolic tests in EDI-. In children with EDI+, metabolic tests

should be first line where concern exists about an inborn error of metabolism.(3) Where no such concern exists, they should be second line or performed if the presentation changes or other results point towards these conditions.

Microarray found a diagnosis in over 10% of our cases, with similar frequencies between EDI- and EDI+. Therefore, we advocate microarray testing in all children with EDI. Fragile X testing is recommended in our guideline for all children who have a family history of EDI / learning difficulties, but this was rarely followed. Ironically, the affected child had no additional clinical features or family history. We recommend Fragile X testing as second line if the microarray is normal in children with a family history of learning difficulties and / or dysmorphic features. Cases that are not tested should be evaluated over time, and Fragile X requested if the child develops features consistent with the diagnosis. Where no diagnosis is found after initial investigations in children with EDI+ or a relevant family history, referral to a clinical geneticist should be considered. We await further data from gene exome studies on their usefulness when a microarray is negative.

The role of MRI in EDI is controversial, particularly as sedation or general anaesthetic is required for those who cannot lie still. Consensus statements in 1997 and 2003 recommended MRI only in children with EDI and additional symptoms, based on a belief that children with EDI and no additional symptoms were unlikely to have structural brain abnormalities.(1, 5) There was a paucity of data to support this view. Our previous analysis between 1998 - 2006 showed 22.2% of participants with EDI- and 27.6% with EDI+ had specific abnormalities, but methodological flaws existed with this data.(31) A prospective study between 2007-2008 the rates of specific abnormalities were 7.5% for EDI- and 28% (21/75) for EDI+.(32) Our current data shows

that MR imaging has the highest diagnostic rates of any tests, with 13.3% in children without additional features and 24% in those with additional features. The lack of a statistical difference between groups is probably a type 2 statistical error.

Clinically, we advocate a common-sense approach. In a child with EDI-, MRI should not be a first line test because of the anaesthetic and/or sedation risks. Where no diagnosis is found on first line laboratory testing, MRI should be discussed with the family, including the likelihood that no specific treatment is available for any abnormality, and the risks of general anaesthesia. In those with EDI+, MRI should be first line if a high risk of specific MRI abnormalities is likely: skeletal dysplasia (42.9%), signs of upper motor neurone involvement (39.2%), refractory or focal seizures (approximately 37.0%), ophthalmological signs (35.9%), failure to thrive not explained by poor calorific input (35.9%), antenatal concerns such as maternal drug use or hydrops (31.3%), feeding / swallowing difficulties (30.4%), gait or movement abnormalities (28.2%), central mediated hypotonia (27.7%), and airway problems (27.3%). In other children, MRI could be second line test following discussion with the parents or deferred.

It is our unit's policy to perform MR spectroscopy in all children with EDI, to detect conditions like cerebral creatine deficiency.(32) We found a further case of creatine transporter deficiency using MRS, a child with large lactate peak suspected to have a defect in pyruvate metabolism, and third participant with a non-specific reduction in choline levels. Because MRS adds around 8 minutes to acquisition times, and creatine deficiencies are treatable, we recommend MRS for children with EDI when MRI is performed.

Limitations with our data

As with previous retrospective data on the investigation of children with EDI,(31) our data has many methodological flaws. We relied upon the documentation in medical notes and clinic letters to phenotype our participants, and it is possible that features may have been missed by clinicians or not documented. Many recommended investigations were not performed in all participants and we do not know why clinicians ordered specific additional tests. Finally, because data results from review in busy clinics, we have no formal developmental assessment to confirm the diagnosis, assess severity, or domains affected.

New recommendation on how to investigate EDI

There is a pervasive view amongst paediatricians that it is kinder to perform all necessary investigations in one go, but our results show this to be a wasteful approach. Cost savings could be redirected to other areas of care, such as therapy or psychology. We propose a diagnostic algorithm in figure 1 based on our data. Guidelines cannot cover every clinical eventuality and should not stop clinicians ordering additional investigations where a high degree of suspicion exists for a specific condition.

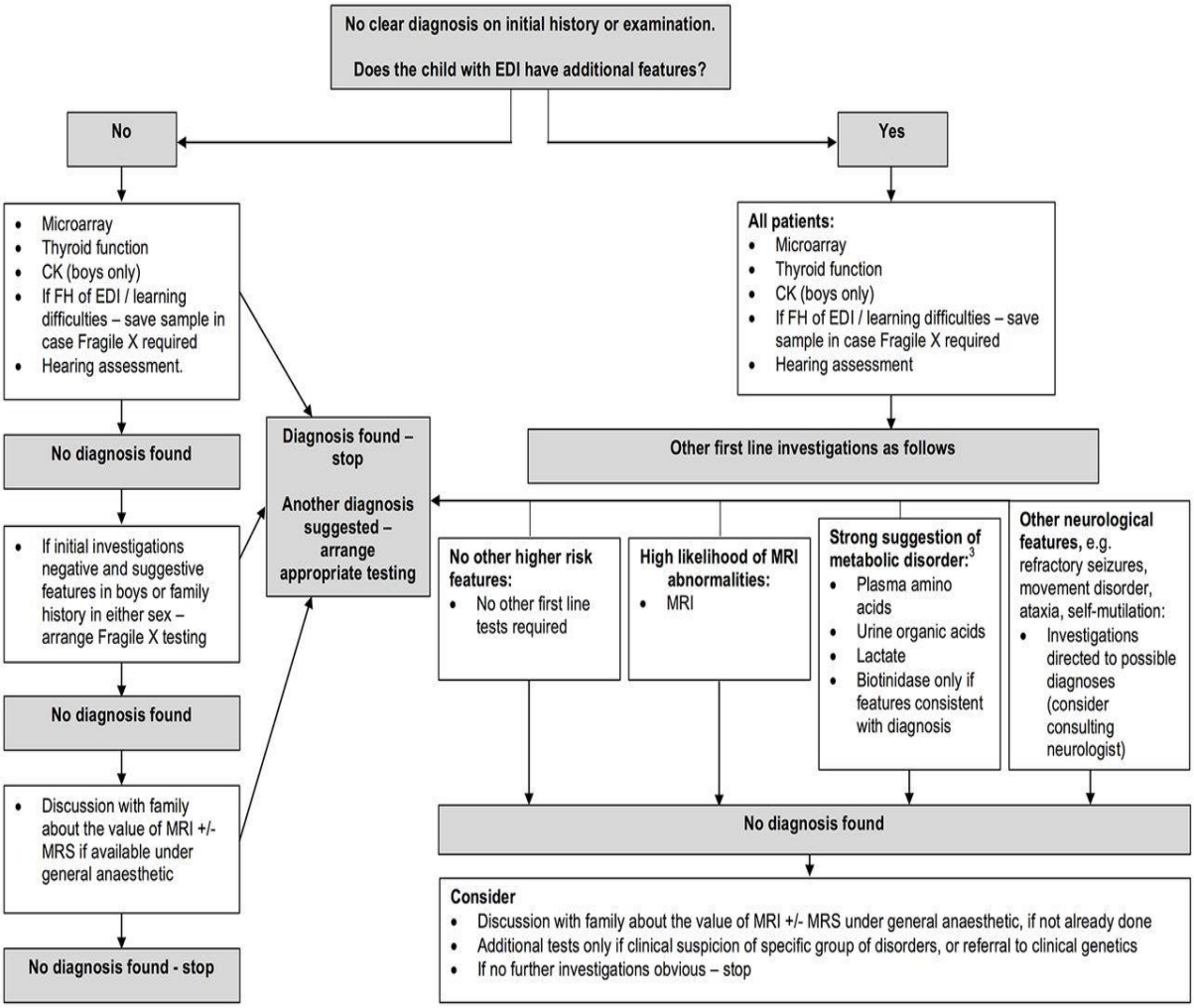

Figure 9.8.1 Proposed diagnostic algorithm for investigation of EDI

CONCLUSIONS

Many investigations recommended as “first line” to determine a cause of EDI are rarely diagnostic and can be safely deferred without missing diagnoses. This has cost saving implications to the NHS. We recommend a streamlined guideline based on our results. A paucity of evidence exists on the best way to investigate EDI. Previous work and recommendations are based on retrospective studies with poor participant phenotyping and inconsistent choice of investigations. A prospective study is needed to evaluate the optimal and most cost-efficient way to investigate children with EDI

according to the degree of their EDI, the domains affected, and the additional features evident.

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11 Dedication and thanks

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