Original Article

Magnetic Resonance Imaging in Evaluation of Periventricular Leukomalacia

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Abstract

Background: Improvements in perinatal care have resulted in increased survival of infants born prematurely, however neurological damage due to ischaemic infarction of the periventricular white matter is a problem of enormous medical, social and economic importance. Such vascular insult leads to destruction of the periventricular white matter, termed periventricular leukomalacia (PVL). This abnormality is the leading cause of significant morbidity in the survivors of premature birth. Magnetic Resonance Imaging (MRI) is perhaps the only imaging modality, which can accurately detect and quantify periventricular leukomalacia.
Methods: Magnetic Resonance Imaging was carried out in 45 children in the age group of 4 weeks to 8 years, with history of premature birth and perinatal hypoxia. These children had neurological deficits ranging from cortical blindness, spastic diplegia, spastic quadriplegia to severe mental retardation. The procedure was carried out on a 1.5 Tesla (Siemens Magnetom Avanto) MR system using available protocols for imaging the paediatric brain.
Result: The study revealed that MR imaging could accurately identify areas of ischaemic infarction of the periventricular white matter both in the early as well as in the late stages. The pattern of abnormalities detected on MRI of the brain in these patients can be considered specific for PVL in the clinical background of premature birth and perinatal hypoxia.
Conclusion: MRI is the ideal imaging modality to detect, quantify and accurately map the areas of brain affected by this hypoxic-ischaemic process. It is presently the gold standard for evaluating the neuroparenchyma in those with perinatal hypoxia. Advanced MR techniques like Diffusion Weighted Imaging (DWI), Proton MR Spectroscopy and DTI have shown great promise in our understanding of the pathophysiology and anatomic considerations of this disease process.

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Key Words : Hypoxic ischaemic encephalopathy; Magnetic resonance imaging; Periventricular leukomalacia

Introduction

Amongst all problems in neonatal medicine, brain injury in the premature infant, is of particular importance as it has tremendous medical, social and financial implications. Periventricular leukomalacia (PVL) is the major neuropathologic form of this brain injury, which leads to significant neurologic morbidity encountered in survivors of premature birth. PVL is defined as ischaemic infarction due to hypoperfusion of the end arteries that supply the white matter located around the lateral ventricles of the premature infant's brain [1].

PVL is the 2nd most common hypoxic brain injury in premature infants accounting for 4 to 26%, intraventricular and periventricular haemorrhage being more common, which account for 30 to 55% of all hypoxic brain injury [2,3]. It is rarely fatal but has far reaching consequences due to the diversity of neurological damage and morbidity associated with it. The common clinical presentations range from spastic diplegia, spastic quadreplegia, cortical blindness, deafness and mental retardation. However the clinical findings of this abnormality in the neonatal period are not distinctively sufficient to allow for a firm and accurate diagnosis to be made.

Imaging plays an important role to establish the presence and effects of this condition. The use of cranial ultrasonography for diagnosing PVL was established in the early 1980's, since then this modality of imaging has been in the forefront in the diagnosis and follow up of PVL [4]. Ultrasonography reveals an increased echogenicity of the periventricular white matter, which appears within 24 to 48 hours after a hypoxic-ischaemic incident. The affected periventricular white matter is usually as bright as or brighter than the choroid plexus, in contrast to a normal periventricular white matter, which is less bright than the choroid plexus. Two to four weeks later, cysts appear in these hyperechoic areas, which finally resolve with development of ventricular enlargement. The spectrum of leukomalacia diagnosed

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with sonography was described by Vries et al [5]. Although cranial sonography is convenient and readily available, it also has its limitations, it can depict only 28 to 80% of histologically proved PVL [6]. One of the difficulties is in differentiating between a normal periventricular halo and early PVL; moreover, it may be difficult to assess the severity of echogenicity and finally there is substantial intra- and inter observer variability [7].

In the past two decades MR imaging has been used as the gold standard in the diagnosis and follow- up of periventricular leukomalacia in both term and premature infants as it can depict the precise site and extent of hypoxic-ischaemic brain injury at an earlier stage and allows a wider differentiation of lesions as compared with sonography alone. The patterns of hypoxic-ischaemic injuries are well documented and include abnormally increased signal in the periventricular region on T2-weighted images, white matter loss, ventricular dilatation, multicystic encephalopathy and basal ganglia necrosis.

The aim of the present study was to characterize features of hypoxic-ischaemic brain injury on MR imaging in neonates with history of perinatal hypoxic insult and neurological deficits.

Material and Methods

Patient population and patient preparation

A total of 45 patients (25 males and 20 females) with age ranging from four weeks to eight years were included in this cross sectional study. A detailed perinatal history was elicited from the parents of the child with specific reference to perinatal complications, birth weight, gestational age at birth and any neurological deficits. The detailed clinical data of these patients are summarized in Table 1. Children with neurological deficits were clinically evaluated in detail and the same has been elucidated in Table 2.

Table 1

Clinical data of the patients (n=45)

Gestational age at birth :	
< 30 weeks	12
31-34 weeks	22
34.1-38 weeks	08
> 38 weeks	03
Birth weight :	
< 1000 g	06
1001-1500 g	16
1501-2500 g	18
> 2500 g	05
History of perinatal complications :	
Perinatal asphyxia	29
Respiratory distress syndrome	03
Neonatal seizures	11
Neonatal hypoglycaemia	02
Multiple complications	34

MR Imaging protocol

MR imaging of the brain was performed as soon as the infants were in a stable respiratory and circulatory condition. The referring physician and anesthetist were consulted for the type of sedation (general anesthetic sedation, deep sedation or conscious sedation) for every case. The patients were positioned head- first in supine position with a head coil and imaging was performed using 1.5 Tesla MR Equipment (Siemens Magnetom Avanto, Erlangen, Germany). The heart rate, transcutaneous oxygen saturation was continuously monitored and supplemental oxygen administered.

The images were acquired with a 128 x 256 matrix, a field of view of 18 to 20 cm, and a section thickness of 4 mm with an interslice gap of 2mm. T1-weighted spin-echo (SE) images (480/20/2 (TR/TE/excitations)) were obtained in the sagittal and axial planes. Inversion recovery images (4000/30 (TR/TE), TI = 2500) and T2-weighted turbo spin echo images (3000/30/80/1) were obtained in the axial and coronal planes.

Results

Data collection and image analysis

The results of the cranial MR examinations were analyzed and assessed for presence of areas of altered signal intensity within the periventricular white matter relative to the remainder of the cerebral hemispheric white matter, presence of areas of altered signal intensities in other parts of the neuroparenchyma, loss of or paucity of periventricular white matter, ventricular enlargement with irregularity of the wall, morphology and signal characteristics of the corpus callosum, associated abnormalities, if any.

Based on the MR findings a scoring system was formulated to evaluate the severity of the hypoxic changes in the brain parenchyma.

Grade 1 - Normal MR findings.

Grade 2 - Areas showing increased signal on long TR sequences.

Grade 3 - Few punctate haemorrhages in the white matter.

Grade 4 - Multiple, more than six areas of punctate haemorrhages in the white matter and /or larger focal haemorrhages but less than 2 in number.

Grade 5 - Extensive changes of increased signal intensities on long TR sequences with areas of punctate or focal haemorrhages.

Grade 6 - Diffuse signal intensity changes with haemorrhagic lesions or cystic lesions involving both periventricular and subcortical white matter [8].

Presence of irregular outline of the ventricular walls,

Table 2

Various neurological deficits (n=45)

Cortical visual impairment (unilateral)	06
Cortical visual Iipairment (bilateral)	02
Spastic diplegia	20
Spastic quadreplegia	08
Mental retardation	09

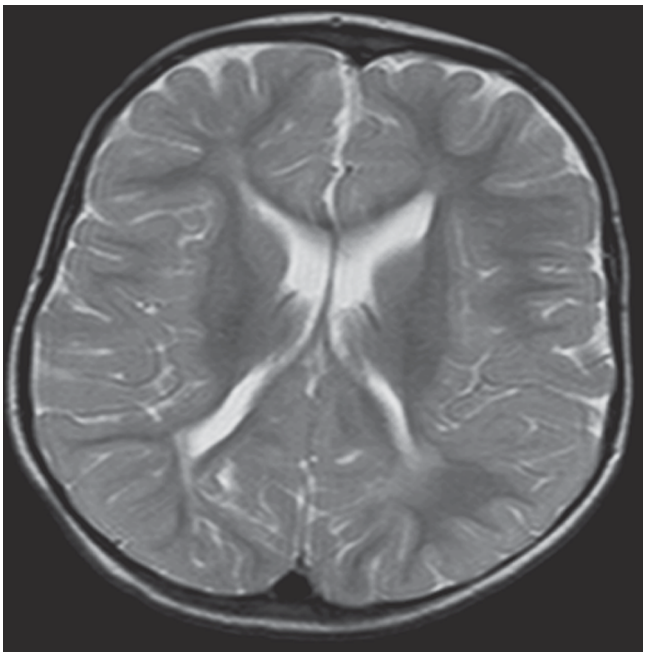

Fig. 1 : Axial T2 weighted turbo spin echo image showing hyperintense signals in the periventricular white matter. Paucity of white matter is also seen in the periventricular region with the grey matter reaching upto the ventricular margins. These findings represent grade 2 lesions.

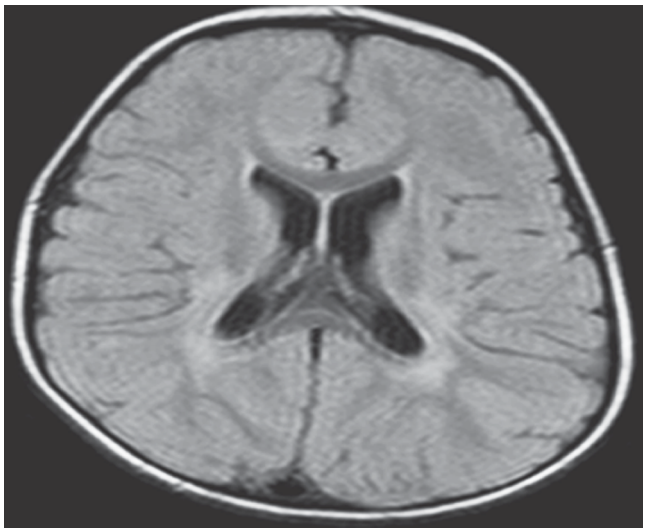

Fig. 2 : Axial FLAIR (Fluid attenuated Inversion Recovery) image showing hyperintense signals in the periventricular white matter.

thinning and bowing of the corpus callosum were also evaluated and these provided additional findings to characterise the severity of the hypoxic brain injury. The various abnormalities detected on MR scans in these patients are listed in Table 3.

Four children had normal MR findings. Thirteen children had presence of periventricular zone of increased signal intensity on T2 weighted and inversion recovery images (Figs. 1 & 2), appearing hypointense on T1-weighted images (Fig. 3), which corresponded to grade 2 lesions. There was a specific predilection for involvement of the peritrigonal areas. The corpus callosum was involved in a majority of children

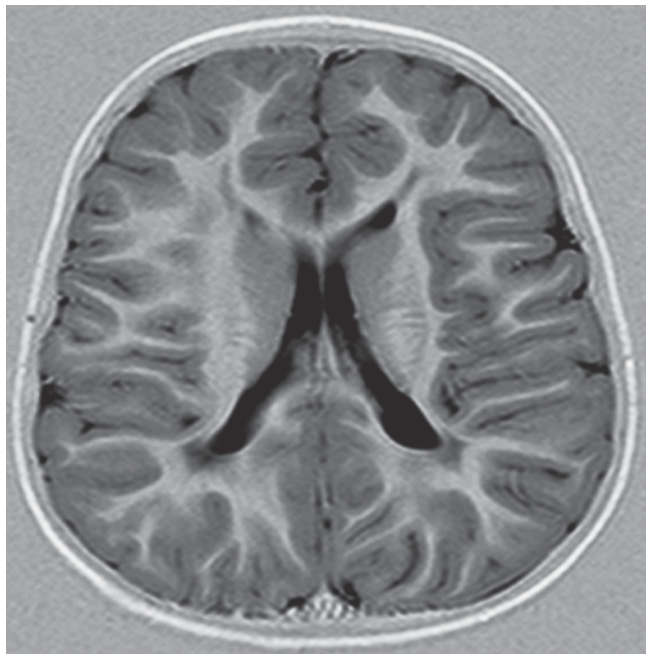

Fig. 3 : Axial T1 weighted images showing hypointense signals in the periventricular white matter with wavy outline of the ventricular walls consistent with irregular loss of periventricular white matter.

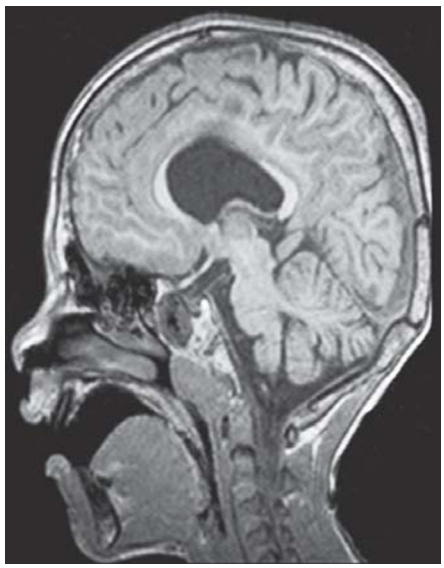

Fig. 4 : Mid-sagittal T1 weighted image showing thinning with upward bowing of the mid-body of the corpus callosum.

Table 3

Result (MRI findings) (n=45)

Normal (Group I)	04
Group II	13
Group III	08
Group IV	09
Group V	05
Group VI	06

which ranged from focal thinning and upward bowing (Fig. 4) to diffuse thinning. Haemorrhagic lesions were seen in 16 children, out of which, 8 showed multiple small punctate

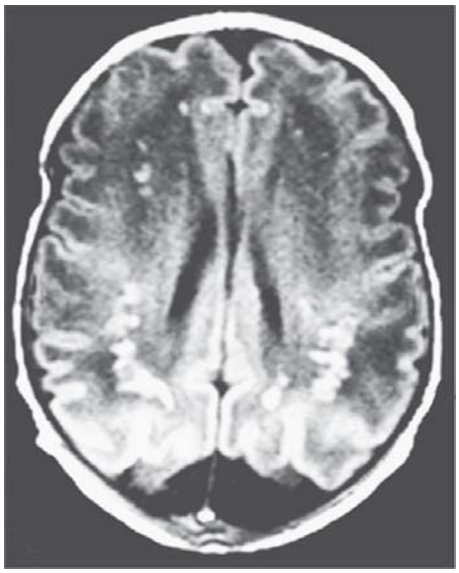

Fig. 5 : Axial T1 weighted image showing multiple focal hyperintense areas in the white matter consistent with areas of haemorrhage. These findings represent grade 4 lesions.

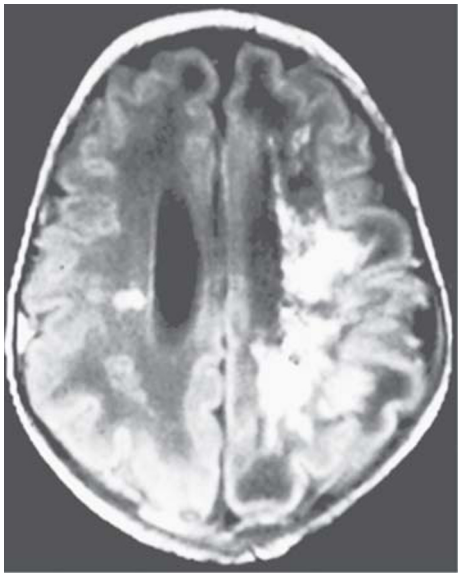

Fig. 6 : Axial T1 weighted image showing multiple large areas of haemorrhage within the white matter on the Lt side with multiple smaller focal haemorrhages on the opposite side consistent with grade 5 lesions.

haemorrhages corresponding to grade 3 lesions, these foci of haemorrhages were predominantly located in the periventricular and the subcortical areas, whereas nine children had larger areas of haemorrhages corresponding to grade 4 lesions (Fig. 5). Five children had extensive periventricular haemorrhagic lesions, with presence of haemorrhages in the deep white matter also, corresponding to grade 5 lesions (Fig. 6). Similar results have been published by Keeney et al in their study. In the majority of the children, the haemorrhagic lesions were distributed along the ventricles in the parieto-occipital regions, with a few haemorrhagic in the subcortical white matter as well. Multiple periventricular and subcortical cysts were seen in six patients corresponding to grade 6 lesions, the cystic lesions showed CSF signal

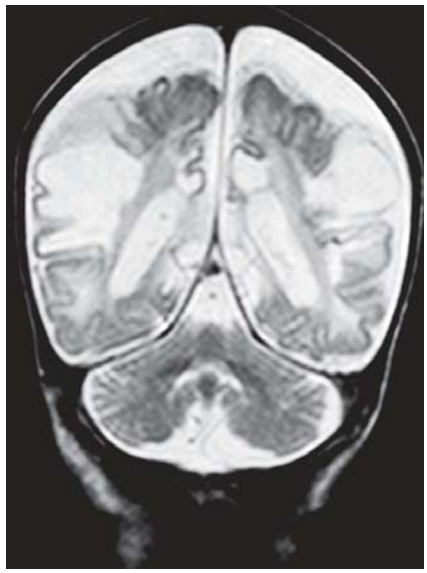

Fig. 7 : Coronal T2 weighted image showing multiple subcortical cysts with contents showing CSF signal intensity consistent with grade 6 lesion.

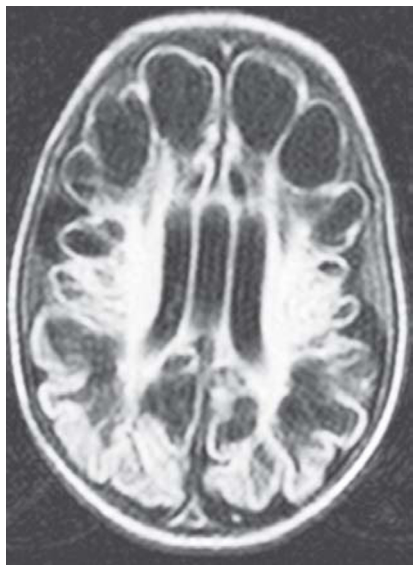

Fig. 8 : Axial FLAIR image showing multiple subcortical cysts of CSF signal intensity consistent with cystic encephalomalacia.

intensities on all sequences consistent with findings of cystic encephalomalacia (Figs. 7 & 8).

Discussion

Maintenance of normal cerebral blood flow is essential for brain development, unfortunately this is easily disturbed even with minor stresses during the prenatal and perinatal period [9]. Cerebral hypoperfusion which along with the presence of oxygen free radicals induce cerebral ischemia in the periventricular white matter which has selective vulnerability in the preterm neonate to ischemia, being in the arterial watershed zones. Apart from ischaemia being the cause of PVL, Leviton et al proposed that maternal infection, placental inflammation and vasculitis may also contribute to the pathogenesis

of this condition. They observed that foetal inflammatory response, as reflected by foetal vasculitis (polymorphonuclear leukocyte infiltration in the chorionic plate or umbilical cord) damages the fetal brain. Furthermore, various maternal cytokines have also been implicated in the pathogenesis of PVL. Following the initial insult whether ischemia, vasculitis or cytokine-mediated white matter damage occurs affecting mainly the oligodendroglia. This leads to periventricular leukomalacia which is histologically characterized as "softening" of the white matter which can progress to focal cystic degeneration of the neuroparenchyma. Approximately half of the deaths due to cerebral hypoxic-ischaemic injury occur in the first month of life and these neonates with severe neurological disabilities often die from aspiration pneumonia and other related infections. Among those who survive hypoxic insult to the brain, the most serious neurological sequelae are mental retardation, epilepsy and cerebral palsy which are seen in about 80%, about 10% develop moderate disabilities and only 10% are free from neurological complications [10]. Our study also shows similar trends with 82% (37 out of 45) of cases having manifested with major neurological complications (Table 2).

Early diagnosis of PVL is particularly important since clinical substantiation of ischemic brain damage is difficult as the neonate usually presents with nonspecific clinical features such as seizures, hypotonia or lethargy. This has led to a greater dependence on diagnostic imaging in evaluating this condition. In our series though majority of cases had history of perinatal asphyxia and seizures, two neonates presented with hypoglycemia with subtle clinical features. Cranial ultrasonography has been in use since the early 1980s to diagnose and characterize periventricular leukomalacia in the neonatal period. With improvement in technology and expertise in sonography more information is available about the temporal profile of the sequence of events of this condition. In the acute phase, an increased echogenicity of the periventricular white matter was seen which appeared within 24 to 48 hours after the hypoxic-ischemic insult. The affected periventricular white matter was as bright as or even brighter than the choroid plexus. After four weeks, cysts appeared in the areas of increased echogenicity which subsequently resolved with the development of ventricular enlargement. Although cranial sonography has been widely used to evaluate hypoxic ischaemic brain damage in infants it also has its limitations. Studies have shown that cranial sonography can depict only 28 to 80% of histologically proved PVL [11], moreover differentiating a normal periventricular echotexture and early PVL may be difficult using sonography. Furthermore, the severity of periventricular echogenicity may not be accurately assessed by this modality. Apart from this intra- and inter-observer disagreement has been substantial in some studies [12].

With the availability of MRI early as well as late sequelae of neonatal hypoxic-ischemic brain injury has been well documented. Injury patterns seen on MRI of the brain can be divided into early and late stages. Patterns of early changes include focal or diffuse areas of restricted diffusion as seen on diffusion weighted imaging (DWI) with a corresponding reduced Apparent Diffusion Coefficient values (ADC) [13]. Such changes are seen only on DWI and may not be detected on routine T2 weighted or inversion recovery sequences. Subsequently changes seen on conventional T2 weighted and inversion recovery sequences include focal areas of increased signals in the periventricular white matter especially the peritrigonal white matter and focal areas of increased signal on T1 weighted images indicating periventricular haemorrhage. In our series 35% (16 out of 45) cases had findings of haemorrhage on MR examination. Late findings of PVL are due to loss of white matter leading to gliosis and cavitation with relative sparing of the overlying cortical mantle, this leads to dilatation of the lateral ventricle with irregularities of the ventricular walls [8]. We had six cases of grade 6 PVL having cystic lesions in the affected region. Our results are in tandem with Miller et al where the percentages of cystic PVL are low [13]. Thinning of the posterior part of the body and splenium of the corpus callosum with upward bowing are also secondary manifestations.

Few studies have compared the neurological deficit outcome as a result of PVL vis a vis its grade. However Woodward et al [14] in their prospective study have concluded that the association of neurodevelopemental delay and grades of PVL are multifactorial. In their study of 167 very preterm infants at two years of age they have found moderate to severe useful markers for the elevated risk of severe cognitive delay, severe psychomotor delay, cerebral palsy and neurosensory impairment. Postnatal use of dexamethasone was a significant factor in deciding the final outcome.

Diffusion-weighted MR imaging (DWI) has already become an accepted protocol to evaluate cerebral damage after acute stroke in adults, however its role in evaluation of neonates with hypoxic injury to the brain is less well assessed. Studies have shown that DWI reveals areas of hyperintensities in the periventricular and deep white of the brain with a corresponding decrease in apparent diffusion coefficient (ADC) values when cranial sonography and conventional MRI are normal, this is consistent with areas of restricted diffusion as seen in early ischaemic injury [15]. Cerebral

ischaemia causes depletion of cellular energy stores which leads to failure of the Na-K/ ATPase ionic membrane pump which causes shift of water molecules from the extracellular to the intracellular compartment, thereby decreasing the diffusion of water. This can be visualized immediately after the insult using DWI, which shows hyperintense signals with a corresponding decrease of the ADC values. These findings have been confirmed on neuro-histopathological examination on autopsy specimens, which has established that apart from neuronal degeneration in these regions there was also intracellular oedema also [16].

Proton MR Spectroscopy (H-MRS) has further supplemented the findings of conventional and DW imaging in hypoxic-ischaemic brain injury. MRS of the affected regions of the neonatal brain have revealed an indirect evidence of neuronal damage by showing a decrease in the N-acetyl- aspartate (NAA) levels and increase in NAA to choline and creatine ratios. Accumulation of lactate is readily identified on MR spectroscopy as an increase in lactate peaks which occurs when oxidative phosphorylation is impaired and anaerobic glycolysis is enhanced, as in acute ischaemia [17]. Thus the findings on proton MR spectroscopy further support the view that the cerebral white matter lesions identified on seen on DWI was ischaemic.

Abnormalities in tone and movement associated with PVL have been attributed to injury to the descending corticospinal tracts. In our series 28 of 45 cases had spastic di or quadriplegia. However, damage to these pathways has not been clearly demonstrated by conventional MRI as it cannot differentiate individual WM tracts. White matter tractography is a recently developed rapidly evolving MR technique, based on diffusion tensor imaging (DTI) which can spatially map specific white matter tracts to provide neuroanatomic localization. We did not have this feature in our MR machine and hence did not use it in these cases. It appears that this modality may have a significant role to play in the evaluation of early PVL as studies done in preterm newborns with perinatal hypoxia have revealed white matter tract damage before clinical motor impairment is obvious [18]. DTI imaging of white matter in children with cerebral palsy is a technique which has great potential and will be helpful in the understanding of the pathophysiology of motor disability in this condition.

The main differential diagnosis affecting children is that of leukodystrophies like adenoleukodystrophy. However they have in common a genetic origin and involve the peripheral as well as the central nervous system. Each is caused by a specific inherited biochemical defect in the metabolism of myelin proteolipids that results in abnormal accumulation of a metabolite in brain tissue. Progressive visual failure, mental deterioration and spastic paralysis develop early in life however variants of these diseases have a more delayed onset and a less progressive course. The clinical profile, pattern of contrast enhancement and use of MR spectroscopy can help in making a certain diagnosis.

Metabolic disorders like Lowe's syndrome and Hurler's disease are associated with cystic changes in the cerebral white matter. However the location of lesions in the brain, systemic skeletal manifestations and biochemical abnormality can help in reaching the correct diagnosis.

The involvement in PVL tends to be symmetrical and is often associated with regional loss of white matter volume and ventricular dilatation. The lesions have scalloped outer margins, and the ventricular surface may also be irregular due to coalescence of cystic components with the adjacent ventricles as in grade 6 lesions.

The maturation of white matter in the region of centrum semiovale progresses nearly all subjects have an area of hyperintensity in the region lateral to the ventricles, more prominently dorsal and superior to the lateral ventricular trigone on T2W sequence. It is proposed that these areas are due to delayed mylination of the fibre tracts of association areas of posterior and inferior parietal and posterior temporal cortex. These areas were named as 'terminal zones' by Yakovlev and Lecours. However PVL can be distinguished from the terminal zone by certain characteristics like more sharp definition, its location more inferior as well as lateral to the trigone and near to optic radiation. In addition PVL is very bright in T2W sequence and since there is loss of brain matter there is irregularity of ventircular wall, abnormally deep cortical sulci with the cortex sometimes extending to the ventricular surface. Lastly, a layer of white matter intervening the ventricular wall and the area of brightness is seen in terminal zone and it is missing in case of PVL.

Large Circhow-Robin spaces in this region can also sometimes confuse the interpretor. However all such subjects show no neurological deficit and the lesion follows cerebro-spinal fluid intensity on all sequences.

Thus MRI with its advanced imaging techniques is the ideal imaging modality to detect, quantify and accurately map the areas of brain affected by this hypoxic ischemic process, it can detect from the subtle to the most obvious changes associated with hypoxic – ischaemic injury to the brain. Newer additions in MR imaging like DWI, H-MR spectroscopy and diffusion tensor imaging of the white matter tracts are adding a

new dimension in understanding this disease process and its management.

Conflicts of Interest

None identified

Intellectual Contribution of Authors

Study Concept : Gp Capt A Alam
Drafting & Manuscript Revision : Wg Cdr S Sahu
Statistical Analysis : Wg Cdr S Sahu
Study Supervision : Gp Capt A Alam

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