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## Role of MRI in the evaluation of white matter diseases of Brain

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### Abstract

**Aim:** The role of magnetic resonance imaging in evaluation of white matter diseases and in their early diagnosis.

**Methods:** 50 patients who were clinically suspected of white matter diseases underwent MR imaging using 1.5T scanner (SIEMENS MAGNETOM Aera) in this prospective study period of 2 years in the Department of Radio-diagnosis, Guru Nanak Dev Hospital, Amritsar. Patients from all the age groups including both sexes were included.

**Results:** Out of 50 cases examined, there were 23 cases (46%) of hypoxic ischemic encephalopathy, 10 cases (20%) of multiple sclerosis, 6 cases (12%) of posterior reversible encephalopathy syndrome, 3 cases (6%) each of metachromatic leukodystrophy and progressive multifocal leukoencephalopathy, 2 cases (4%) of acute disseminated encephalomyelitis and 1 case (2%) each of Canavan's disease, Pelizaeus-Merzbacher Disease and central pontine myelinolysis. Slight male predominance (58%) was seen with most of the cases of pediatric age group (62%). The most commonly involved part was supratentorial region in 76% cases with asymmetric pattern of distribution seen in 84%.

**Conclusions:** MRI is very sensitive in detecting subtle white matter lesions, FLAIR sequence further enhances its sensitivity. The present study concludes that MRI in conjunction with clinical findings, plays a pivotal role in the identification, localization and characterization of underlying white matter pathology and its further follow up.

**Keywords:** MRI, white matter diseases, hypoxic ischemic encephalopathy, multiple sclerosis.

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### Introduction

With the application of MRI in clinical aspect, it became obvious that we are being given the very modest amount of information by CT on diverse diseases involving white matter.<sup>1</sup> MRI has practically replaced all other imaging modalities in the evaluation of white matter pathologies as it provides brilliant gray-white matter differentiation and also has multiplanar imaging capability and these properties make it the modality of choice in demyelinating diseases.<sup>2</sup> MRI can provide unparalleled structural and

even functional information with so many available pulse sequences that allow detailed investigation of the various properties of different pathological tissues.<sup>3</sup> Our understanding towards the approach to demyelinating diseases has drastically altered since the introduction of MRI. Use of structural and metabolic quantitative MRI techniques, such as magnetization transfer MRI, diffusion-weighted MRI and proton MR spectroscopy, is on the rise in the study of white matter pathologies, which can provide us unimaginable information regarding underlying pathologies.

A wide-ranging number of pathologies affect white matter. Histologically, white matter disorders are typically divided into two groups: Dysmyelinating diseases and Demyelinating diseases. Dysmyelinating disorders, aka Leukodystrophies, result from an inherited enzyme deficiency which will lead to the defective formation, turn-over or maintenance of myelin and the Demyelinating diseases literally imply a loss of myelin due to the primary involvement of oligodendroglia or myelin membranes. Most of the Dysmyelinating disorders are of metabolic cause and usually occur in infants. While in older and adult children, white matter diseases are generally of demyelinating type or the combination of both.<sup>3,4</sup> Recognizing various MRI patterns of the disease is important to systematically explore all the important details of the abnormalities on MR images to reach the particular diagnosis.<sup>5</sup> When white matter disease is encountered in an imaging study, characterization of the white matter involvement as multifocal, confluent/diffuse or selective, becomes very useful approach. This approach, combined with the clinical information of patient's demographics, clinical history, and physical findings, helps the radiologist to narrow down the differential diagnosis.<sup>6</sup>

### Aims and Objectives

- To evaluate the role of magnetic resonance imaging in white matter diseases.
- To establish an accurate diagnosis and to narrow down the differential diagnosis of various white matter diseases.
- To assess the severity and extent of the underlying lesion in various conditions of white matter diseases.

### Materials and Methods

The study was conducted after approval from the institutional thesis and ethical committee. The main

source of data for the study is patients from Guru Nanak Dev Hospital attached to Government Medical College, Amritsar.

50 patients were randomly selected from the referred patients with the clinical suspicion of white matter disorders and imaging was done using SIEMENS MAGNETOM Aera 1.5 Tesla Machine in the Department of Radiodiagnosis of Guru Nanak Dev Hospital, Amritsar. Informed consent was taken after explaining about and before any procedure in the vernacular language of patient.

#### Inclusion Criteria:

- Patients with clinical suspicion of white matter diseases.
- Incidental finding of white matter diseases/ lesions.
- Patients of all age groups.

#### Exclusion Criteria:

The study excluded:

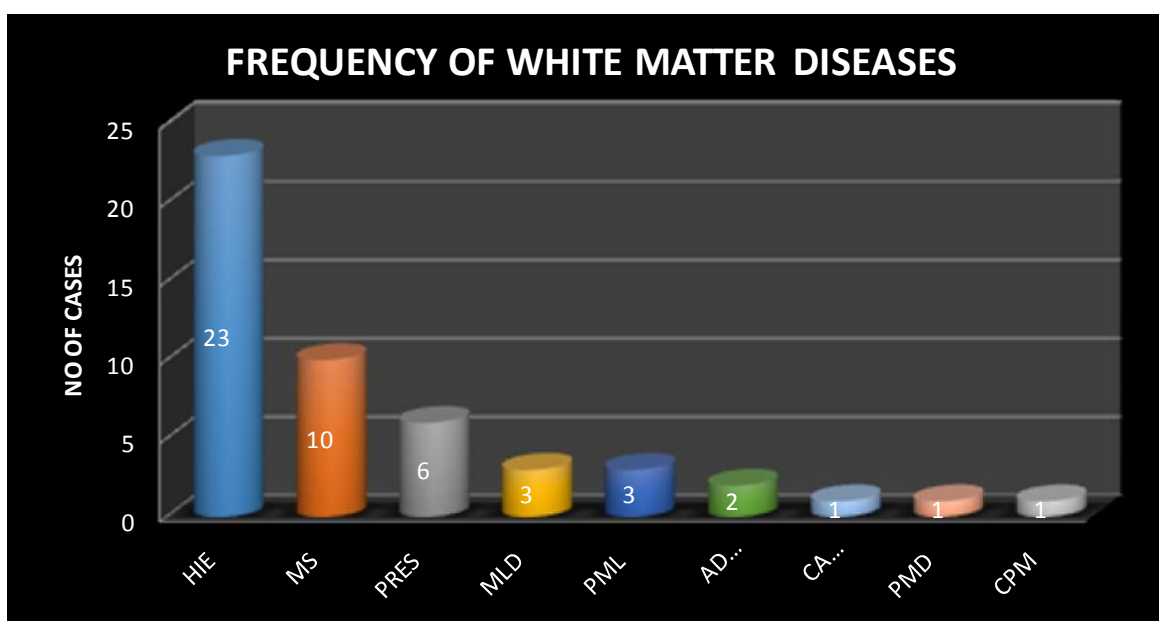
- Patients with age related ischemic demyelination and post-traumatic white matter injury.
- Patients having history of claustrophobia, metallic implants and who refused to give consent for MR imaging.

T1W, T2W, FLAIR, sequences were obtained in each patient in various planes. DWI, SWI and MR spectroscopy were included in the study when required. Contrast (Gadolinium-DTPA) at dose of 0.1mmol/kg body weight was given wherever necessary. None of the patients had any adverse reactions following Gadolinium injections.

**Observations and Results**

**Table 1: Incidence and frequency of various white matter diseases (n=50)**

SR NO.	DIAGNOSIS	NO. OF CASES	PERCENTAGE (%)
1	HIE	23	46
2	MS	10	20
3	PRES	6	12
4	MLD	3	6
5	PML	3	6
6	ADEM	2	4
7	CANAVAN'S DISEASE	1	2
8	PMD	1	2
9	CPM	1	2
	<b>TOTAL</b>	<b>50</b>	<b>100</b>

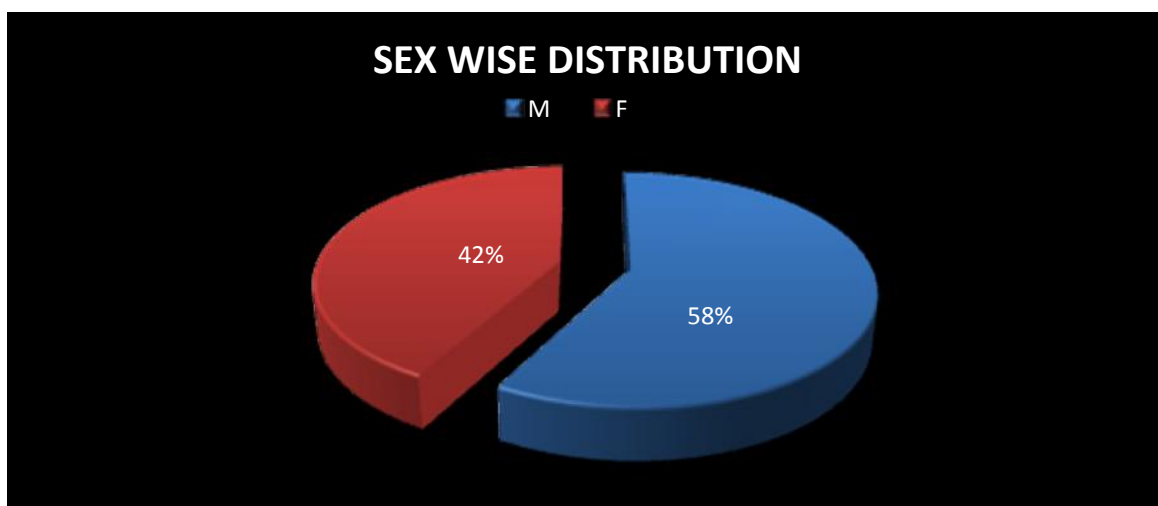


**COMMENTS:** The most common disease encountered in the age group below 20years was hypoxic ischemic encephalopathy which was seen in

23 patients (46%) and in age group above 20 years was multiple sclerosis which was seen in 10 patients (20%).

**Table 2: Sex distribution of cases (n=50)**

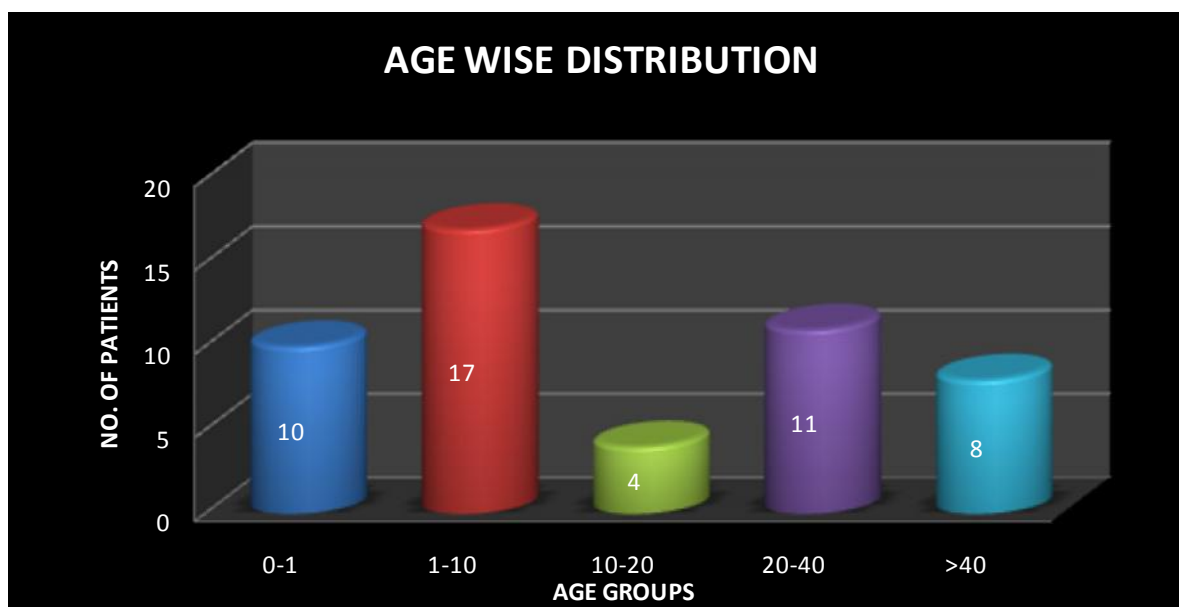
SR NO.	SEX	NO. OF CASES	PERCENTAGE (%)
1	M	29	58
2	F	21	42
	<b>TOTAL</b>	<b>50</b>	<b>100</b>



**COMMENTS:** White matter diseases were more common in males (58%) than in females (42%) with a sex ratio of 1.38:1.

**Table 3: Age distribution of cases (n=50)**

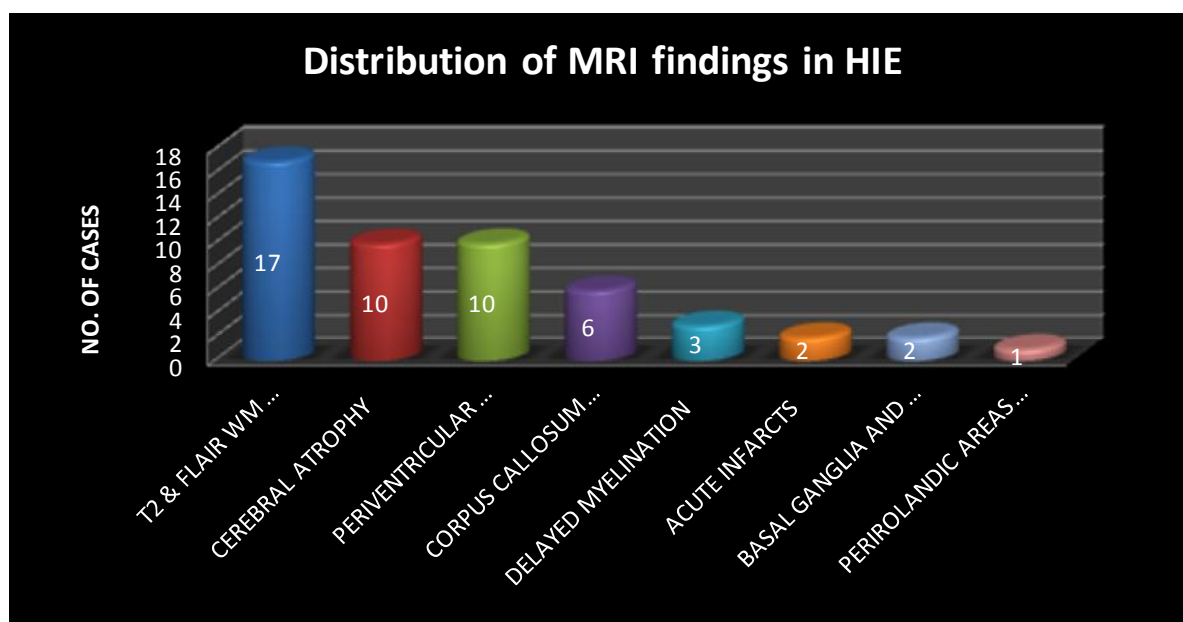
SR NO.	AGE GROUPS (YEARS)	NO. OF PATIENTS	PERCENTAGE (%)
1	0-1	10	20
2	1-10	17	34
3	10-20	4	8
4	20-40	11	22
5	>40	8	16
	<b>TOTAL</b>	<b>50</b>	<b>100</b>



**COMMENTS:** The commonest age group affected was 1-10 years (34%).

**Table 4: Distribution of MRI findings in HIE (n=23):**

SR NO.	MRI FINDINGS	NO. OF CASES	PERCENTAGE (%)
1	T2 & FLAIR WM HYPERINTENSITIES	17	73.91
2	CEREBRAL ATROPHY	10	43.47
3	PERIVENTRICULAR LEUKOMALACIA	10	43.47
4	CORPUS CALLOSUM THINNING	6	26.08
5	DELAYED MYELINATION	3	13.04
6	ACUTE INFARCTS	2	8.69
7	BASAL GANGLIA AND THALAMI	2	8.69
8	PERIROLANDIC AREAS HYPERINTENSITIES	1	4.34



**COMMENTS:** Out of 23 cases of HIE, T2 and FLAIR white matter hyperintensities were seen in the maximum number of cases (17) followed by cerebral atrophy (10 cases) and periventricular leukomalacia (10 cases).

**Discussion**

**Normal Myelination**

Normal brain myelination is a dynamic process that begins by the fifth month of fetal life and takes place

rapidly during the first 2 years, by which time it is nearly completed. In general, myelination progresses from caudal to cephalad, from dorsal to ventral and from central to peripheral.<sup>7</sup>

**MR Myelination milestones:**

Structure	High Signal (T1WI)	Low Signal (T2WI)
Posterior fossa:		
Dorsal Medulla/ Mid Brain	Birth	Birth
Sup & Inf. Cerebellar Peduncles	Birth	Birth
Middle Cerebellar Peduncles	1 month	3 months
Cerebellar White Matter	1 to 3 Months	8 to 18 Months
Supratentorial:		
Internal Capsule		
Posterior limb	Birth	Birth
Anterior limb	3 Month	3-6 Month
Thalamus	Birth	Birth
Pre/Post Central Gyri	1 Month	8-12 Months
Corpus Callosum		
Splenum	3-4 Months	6 Months
Genu	6 Months	8 Months
Centrum Semiovale	Birth to 1 Month	3 Months
Optic Radiation	3Months	3Months
Subcortical U-Fibers	3-8 Months	8-18 Months
	(Occipital First)	(Frontal Last)

In the study, out of these 50 patients, 29 were males (58%) and 21 were females (42%). The most common age group affected was between 1-10years (17 cases) (34%). The most common disease encountered in the age group below 20 years was hypoxic ischemic encephalopathy and in age group above 20 years was multiple sclerosis. These findings were comparable with the findings of Lakhkar et al, Ahsan et al and Arora et al where multiple sclerosis was the most common white matter disease in their studies with mean age groups of 27.6 years, 33 years and 24.7 years respectively.<sup>2,8,9</sup> Also, with the studies done by Khaldkar et al, Conolly et al on hypoxic ischemic encephalopathy in which most commonly affected age group was 1-5 years.<sup>10,11</sup>

In the study, we found that FLAIR sequences had a better sensitivity for subtle demyelinating foci especially those with periventricular locations thus correlating with the study done by Ashikaga et al.<sup>12</sup>

The supratentorial neuroparenchyma (38 cases) (76%) was most commonly involved in our study. Under distribution, the periventricular white matter (28 cases) (56%) was most commonly involved. Asymmetric pattern of involvement was most common and seen in 42 cases (84%) compared to symmetric involvement

which was seen in 8 cases (16%). These findings correlate well with the similar studies done by Lakhkar et al, Ahsan et al and Arora et al.<sup>2,8,9</sup>

Intravenous contrast was administered in all the cases of multiple sclerosis (10 patients), progressive multiple leukoencephalopathy (3 patients) and acute disseminated encephalomyelitis (2 patients). 2 cases (20%) of multiple sclerosis and 1 case of ADEM (50%) showed enhancement of lesions. No enhancement is seen in any case of PML in our study. There was no incidence of any contrast reaction noted in this study.

**Hypoxic Ischaemic Encephalopathy** was diagnosed in 23 of the 50 cases (46%) in the study and was most common diagnosis in the age group of less than 20 years. 18 of these were males (78.26%) and 5 females (21.73%) with a ratio of 3.1:1. These findings were consistent with that Lakhkar et al who showed a 3:1 male predominance in their study.<sup>2</sup> Also with the study of Qureshi et al in which 79.6% of cases were males and 20.4% were females.<sup>13</sup>

Maximum patients of HIE were of age group 1-10 years correlating with the study of Khaldkar et al and Conolly et al in which maximum patients were between the age group of 1 to 5 years.<sup>10,11</sup>

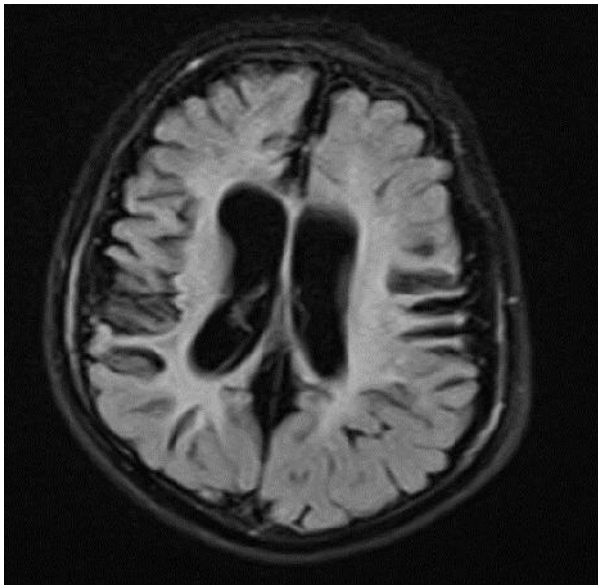


In our study, 13 patients (56.52%) were preterm neonates and 10 patients (43.47%) were term neonates. In the study done by Khaldkar et al on 100 patients 36% patients were preterms and 64% had term.<sup>10</sup> In another study done by Qureshi et al on 181 infants, 77.9% were full term and 19.1% were premature.<sup>13</sup> The variation in the results of our study from these studies can be due to the difference in the sample size.

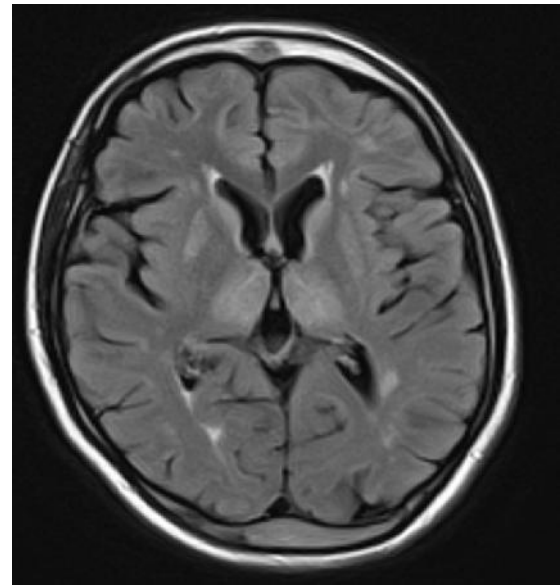
Most common MRI finding was hyperintense signals on T2W and FLAIR images involving the periventricular and subcortical white matter and was seen in 17 cases (73.91%) followed by Cerebral atrophy in 10 cases (43.47%), Periventricular leukomalacia in 10 cases (43.47%), Corpus Callosum thinning in 6 cases (26.08%), Delayed myelination in 3 cases (13.04%), Acute infarcts in 2 cases (8.69%) and Bilateral basal ganglia and thalamic involvement in 2 cases (8.69%). Periorlandic white matter hyperintensities were seen in 1 case (4.34%). Our study correlates well with the study done by Khaldkar et al

on 100 patients of perinatal asphyxia in which they found that maximum number of cases showed generalized cerebral atrophy (61%), followed by T2W hyperintensities (50%), cystic encephalomalacia (44%), delayed myelination (39%), corpus callosum thinning (33%), acute infarcts (19%), cerebellar atrophy (17%), periventricular leukomalacia (12%) and germinal matrix hemorrhage (0.3%).<sup>10</sup> The variation in the results can be due to the difference in the sample size.

In our study, 5 (21.74%) out of 23 patients presented with cerebral palsy. 3 (60%) of these were preterm and 2 (40%) patients were full term. Periventricular leukomalacia was seen in all the three preterm patients. Cerebral atrophy and corpus callosum thinning seen in two of these three preterm patients. T2 hyperintensities were seen in both of the full term patients suffering from cerebral palsy. Our findings correlate with the findings of Khaldkar et al and Truwit et al.<sup>10,14</sup>



(a)



(b)

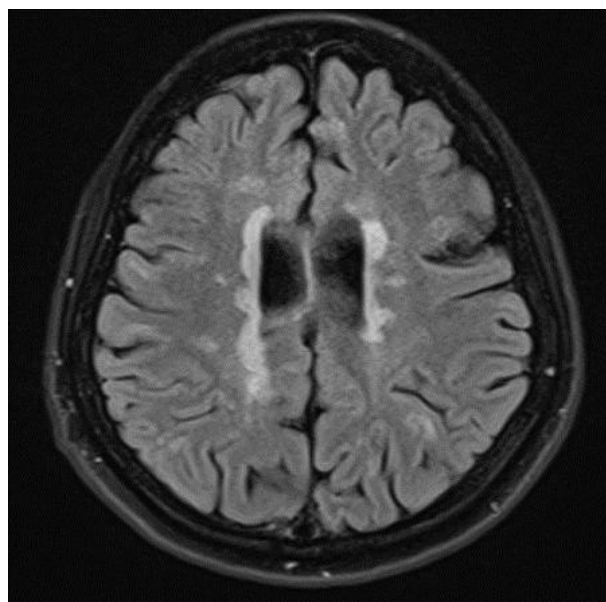
**Figure 1 :** (a) Axial FLAIR image in a patient with history of birth asphyxia demonstrating dilated sulcal spaces, thinning of cortex and paucity of white matter in subcortical and periventricular regions, gliotic changes and cerebral cortical atrophy. (b) Axial FLAIR image at ganglionic level in another patient showing hyperintense signals in the lentiform nucleus and thalami, consistent with severe HIE.

**Multiple Sclerosis** was diagnosed in 10 patients (20%) and was the most common white matter disease in the age group above 20 years. 8 (80%) of the 10 patients were females and 2 (20%) males. 6 (60%) of these patients were in age group of 20-40 years and 4 (40%) were in age group more than 40 years. These findings were consistent with that of Lakhkar et al and Mani et al who suggested that there is a definite female predominance of the disease in Indian population.<sup>2,15</sup> The most common presenting complaint in our study was limb weakness with loss of balance (7 patients) (70%) followed by blurring of vision (4 patients) (40%). Visual impairment was the commonest initial symptom in the study of Lakhkar et al (73.3%) and Mani et al (47%) followed by weakness in 46.6% and 27% patients respectively.<sup>2,15</sup> The variation in our study can be due to small sample size.

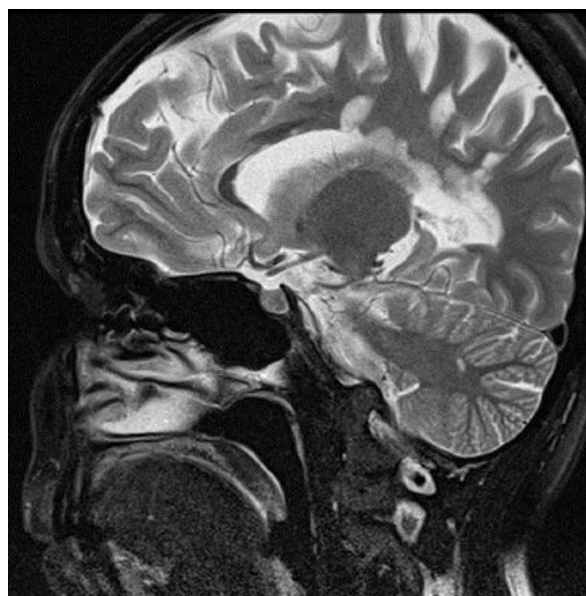
The most common site of lesion in cases of MS in our study was the periventricular area with Dawson's

fingers periventricular extension, seen in 8 patients (70%) showing as bilateral periventricular hyperintensities on T2 and FLAIR images which were hypointense on T1 weighted images. In their study, Offenbacher et al have also noted the periventricular area as the commonest location. These lesions were in the range of 10mm in size.<sup>16</sup> Other sites of involvement in our study were brainstem (20%) (2 patients), cerebellum (30%) (3 patients) and optic nerve (1 patient) (10%). Cord involvement was noted in 2 cases (20%). Our study correlated with the study of Lakhar et al and Offenbacher et al who had also noted the periventricular area as the commonest location.<sup>2,16</sup> Lakhar et al found brain stem (40%), cerebellum (6.6%), spinal cord (20%) and cerebellum (20%) to be commonly involved sites.

On contrast study, patchy enhancement of few lesions was seen in two patients (20%). On Proton MR Spectroscopy, we found reduced N-acetyl aspartate levels and increased choline levels correlating with the study of Katdare et al and Geurts et al.<sup>17,18</sup>



(a)



(b)

**Figure 2:** (a) Axial FLAIR images showing hyperintense plaques in the b/corona radiata and the periventricular location of confluent hyperintense plaques, (b) T2 Sagittal image demonstrating hyperintense lesions arranged perpendicular to the lateral ventricle giving the typical appearance of Dawson's Fingers d/t periventricular extension.

**Posterior reversible encephalopathy syndrome** was diagnosed in 6 (12%) patients in this study. 5 of them were females (83.34%) and 1 of them was male (20%) and age group varied through a wide range of 19-61 years. 4 patients (66.66%) had features of

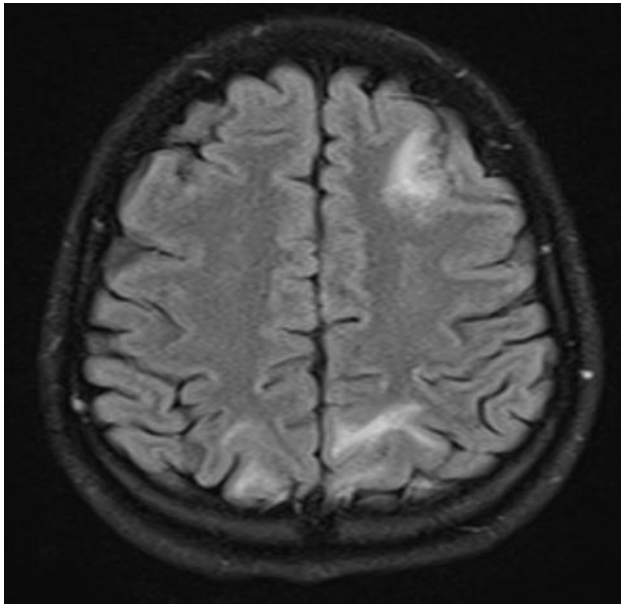
pregnancy induced hypertension. Other patients were found to have predisposing conditions like uncontrolled hypertension (1 patient) (16.67%), chronic renal failure (1 patient) (16.67%) and SLE (1 patient) (16.67%).



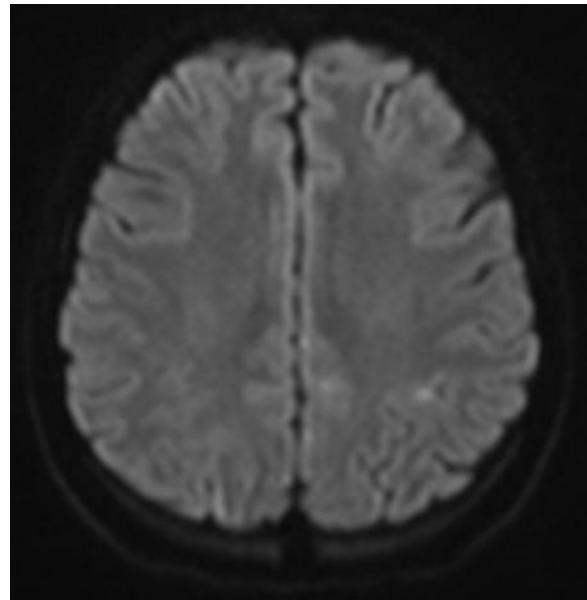
The most common clinical presentation was headache (6 patients)(100%), seizures (5 patients)(83.33%), altered sensorium (4 patients)(66.66%) and blurred vision(3 patients )(50%) correlating with the study of Raman et al and Fugate et al.<sup>19,20</sup>

MRI findings showed areas of high signal intensities with a fairly symmetric pattern. The most commonly involved area was the parietal lobe white matter (100%), followed by occipital lobes (83.33%) and

frontal lobes (83.33%). Cerebellar deep matter involvement was seen in 1 patient (16.66%). These findings were consistent with Raman et al who also found the parieto-occipital lobes to be most commonly involved (100%) followed by frontal lobes (30.4%) and also with the study of Fugate et al in which parieto-occipital lobes were most commonly involved (94%) followed by frontal lobe (77%).<sup>19,20</sup> All the patients recovered clinically completely.



(a)



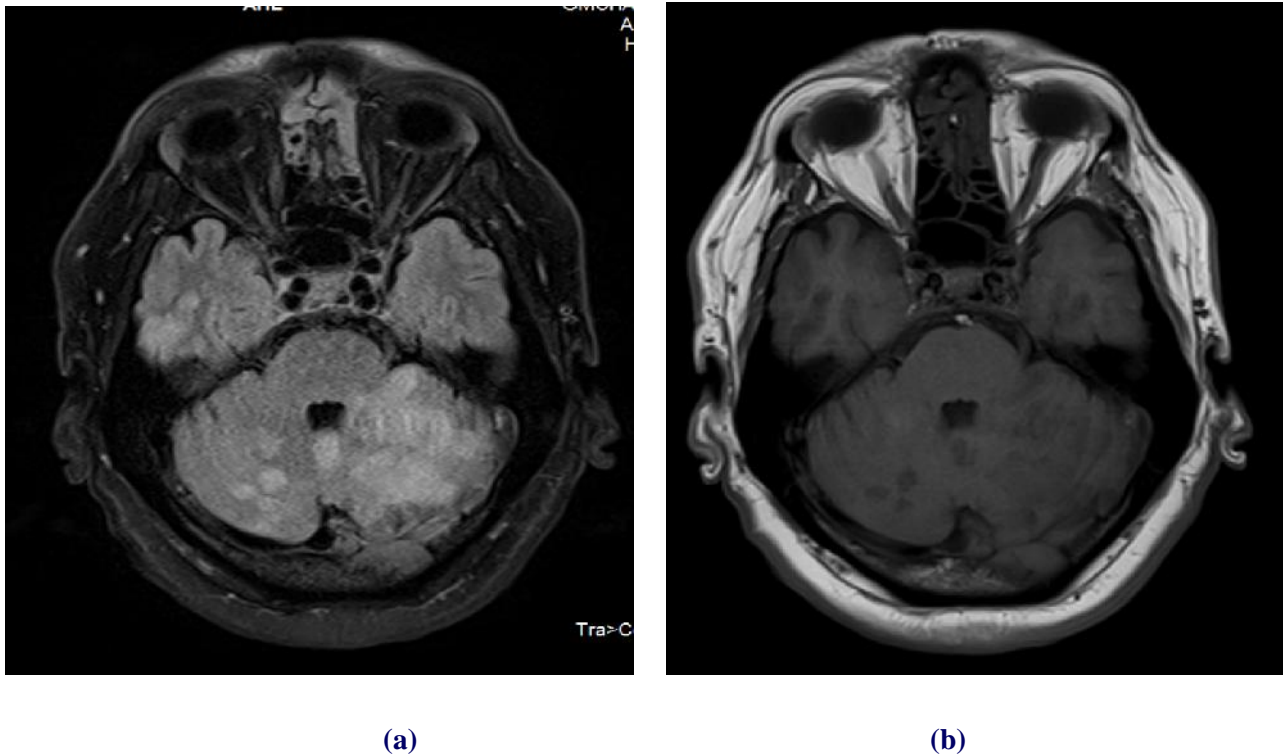
(b)

**Figure 3:** (a) Axial FLAIR, (b) Axial DWI images in a 19 yr old gravid female with sudden onset headache images showing hyperintense signals in subcortical white matter of bilateral parietal lobes at parasagittal regions which show no diffusion restriction.

**Progressive multifocal leukoencephalopathy** was diagnosed in 3 patients (6%) in our study. All were HIV positive, 2 males and 1 female with age range of 30-45 years. This finding was consistent with the study of Krupp LB et al who reported that PML has a stronger association with AIDS than with any other disease.<sup>21</sup> The most common clinical presentation was motor weakness and seen in 2 patients (66.6%) followed by convulsions in 1 patient (33.34%) correlating with Augusto et al.<sup>22</sup>

On MRI, subcortical and deep fronto-parietal white matter involving subcortical U-fibers was involved in

all 3 patients (100%). 1 patient (33.34%) showed the involvement of the posterior fossa by asymmetrically involving cerebellar deep white matter. 1 patient (33.34%) showed a restriction on DWI. No contrast enhancement was seen in any of the cases. No associated mass effect was seen with lesions. Our findings correlate with findings of Lakhar et al, Augusto et al and Gowdar et al which revealed multifocal bilateral parietal, occipital, periventricular, subcortical U fibres, deep gray matter and bilateral cerebellar white matter hyperintensities on T2 weighted and FLAIR images.<sup>2,22,23</sup>

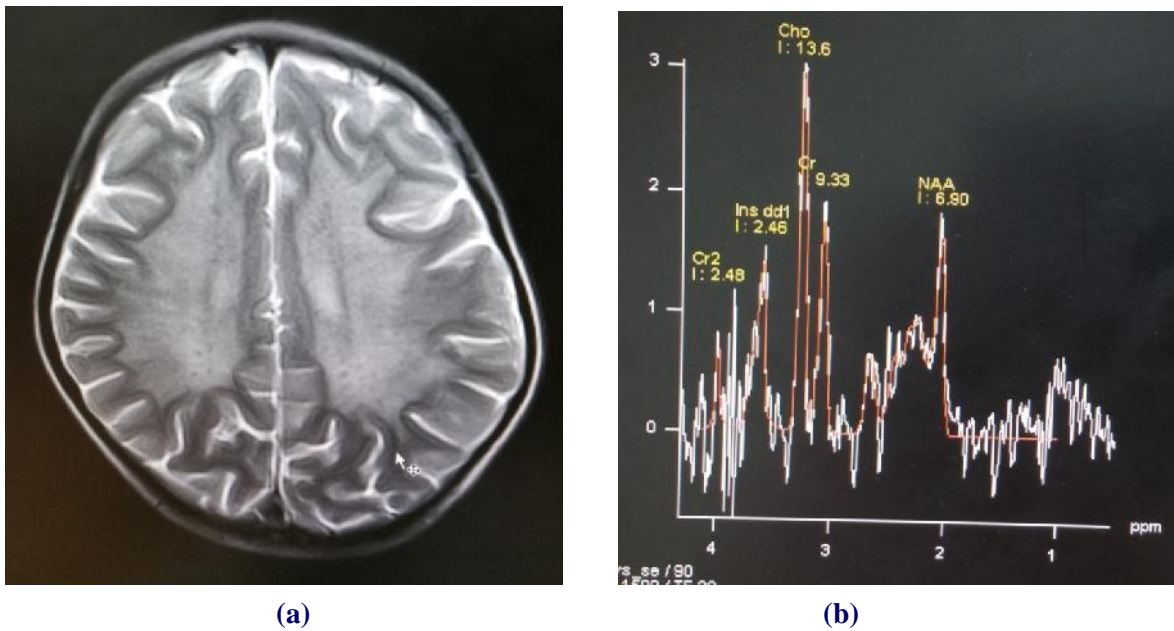


**FIGURE 4 :** In an immunocompromised female, with sudden onset cerebellar signs (a) Axial FLAIR images showing asymmetrical, multifocal hyperintense lesions involving the bilateral cerebellar white matter (L>R) and left middle cerebellar peduncle. Lesions are also seen involving right temporal lobe. No mass effect is seen (b) Corresponding Axial T1 image show hypointense lesions in subcortical white matter.

**Metachromatic leukodystrophy** was diagnosed in 3 patients (6%) . All of them were males, age group being in the range of 1 to 3 years that comes under the late infantile type of MLD correlating with the study of Kim et al.<sup>24</sup> Clinical presentations were in the form of seizures, progressive limb weakness, loss of head control, deterioration in vision and behavioral changes.

MRI of all these patients (100%) showed bilaterally symmetrical confluent hyperintensities involving

bilateral supratentorial periventricular white matter giving tigroid pattern predominantly in fronto-parieto-occipital lobes. These findings were consistent with those of Kim et al who showed bilateral, symmetrical and confluent high signal intensities on T2 weighted imaging.<sup>24</sup>They reported 100% incidence of periventricular white matter and centrum semiovale involvement. The diagnosis was biochemically confirmed in these patients showing reduced serum aryl sulfatase levels.



**FIGURE 5:** (a) Axial T2W in an child showing bilaterally symmetrical and confluent areas of hyperintense signals in fronto-parietal periventricular deep white matter regions with sparing of Subcortical U- fibres with mild corticocerebral atrophy. (b) Proton MRS revealing decreased NAA and elevated choline levels.

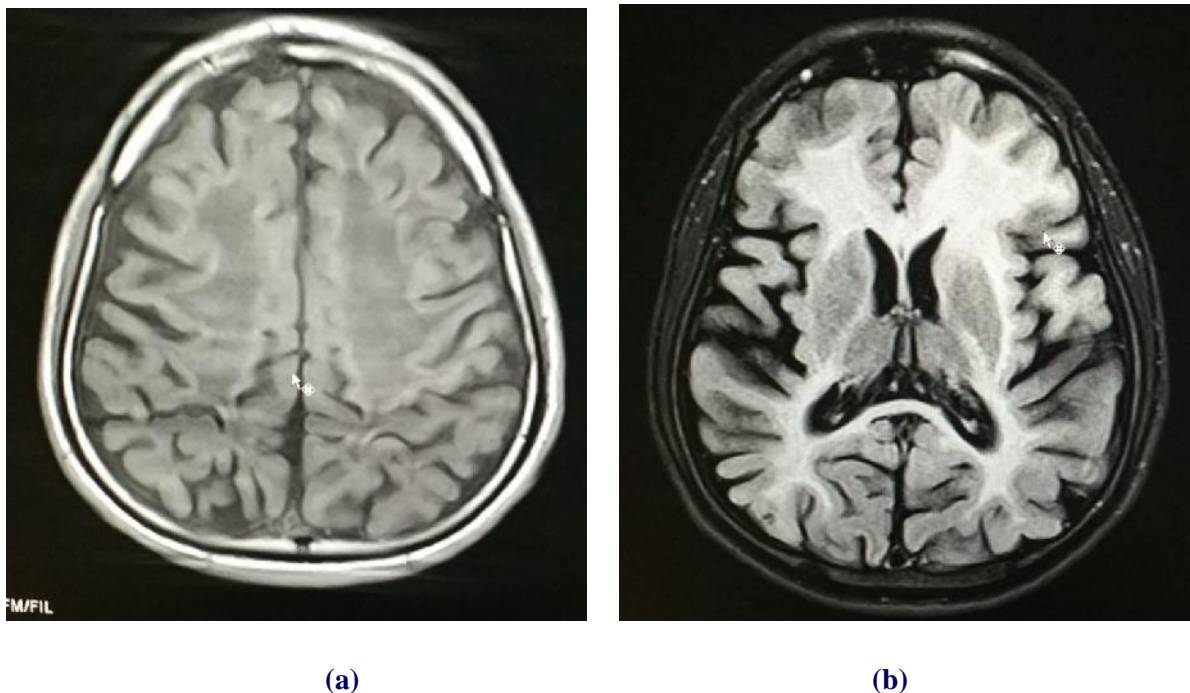
**Acute disseminated encephalomyelitis** was seen in 2 (4%) patients in our study, both having a history of fever. The age group involved was of a pediatric group of which 1 was male and 1 female. One of them had a history of immunization. Both (100%) of them presented with altered sensorium, while one (50%) of them had convulsions. Gowder et al and Elhassanien et al in their study found that ADEM most commonly occurs in the pediatric age group of about 2-16 years.<sup>23,25</sup>

On MRI of these cases hyperintense lesions were seen on T2W and FLAIR images which were located in the supratentorial cerebral white matter of fronto-parieto-temporal regions involving subcortical U-fibers in both cases (100%) and both supra and infratentorial white matter in 1 patient (50%), with asymmetric and patchy involvement. Brainstem involvement was seen in 1 patient (50%). Thalamus was also involved in 1 case (50%). Patchy and ring type enhancement is seen in one (50%) of the cases. These findings were comparable with those Gowder et al. Their MRI findings included hyperintense lesions involving bilateral frontal (75%), parietal (62.5%), temporal (50%), occipital (25%), deep grey matter (12.5%), periventricular region (37.5%), subcortical U fibres (50%), cerebellar white matter (50%) and brain stem (50%).<sup>23</sup>

**Canavan's disease** was diagnosed in 1 patient (2%), a 1.6 year old male child with gradual decrease in

activity, interaction, neuroregression and macrocephaly. MRI showed the complete involvement of supra and infratentorial white matter. No lobar predominance of white matter abnormalities seen. These abnormal areas showed hypointense signal on T1W and hyperintense signal on T2W images. MR spectroscopy showed marked increase in N-acetyl aspartate peak. Our findings were consistent with the study of Michel and Given and with Karimzadeh et al in which they reported symmetric white matter hyperintensities at T2 weighted brain MRI images and found peaks of NAA on MRS even before any evidence of NAA in serum and urine.<sup>26,27</sup>

**Pelizaeus-Merzbacher Disease** was diagnosed in 1 patient (2%). A 6 years old male child presenting with difficulty in speech, abnormal eye movements, gradual onset quadriparesis. MRI showed hyperintense signals on T2W images diffusely in the whole cerebral white matter. Diffuse Cerebral and cerebellar atrophy was also noted. MRS showed normal values of NAA and Choline. No abnormal peak was noted. Our findings correlate with the study of Nezu et al who studied 4 cases of PMD and suggested three subtypes on basis of patterns of the disease.<sup>28</sup> Our case findings are consisting of their type II pattern of hyperintensity that is involving hemispheres diffusely without brainstem lesions and also proton MRS in their study revealed no apparent abnormal peaks.



**Figure 6:** In a 6 years old male patient with visual impairment, (a) Axial T1W image shows diffuse symmetrical hypointense signal involving cerebral white matter indicating lack of myelination with sulcal prominence. (b) Axial FLAIR image at the ganglionic level shows paucity of white matter with diffuse cerebral atrophy.

**Central Pontine Myelinolysis** was diagnosed in 1 patient(2%), a 48 years aged male, who had definite predisposing factors like hyponatremia and alcoholism. On MRI, hyperintense lesion characteristically involving central pons with peripheral sparing was seen correlating with the findings of the study of Chatterjee et al and Musana et al, consisting of symmetric hyper signal intensity focus in the central part of the pons with an unaffected outer rim at T2-weighted and FLAIR imaging.<sup>29,30</sup>

## Conclusion

The advent of MRI has revolutionized the concept of understanding of white matter diseases. Being noninvasive and devoid of radiation hazard, MRI is considered far more superior any other modality and is considered the imaging modality of choice in white matter diseases. Its multiplanar imaging capability and excellent grey white matter resolution makes MRI very sensitive in detecting subtle white matter demyelinating foci. Correct diagnosis can be made by the conjunction of MRI findings and clinical findings alone in majority of patients and hardly confirmation by biopsy is needed. Advances in new techniques further encourage a multimodal approach with the help

of a variety of sequences sensitive to different brain tissue characteristics. Together, these techniques will be able to provide clues to the early stages of disease and hence early diagnosis.

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**Conflict of interest:** None declared

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