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Original Research Article

A retrospective study on acquired demyelinating diseases in children

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ABSTRACT

Background: Acquired demyelinating diseases (ADS) constitute a heterogeneous group of central nervous system disorders of autoimmune origin that causes significant physical and cognitive disabilities. Early recognition and prompt management causes significant improvement in acute episodes of demyelinating disorders.
Methods: 33 children diagnosed with demyelinating disorders at Lokmanya Tilal municipal medical college and hospital in Mumbai were enrolled. The study was conducted between January 2013 and November 2022. Demographic data, clinical profile, CSF study, serum antibody, radiological findings were collected and results were analyzed. Statistical Data was analysed using statistical software GraphPad in Stat.V3.0. Data were presented in tables and figures whenever needed. P value <0.05 considered as significant.
Results: Of 33 patients, 21 (63%) were cases of acute disseminated encephalomyelitis (ADEM), 6 (18.1%) of transverse myelitis (TM), 1 case of ADEM + TM (3%), 3 (9%) of neuromyelitis optica, 1 (3%) of Optic neuritis and 1 (3%) of multiple sclerosis. ADEM patients presented with encephalopathy and multifocal neurological deficits, 40% were MOG positive. Two patients were of multiphasic ADEM. Patients of transverse myelitis had paraparesis or quadriparesis and sensory + bladder involvement. Patients with NMO presented with bilateral visual impairment with limb weakness and bladder involvement. Steroids were the primary treatment, 3 patients (9%) required intravenous immunoglobulin (IVIG) and 1 (3%) patient received plasma exchange therapy.
Conclusions: ADEM is the most common ADS. Early diagnosis and management with steroids therapy improves outcome in most of the patients. Non response to steroids warrants second line treatment options like IV Immunoglobulin (IVIG) or Therapeutic plasma exchange.

Keywords: Pediatric demyelinating disorders, ADEM, Transverse myelitis, MOG

INTRODUCTION

Acquired demyelinating diseases (ADS) constitute a heterogeneous group of central nervous system disorders of autoimmune origin and cause significant physical and cognitive disabilities. The spectrum includes monophasic, multiphasic, and progressive disorders ranging from highly localized forms to multifocal or diffuse variants.[1]

Monophasic events may be classified as clinically isolated syndrome (CIS), characterized by monofocal or polyfocal deficits without encephalopathy or acute disseminated encephalomyelitis (ADEM), characterized by polyfocal deficits and encephalopathy.[2]

Recurrent disorders include multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD) and serum antibodies to myelin oligodendrocyte glycoprotein (MOG)- associated demyelination.[3] International pediatric multiple sclerosis study group (IPMSSG) has proposed the criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders for diagnosis and research purpose.[4]

Steroids causes significant improvement in acute episodes of demyelination in these disorders. However, recurrent demyelinating disorders like multiple sclerosis and NMO require long-term immunomodulation.[5] The objective of this study was to extend insight into and

improve diagnosisof these syndromes by describing their clinical, immunological and radiological features.

METHODS

Study design

Prospective plus retrospective observational study was used.

Study place

Study conducted at department of paediatrics, Lokmanya Tilak Municipal medical college and hospital, Mumbai.

Duration of study

The study conducted from January 2013 to December 2022.

Sample size

A total of 33 patients were enrolled in the study based on the sample size calculation by SPSS statistical analysis package. The sampling method used was convenience-based sampling for the study.

Inclusion criteria

All children in the age group between 1 year to 12 years who present with clinical, radiological, and immunological features of acquired demyelinating disorders were included in the study.

Exclusion criteria

Parents/ guardians not willing to give written informed consent to enrol their child in the study were excluded from the study.

Sample method

Prospective cases data was obtained from patients in pediatric care services from July 2019 to December 2022 and for retrospective cases data was obtained from prefilled proformas preserved in the department from January 2013 to July 2019. Total 33 cases were identified for acquired demyelinating syndrome and studied in detail.

The study was initiated only after institutional ethics committee permission was obtained. The study was performed in accordance with the ethical principles specified in the declaration of Helsinki and as per the guidelines of good clinical practice.

Statistical analysis

After data collection, data entry was done in a Microsoft Excel sheet. Data analysis was done with the help of statistical software GraphPad InStat.v3.0 .Data were presented in tables as well as figures, wherever needed descriptive statistics were used to note down the distribution of patients based on age, gender, patient history details, and other findings. A p value of less than 0.05 was considered significant wherever applicable.

Brief methodology details

After enrollment, demographic details such as age, sex and socioeconomic status were noted in the predesigned proforma. Patient details were noted as follows-Detailed patient history, complete physical and neurological examination and laboratory investigations-Rotine blood (CBC, liver and renal function test), serum antibodies for MOG and AQP-4, CSF analysis and MRI (brain/spine) scan.

The diagnosis of ADS was based on the acute onset of neurologic signs and symptoms together with brain MRI evidence of multifocal, hyperintense lesions on T2-weighted according to IPMSSG 2010 criterion.

RESULTS

The 33 pediatric ADS cases age group 1 to 12 years old, were analyzed.

Of these, 22 (66.6%) cases were of acquired demyelinating encephalomyelitis (ADEM), 6 (18.1%) of transverse myelitis (TM), 3 (9%) of neuromyelitis optica (NMO), 1 (3%) of optic neuritis (ON) and 1 (3%) of multiple sclerosis (MS).

The mean age of presentation was 7.7 years (range: 2-12 years).

Of 33 cases, 16 (48%) were male and 17 (51%) females with male/ female ratio of 0.9:1.

Table 1: Frequency distribution of age groups with acquired demyelinating diseases.

Age groups (Years)	ADEM (%)	TM (%)	NMO (%)	MS (%)	ON (%)	Total (%)
1 to 4	5 (22.7)	1 (16)	0 (0)	0 (0)	0 (0)	6 (18.1)
5 to 8	9 (40.9)	1 (16)	1 (33.3)	0 (0)	0 (0)	11 (33.3)
9 to 12	8 (36.3)	4 (66.6)	2 (66.6)	1	1	16 (48.4)
Total	22 (66.6)	6 (18.1)	3 (9)	1 (3)	1 (3)	33 (100)
Mean ± SD	7.04±3.09	8.5±3.34	9.16±2.3	12	12	7.7±3.07

Table 2: Frequency distribution of gender of patients with acquired demyelinating diseases.

Gender	ADEM (%)	TM (%)	NMO (%)	MS (%)	ON (%)	Total (%)
Male	14 (63.6)	1 (16.6)	0 (0)	0 (0)	1 (100)	16 (48.4)
Female	8 (36.3)	5 (83.3)	3 (100)	1 (100)	0 (0)	17 (51.1)
Total	22 (66.6)	6 (15.1)	3 (9)	1 (3)	1 (3)	33 (100)
M: F ratio	1.75:1	0.2:1	0:3	0:1	1:0	0.94

Table 3: Clinical features of pediatric demyelinating disorders.

Clinical features	ADEM, (n=22) (%)	TM, (n=6) (%)	NMO, (n=3) (%)	ON, (n=1) (%)	MS, (n=1) (%)
Encephalopathy	22 (100)	-	1 (33.3)	-	-
Seizures	7 (31.8)	-	-	-	-
Fever	4 (18.1)	-	-	-	-
Visual disturbances	-	-	3 (100)	1 (100)	-
Unilateral	-	-	-	1 (100)	-
Bilateral	-	-	3 (100)	-	-
Limb weakness	11 (50)	6 (100)	3 (100)	-	1 (100)
Hemiparesis	3 (13.6)	-	-	-	-
Paraparesis	1 (4.5)	5 (83)	3 (100)	-	-
Quadriparesis	7 (31.8)	2 (33)	-	-	1 (100)
Cerebellar signs	6 (27.2)	-	-	-	-
Sensory involvement	-	6 (100)	1 (33.3)	-	-
Meningism	14 (63.6)	-	-	-	-
Bowel and bladder involvement	2 (9)	6 (100)	2 (66.7)	-	-
Recurrent history	2 (9)	-	-	-	1 (100)

Table 4: Radiological findings of pediatric demyelinating disorders.

Radiological findings	ADEM, (n=22) (%)	LETM, (n=6) (%)	NMO, (n=3) (%)	ON, (n=1) (%)	MS, (n=1) (%)
Areas involved					
Cerebral cortex	20 (90.9)	-	2 (66.6)	-	1 (100)
Thalamus	12 (54.5)	-	1 (33.3)	-	-
Brainstem	9 (40.9)	-	2 (66.6)	-	-
Cerebellum	6 (27.2)	-	1 (33.3)	-	1 (100)
Spine	1 (4.5)	6 (100)	3 (100)	-	-
Optic nerve	-	-	3 (100)	1 (100)	-
Contrast enhancement	4 (18)	-	1 (33.3)	-	1 (100)

LETM-Longitudinally extensive transverse myelitis (>3 spinal segments); ADEM-Acute disseminated encephalomyelitis; NMO-Neuromyelitis optica; ON-Optic neuritis; MS-Multiple sclerosis.

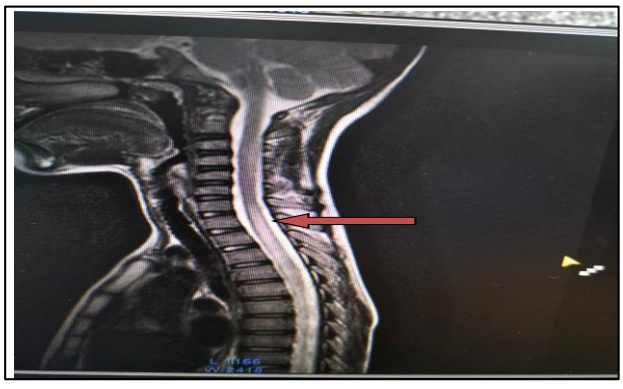

Figure 1: Long segment abnormal cord signal intensity from C7-D8 vertebral level (Longitudinally extensive transverse myelitis).

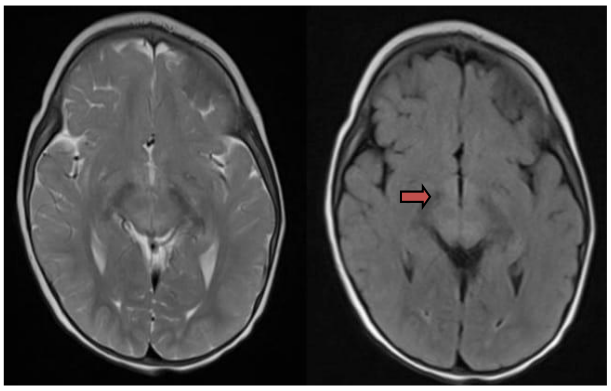

Figure 2 and 3: MRI brain-hyperintense lesions in midbrain, brainstem, visualized cervical spine.

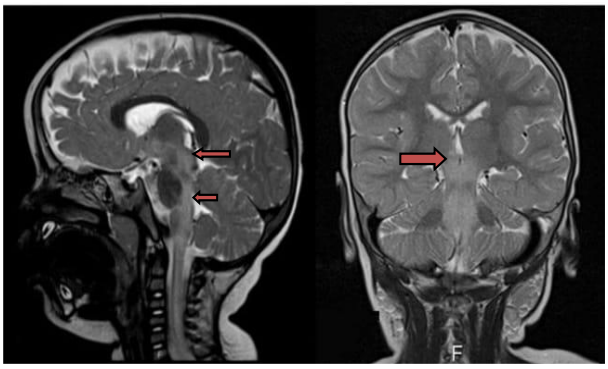

Figure 3: MRI brain-hyperintense lesions in brainstem, visualized cervical spine.

In our study out of 33 cases, 20 cases were ADEM and 2 were MDEM. The mean age of onset for ADEM was 7 years (range 1-12 year). M:F ratio was 0.9:1. History of preceding illness were present as upper respiratory infection /acute febrile illness in 19 (86.3%) and mean duration between preceding events and onset of symptoms was 7.24±2.9 days. All patients diagnosed with ADEM had encephalopathy. In 6 patients (28.6%) cranial nerves were also affected.

CSF analysis were abnormal in 67% of cases, typically showing a lymphocytic pleocytosis with an elevated protein in 47% cases. Bacterial and viral PCR were negative in all patients. CSF oligoclonal bands was positive in 2 patients with MDEM. Serum MOG antibodies done in 19 out of 22 patients and was positive in 7 (36%) patients. MOG antibody was tested in only 1 patient of MDEM which was negative. MRI Brain with spine showed T2 hyper-intensities in multiple locations in all patients with contrast enhancement in 23% patients. Areas involved in descending order of frequency were subcortical white matter (85%) cases, basal ganglia (80%), thalamus (57%), brainstem (42%), cerebellum (28%) and spinal cord involvement (5%) cases.

All patients were treated with pulse dose of methyl prednisolone followed by a short course of oral corticosteroids (OCS) for 4 weeks. The 19 (86%) patients responded to steroids. Two (9%) patients required IVIG (Intravenous immunoglobulin).

On follow up at 3 months, 3 patients out of 14 had neurocognitive deficit with recurrent headaches. Eight patients were lost to follow up.

Six patients were diagnosed as transverse myelitis with mean age of presentation of 8.5 years (range 4-12 year) and M:F ratio was 0.25:1. Four patients (66%) had respiratory infections as preceding illness and mean duration of onset of symptoms from preceding illness was 4.25±3.9 days (range 3 to 28 days). In 4 (66.6%) patients, sensory level was at the thoracic region and in 1 (16%) was at cervical region and 1 (166%) had no sensory symptoms.

CSF analysis revealed pleocytosis in 4 (66.6%) patients and elevated proteins.

MOG, NMO antibodies were negative in all patients but 1 patient was positive for serum IgG COVID antibodies. MRI spine showed spinal cord involvement in the thoracic region 4 (57%) and thoracolumbar in 1 (14%), 2 (28%) complete cord except cervical region. MRI brain was normal in all patients.

All patients with TM were treated with high dose MPS with tapering of OCS over 4-6 weeks. One patient received PLEX (Therapeutic Plasma exchange) due to non-response to IV steroids. 50% patients had residual paraparesis and bladder incontinence at the time of discharge and 16% at 3 months follow up and 2 (33.3%) patients had 100% recovery at 3 month follow up.

In our study 3 patients were diagnosed as NMO, mean age of presentation was 9.1±2.3 years, all were female in gender.

CSF analysis showed elevated cell count and proteins in 1 patient. Serum NMO antibodies were positive in two patients (66%). On MRI brain all patients had T2 hyperintensities involving multiple nonspecific areas of brain and bilateral optic nerve involvement, with spinal involvement ≥3 segments (LETM).

All 3 patients were treated with high dose MPS with slow tapering of OCS along with IVIG in one patient. Two patients were followed up at 3 months had visual impairment.

We had only 1 patient with optic neuritis, a 12-year-old with unilateral visual loss. His CSF analysis was normal; MRI brain showed unilateral enhancement of optic nerve. Child was treated with high dose MPS and tapering of OCS over 6 weeks with significant improvement in vision at 3 month follow up.

One patient was diagnosed with multiple sclerosis, a 12-year female, with quadriparesis and past history of recurrent episodes. CSF studies were normal. MRI brain studies showed T2/ FLAIR resolving bilateral cerebellar lesions and new hyperintensities involving the periventricular, pericallosal and cerebellar region involving white matter.

DISCUSSION

This study describes the clinical features, CSF analysis and radiological findings of the pediatric acquired demyelinating disorders. ADEM was the most common acquired demyelinating disorder in our study with mean age of presentation being 7 years which was similar to 5.5 and 6.14 years seen in other similar pediatric studies done by Torisu H, Singhi PD et al.[6,7]

Female preponderance in our ADEM patients was similar

to study conducted by Yamaguchi et al. Although some studies have reported equal sex distribution.[8] Most common presentation in ADEM patients was encephalopathy with multifocal motor deficit and meningism similar to other studies.[6-8] Cranial neuropathies and cerebellar signs were present in 28% patients. In our study, seizures were present in 31%, whereas study done by Hynson et al had seizure in 13% patients only. CSF abnormalities either lymphocytic pleocytosis or elevated protein content vary from 28% to 85% in various studies in our study it was 67% cases.[9]

MRI is highly sensitive in detecting white matter abnormalities and investigation of choice for demyelinating disorders. ADEM present with multiple hyperintense bilateral, asymmetric patchy and poorly marginated lesions on T2 weighted and FLAIR images on MRI. ADEM lesions typically involve the subcortical and central white matter and cortical gray white matter junction. Most of patients in our study present with subcortical white matter and brainstem involvement with occasional spinal cord involvement. Deep grey matter lesions involving basal ganglia and thalamus 54% which is similar to studies showing 49% to 60%.[6,10] Most of the patients responded well to the pulse dose of steroids on 3 month follow up.

Acute transverse myelitis should be suspected in any patient with acute spinal cord dysfunction when there is no evidence of spinal cord compression, injury, or irradiation. In our study patients with transverse myelitis present with paraparesis or quadriparesis with neurogenic bladder and sensory dysfunction. However, all pediatric TM may not present with sensory symptoms/ level.

All patients were treated with high dose methyl-prednisone, non-response was treated with IVIG and PLEX in 1 child each.

Patients with NMO presented with visual deficits, limb weakness and bladder dysfunction. Serum anti aquaporin-4 antibodies were positive in two-third of patients, similar findings were reported by Lotze et al and Collongues et al in their studies.[13,14] MRI brain with spine showed optic nerve and spinal involvement, all patients were treated with high dose steroids and IVIG. 50% patients had good outcome in our study.

Limitations

Most of the sample size is from retrospective design and hence the exact outcome of the patients in the form of degree of impairment, amount and time of recovery is not elicited. This is not a population-based study, hence bias is unavoidable, as this study included the majority of cases from the retrospective cohort group reported from a single center.

CONCLUSIONS

Children presenting with new, subacute focal neurological deficits with history of some preceding event and in absence of trauma, metabolic derangements, or structural abnormalities should be suspected of having acquired CNS demyelination. These patients should be investigated with CSF analysis, serum antibodies and neuroimaging. ADEM is the most common among ADS. Early diagnosis and management with steroid therapy improves outcome in most of the patients.

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