Clinico-radiologic Spectrum and Outcome of Pediatric Acquired Demyelinating Disorders of Central Nervous System: A Retrospective Indian Tertiary Care Hospital Cohort

Ramakrishna Prithviraj[1] Bidisha Banerjee[1] Ullas V. Acharya[2] Muhammed Hafis[3] Sruthi Sashidharan[3]

[1] Division of Paediatric Neurology, Department of Paediatrics, Manipal Hospitals, Bengaluru, Karnataka, India
[2] Division of Neuroradiology, Manipal Hospitals, Bengaluru, Karnataka, India
[3] Department of Paediatrics, Manipal Hospitals, Bengaluru, Karnataka, India

Address for correspondence Bidisha Banerjee, MD, DM, Division of Paediatric Neurology, Department of Paediatrics, Manipal Hospitals, HAL Airport Road, Bengaluru 560017, Karnataka, India (e-mail: drbidisha@yahoo.co.in).

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Abstract

Background Pediatric acquired demyelinating syndrome (ADS) constitutes a group of treatable disorders with acute neurologic dysfunction. Neuroimaging has played a significant role in diagnosis of ADS. We describe clinico-radiologic spectrum, outcomes, and comparison of the groups: acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorder (NMOSD), clinically isolated syndrome (CIS), multiple sclerosis (MS), and myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD).

Methods Retrospective review of 70 children with ADS at a tertiary care hospital over 15 years (2008–2023) was performed. Diagnosis was assigned as per International Pediatric Multiple Sclerosis Study Group criteria 2016. Fisher's exact and chi-square tests were applied.

Results Thirty-nine boys and 31 girls aged 8.2 ± 4.0 years with CIS ($n = 27$), ADEM ($n = 16$), NMOSD ($n = 13$), MS ($n = 1$), and MOGAD ($n = 13$) were included. Clinical syndromes with positive significant association included polyfocal symptoms, encephalopathy in ADEM, optic neuritis (ON) in MOGAD, brainstem, area postrema syndrome in NMOSD. MOGAD presented with atypical presentations like prolonged fever (PF; 76.9%) and aseptic meningitis (23%). Seropositivity for myelin oligodendrocyte glycoprotein immunoglobulin-G was 62% and for NMO-IgG 2.6%. Neuroimaging of MOGAD showed lesions predominantly in basal ganglia/thalami (69.2%), optic nerve (46.2%), and cerebellum (46.2%). Imaging patterns between ADEM and MOGAD were comparable except for more ON ($p = 0.004$), spinal cord ($p = 0.01$), and cerebellar lesions ($p = 0.03$) in MOGAD. Area postrema lesion was unique to NMOSD. All patients received immunotherapy, of whom 91.4% ($n = 64$) had good recovery, 8.6% ($n = 6$) had functional limitation on modified Rankin scale at discharge, and 12 (17.1%) relapsed.

Keywords
- acute disseminated encephalomyelitis
- neuromyelitis optical spectrum disorder
- clinically isolated syndrome
- MOG antibody disease
- basal ganglia/thalami

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Conclusion The largest group was CIS. Seropositivity of MOG was high with atypical presentations like PF and aseptic meningitis. Specific neuroimaging patterns correlated with ADS categories. Short-term outcome with immunotherapy was favorable in spite of relapses.

Introduction

Pediatric acquired demyelinating syndromes (ADSs) are common and constitute treatable cause of acute neurologic dysfunction. Their global incidence is lower when compared with adults, ranging from 0.6 to 1.66 per 100,000 children.[1–3] They include a broad spectrum of immune-mediated demyelinating diseases of the central nervous system (CNS), including acute disseminated encephalomyelitis (ADEM), optic neuritis (ON), acute transverse myelitis (ATM), neuromyelitis optica spectrum disorder (NMOSD), multiple sclerosis (MS), and myelin oligodendrocyte glycoprotein antibody-associated disorders (MOGAD). Children present with a wide range of neurological symptoms depending on the site of inflammation and severity of demyelination. Substantial overlap exists in clinical and radiological presentations, making it challenging to distinguish one from the other in an individual. However, neuroimaging plays an important role in the diagnosis and follow-up of ADS.[4,5] Early diagnosis and treatment may improve the neurological outcome.[3,6,7] Specific biological markers including serum aquaporin-4 immunoglobulin-G (AQP4-IgG), myelin oligodendrocyte glycoprotein immunoglobulin-G (MOG-IgG), cerebrospinal fluid (CSF) immunoglobulins, and oligoclonal bands (OCBs) have expanded the knowledge and definitions of distinct disease entities within ADS.[7,8] The high specificity of AQP4-IgG for NMO has allowed the identification of seropositive patients with atypical presentations of NMOSD.[8] MOGAD is a distinct disease entity with higher incidence in pediatric population. The current estimated range of incidence in pediatric population (0.31 per 100,000) is higher than in adults (0.13 per 100,000) and occurs with a relatively equal sex ratio, particularly in younger children compared with pediatric MS and NMOSD.[9,10] In recent years, several studies have detected association of MOG-antibody (MOG-Ab) in 20 to 40% of children with a first episode of acute inflammatory demyelination.[10–12] They may have monophasic or relapsing course but do not meet the criteria for MS or other neuroinflammatory disorders and are better categorized as MOGAD.[13] Atypical presentation such as prolonged fever (PF), cortical encephalitis, and aseptic meningitis have been reported, expanding the spectrum.[10,14] Geographic and racial differences in distribution of ADS subtypes have been reported.[1,3,10,12] However, studies from the Indian subcontinent describing the spectrum and outcome of ADS subtypes are scarce.[15–17] Despite the variable presentation and radiologic lesions, treatment outcomes were generally observed to be favorable with few relapses. This prompted the retrospective chart review in the backdrop of evolving biomarkers and classification of ADS categories. Hence, this retrospective study was done to delineate the clinico-radiologic spectrum and outcome, and to compare the clinical presentation and neuroimaging features between ADEM, NMOSD, clinically isolated syndrome (CIS), MS, and MOGAD. Our objective was to additionally study the prevalence of MOG-Ab positivity among the ADS spectrum and to describe clinical and radiological profile, and outcome of the MOGAD group.

Methods

In this retrospective observational study, we included consecutive children under 18 years of age with ADS who presented to the Pediatric Neurology Clinic, Pediatric Emergency, and Pediatric Intensive Care Unit at a single tertiary care hospital between April 2008 and May 2023. They were diagnosed with ADS subtypes if they fulfilled the International Pediatric Multiple Sclerosis Study Group criteria (IPMSSG 2016).[5,13] Children diagnosed with infectious, metabolic, vascular, neurodegenerative or neoplastic CNS diseases were excluded. Electronic medical records of a total of 70 cases were retrospectively analyzed for clinical, laboratory, and radiological data. Institutional ethics committee approval was obtained on December 14, 2022, and consent was waived off due to retrospective nature of the study. Neuroimages including MRI brain and/or spine with and without contrast were reviewed by neuroradiologist. Serum NMO-IgG and MOG-IgG antibodies were analyzed by cell-based immunoassay and OCBs were analyzed in paired CSF and serum samples.

Treatment Protocol

A typical treatment regimen included intravenous (IV) methylprednisolone (MPS) at a dose of 30 mg/kg/day (maximally 1,000 mg/d) for 5 days, followed by an oral prednisolone taper over 6 to 12 weeks starting with a dose of 1 mg/kg/day. In steroid-unresponsive cases, IV immunoglobulin (IVIG) in combination with corticosteroids was used as a second-line treatment, total dose being 2 g/kg, administered over 2 to 5 days. Plasma exchange (PLEX) with three to seven exchanges was used in refractory patients.[18] Outcome at discharge was graded based on the modified Rankin scale (mRS) which grades disability as grade 0: no symptoms at all; grade 1: no significant disabilities despite signs in clinical examination; grade 2: slight disability, unable to carry out all previous activities, but same independence as other age- and sex-matched children; grade 3: moderate disability, requiring some help, but able to walk without assistance; grade 4: moderately severe disability, unable to walk without

Table 1 Association of clinical syndromes with acquired demyelinating syndrome subtypes

Spectrum	ADEM ($n=16$)	MOGAD ($n=13$)	CIS ($n=27$) and MS ($n=1$)	NMOSD ($n=13$)	Total ($n=70$)	*p*-Value
Encephalopathy	16 (100%)	3 (23%)	3 (10.7%)	2 (15.4%)	24 (34.2%)	NA
Polyfocal CNS events	**12 (75%)**	6 (46.2%)	7 (25%)	4 (30.7%)	29 (41.4%)	**0.008**
Cerebellar Involvement	2 (12.5%)	7 (53.8%)	7 (25%)	5 (38.4%)	21 (30%)	0.12
Brainstem	4 (33.3%)	**6 (46.2%)**	10 (35.7%)	**10 (76.9%)**	30 (42.8%)	**0.03**
Optic neuritis	0	**6 (46.2%)**	6 (21.4%)	4 (30.7%)	16 (22.8%)	**0.02**
Myelitis	0	3 (23%)	6 (21.4%)	5 (38.4%)	14 (20%)	0.07
Area postrema syndrome	0	0	0	**4 (30.7%)**	4 (5.7%)	**0.003**
Diencephalic/ Cerebral syndrome	2(12.5%)	0	6 (21.4%)	4 (30.7%)	12 (17.1%)	0.56

Abbreviations: ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; CNS, central nervous system; MS, multiple sclerosis; NA, not applicable; NMOSD, neuromyelitis optica spectrum disorder.
Note: *p*-Values which are significant and correspnding columns with highest percentages are highlighted in bold for ease of reader.

assistance; grade 5: severe disability, bedridden, requiring constant nursing care and attention; grade 6, dead.[19]

In those with relapsing course, acute episode was initially treated with 5 days of IV pulse MPS followed by slow taper of oral corticosteroids (OCSs). If no improvement, then IVIG and second-line immunosuppressants like rituximab were offered. For maintenance, low-dose OCSs (5–10 mg/d) were used in relapses for 6 to 12 months as needed with clinical monitoring and steroid-sparing agents like azathioprine were discussed.

Statistical Analysis

Continuous and categorical measurements were presented as mean ± standard deviation, percentage respectively, median and interquartile range (IQR) for quantitative variables and data were tabulated and descriptive analysis was performed. All quantitative variables were checked for normal distribution within each category. Fisher's exact and chi-square tests were used for significance of association between categorical variables. All statistical analyses were performed using the SPSS Statistics for Windows, version 22.0. A p-value <0.05 was considered significant.

Results

Seventy children with ADS including 39 (55.7%) boys and 31 (44.3%) girls with a mean age of presentation being 8.2 ± 4.0 years were analyzed. The spectrum included 27 cases of CIS, 16 cases of ADEM, 13 cases of NMOSD, 13 cases of MOGAD, and 1 case of MS. Mean age of presentation in CIS was 8.6 ± 4.2 years, ADEM 6.1 ± 4.4 years, NMOSD 9.8 ± 2.8 years, and MOGAD 7.7 ± 3 years. Clinical symptoms included fever (25, 35.7%), headache (20, 28.6%), vomiting (18, 25.7%), seizures (13, 18.5%), drowsiness (24, 34.2%), visual disturbances (19, 27.1%), gait difficulties (26, 37.1%), hemiparesis (8, 11.4%), swallowing difficulty (6, 8.6%), speech disturbance (6, 8.6%), and bladder dysfunction (12, 17.1%). Antecedent trigger was noted in 51.4% of cases which included infection (48.6%) and vaccine (2.8%). Median duration of symptoms was 3 days (IQR 2, 6). PF was noted in 10 cases of MOGAD (76.9%); 4 (30.7%) cases of NMOSD had intractable vomiting. All cases of ADEM had encephalopathy and 50% of them had seizures at onset. Other symptoms included paraesthesia, unilateral limb pain, ptosis, and facial asymmetry. The association between clinical syndromes and ADS spectrum has been tabulated (►**Table 1**).

Significant positive associations were observed between clinical syndromes and ADS subtypes: ADEM cases had presented predominantly with polyfocal symptoms ($p=0.008$), NMOSD had area postrema syndrome ($p=0.003$), brainstem signs were seen in both NMOSD and MOGAD ($p=0.03$); majority of MOGAD had ON but none in ADEM ($p=0.02$). NMO-IgG seropositivity was observed in 2.6% ($n=1$) and MOG-IgG in 62% ($n=13$). Thirty cases underwent CSF analysis, 46.7% (14) revealed pleocytosis or raised protein; intrathecal OCBs were seen in 5.8% ($n=1$). One case of ADEM which progressed to intractable movement disorder was positive for N-methyl-D-aspartate (NMDA) receptor antibody in CSF. Six cases of ON which underwent visual evoked potential showed prolonged P100 latencies. MRI of brain, orbit, and spine with or without contrast was done to study distribution and characteristics of lesions as shown (►**Table 2**).

In MOGAD cases, predominant involvement of basal ganglia/thalami, optic nerve, and cerebellum was seen (►**Fig. 1**), whereas NMOSD showed predominant optico–spinal, brainstem, and area postrema lesion as shown (►**Fig. 2**). Radiological abnormalities and the ADS spectrum had statistically significant correlation; there were more optic nerves ($p=0.02$) and cerebellar lesions ($p=0.01$) in MOGAD, area postrema ($p=0.003$) in NMOSD, myelitis ($p=0.03$) in NMOSD/MOGAD, and basal ganglia/thalami ($p=0.005$) in MOGAD/ADEM. Imaging patterns between ADEM and MOGAD were comparable except for more ON ($p=0.004$), spinal cord ($p=0.01$), and cerebellar lesions ($p=0.03$) in MOGAD, while MOGAD and NMOSD were comparable except for basal ganglia/thalami ($p=0.005$) and bilateral lesions ($p=0.02$) in MOGAD.

All cases received supportive care and immunotherapy as per the protocol. Acute treatment with pulse MPS was done in all, IVIG in 11 cases with steroid unresponsiveness, and

Table 2 Neuroimaging features of acquired demyelinating syndrome spectrum

Spectrum	ADEM (16)	MOGAD (13)	CIS (27) and MS (1)	NMOSD (13)	Total (70)	*p*-Value
Optic nerve involvement	0	**6 (46.2%)**	4 (14.2%)	3 (23%)	13 (18.6%)	**0.02**
Spinal cord lesion	0	**5 (38.5%)**	8 (28.5%)	**5 (38.5%)**	18 (25.7%)	**0.03**
Area postrema	0	**0**	0	**4 (30.8%)**	4 (5.7%)	**0.003**
Brainstem lesion	4 (25%)	7 (53.8%)	11 (39.2%)	7 (53.8%)	29 (41.4%)	0.28
White matter	**16 (100%)**	9 (69.2%)	11 (39.2%)	6 (46.1%)	42 (60%)	**0.0009**
Corpus callosum	3 (18.7%)	2 (15.4%)	5 (17.8%)	1 (7.7%)	11 (15.7%)	0.34
Basal ganglia /thalamus	**9 (56.2%)**	**9 (69.2%)**	7 (25%)	2 (15.4%)	27 (38.5%)	**0.005**
Gray matter	4 (25%)	6 (46.2%)	2 (7.1%)	3 (23%)	15 (21.4%)	0.07
Postcontrast enhancement	6 (54.5%)	6 (46.2%)	6 (21.4%)	8 (61.5%)	26 (37.1%)	0.106
Lesion margin	9 (56.3%)	4 (30.7%)	4 (14.3%)	1 (7.7%)	18 (25.7%)	**0.01**
Bilaterality	16 (100%)	**10 (76.9%)**	9 (32.1%)	4 (30.8%)	39 (55.7%)	Not applicable
Cerebellum	1 (9%)	**6 (46.2%)**	5 (17.8%)	1 (7.6%)	13 (18.5%)	**0.01**

Abbreviations: ADEM, acute disseminated encephalomyelitis; CIS, clinically isolated syndrome; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.
Note: *p*-Values which are statistically significant and the respective highest proportion of subcategories in columns have been highlighted for ease of reading.

PLEX in 2 refractory cases, followed by oral maintenance steroid therapy for median duration of 8 weeks (IQR 4, 12). Mean hospital stay was 6.6 ± 5.9 days. At discharge, good recovery occurred in 64 (91.4%) cases; 6 cases (8.6%) had functional limitation.

Good recovery was observed in 93.4% with ADEM, 84.6% with NMOSD, 92.3% with MOGAD, and 92.8% of CIS without significant neurodeficits. Outcome of the cases at discharge was graded by mRS: grade 0 in 26 (37.1%), grade 1 in 30 (42.9%), grade 2 in 8 (11.4%), grade 3 in 6 cases (8.6%) but none had grade 4 to 6. Moderate disability (grade 3) with functional limitation included, one with ADEM-residual truncal ataxia and choreoathetoid movement, two NMOSD cases had neurological deficits, and one was nonambulatory, two cases with ATM, and one with MOGAD had lower limb weakness and bladder dysfunction. Comparison and statistical analysis of treatment outcomes between MPS versus combination immunotherapy groups revealed no significant difference in the proportion that had recovered. However, on analyzing the proportions in subcategories of mRS, we found that the slight and moderate disability was higher in the combination immunotherapy ($p < 0.000$).

On median follow-up of 8 months (IQR 3, 17), we observed good recovery in 66 (94.3%) cases and residual deficits were seen in 4 (5.7%) cases with no significant functional limitation. Twelve (17.1%) cases had relapsed with a median duration of 3 months (IQR 1.4, 6.3) after the first episode, which included six cases of NMOSD, five cases of MOGAD, and one case with MS. The child with MS had moved to another country following his first episode and was lost to follow-up.

Of the 29 cases (41.4%) that had follow-up MRIs, 8 had new lesions which included 2 NMOSD—one had cortical enhancing lesion, and the other with ON had relapsed with a new spinal lesion (longitudinally extensive transverse myelitis [LETM], C3–C6) as well as a resolving ON lesion. Child with MS had juxtacortical white matter lesion, while five MOGAD cases had new lesions that involved cortical white matter, basal ganglia, cerebellar lesions (dentate nuclei and middle cerebellar peduncle [MCP]), and optic nerve without chiasmal involvement.

Myelin Oligodendrocyte Glycoprotein Antibody-associated Disorders' Spectrum

On evaluating 21 children with ADS, 13 were positive (62%) for MOG antibodies presenting as ADEM in 4 cases (30.8%), ON in 4 cases (30.8%), ATM in 2 cases (15.4%), CIS in 2 cases (15.4%), and NMOSD in 1 case (7.7%). Female preponderance with 69.2% ($n = 9$) of girls was observed with median age of 8 years (IQR 5, 10) whereas ADEM cases showed median age of 10 years (IQR-8.6, 10.5) and 5.5 years (IQR-5, 8.7) in CIS (including ON and ATM). Among them, 10 cases (76.9%) had antecedent trigger and presented with PF (10, 76.9%), headache (6, 46%), vomiting (4, 30.7%), seizures (1, 7.7%), drowsiness (3, 23%), visual disturbances (5, 38.5%), gait disturbances (6, 46%), and bladder issues (3, 23%). Three of those with PF (>7 d), had aseptic meningitis, and one child presented primarily for fever of unknown origin. All cases of ON had vision loss or markedly reduced visual acuity and papillitis, bilateral in all except one. Mean duration of symptoms was 3.7 ± 2.1 days. Most common presenting clinical syndrome was cerebellar (7, 53.8%) followed by polyfocal CNS symptoms (6, 46%), brainstem signs (6, 46%), ON (6, 46%), encephalopathy (3, 23%), and myelitis (3, 23%). Radiologically, lesions were observed involving white matter (69.2%), basal ganglia/thalamus (69.2%), brainstem (53.8%), cerebellum (46.2%), optic nerve (46.2%) followed by spine (38.5%). Within optic nerve, the anterior segment was involved with perineuritis and chiasma was spared. LETM showed predominant cervical–thoracic cord lesion (C3–C6, C6–T1); however, no conus involvement was seen. None of the MOGAD cases were positive for NMO-IgG antibodies. CSF

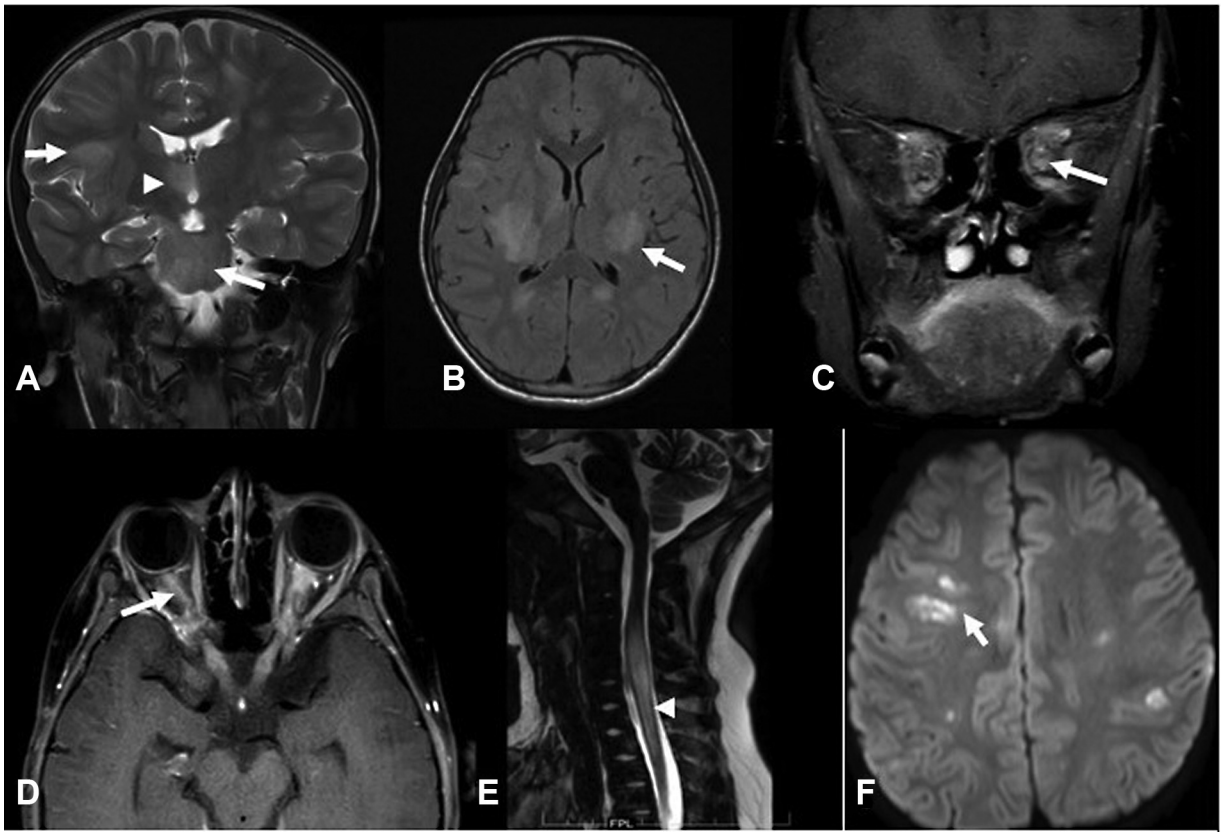

Fig. 1 MOGAD spectrum. (**A**) Coronal T2-weighted images show hyperintensities in white matter and brainstem (white arrows) and thalamus (right; arrowhead). (**B**) Axial FLAIR images showing hyperintense signals across bilateral basal ganglia (white arrow). (**C, D**) Coronal and axial T1 fat sat contrast images showing bilateral optic neuritis, papillitis, perineuritis with sparing the chiasma. (**E**) Sagittal T2-weighted images of transverse myelitis showing long-segment intramedullary hyperintense signal across C3 to T1 level (arrowhead). (**F**) Axial diffusion-weighted images showing foci of diffusion restriction in white matter (white arrow). MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disorder.

analysis showed pleocytosis in 66.6% ($n = 4$) with raised protein and no intrathecal OCBs. Elevated erythrocyte sedimentation rate (ESR) was observed in 53.8% ($n = 7$) of cases with mean being 39 ± 20.4 mm/h. Serological monitoring was advised to all with MOGAD during 6 to 12 months follow-up or long-term immunomodulation therapy by OCSs. It was available in eight MOG-positive cases, including five relapses and two cases had persistent MOG seropositivity (>6 months) after last episode even when asymptomatic.

All children with MOGAD received immunotherapy with pulse MPS for 5 days and followed by oral steroid maintenance. IVIG was given in one and PLEX in one case. At discharge, good recovery was observed in 92.3% of patients, only one child (7.7%) had functional limitation due to neurogenic bladder who recovered later with maintenance immunotherapy. Functional outcome of the cases at discharge by mRS was grade 0 in five cases, grade 1 in six cases, grade 2 in one case, grade 3 in one case while none had grade 4 to 6.

At median follow-up of 9 months (IQR 3, 15), complete recovery was observed in all cases. Five (38.4%) had relapsed with new signs and symptoms predominantly involving the optic nerve and spinal cord in which two of the cases had relapsed at the time of tapering the oral maintenance steroids within 6 months of the first episode. Relapses showed presentations as tabulated (►**Table 3**). Relapses were treated with another course of pulse steroid followed by maintenance OCSs, had good recovery, and in one MOGAD case second-line therapy was required with no functional limitation.

Discussion

This retrospective study describes the clinical, diagnostic, and therapeutic profile of children with ADS from India. Majority presented as CIS followed by ADEM, equal numbers with NMOSD and MOGAD, and one as MS. We observed boys being more affected in the cohort; however in NMOSD and MOGAD female predilection was noted though few studies report no gender predilection at first presentation of ADS.[3,15] In our cohort, NMOSD presented in older children followed by CIS, MOG, and ADEM conforming to the fact that ADEM presents at a younger age and NMOSD later.[3,20] We know that preceding infections may induce the development of ADS, particularly ADEM where 70 to 80% of cases report preceding prodromal illness.[3,15,20] We observed antecedent triggers in the form of infection and vaccine in 51.4% of cases. Children had a wide spectrum of presentation with fever, drowsiness, seizures, vision issues, vomiting, and gait disturbances as

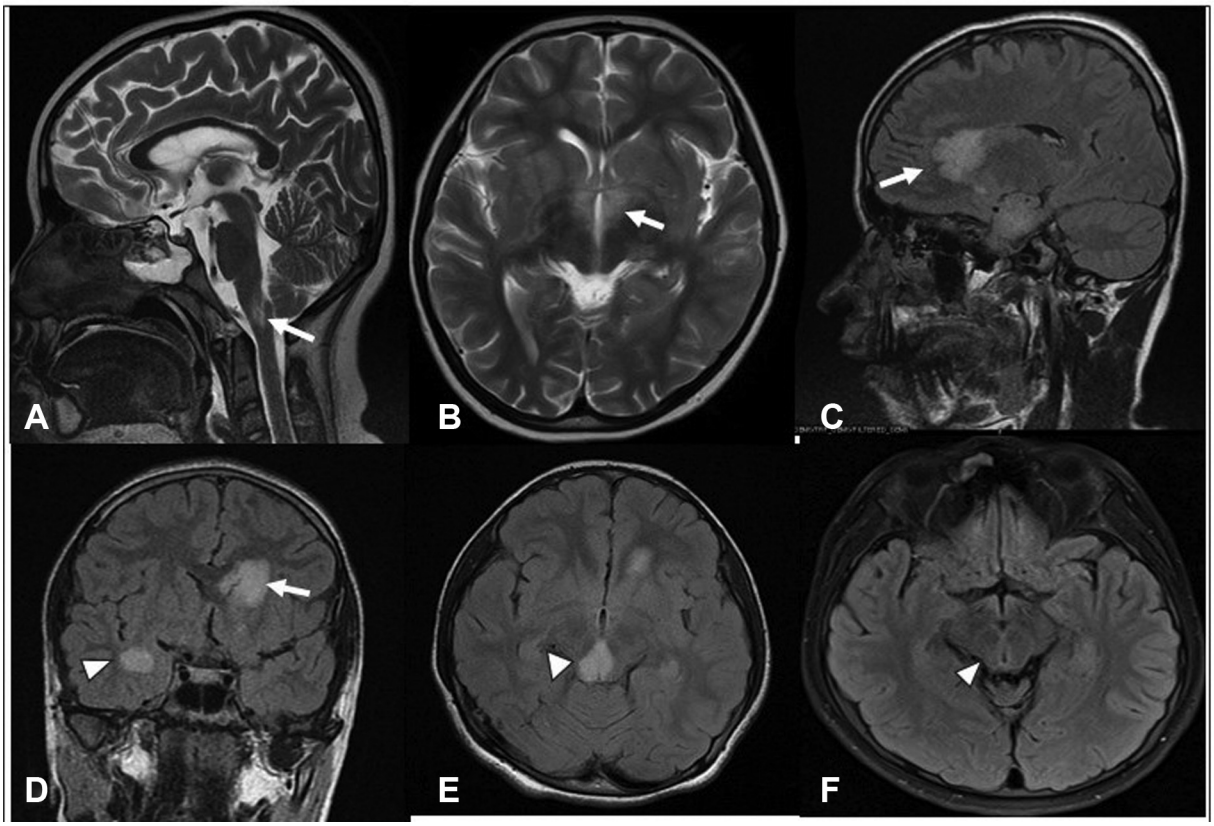

Fig. 2 NMOSD spectrum. (**A**) Sagittal T2-weighted image shows hyperintense lesion at area postrema (white arrow). (**B**) Axial T2 image showing hyperintensities involving hypothalamus (white arrow) diencephalic syndrome. (**C, D**) Sagittal and coronal FLAIR image showing hyperintense lesion in left periventricular area (white arrow) and right mesial temporal lobe (arrowhead). (**E, F**) Axial FLAIR images showing periventricular hyperintensities (arrowhead) in posterior midbrain and resolution in follow-up scan. NMOSD, neuromyelitis optica spectrum disorder.

described in other studies.[15,20] But there were few peculiar features like PF especially in MOG-Ab-positive group which was also observed as a presenting or associated symptom in MOG-associated ADS by Udani et al.[14] Intractable vomiting was observed in children with NMOSD with area postrema syndrome which has been reported in seropositive NMOSD.[21] Major presenting phenotypes included polyfocal neurological symptoms in 41.4%, brainstem signs in 42.8%, and encephalopathy in 34.2%. Presence of encephalopathy is one of the essential criteria for diagnosis of ADEM. We observed that all children with ADEM and 23% of MOGAD cases had encephalopathy which is comparable to studies by Gowda et al and Alper et al where 53 and 42% of cases, respectively, presented with encephalopathy.[15,22] Seizures at onset of illness in 50% of ADEM children was comparable with other studies of ADEM.[15,20] A study on ADS by Kilic et al in 2021, reported ADEM cases with more polyfocal neurological symptoms with seizures in 33.3% and encephalopathy in 93.3% of patients.[20]

With the recent availability of biomarkers, MOG-IgG and NMO-IgG, there is increased testing for autoantibodies in the children with ADS. We found MOG-IgG seropositivity of 62% which is comparable to pediatric cohorts[3,10,23] but higher compared with a study by Sankhyan et al from North India.[16] Most of the children with NMOSD had seronegative/unknown status for AQP4-IgG but neuroimaging features helped in the diagnosis. However, most of these children were diagnosed before testing for serum MOG-Abs became available hence, we cannot rule out the possibility of few of these being MOGAD. Proportion with abnormal CSF (46.7%) was comparable to other studies reporting CSF abnormalities in ADS.[15,16,24] Neuroimaging plays a crucial role in diagnosing ADS and further phenotyping them. Brain MRI showing T2 and FLAIR hyperintense lesions involving bilateral subcortical white matter, optic nerve, MCP, basal ganglia/thalamus were observed in MOGAD and ADEM, which has been reported.[4,25] MOGAD was distinct from ADEM with more ON, myelitis, and cerebellar lesions. Children with CIS spectrum had radiological picture corresponding to their polyfocal signs and symptoms without fulfilling the MRI criteria of MS (2017 McDonald criteria).[26] Area postrema, periventricular lesions were seen in NMOSD which is explained by the distribution of aquaporin channels. These findings are in agreement with other studies on mixed cohort of ADS (pediatric and adult) showing similar pattern of neuroimaging features.[4,15,23,27] These specific neuroimaging features of each spectrum observed in our study as well as others, helped in further categorization in patient with first attack of demyelination.[8,22,26,28]

Immunotherapy in the form of IV pulse MPS was the first line of treatment with additional PLEX and IVIG in small

Table 3 Myelin oligodendrocyte glycoprotein antibody-associated disorders' relapses: presentation and magnetic resonance imaging features

Relapse cases: MOGAD							
S.No.	**Clinical presentation**	**Initial diagnosis**	**Relapse (final diagnosis)**	**Interval between relapse**	**Previous/Initial MRI**	**Follow-up MRI**	**Status**
1	Fever: 10 days, unsteadiness of gait, vomiting, sleepiness	ADEM	Optic neuritis **(ADEM-ON)**	2 months (on steroid taper)	Bilateral white matter lesion	Bilateral optic nerve thickened with enhancement Subtle C3–C6 signal changes without enhancement	Recovered
2	Walking difficulty: 1 day and weakness of leg	TM	ON **(NMOSD)**	2.5 months	Brain and whole spine normal (done outside)	Bilateral ON (Right > Left) without chiasma lesion, few patches of diffusion restriction Spinal lesions C3–T1 > 2/3 cord involvement	Recovered
3	Fever: 6 days, decreased vision: 3 days	ON	ADEM	9 months	Optic nerve thickening and bulky (Right > Left) with postcontrast enhancement No brainstem/BGA/thalami lesion	Corpus callosum, globus pallidus, cerebellum, and brainstem lesions	Recovered
4	Fever: 7 days, headache	ADEM	ADEM	4.5 years	Bilateral white matter, basal ganglia/thalamic lesion, brainstem lesion, leptomeningeal enhancement	New lesion (cerebellum–MCP), leptomeningeal enhancement	Relapses+
			ADEM	5 years			
			Aseptic meningitis	1 month			
			ON **(MDEM-ON)**	(On steroid taper)			
5	Fever for 7 days, headache: 1 day Blurring vision: 1 day Seizure (left focal)	Focal meningitis	ON	2 Months	Right focal leptomeningeal enhancement	ON thickening with perineuritis and sparing chiasma Resolved previous lesion, rest normal	No further relapse, persistent antibody positive

Abbreviations: ADEM, acute disseminated encephalomyelitis; ADEM-ON, acute disseminated encephalomyelitis with optic neuritis; BGA, basal ganglia; MCP, middle cerebellar peduncle; MDEM-ON, multiphasic acute disseminated encephalomyelitis with optic neuritis; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disorder; NMOSD, neuromyelitis optica spectrum disorder; ON, optic neuritis; TM, transverse myelitis.

proportion of patients who showed a poor response to pulse steroids. Majority showed good recovery (91.4%) at discharge comparable to other studies.[15,16,25] Twelve (17.1%) relapsed after first episode of NMOSD, MOGAD, and MS. Recent studies have suggested second-line immunotherapy with agents like rituximab and steroid-sparing agents like azathioprine are being used in those who are refractory to treatment and in relapses.[20,29,30] But in our cohort steroid-sparing agents were not used. As many of these children were from other states, they had to be followed by the local pediatrician who would not be comfortable with the use of azathioprine or mycophenolate. Relapses were managed with a longer tail of low dose (5–10 mg) OCSs as tolerated for at least 6 months.

Myelin Oligodendrocyte Glycoprotein Antibody-associated Disorders

Among MOGAD, most common presentation reported is ADEM occurring in 53% of patients, followed by ON (30%), transverse myelitis (TM; 18%), and limited cases of NMOSD like phenotype (ON + TM) as per recent EU consortium report.[10] We observed ADEM and ON to be a common presentation followed by TM and NMOSD.[10] But other studies have reported ON to be common.[16,24,31] We observed female predominance as noted earlier.[12,17,23] However, EU consortium reported equal gender distribution in MOGAD with a slight female preponderance in older children.

In our study, the median age at onset was 8 years which was less compared with previous studies, with median age of onset being 10.5 and 14 years.[17,24] Children with ON had vision loss or reduced visual acuity and papillitis on clinical examination as reported by Chen et al.[32] Unilateral ON at presentation was more common in seropositive NMOSD, MS in adults whereas bilateral ON at presentation was common in MOGAD.[25,31] We report 75% ($n = 3$) with bilateral and 25% ($n = 1$) with unilateral ON which is in agreement with the study published in 2020 by Wendel et al.[33] Few cases of MOGAD have also been reported with unilateral ON.[14,34]

Atypical presentation with PF and aseptic meningitis, seizures without encephalopathy, overlapping syndromes of MOG-Abs and other autoantibodies (e.g., Anti Nuclear antibody (ANA), N-Methyl-D-aspartate (NMDA) receptor antibodies) in patients with anti-NMDAR encephalitis, have been reported recently in MOGAD.[10,14] PF and raised inflammatory markers like ESR/C-reactive protein and cytokines, mainly interleukin-6, indicates the underlying systemic inflammation.[11,14] Few of these atypical presentations have been described as part of MOG-Ab-associated disorders by Udani et al in 2021, where 12 children were reported with PF with leukocytosis and elevated inflammatory markers including three with aseptic meningitis.[14] In our cohort of MOGAD, we also observed PF in 76.9% ($n = 10$) and elevated ESR in 53% ($n = 7$) of cases; three cases of PF had aseptic meningitis, including one with focal seizures. Distinct presentation with gray matter lesions and seizure without encephalopathy has been increasingly recognized in MOGAD.[10,35] Hence, observation of isolated seizures without clinical features of ADEM, during the initial episode of MOG-Ab-associated demyelination suggest association between MOG antibodies and autoimmune epilepsy.[36]

Predilection for involvement of white matter (69.2%), basal ganglia/thalamus (69.2%), and optic nerve (46.2%) was seen in our study which was comparable to other studies reporting lesions in MOG-Ab-positive ADEM and ADEM with ON (ADEM-ON) at initial presentation.[12,15,23,37] We also observed our MOGAD cohort to have lesions in the brainstem (53.8%), cerebellum (46.2%), especially MCPs, and two cases showed hyperintense lesion in corpus callosum, which were also reported in other pediatric and adult studies.[4,27,28,37] A study by Zhang et al showed cerebellar lesions in 58.3% and corpus callosum in 16.7% of subjects.[25] MOG-ON showed high rates of longitudinal involvement of the optic nerve in mixed pediatric and adults cases, with relative sparing of the optic chiasm and tracts, similar to our results.[25,33] Additionally, perineural enhancement and inflammation has been described in both adult and pediatric cohorts distinguishing MOG-Ab-positive from AQP4-Ab-positive and MS patients with ON.[4,32,34] Therefore this pattern of ON lesion can help differentiate between these two disorders.

Few peculiar lesions including areas of restricted diffusion suggestive of cytotoxic edema were seen in two MOGAD cases which is uncommon in pediatric MOGAD but may be present in younger patients with ADEM.[4,27] Enhancing lesions post gadolinium contrast injection was observed in 60% ($n = 10$), which is comparable with other studies.[4,31] Subclinical spine lesions (LETM) were observed in ADEM, without frank symptoms, emphasizing the importance of screening for spinal cord lesions in patients without symptoms of myelopathy. Our study depicted equal prevalence of myelitis in MOGAD and NMOSD with no specific area predilection and statistical association and hence did not help in differentiating both. Although lumbar and conus involvement are unique to MOG-Ab-positive patients we did not see any children with conus involvement as described in mixed cohorts.[17,28,37]

Six cases of MOGAD underwent CSF analysis of which 66.6% ($n = 4$) had abnormality as in other studies with mild pleocytosis and elevated protein and one had type IV OCB.[16,17,38] We observed 62% MOG positivity higher than other recent pediatric cohort.[16,33] Dale et al and Zhang et al reported 40 to 68% MOG positivity in children with ADEM.[11,25] Elevated ESR is comparable to other study which suggests underlying systemic inflammation in the acute phase of illness.[11] None of our MOGAD–NMOSD were positive for AQP4-IgG which is in concordance with literature where AQP4-IgG seropositivity is rare in MOGAD. Hence, anti-MOG antibodies should be tested in children with AQP4-seronegative NMOSD.[39]

All cases had good treatment response with first-line immunotherapy with pulse steroid, IVIG, and PLEX in isolation or combination. Only one case required PLEX with IVIG and supportive care. Relapse was seen in 38% ($n = 5$) of MOGAD, which is lower than that reported (50–80%) earlier.[17,40] Relapses may occur with further episodes of ADEM as multiphasic ADEM (MDEM), ADEM-ON, or with transverse myelitis (ADEM-TM). In our cohort, two with ON had

relapsed during tapering of steroid which was also observed by Ramanathan et al.[30] Multiphasic presentation with lesions over deep and subcortical white matter, optic nerve without chiasmal lesion, thalamus, dorsal cord, and brainstem lesions, leptomeningeal enhancement with few resolved and new lesions were seen helping us to categorize as MDEM, ADEM-ON which have been also reported.[7,12,20] In our cohort, relapses were more commonly restricted to the optic nerve or spinal cord and two cases with aseptic meningitis had leptomeningeal enhancement specific for MOGAD.

Studies on MOG found that patients with persistent MOG-Ab with high titers seropositivity after treatment were more likely to relapse.[7,12] Two cases had persistent antibody positivity even after 6 months but only one relapsed in initial taper but none later on follow-up. We observed the relapses of ON but they had good recovery on maintenance steroid therapy, while myelitis had prolonged recovery comparable with other studies in MOGAD group.[20,30]

Study Strength

This is a reasonably large pediatric ADS cohort from India. Biomarker analysis was helpful to classify the MOG-associated disorders. Neuroimaging available in almost all helped in differentiating the ADS subtypes with clinical correlation.

Study Limitations

Since it was a retrospective cohort, nonuniform data on certain parameters made interpretation difficult. As the study was over a long period of many years, hence biomarkers were available or done in the later part only, these again have the potential to bias observations. MRI was not done in all patients on follow-up due to affordability issues. These are particularly important for CIS patients to determine the resolution of lesions and recurrence.

Conclusion

Categorization of the ADS spectrum according to latest IPMSSG classification and availability of novel biomarkers helped us to differentiate ADS subtypes. If child presents with encephalopathy, acute diminished vision, PF, high ESR, neuroimaging confirming findings of ON with additional brain lesion (ADEM-like, basal ganglia/thalamus, MCP, leptomeningeal enhancement), there should be high index of suspicion for MOGAD. Radiological features of ADEM and MOGAD group are comparable with additional optico–spinal, cerebellar lesions in MOGAD. Immunotherapy with steroids is favorable. The presence of MOG antibodies is helpful for prognostication and determining relapse risk.

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Conflict of Interest
None declared.

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