Original Article

Acquired demyelinating disorders of central nervous system: A pediatric cohort

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Abstract

Objective: This is a retrospective chart review of consecutive children with acquired demyelinating disorders presenting to a north Indian tertiary care hospital over 4 years. The aim of this review is to describe all the patients (with single event as well as those with recurrences) with detailed description of those who recurred. **Materials and Methods:** Overall 35 cases were reviewed and their clinical presentations, diagnosis, management, and follow-up are being presented. **Results**: Out of 35 cases, 24 did not show any recurrences (seven acute disseminated encephalomyelitis (ADEM) and 17 clinically isolated syndromes). Amongst the 11 patients with recurrent demyelination, majority were multiple sclerosis (8/11, 72.7%) followed by neuromyelitis optica (NMO; 2/11), and multiphasic ADEM (1/11). The median disease duration and follow-up since onset for those with recurrent episodes is 4 years (2.5-4.5 years). Steroids caused significant improvement in acute episodes of demyelination. However, recurrent demyelinating disorders like multiple sclerosis and NMO required long-term immunomodulation. Azathioprine currently is the most favored long-term immunomodulator used in NMO. Interferon-β and glatiramer acetate are currently recommended for multiple sclerosis. However, azathioprine may be a suitable alternative in a resource-limited setting. **Conclusion**: The consensus definitions for these groups of disorders need further validation in the pediatric age group. Studies with larger population size are required to characterize features that predict future recurrences.

Key Words

Acquired demyelination, azathioprine, central nervous system, multiple sclerosis, neuromyelitis optica

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Introduction

Inflammatory demyelinating diseases of the central nervous system comprise of monofocal or polyfocal, monophasic, multiphasic, or progressive group of disorders of autoimmune origin. These include Acute Disseminated Encephalomyelitis (ADEM), Multiple Sclerosis (MS), Clinically Isolated Syndrome (CIS) and Neuromyelitis Optica (NMO).[1,2] Although these disorders are associated with significant morbidity, early diagnosis results in improved functional and neurological outcome.[3]

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The definitions for pediatric demyelinating disorders are evolving.[4,5] Individual attacks are managed acutely by immunotherapy (primarily parenteral steroids followed by short course of oral steroids). However, disease modifying therapies in the form of long-term immunomodulators and steroid sparing agents are required for recurring entities, viz., MS and NMO.[6,7] Timely diagnosis and institution of appropriate therapy determines prognosis and outcome.[8]

One aspect of these groups of disorders that have always intrigued researchers is predicting the recurrence risk after the first attack. Interestingly, patients can be labeled as MS or NMO even after the first clinical attack [Tables 1 and 2; current consensus guidelines for diagnosis of MS and NMO, respectively].[4,5] It is crucial to pick up these cases early for institution of disease modifying therapy. However, clinical and radiological criteria are still evolving for the pediatric age group.[9]

This is a retrospective chart review of pediatric patients with central nervous system demyelinating disorders.

Table 1: Current consensus diagnostic criteria for multiple sclerosis (based on 2010 McDonald criteria)

Clinical criteria	Additional features
≥2 attacks; objective clinical evidence of two or more lesions or history-based evidence of a previous attack[1]	Not required
≥2 attacks with objective clinical evidence of one lesion	DIS as documented by ≥1 lesion in T2-weighted MRI in atleast 2 out of 4 of these sites (periventricular, juxtacortical, infratentorial, spinal cord)
1 attack, however objective clinical evidence of ≥2 lesions	DIT as demonstrated by both enhancing and nonenhancing lesions at the same time or a new lesion on follow-up MRI compared to a previous scan
An isolated CIS	Both DIS and DIT
PPMS	A year of disease progression with any two of the below three DIS (≥1 in supratentorial and infratentorial sites except spinal cord) DIS (≥2 in spinal cord) Positive CSF oligoclonal bands

DIS = Dissemination in space, DIT = Dissemination in time, CIS = Clinically isolated syndrome, PPMS = Primary progressive multiple sclerosis, CSF = cerebrospinal fluid, MRI = Magnetic resonance imaging

Table 2: Current consensus diagnostic criteria for pediatric neuromyelitis optica

Optic neuritis
Transverse myelitis
One of the two
a) LETM (involvement of 3 or more spinal segments)
b) NMO IgG seropositivity

LETM = Longitudinally extensive transverse myelitis, NMO = Neuromyelitis optica, IgG = Immunoglobulin G

Materials and Methods

This is a retrospective chart review of pediatric case records of demyelinating events presenting to a tertiary care teaching center in north India. Overall 35 cases of acquired, acute onset, first episode of central nervous system demyelination presented over a 4-year period (July 2009-April 2013), out of which 11 patients showed recurrence. The final diagnoses of the subtype of demyelination in 35 cases were established in concordance with the definition proposed by International MS Study Group and revised McDonald criteria.

All the cases after they presented to the current center were subjected to magnetic resonance imaging (MRI) brain, orbit and spine with contrast, brainstem-evoked response audiometry, and visually-evoked response evaluation in the presenting as well as recurrent episodes. In the 11 recurrent cases, two patients presented to the current center in their first episodes. Cerebrospinal fluid (CSF) oligoclonal bands (OCBs) were assayed (isoelectric focusing using gel electrophoresis) in all patients when they presented with a recurrent episode and also in first episodes with clinically isolated syndromes (other than acute transverse myelitis (ATM)). Serum anti-NMO antibodies (enzyme-linked immunosorbent assay) were done if patients presented with isolated transverse myelitis or optic neuritis or both or in ADEM-like presentation with MRI brain lesions characteristic of NMO. The cases with isolated transverse myelitis or optic neuritis were also subjected to antibody testing as the current consensus guideline for diagnosing pediatric NMO does not mention longitudinally extensive transverse myelitis (LETM) as an obligatory criteria.[5] Moreover in NMO, optic neuritis and transverse myelitis can occur in isolation and follow each other sequentially even after years. Cases which were being followed-up prior to availability of serum anti-NMO antibody assay in the current center, were subjected to it (after it was available) only if they had any recurrence in a relevant clinicoradiological scenario. Demyelinating events which happen as a part of infection rather than parainfectious etiology were not ruled out. This was because most of the events presented clinically in a classical parainfectious manner; and moreover, appropriate microbial tests to rule out infections were not available in the current setup.

In appropriate clinicoradiological scenarios, neurometabolic (arterial and CSF lactate, arterial pH, blood sugar, serum ammonia, blood tandem mass spectrometry, urine gas chromatography mass spectrophotometry, serum ceruloplasmin, and 24-h urinary copper) and autoimmune work up (antinuclear antibody, antithyroid antibodies, and antineutrophilic cytoplasmic antibodies) were done.

Results

All cases presented till December 2010 were classified according to the consensus definition proposed by International MS Study Group, from January 2011, the 2010 revised McDonald criteria was used. Subsequently, all cases were reclassified using the 2010 revised McDonald criteria.

Out of 35 cases, 24 did not show any recurrences (seven ADEM and 17 CIS (isolated ATM, eight; optic neuritis with myelitis, three; isolated optic neuritis, two; basal ganglia syndrome, two; and hemispheric syndrome, two)). The median age at initial presentation for those who did not have recurrent events (n = 24) was 7 years (range: 1-12 years).

Amongst the 11 patients with recurrent demyelination, majority were multiple sclerosis (8/11, 72.7%) followed by NMO (2/11, both seropositive) and multiphasic ADEM (1/11). The median age at initial presentation for those with recurrences (n = 11) was 5 years (range: 3-12 years). The clinical, salient laboratory, and radiological investigations of all patients with recurrent demyelination have been detailed in Tables 3 and 4.

All patients with multiple sclerosis fulfilled the revised McDonald diagnostic criteria. The median time interval between first and second episodes in MS patients was12 months (4-36 months). Overall 23 events of demyelination were noted in eight patients with MS, out of which only three (13%) were polyfocal, rest being monofocal (20/23,86.9%). Of the

Table 3: Clinical and laboratory features of recurrent demyelinating cases with final diagnosis

Patients (n = 11)	Age at onset /sex	1st episode	2nd episode	3rd episode	4th episode	Finaldiagnosis	Total disease duration
Patient 1	3 years/male	Febrile encephalopathy with complete recovery*	2 years later: Febrile encephalopathy with focal status epilepticus with complete recovery	1 year later: Febrile encephalopathy with ataxia with complete recovery		Multiphasic ADEM	4.5 years
Patient 2	6 years/male	Psychiatric features with complete recovery	4 months later: Psychiatric features with hemiparesis with upper motor neuron facial nerve palsy with complete recovery*	2 years later: Febrile encephalopathy with complete recovery		NMO (serum anti-NMO antibody positive)	3.5 years
Patient 3	4 years/male	Febrile encephalopathy with complete recovery	1 year later: Monoparesis with complete recovery	2 years later: Hemiparesis with partial recovery	1 year later: Paraparesis with partial recovery*	Multiple sclerosis	4.5 years
Patient 4	5 years/male	Hemiparesis with complete recovery	3 years later: Hemiparesis with pancerebellar features with complete recovery*			Multiple sclerosis (CSF OCB +ve)	4.5 years
Patient 5	12 years/ male	Acute onset vision loss with complete recovery	1 year later: Encephalopathy with complete recovery	2 years later: Hemiparesis with pancerebellar features with ongoing recovery*		Multiple sclerosis (CSF OCB + ve)	4.5 years
Patient 6	9 years/male	Paraparesis with significant recovery*	3 years later: Paraparesis and acute onset vision loss with significant recovery*			Multiple sclerosis	4 years
Patient 7	9 years/ female	Monoparesis with acute onset vision loss with complete recovery	3 months later: Monoparesis with acute onset vision loss with complete recovery*	3 years later: Acute onset vision loss with partial recovery		NMO (serum anti-NMO antibody positive)	4.5 years
Patient 8	5 years/ female	Febrile encephalopathy with complete recovery	4 months later: Febrile encephalopathy with complete recovery	5 months later: Hemiparesis with near complete recovery*		Multiple sclerosis (CSF OCB + ve)	3.5 years
Patient 9	5 years/male	Acute onset vision loss with complete recovery	3 months later: Quadriparesis with partial recovery	3 months later: Hemiparesis with ongoing recovery*		Multiple sclerosis	3.5 years
Patient 10	9 years/male	Focal seizures without encephalopathy with complete recovery	1 year later: Diplopia with decreased vision with complete recovery	1 year later: Diplopia with decreased vision with complete recovery*		Multiple sclerosis	2.5 years
Patient 11	4.5 years/ female	Left hemiparesis with left focal seizures without encephalopathy with partial recovery	1 year later: Left hemiparesis with left focal seizures without encephalopathy with near complete recovery*	1 year later: Paraparesis with complete recovery		Multiple sclerosis (CSF OCB + ve)	2.5 years

Episodes in * are the one in which the patient presented to the current center. ADEM = Acute disseminated encephalomyelitis, ATM = Acute transverse myelitis, NMO = Neuromyelitis optica, CSF = Cerebrospinal fluid, OCB = Oligoclonal bands

Table 4: Radiological features of recurrent demyelinating cases

Patient	1st episode	2nd episode	3rd episode	4th episode
1	Brainstem, subcortical white matter, thalamus, dorsal spine	Normal	Dorsal spine, brainstem, periventricular white matter	
2	Bilateral asymmetrical deep and subcortical white matter as well as grey matter, basal ganglia, pons	Same as previous	Bilateral periventricular white matter, thalamus, midbrain, cervical spine	
3	Left cerebellum	Right frontoparietal deep and subcortical white matter	Left periventricular, basal ganglia and thalamus	Right frontoparietal deep and subcortical white matter, left cerebellum, sequelae of lesions of 3rd episode
4	Not available	Bilateral asymmetrical periventricular white matter, cervical cord, medulla, cerebellum		
5	Normal	Bilateral asymmetrical periventricular white matter	Bilateral asymmetrical subcortical white matter	
6	Dorsolumbar spinal cord	Dorsolumbar spinal cord, bilateral asymmetrical deep and subcortical white matter		
7	Optic nerve, callososeptal interface, deep and subcortical white matter	Optic nerve, deep and subcortical white matter, basal ganglia	Optic nerve, deep and subcortical white matter, cervical spinal cord	
8	Not available	Not available	Bilateral confluent basal ganglia, internal capsule, deep and subcortical white matter, left cerebral peduncle and bilateral brachium pontis	
9	Normal	Bilateral asymmetrical periventricular and deep white matter	Same as before	
10	Bilateral asymmetrical deep and subcortical white matter, left thalamus	Bilateral asymmetrical deep and subcortical white matter, left thalamus, bilateral optic nerve	Bilateral asymmetrical deep and subcortical white matter, callososeptal interface, left thalamus, bilateral optic nerve	
11	Bilateral asymmetrical deep and subcortical white matter tumefactive lesion	Same as before	Bilateral asymmterical deep and subcortical white matter lesion with contrast enhancement, new areas compared to before, spine normal	

20 monofocal MS events, predominant clinical manifestations were hemispheric syndrome in six (30%) followed by encephalopathy (5,25%) and visual symptoms in four (20%). Hemispheric syndrome with pancerebellar features was present in two polyfocal events, the other event being a paraparesis with visual manifestations.

Of the patients with an isolated episode of optic neuritis and/or myelitis who presented after the availability of anti-NMO antibody assay in the current center, only one showed antibody positivity. Of the two patients with anti-NMO antibody positivity in the recurrent group, one (patient 7) fulfilled the current consensus diagnostic criteria. The other patient (patient 2) had three episodes of encephalopathy with subclinical cervical myelopathy without any evidence of visual involvement.

Only one patient had multiphasic ADEM who presented with recurrent episodes of encephalopathy.

All the patients who presented with visual complaints had impaired visually-evoked responses; subclinical responses were present in none. None of the patients had abnormal brainstem-evoked audiometric responses. Routine CSF microscopy and biochemistry were normal in all; however, positive OCBs were seen in four patients (patient 4,5,8, and 11) [Table 3] with multiple sclerosis.

None of the patients had abnormality in neurometabolic or autoimmune work up in relevant clinicoradiological scenarios.

In those patients with single demyelination events, radiologically ADEM cases showed predominantly asymmetric involvement of deep and subcortical white matter with occasional involvement of deep grey matter, brainstem, and spinal cord. Patients with isolated ATM-like presentation had patchy involvement mainly of cervical and dorsal cord. Other patients of CIS had radiological picture corresponding to their clinical presentation.

The radiological features of recurrent demyelinating disorders are elaborated in Table 4. In multiple sclerosis, lesions were present predominantly in juxtacortical and periventricular

locations [Figure 1] followed by infratentorial (brainstem and cerebellum) sites and spinal cord. In anti-NMO antibody positive patients, lesions were present in cervical cord and deep and subcortical white and grey matter with optic nerve involvement seen in only one of the three patients. The classical LETM described in NMO was seen in the patient (anti-NMO antibody positive) with an isolated event of myelitis [Figure 2].

Thalamic and basal ganglia lesions were present in both MS and NMO patients.

The multiphasic ADEM patient had lesions spread over deep and subcortical white matter, thalamus, dorsal cord, and brainstem.

Individual episodes were treated with intravenous pulse methylprednisolone therapy followed by oral steroids for 2-3 weeks. Those with active infection were given intravenous immunoglobulin instead of steroids. In all patients with isolated single episode of demyelination, except for three patients with ATM, complete clinicoradiolgical recovery was observed. The three ATM patients showed radiological evidence of myelomalacia with clinical evidence of paraparesis as sequelae. One patient, who tested positive for serum anti-NMO antibody in the first event with ATM, has been started on oral azathioprine (2 mg/kg/day) without any recurrence for 1 year.

All patients with NMO and MS are being continued on azathioprine in a dosage of 2-3 mg/kg/day without any side effects. Except for two patients (patient 7 with NMO and 11 with MS) none of them have had a radiological or clinical recurrence after starting azathioprine, although sequelae are present in 50% patients (5/10). The patient with multiphasic ADEM is in remission and not on any long term immunomodulation. The median disease duration and follow-up since onset for those with recurrent episodes is 4 years (2.5-4.5years).

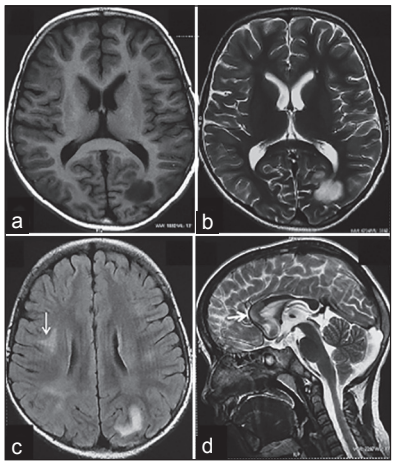

Figure 1: Axial MRI brain show a focal lesion in left occipital lobe which is hypointense on T1W (a) and hyperintense on T2W (b) images. Axial FLAIR image (c) at a higher level shows multiple other bilateral lesions in white matter, some of which are oriented perpendicular to the lateral ventricle (arrow). T2W sagittal image (d) shows the involvement of anterior part of the corpus callosum (arrow). MRI = Magnetic resonance imaging, FLAIR = Fluid-attenuated inversion recovery, T1W = T1-weighted, T2W = T2-weighted

Discussion

The current cohort describes clinical and diagnostic features, treatment, and follow-up in children with demyelinating disorders with emphasis on those with recurrences. In the first event it may be difficult to identify the ones that are going to recur, but every effort should be made to identify the ones that are at risk of recurrence. The pediatric clinicoradiological characteristics of NMO and MS are different from adults to some extent. The adult characteristics are better validated and more studies are required to delineate the pediatric features.[10,11]

Clinically, the predominant presentation in MS is polyfocal in children compared to monofocal in adolescents and adults.[12] Interestingly in the current cohort, the predominant presentation was monofocal, although the median age at onset was 5 years. The most frequent monofocal presentations reported in pediatric MS are motor and brainstem dysfunction followed by sensory features and ataxia.[13,14] In the current cohort although motor manifestations were the predominant finding, the next common presentation was encephalopathy. An ADEM-like presentation has been described in pediatric MS patients to the tune of 2-18%.[5,9,15-17] Thus, this cohort reinforces the fact that an ADEM-like presentation does not preclude a diagnosis of MS. Moreover, it seems that the concept of waiting for two non-ADEM events to occur for labeling MS and starting long-term immunomodulation[18] needs reevaluation and modification, particularly in the pediatric age group. The fact that the predominant pattern of pediatric MS is relapsing remitting and is supported by the current cohort.[9,19] The two recurrent NMO cases also had atypical clinical presentations. One presented with three ADEM-like events; whereas, the other one presented with monoparesis and impaired vision. Upto 16% pediatric NMO patients present with isolated cerebral syndrome; whereas in adults, brain lesions are mostly asymptomatic.[18]

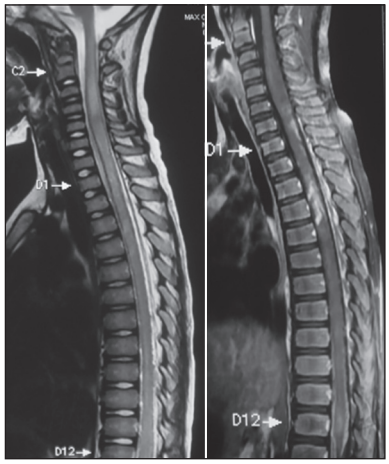

Figure 2: Sagittal MRI whole spine in an 8-year-old child showing hyperintense signal on T2 in the spinal cord extending from C2 vertebral level till the conus with patchy areas of contrast enhancement consistent with transverse myelitis

CSF OCB positivity is not mandatory for the diagnosis of MS. Moreover, they can be negative initially in the course of illness. However, they are useful in scenarios like primary progressive MS and in unusual clinical situations (ADEM-like presentations) as exemplified in the current cohort by patient 8 and 11, respectively.[4,6] Similarly in NMO, the pediatric consensus diagnostic criteria does not have serum anti-NMO positivity as an essential feature.[20] Upto 78% children with NMO demonstrate anti-NMO seropositivity.[21] In the current cohort, patient 6 although clinically fits into an NMO-like picture, was seronegative and has been labeled as opticospinal MS.[22] However, those patients who have presented with isolated episode of optic neuritis and/or myelitis (including long segment), not all have been tested for anti-NMO antibody positivity, as the test has been made available in the current center only in recent past. Evidence shows that anti-NMO antibody positivity is to the tune of 40-50% in patients with LETM. It is negligible in patients with smaller lesions. Moreover in patients with seropositive LETM, recurrence in terms of myelitis or neuritis is around 50%.[23,24]

Another immunological assay of interest is myelin oligodendrocyte glycoprotein (MOG). It is particularly useful in pediatric ADEM and MS. However in recent times, it has also been found to be positive in seronegative NMO. In the current cohort, none of the cases were subjected to this assay because of nonavailability. The therapeutic implications of this assay is that seropositive patients are more likely to benefit from plasmapheresis and/or B-cell directed therapy.[25,26]

Clinicoradiologically, all patients with MS in the current cohort fulfilled the criteria of dissemination of space and time according to the revised McDonald criteria.[4] Multifocal extensive bilateral diffuse white matter involvement has been classically described in ADEM and it is usually one of its differentiating features from MS. Rarely this has been described in pediatric MS and has been documented in patient 6 in the current cohort [Figure 3].[27] However, one has to keep a very high index of suspicion in view of close radiological mimickers like leukodystrophies and mitochondrial disorders. Patient 2 with NMO who presented with recurrent cerebral syndrome, radiologically demonstrated predominant periventricular and subcortical white matter involvement [Figure 4], which is in concordance with existing literature. This is because these regions are densely populated with aquaporin-4 channels.[18,28] Interestingly, patient 7 with NMO showed callososeptal interface signal changes [Figure 5] which are characteristic of MS.[11]

Researchers have tried to predict future risk of MS on the basis of features of the first demyelinating event. Before the international consensus definitions were developed, in a large prospective study with 296 French children, age more than 10 years and optic neuritis were predictive of increased risk of relapse, whereas encephalopathy and myelitis were associated with low risk of further attacks.[14] Dale *et al*., in their review mentioned that patients with a CIS presentation (except ATM) in their first episode are more likely to have recurrent episodes.[6] Recently, Banwell *et al*., prospectively followed 302 Canadian children and proposed that in the presence of T2 lesions on MRI brain, age >11.85 years, and absence of encephalopathy predict a higher risk of developing MS later in life.[15]

In the current cohort, the median age was lower for those with recurrent episodes as compared to those with single episode. However, there was a definite trend showing that an initial isolated ATM-like event was unlikely to recur. The factors in first episode of demyelination which has been stated to favor recurrence and their distribution in the current cohort have been enumerated in Table 5.

Radiologically, presence of periventricular perpendicular ovoid lesions (PVPOLs) in an initial demyelinating event should be considered strongly for future development of MS even in the presence of encephalopathy.[29] In the current cohort, these were seen in patient 10 with MS in one of the recurring episodes [Figure 1]. Interestingly, patient 7 who was finally diagnosed as seropositive NMO had PVPOLs in first episode of demyelination. Tumefactive lesions which are classically seen with ADEM[10] have been demonstrated in the current cohort in a primary progressive OCB positive MS patient (patient 11) [Figure 6].

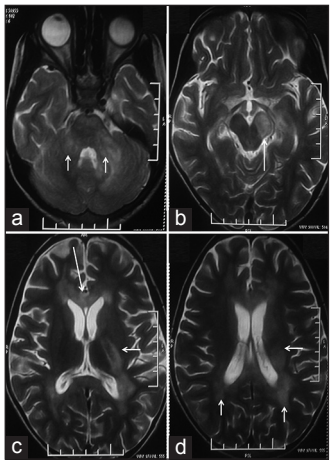

Figure 3: T2-weighted axial MRIbrain at multiple levels showing multifocal bilateral hyperintense lesions involving bilateral brachium pontis (arrows in a), left cerebral peduncle (arrow in b), corpus callosum (long arrow in c), left internal capsule (short arrow in c), and deep periventricular white matter (arrows in d)

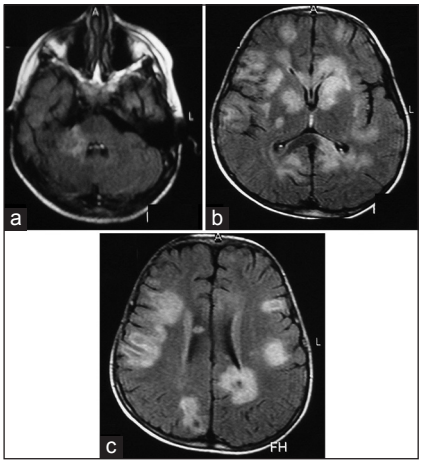

Figure 4: Axial FLAIR MRI brain showing bilateral asymmetrical multiple hyperintense focal lesions involving right brachium pontis (a), basal ganglia (b), corpus callosum, and subcortical and deep white matter(c)

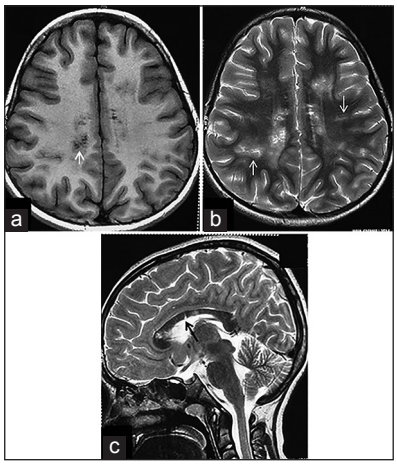

Figure 5: MRI showing bilateral multiple focal hypointense lesions on T1W axial (a) and bilateral multiple focal hyperintense lesions on T2W axial (b) and sagittal (c) involving centrum semiovale with predominant periventricular distribution. The perpendicular orientation of few lesions to the ventricles (arrows in b) represents the 'periventricular perpendicularly oriented lesions(PVPOLs)'. Note the characteristic involvement of the callososeptal interface (arrow in c)

Table 5: Distribution of factors favoring recurrence in the first episode of demyelination in those with recurrent episodes in the current cohort

Factors in first episode of demyelination favoring recurrence	Distribution in current cohort
Age >10 years	Patient 5 (*n*=1/11)
Optic neuritis	Patients 5,7, and 9 (*n*=3/11)
CIS (except ATM)	Patients 4,5,7,9,10, and 11 (*n*=6/11)
Presence of T2 lesions in MRI brain	Patients 1,2,3,7,10, and 11 (*n*=6/9)
Absence of encephalopathy	Patients 4,5,6,7,9,10, and 11 (*n*=7/11)
Periventricular perpendicular ovoid lesions	Patient 7 (*n*=1/9)

CIS = Clinically isolated syndrome, ATM = Acute transverse myelitis, MRI = Magnetic resonance imaging

Azathioprine is one of the commonly used long-term immunomodulators in patients with NMO[11] which also has been followed for current cohort with encouraging results. Current recommendation for treating pediatric MS suggests glatiramer acetate and interferon-β as the first-line drugs. Second line includes immunomodulators like azathioprine.[30,31] The current status of azathioprine in MS is one of a promising disease modifying agent with favorable risk-benefit ratio, which should be evaluated in randomized trials with interferon, as inferred by the Cochrane systematic review group.[31] In a developing country like ours, factors like cost of the drugs, transportation expenses for coming to the hospital, and awareness for the requirement of repeated parenteral therapy are significant barriers for treatment of chronic conditions like MS. In the current cohort, all patients of MS have been started on azathioprine only. Except one, none of the patients had a clinical or radiological recurrence after starting azathioprine and the sequelae of previous episodes were improving in all. In view of the logistic reasons described above, none of them had been started on glatiramer acetate and interferon-β.

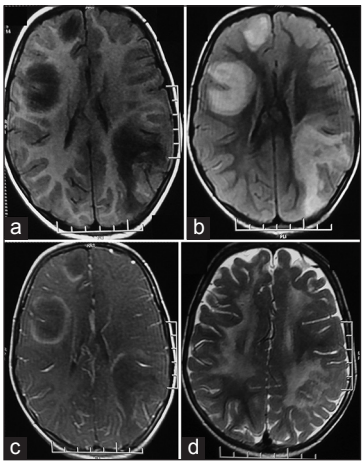

Figure 6: Axial T1W (a), FLAIR (b), and post-contrast T1W (c) images showing bilateral large tumefactive lesions appearing hypointense on T1, hyperintense on FLAIR, and peripheral rim enhancement on post gad images. Follow-up MRI axial T2W image (d) done 1 year later shows marked regression in the size of the lesions

The current study has certain limitations, viz., retrospective design and limited sample size. However, it still highlights certain important aspects of these disorders. Strong clinical suspicion along with radiological support can help diagnose pediatric central nervous system demyelinating disorders. Currently proposed diagnostic criteria require validation in pediatric population. Factors that predict recurrence in the adult population may not be extrapolated to the pediatric population (particularly in < 10 years age), further studies are required in larger population size. Steroids have a well-established role in the management of an acute demyelinating event. Immunomodulators like interferons and glatiramer acetate are usually recommended for long-term management of MS to prevent relapses. However, in a resource-limited setting, drugs like azathioprine may be useful.

References

1. Cañellas AR, Gols AR, Izquierdo JR, Subirana MT, Gairin XM. Idiopatic inflammatory-demyelinating disease of central nervous system. Neuroradiology 2007;49:393-409.
2. Petzold A. Isolated, relapsing and progressive demyelinating diseases of the central nervous system. J Neurol 2008;255:69-76.
3. Spalice A, Parisi P, Papetti L, Nicita F, Ursitti F, Del Balzo F, *et al*. Clinical and pharmacological aspects of inflammatory demyelinating diseases in childhood: An update. Curr Neuropharmacol 2010;35-148:35.
4. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292-302.
5. Krupp LB, Banwell B, Tenembaum S. International Pediatric MS Study Group. Consensus definitions proposed for pediatric multiple sclerosis and related disorders. Neurology 2007;68:S7-12.
6. Dale RC, Brilota F, Banwell B. Pediatric central nervous system inflammatory demyelination: Acute disseminated encephalomyelitis, clinically isolated syndromes, neuromyelitis optica, and multiple sclerosis. Curr Opin Neurol 2009;22:233-40.

7. Pohl D, Waubant E, Banwell B, Chabas D, Chitnis T, Weinstock-Guttman B, *et al*. International Pediatric MS Study Group. Treatment of pediatric multiple sclerosis and variants. Neurology 2007;68:54-65.
8. Dunder NO, Anler V, Gugen A, Serdoruglu A, Yarar C. Relapsing acute disseminated encephalomyelitis in children: Further evaluation of the diagnosis. J Child Neurol 2010;25:1491-7.
9. Rubin JP, Kuntz NL. Diagnostic criteria for pediatric multiple sclerosis. Curr Neurol Neurosci Rep 2013;13:354-63.
10. Neuteboom RF, Boon M, Catsman Berrevoets CE, Vles JS, Gooskens RH, Stroink H, *et al*. Prognostic factors after a first attack of inflammatory CNS demyelination in children. Neurology 2008;71:967-3.
11. McKeon A, Lennon VA, Lotze T, Tenenbaum S, Ness JM, Rensel M, *et al*. CNS aquaporin-4 autoimmunity in children. Neurology 2008;71:93-100.
12. Yeh EA, Chitnis T, Krupp L, Ness J, Chabas D, Kuntz N, *et al*. US Network of Pediatric Multiple Sclerosis Centers of Excellence. Pediatric multiple sclerosis. Nat Rev Neurol 2009;5:621-31.
13. Banwell B, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M. Multiple sclerosis in children: Clinical diagnostics, therapeutic strategies and future directions. Lancet Neurol 2007;6:887-902.
14. Mikaeloff Y, Suissa S, Vallée L, Lubetzki C, Ponsot G, Confavreux C, *et al*. First episode of acute CNS inflammatory demyelination in childhood: Prognostic factors for multiple sclerosis and disability. J Pediatr 2004;144:246-52.
15. Banwell B, Bar-Or A, Arnold DL, Sadovnick D, Narayanan S, McGowan M, *et al*. Clinical, environmental, and genetic determinants of multiple sclerosis in children with acute demyelination: A prospective national cohort study. Lancet Neurol 2011;10:436-45.
16. Verhey LH, Branson HM, Shroff MM, Callen DJ, Sled JG, Narayanan S, *et al*. MRI parameters for prediction of multiple sclerosis diagnosis in children with acute CNS demyelination: A prospective national cohort study. Lancet Neurol 2011;10:1065-73.
17. Mikaeloff Y, Caridade G, Husson B, Suissa S, Tardieu M. Neuropediatric KIDSEP Study Group of the French Neuropediatric Society. Acute disseminated encephalomyelitis cohort study: Prognostic factors for relapse. Eur J Pediatr Neurol 2007;11:90-5.
18. Pittock SJ, Lennon VA, Krecke K, Wingerchuk DM, Lucchinetti CF, Weinshenker BG. Brain abnormalities in neuromyelitis optica. Arch Neurol 2006;63:390-6.
19. Verhey LH, Shroff M, Banwell B. Pediatric multiple sclerosis: Pathobiological, clinical and magnetic resonance imaging features. Neuroimaging Clin N Am 2013;23:227-43.
20. Makhani N, Banwell B Shroff M. Diagnosing neuromyelitis optica. Neuroimaging Clin N Am 2013;23:279-1.
21. Banwell B, Tenembaum S, Lennon VA, Ursell E, Kennedy J, Bar-Or A, *et al*. Neuromyelitis optica-IgG in childhood inflammatory demyelinating CNS disorders. Neurology 2008;70:344-52.
22. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. Lancet Neurol 2007;6:805-15.
23. Weinshenker BG, Wingerchuk DM, Vukusic S, Linbo L, Pittock SJ, Lucchinetti CF, *et al*. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. Ann Neurol 2006;59:566-9.
24. Alvarenga MP, Alvarenga RM, Alvarenga MP, Santos AM, Thuler LC. Anti-AQP4 antibody in idiopathic acute transverse myelitis with recurrent clinical course: Frequency of positivity and influence in prognosis. J Spinal Cord Med 2012;35:251-5.
25. Mayer MC, Meinl E. Glycoproteins as targets of autoantibodies in CNS inflammation: MOG and more. Ther Adv Neurol Disord 2012;5:147-59.
26. Tanaka K, Tanaka M. Pathogenesis of autoantibodies in demyelinating disorders of the central nervous system. Nihon Rinsho 2014;72:2067-72.
27. Callen DJ, Shroff MM, Branson HM, Li DK, Lotze T, Stephens D, *et al*. Role of MRI in the differentiation of ADEM from MS in children. Neurology 2009;72:968-73.
28. Pittock SJ, Weinshenker BG, Lucchinetti CF, Winger-chuk DM, Corboy JR, Lennon VA. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol 2006;63:964-8.
29. Alper G, Heyman R, Wang L. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow-up: Comparison of presenting features. Dev Med Child Neurol 2009;51:480-6.
30. Kuntz NL, Chabas D, Weinstock-Guttman B, Chitnis T, Yeh EA, Krupp L, *et al*. Treatment of multiple sclerosis in children and adolescents. Expert Opin Pharmacother 2010;11:505-20.
31. Casetta I, Iuliano G, Filippini G. Azathioprine for multiple sclerosis. Cochrane Database Syst Rev 2007;17.

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