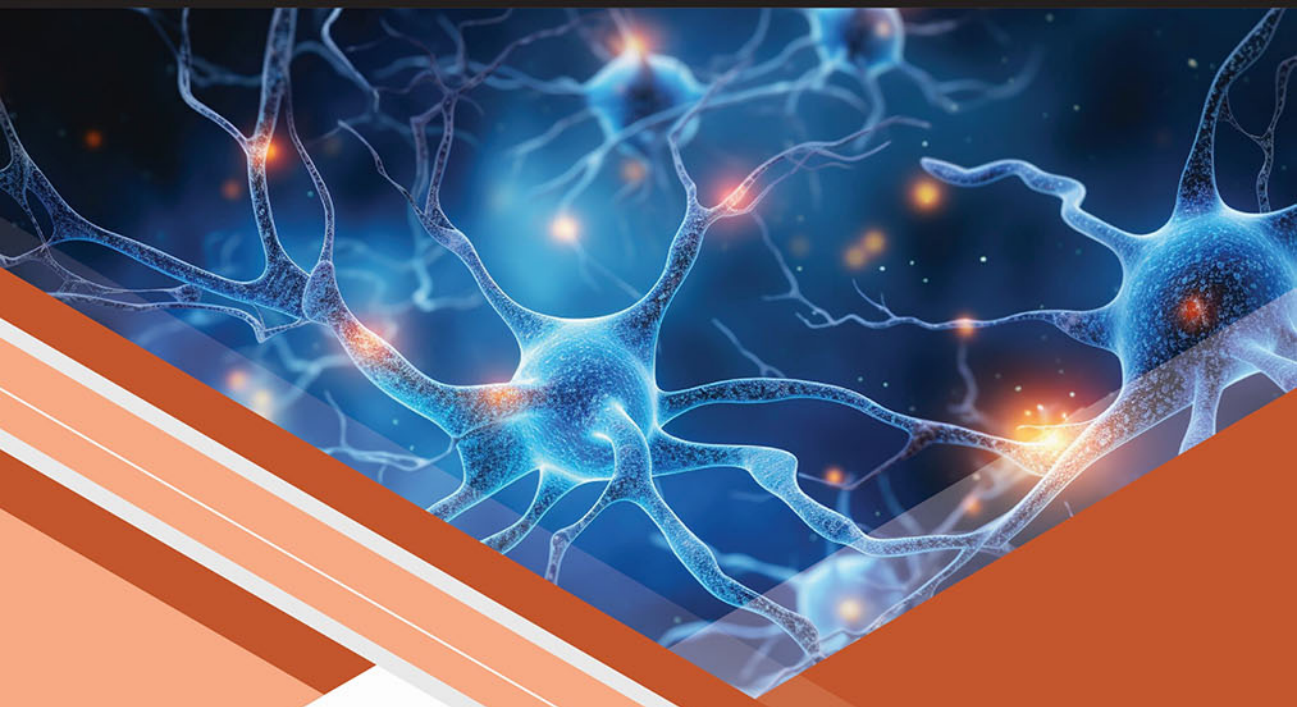

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CHAPTER 6

Pediatric Demyelinating Disorders: Management Update

Lokesh Saini, Kandha Kumar UK

ABSTRACT

Pediatric acquired demyelinating syndromes (ADS) encompass a diverse array of immune-mediated diseases, including acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte glycoprotein antibody-associated diseases (MOGAD), and multiple sclerosis (MS). Due to the overlapping and evolving nature of their symptoms, accurately distinguishing between these conditions based on initial presentation is complex. This chapter addresses the management strategies for these disorders, integrating recent evidence to guide treatment.

Keywords: Pediatric demyelinating disorders, ADEM, NMSOD, MOGAD, Management.

INTRODUCTION

Pediatric acquired demyelinating syndromes (ADS) include a broad spectrum of immune-mediated demyelinating diseases such as acute disseminated encephalomyelitis (ADEM), neuromyelitis optica spectrum disorders (NMOSD), myelin oligodendrocyte-glycoprotein antibody-associated diseases (MOGAD) and multiple sclerosis (MS). As the symptoms overlap and evolve over time, it becomes challenging to delineate the specific etiology based on the initial presentation. This chapter focuses on the management aspect of individual disorders in the context of recent evidence. **Figures 1 to 3** and **Table 1** depict the usual sites of involvement in various demyelinating disorders.[1]

MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY-ASSOCIATED DISEASE

Introduction

The common presentation of MOGAD includes ADEM (45.6%), optic neuritis (ON) (29.5%), transverse myelitis (TM) (11.2%), ON + TM (4.3%), and others (9.5%). Other rare forms of presentation include encephalitis-like phenotype, leukodystrophy-like phenotype, combined central and peripheral demyelination, overlapping syndromes, and nonclassifiable phenotypes.[2,3] Anterior segment ON/papillitis, conus involvement, and H-shaped spinal cord demyelination are strong clinico-radiological handles for early suspicion of MOGAD.

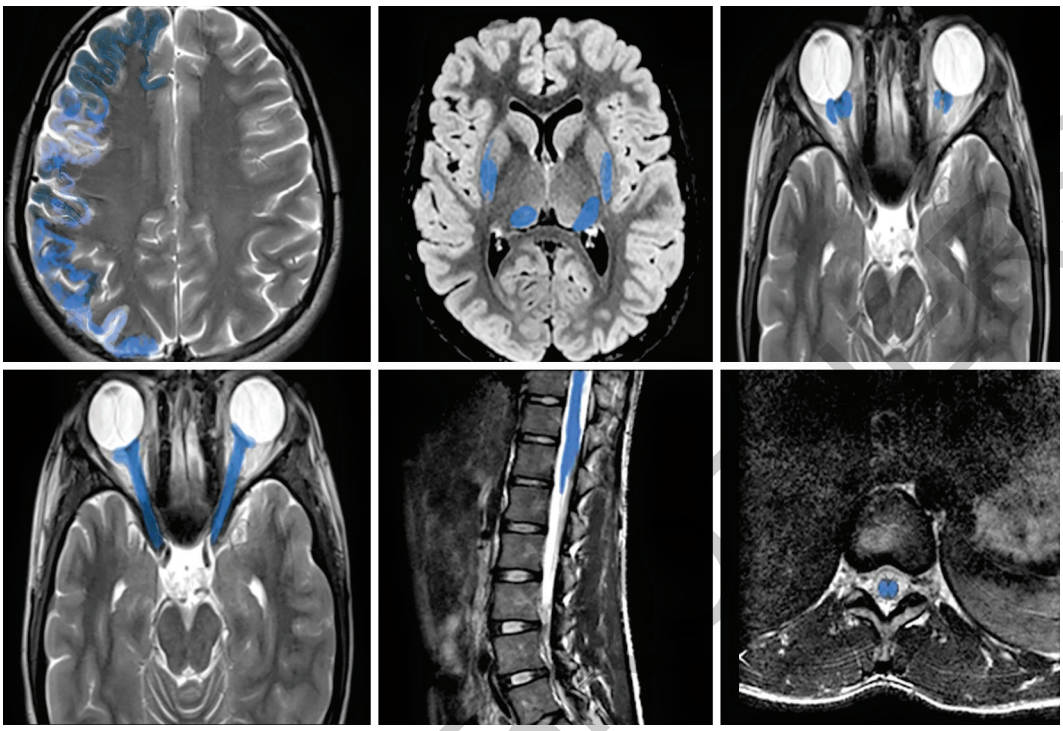


FIG. 1: Usual sites involved in myelin oligodendrocyte-glycoprotein antibody-associated diseases.

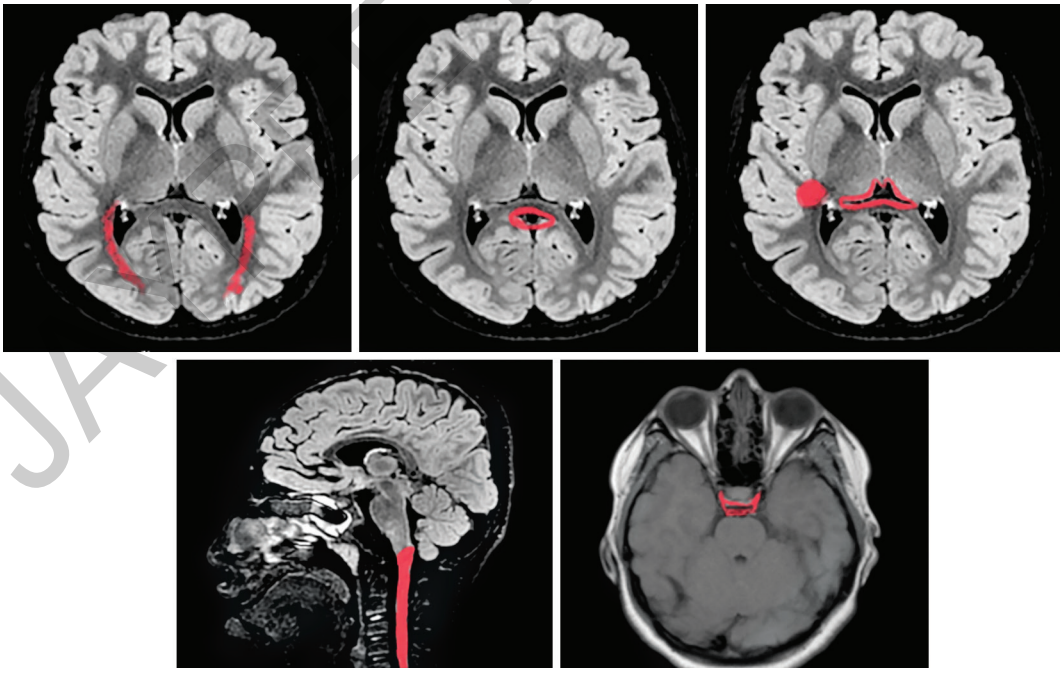


FIG. 2: Usual sites involved in neuromyelitis optica spectrum disorders.

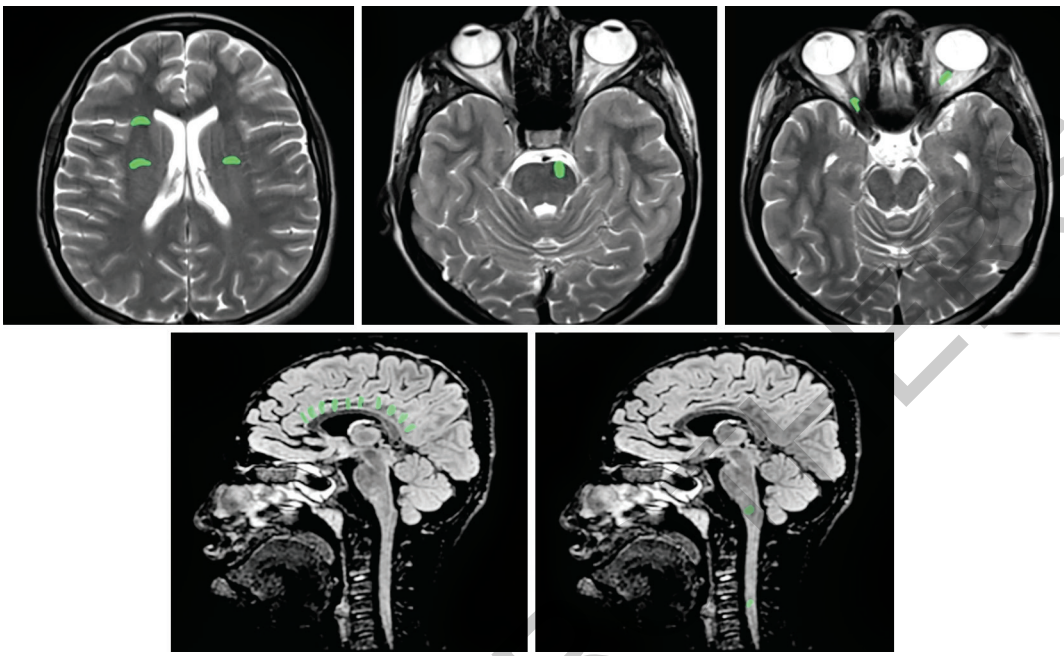


FIG. 3: Usual sites involved in multiple sclerosis.

TABLE 1: Usual sites involved in various demyelinating disorders.

Sites	MOGAD	NMOSD	MS
Brain	Small punctate to large tumefactive lesions in both white and deep gray matter;	Periaqueductal gray matter, area postrema, peri 4th ventricle, corticospinal tracts, rarely thalamus and brainstem	Ovoid lesion involving MS typical sites—juxtacortical, periventricular, and infratentorial. Ring-enhancing lesions are also commonly seen
Spine	Longitudinally extensive lesions involving >3 vertical segments, conus involvement, H-sign due to predominant gray matter involvement, and pencil-thin ependymal enhancement	Longitudinally extensive single lesion commonly involving the cervical cord. Holocord involvement in the axial images	Multiple short lesions; periphery of cord. Ring or nodular enhancement
Optic nerve	Long lesions in the anterior segments, papillitis, perineural sheath enhancement. Involvement can be unilateral or bilateral	Uni-/bilateral, mainly posterior segments, optic chiasma and optic tracts	Unilateral, short lesions, mainly involving the intraorbital portion

(MOGAD: myelin oligodendrocyte-glycoprotein antibody-associated diseases; NMOSD: neuromyelitis optica spectrum disorders; MS: multiple sclerosis)

Other variants of MOGAD include:

- Cortical—encephalitis-like phenotype;
- FLAMES (FLAIR-hyperintense lesions in anti-MOG-associated encephalitis with seizures);
- Leukodystrophy-like phenotype;
- Combined central and peripheral demyelination;
- Overlapping syndromes; and
- Pyrexia of unknown origin.

Pediatric versus Adult Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease

Table 2 depicts the differences between pediatric and adult-onset MOGAD.[2-5]

Special Precautions in Pediatric Myelin Oligodendrocyte Glycoprotein Antibody-associated Disease

Children are more prone to infections following the immunotherapy. Screening for tuberculosis, retroviral infection, and viral hepatitis (hepatitis B and C) before initiating aggressive immunotherapy.

Prophylactic antibiotics including co-trimoxazole (5 mg/kg/day of trimethoprim component thrice a week) and fluconazole (3 mg/kg/day) should be started when children are treated with second-line immunotherapy like rituximab, tocilizumab, etc.

Table 3 depicts the vaccination schedule to be followed when children are on immunosuppressants.[6,7]

Treatment of Acute Attack

All acute attacks of MOGAD despite severity should be treated. Intravenous methylprednisolone (IVMP) at 20–30 mg/kg/day (maximum 1,000 mg) in a single dose for 5 consecutive days should be administered.[4,8-10] MOGAD generally has a very good response to steroids. However, the initial responsiveness to the glucocorticoids may neither necessarily prevent further relapses nor determine the severity and spectrum of clinical disease in further attacks.[4] In a large retrospective study, it was observed that IVMP caused complete resolution in 50% and partial response in 44% of the population.[11] IVMP should be followed

TABLE 2: Differences between pediatric and adult-onset MOGAD.

Characteristics	Pediatric MOGAD	Adult MOGAD
Incidence	0.31/100,000 children/year	0.13/100,000 adults/year
Prevalence among all ADS	35–40% of all pediatric ADS	5% of all ADS in adults
Most common presentation	ADEM like presentation	Optic neuritis and transverse myelitis
Incidence of relapses	Less common (Children <10 years old usually have a monophasic course. Incidence of relapse is 30–50% in children >10 years.)	More common (Incidence of relapse is 50–70% in adult patients)
Prognosis	Children <10 years old have more substantial recovery after the initial attack with a lower likelihood of relapse	Adolescents and adults especially those presenting with optic neuritis and transverse myelitis need long-term maintenance therapy

(ADS: acquired demyelinating syndromes; ADEM: acute disseminated encephalomyelitis; MOGAD: myelin oligodendrocyte-glycoprotein antibody-associated diseases)

TABLE 3: Recommendation for vaccination during immunosuppressant therapy.

Immunosuppressant therapy	Vaccination schedule
High dose prednisolone (2 mg/kg/day)	All vaccines can be administered 1 month after discontinuation of steroids
Moderated dose prednisolone (0.75–2 mg/kg/day)	No live vaccines until discontinuation of steroid therapy
Low dose alternate day steroids	Live vaccines can be administered concurrently
Treatment with rituximab	Avoid live vaccines until the CD-19 count recovers
Treatment with tocilizumab, cyclophosphamide	Avoid live vaccine until 3 months off therapy
Treatment with mycophenolate mofetil, azathioprine	Avoid live vaccine until 1 month off therapy

by oral prednisolone at 1–2 mg/kg/day for 4 weeks followed by tapering over 3 months. Slow tapering of oral steroids over 3–6 months may prevent relapses to a significant extent when compared to rapid tapering.[5,12]

If the Initial Intravenous Methylprednisolone Fails?

If the patient is refractory to the IVMP or shows inadequate response, therapeutic plasma exchange (TPE) should be initiated. A total of 5–7 sessions on every alternate day is recommended.[8] There are multiple studies demonstrating the benefits of TPE in patients who fail to respond to IVMP with complete recovery in 60–76% of the population.[5,11] Intravenous immunoglobulin (IVIg) at 2 g/kg over 2–5 days is an alternative in centers where TPE is not feasible.[8]

Maintenance Therapy

The usual course of MOGAD especially in the pediatric population tends to be monophasic with a very good response to initial treatment. The rationale for maintenance therapy is that, some degree of disability accumulates after each mild attack, increasing the likelihood of long-term morbidity.[13] There are no randomized controlled trials (RCTs) comparing the efficacy of individual immunosuppressants with one another. As per a recent systematic review, rituximab or IVIg can be used as the initial choice for maintenance therapy.[14,15]

Who are the Candidates for Maintenance Therapy?

- Patients with poor recovery after the initial attack defined by, Expanded Disability Status Scale (EDSS) ≥3, Modified Rankin Scale (MRS) ≥3, or visual acuity (VA) ≤0.3, even after 1–3 months of acute treatment.[8]
- Patients with clinical relapse.[8]

Parenteral Therapy

Intravenous Immunoglobulin

Monthly IVIg infusion as a maintenance therapy is also one of the efficacious methods to prevent relapse.[4,12] 1–2 g/kg over 1–5 days every month is recommended.[8] In a cohort study on pediatric MOGAD patients, annualized relapse rate (ARR) was lowest with IVIg when compared to all other maintenance immunosuppressants.[16] Adverse effects include headaches from aseptic meningitis and an increased risk of thromboembolic events. Subcutaneous immunoglobulin (SCIg) also has similar efficacy as that of IVIg and possesses cost-benefit.[17] However, studies are needed to validate its effect on MOGAD patients. Cost is an important limitation for its routine use.

Rituximab

Rituximab is a chimeric monoclonal antibody that targets CD20 on B cells and results in B-cell depletion. There are different protocols

for dosing, frequency, and durations. The regimen usually followed in pediatric MOGAD is 375 mg/m^2/dose every week. Total of 2–4 doses is given by a standardized protocol. This cycle is repeated every 6 months. Monitoring of CD19 and 20 levels before the next dose is recommended. Common side effects are persistent hyperglobulinemia and leukopenia predisposing the patients for serious infections. Prophylactic antimicrobials such as co-trimoxazole and fluconazole may be considered. Despite adequate B-cell depletion, relapse occurs in about 25–86% of the population.[12,18-20]

Tocilizumab

Tocilizumab is an anti-interleukin-6 (IL-6) receptor monoclonal antibody, which is an important IL for B-cell maturation and antibody production. This is administered at a dose of 8 mg/kg through IV infusion every 4 weeks. It has been evaluated in retrospective observational studies for relapsing MOGAD. These studies, though limited in sample size, suggest that tocilizumab reduces ARR significantly.[21,22] However, potential adverse effects include increased infection risk, cytopenias, and elevated liver enzyme levels. Therefore, regular blood monitoring is essential, including a complete blood count and liver enzyme tests at baseline, monthly for the first 3 months, and every 2 months thereafter. Prophylactic antimicrobials such as co-trimaxazole and fluconazole may be considered.

The role of other immunosuppressants including cyclophosphamide, cyclosporin, mitoxantrone, or methotrexate in MOGAD is limited.

Oral Agents

Oral immunosuppressants including azathioprine and mycophenolate mofetil (MMF) are the preferred steroid sparing agents. Bridging therapy with low-dose prednisolone for 3–6 months is recommended, as these agents have an initial drug latency period to elicit immunosuppression.

Mycophenolate Mofetil

The MMF is the preferred oral immunosuppressant over azathioprine and its efficacy has been demonstrated in multiple cohort studies.[23-25] MMF elicits its immunosuppression by inhibiting inosine monophosphate dehydrogenase and thereby preventing T- and B-cell proliferation. The recommended dose is 600–1,200 mg/m^2/day (maximum 2 g/day) in two divided doses.[8] Adverse effects include gastrointestinal toxicity, risk of infections, and cytopenia. It should be used with caution in adolescent girls due to its potential risk for teratogenicity. Periodic monitoring of blood counts and liver function tests is mandatory.

Azathioprine

The recommended dose is 2–3 mg/kg/day in single or divided doses.[8] It is a purine synthesis inhibitor, thereby preventing B- and T- cell proliferation. Thiopurine-S-methyltransferase enzyme activity should be tested before initiating azathioprine as low enzyme activity cumulates the drug toxicity. Retrospective studies demonstrated the efficacy of azathioprine with a 50% reduction in relapse rates.[9,12,16] Adverse effects include infection, rash, transaminitis, bone marrow suppression, and risk of future malignancies. Periodic monitoring of blood counts and liver function tests is mandatory.

When to Withdraw the Maintenance Treatment?

Currently, there are no formal guidelines for the de-escalation and discontinuation of maintenance immunotherapy in MOGAD. Observations indicate that some patients experience long periods of stable disease without treatment and only relapse after several years, sometimes over a decade.

This suggests that continuous maintenance treatment over such extended periods may lead to overtreatment. Generally, it is advisable to consider de-escalating maintenance immunotherapy after 2 years of stable disease without relapses, along with stable visual, motor, autonomic, and cognitive assessments.[8]

Flowcharts 1 and 2 depict an overview on the management of MOGAD.

Special Considerations

Although there are no clear recommendations for the management of MOGAD variant, in children with ON or TM presentation long-term immunotherapy either with a low dose of prednisolone for 9–12 months or IV rituximab can be given. In children presenting with status epilepticus with uncontrolled raised intracranial pressure (ICP) and magnetic resonance imaging (MRI) showing cortical encephalitis, early initiation of second-line immunotherapy such as tocilizumab and TPE along with methylprednisolone can be considered.

NEUROMYELITIS OPTICA SPECTRUM DISORDERS

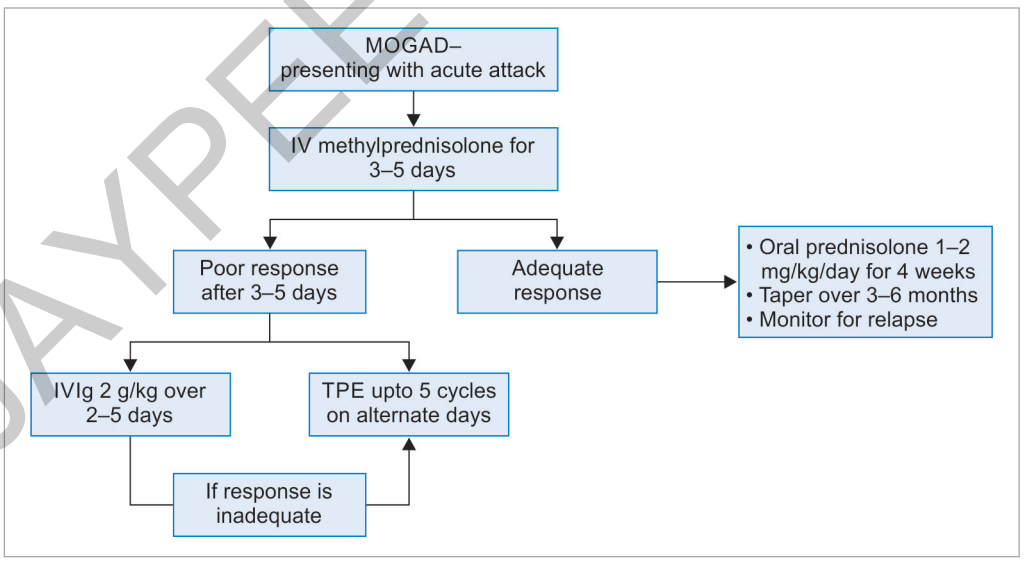
Introduction

Neuromyelitis optica spectrum disorder is an inflammatory disorder of the central nervous system, primarily affecting the spinal cord and optic nerves with involvement of other areas including the area postrema, periaqueductal gray matter, and hypothalamus. The disorder is known for its morbid attacks, chronicity, and a relapsing course. The clinical manifestations include ON, TM, area postrema syndrome, cerebral syndrome, acute brainstem syndrome, diencephalic clinical syndrome, and other overlapping autoimmune diseases.[26]

Management of Acute Attack

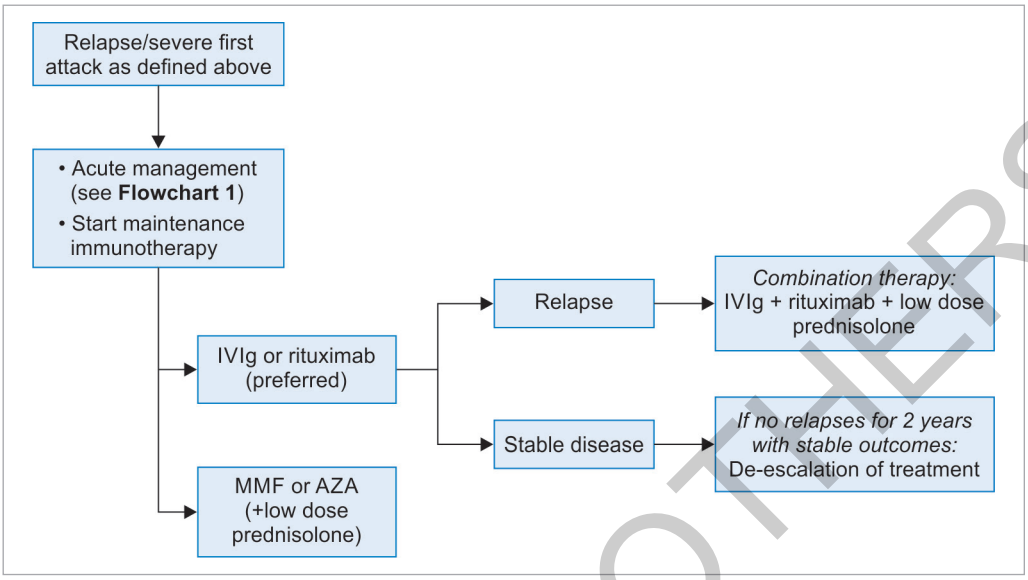
The treatment should be initiated immediately without any delay in NMOSD acute attacks. Acute therapy includes:

- IVMP, 30 mg/kg (maximum 1 g) for 3–5 days.



FLOWCHART 1: MOGAD—management of acute attack.

(IVIg: intravenous immunoglobulin; MOGAD: myelin oligodendrocyte-glycoprotein antibody-associated diseases; TPE: therapeutic plasma exchange)



FLOWCHART 2: Maintenance therapy in MOGAD.
(IVIg: intravenous immunoglobulin, MMF: mycophenolate mofetil; AZA: azathioprine)

- If the patient shows insufficient response, then TPE 5–10 cycles on alternate days should be done.[27]
- In those patients, who showed insufficient response to steroids during previous attacks or sufficient response to apheresis therapy during previous attacks or those with severe myelitis, TPE is recommended as the first-line treatment.[27]

Either plasma exchange or immunoadsorption may be used as apheresis therapy. For patients with severe attacks, concomitant treatment with IVMP and TPE may be used. This is followed by oral prednisolone at 1–2 mg/kg/day for 4 weeks and tapering over 3–6 months. However, the duration of oral steroids depends upon aquaporin 4 antibody-immunoglobulin G (AQP4-IgG) serostatus, disease activity, mode of action, and the expected time to the attack-preventive effect of the subsequent immunotherapy.

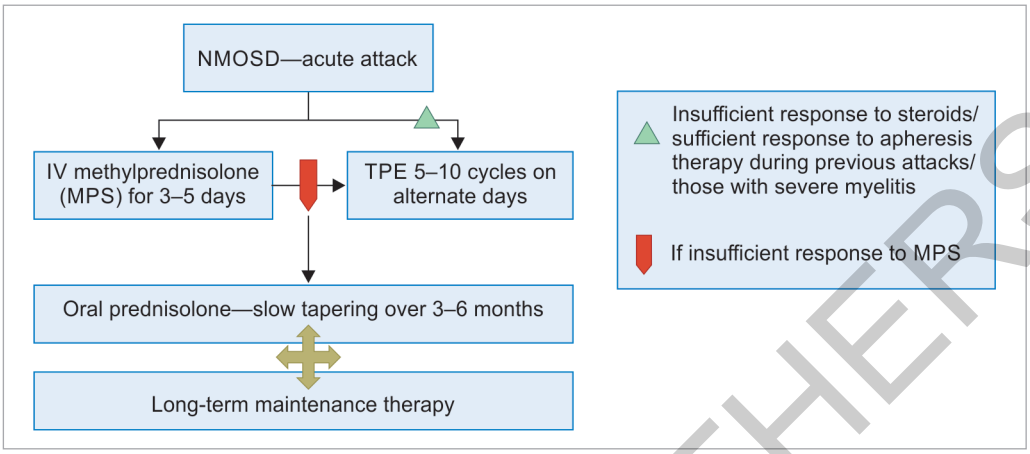
Flowchart 3 depicts the overview of the management of the initial attack of NMOSD.

Long-term Therapy

Indications: Long-term immunotherapy should be given to every patient with AQP4-IgG-positive NMOSD even after the first attack. The available treatment options include rituximab, IVIg, MMF, azathioprine, and upcoming future options include, tocilizumab, eculizumab, satralizumab, inebilizumab, and ofatumumab. The risk of recurrence of AQP4-IgG-positive NMOSD is 50% leading to disabling ON and TM.[28-30]

Rituximab

There are numerous studies demonstrating a significant reduction in annual relapse rates and even complete cessation of further relapses when rituximab is used as a maintenance therapy.[31,32] There are no standard protocols for dosing and frequency of rituximab administration. The commonly followed protocol is 375 mg/m^2/dose every week for 4 weeks. CD19 counts should be



FLOWCHART 3: Overview of the management of the initial attack of NMOSD.

(IV: intravenous; IVMP: intravenous methylprednisolone; NMOSD: neuromyelitis optica spectrum disorders; TPE: therapeutic plasma exchange)

monitored 4 weeks after the last dose and then monthly. There is a higher chance of B-cell repopulation as early as 4 months following rituximab administration.[31] Further cycles are repeated every 6 months or when CD19 >1%.[33] Rituximab may be considered as a first-line maintenance therapy for relapse prevention in pediatric NMOSD patients.[34]

Intravenous Immunoglobulin

There are no studies to elucidate the role of IVIg in the pediatric NMOSD population as a long-term preventive therapy. A retrospective adult study showed a 66% reduction in relapse when IVIg is administered every 2 monthly.[35] Induction with 2 g/kg over 2–5 days during the acute attack followed by 1 g/kg/dose every month as maintenance therapy is recommended.

Mycophenolate Mofetil

The MMF is effective in pediatric NMOSD as a long-term preventive therapy. A large retrospective study showed that the median ARR and EDSS scores were significantly decreased, with 60% of patients being relapse-free.[24] The dose used is 600–1,200 mg/m^2/day in two divided doses. It should be overlapped with low-dose oral prednisolone for an initial 6 months. Periodic monitoring of blood counts and liver function tests is mandatory.

Azathioprine

Role of azathioprine was evaluated in a large cohort study containing both adult and pediatric population. It was found that reductions in relapse rate 89% and 61% remained relapse-free at 18 months after treatment initiation.[36] The recommended dose is 2–3 mg/kg/day in single or divided doses. Periodic monitoring of blood counts and liver function tests is mandatory.

New Treatment

Tocilizumab

There are two open-label studies in adult NMOSD patients showing the efficacy of tocilizumab as a preventive therapy.[37] There are few case reports in pediatric NMOSD, where tocilizumab provided a stable clinical course without relapse in rituximab failed patients.[38,39]

Future Treatments

Eculizumab

Eculizumab is a humanized monoclonal antibody designed to target the C5 complement protein, thereby inhibiting the alternate pathway of the complement cascade which attacks AQP4-expressing cells. Recently, the Food and Drug Administration (FDA) approved eculizumab for treating AQP4-IgG positive NMOSD in adult patients based on the phase 3 results of the PREVENT trial. It showed a relapse-free status in 98% of patients treated with eculizumab when compared to 63% of those receiving a placebo. However, its role in the pediatric population has not been validated.[34] One of the serious adverse effects of eculizumab is infection of capsulated organisms as membrane attack complex (MAC) is inhibited. Vaccination against pneumococcus, meningococcus, and *H. influenzae* should be done before the treatment.

Satralizumab

Satralizumab (SA237), similar to tocilizumab, is a humanized recombinant monoclonal antibody that targets the IL-6 receptor, offering immunomodulatory effects. In a phase 3 trial with 83 patients (composing 7 adolescent patients), satralizumab significantly lowered the risk of relapses, in the seropositive group.[40] Pediatric RCT is still in progress.

Inebilizumab

Inebilizumab is a humanized monoclonal antibody, targeted against CD19 B cells. It provides a broader depletion of B-cell lineage when compared to rituximab. In a phase 3 trial, with 230 adult patients with active NMOSD (93% seropositive), treatment with inebilizumab significantly reduced the risk of clinical relapses, disability progression, MRI lesion activity, and the need for hospitalizations compared to the placebo group. Experience in the pediatric population is not yet clear.

Duration of Long-term Therapy

There are no clear data, to recommend the duration and de-escalation of immunotherapy in NMOSD patients. Immunotherapy should be continued in stable AQP4-IgG-positive NMOSD patients, and must be closely monitored, if treatment is temporarily or permanently discontinued due to side effects or patient choice. In seronegative NMOSD patients who have been stable for over 5 years, reevaluation of immunotherapy may be considered.

ACUTE DISSEMINATED ENCEPHALOMYELITIS

The ADEM is a postinfectious demyelinating disorder of the central nervous system, triggered by an environmental stimulus (viral infection, vaccines) in genetically susceptible individuals.[41] The classic ADEM presents with acute febrile encephalopathy with multifocal neurological deficits, has a monophasic course, and responds well to immunotherapy.[42] Other variants include acute hemorrhagic leukoencephalitis, acute hemorrhagic encephalomyelitis, and acute necrotizing hemorrhagic leukoencephalitis of Weston Hurst.[43] As the most common presentation of MOGAD is an ADEM-like phenotype, serological testing for myelin oligodendrocyte glycoprotein (MOG) antibodies is recommended in all patients with suspicion of ADEM.[2]

Management

The initial management includes broad-spectrum antibiotics and acyclovir (until infective etiology is ruled out), antiraised ICP measures and seizure management. Once the possibility of ADEM is strongly considered, IVMP at 30 mg/kg/dose for 3–5 days is the

initial treatment of choice.[44] This is followed by oral prednisolone at 1–2 mg/kg/day for 2 weeks followed by tapering over 4–6 weeks. If there is an inadequate clinical response to IVMP, TPE (in case of associated TM) or IVIg constitutes the second-line therapy.[44] Only patients with severe variants of ADEM will require second-line immunotherapy. For patients with a relapse of disease, we suggest intravenous (IV) glucocorticoids for acute management. There should be a careful review of the initial diagnosis for such patients to determine if their relapse represents multiphasic ADEM or another demyelinating syndrome such as MOG antibody-associated disease, MS, or NMOSD.

PEDIATRIC ONSET MULTIPLE SCLEROSIS

Multiple sclerosis characteristically being the disease of young adults, pediatric-onset MS (POMS) represents about 5% of total cases. The clinical course, management, and prognosis differ in the pediatric population. Relapsing-remitting multiple sclerosis (RRMS) is more common and constitutes about 97–99% of all POMS.[42,43]

Treatment of Acute Attack

Glucocorticoids remain the mainstay treatment for acute attacks. IVMP at 30 mg/kg/day for 3–5 days is the first-line treatment for an acute attack, followed by a short course of tapering oral steroids. If the patient relapses while tapering the steroid, either repeat IVMP or IVIg can be given. TPE is an alternative.

Disease-modifying Therapy for Pediatric-onset Multiple Sclerosis

The DMTs not only reduce the frequency of relapses but also decrease the T2 lesion load by targeting specific inflammatory elements that predominate during the relapsing-remitting course of MS. Nearly all DMT use in POMS, except fingolimod is off-label. Based on the results of the PARADIGMS trial comparing the efficacy of fingolimod versus interferon β-1a, FDA has approved oral fingolimod in children >10 years of age.[44] The dose is 0.25 mg once daily orally if weight is <40 kg and 0.5 mg once daily if weight is >40 kg. Adverse effects include bradycardia, cardiac arrhythmias, persistent lymphopenia, transaminitis, and basal cell carcinoma.[45]

There prevails a huge controversy between the use of escalation versus induction therapy. Considering the increased inflammatory load, young age at when the disability occurs, high relapse rates studies are favoring the initiation of high-efficacy early treatment (HEET) followed by maintaining on safer medications. In a recent observational study comparing the effectiveness of HEET (fingolimod, natalizumab, ocrelizumab, and alemtuzumab) versus medium efficacy treatment (MET) (interferon β-1a, glatiramer acetate, dimethyl fumarate, and teriflunomide) in POMS, it was found that patients starting with METs had much higher clinical disease activity than those initiated with HEET.[46]

Other DMTs approved in adult MS and which are under trial for pediatric use include

- *First-line DMTs*: Interferon β-1a, interferon β-1b, glatiramer acetate, and dimethyl fumarate.
- *Second-line DMTs*: Teriflunomide, natalizumab, alemtuzumab, cladribine, rituximab, and ocrelizumab.[47]

CONCLUSION

The clinical presentation, radiological hallmarks, treatment, and prognosis are distinct in pediatric-acquired demyelinating disorders. It is important to distinguish monophasic forms from relapsing phenotypes so that the use of chronic immunotherapy can be made more vigilant. MOG antibodies are detected in over 33% of all pediatric patients

during the initial demyelination episode. AQP4 antibody positivity had high relapsing rates with significant long-term disability. Numerous clinical trials on novel therapeutic agents are in progress, and especially those on POMS are highly promising.

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Advances in
CNS Demyelinating Disorders

This book provides a comprehensive review of the latest research and clinical practices in the management of central nervous system (CNS) demyelinating disorders, including multiple sclerosis, neuromyelitis optica, myelin oligodendrocyte glycoprotein disorders, and seronegative CNS demyelinating disorders. It is designed for clinicians and students seeking to expand their understanding of these disorders. Each chapter examines the therapeutic approaches and highlights practical perspectives on dealing with CNS demyelinating disorders. It underscores the importance of personalized treatment plans and emphasizes the need for ongoing research to improve outcomes for those affected by these conditions.

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