Severe MOG Antibody-Associated Encephalitis in Children: Clinical Features, Diagnostic Challenges, and Immunotherapy Escalation – A Practical Review

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Abstract

Background: Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) has emerged as a distinct autoimmune neuroinflammatory disorder in childhood, characterized by a wide clinical spectrum ranging from monophasic acute disseminated encephalomyelitis to recurrent optic neuritis and severe encephalitis. Among these phenotypes, MOG antibody–associated encephalitis (MOG-E) represents a particularly challenging entity due to its variable presentation, potential for rapid neurological deterioration, and incomplete understanding of its pathobiology. Severe MOG-E in children is increasingly recognized in tertiary pediatric neurology settings, yet its clinical features often overlap with infectious, post-infectious, and other autoimmune encephalitides, complicating early diagnosis and delaying optimal treatment.

This practical review aims to synthesize current evidence on the clinical presentation, diagnostic hurdles, and immunotherapy strategies specifically relevant to *severe* pediatric MOG-E. We highlight the characteristic but not universally present features—including refractory seizures, encephalopathy, multifocal deficits, cortical or deep gray matter involvement on MRI, and cerebrospinal fluid abnormalities—that must be interpreted with caution in emergency and intensive care settings. Diagnostic challenges arise from fluctuating antibody titers, imperfect assay specificity, MRI patterns that may mimic infectious encephalitis or NMDA receptor encephalitis, and the absence of universally accepted criteria for defining severity in MOG-E.

Given the absence of randomized pediatric trials, treatment escalation strategies rely heavily on observational data and expert consensus. High-dose corticosteroids remain first-line therapy, but severe or steroid-refractory cases often require rapid escalation to intravenous immunoglobulin, plasma exchange, or targeted immunotherapies such as rituximab, mycophenolate mofetil, or emerging IL-6 pathway inhibitors. Prompt recognition of inadequate early response is essential to prevent prolonged ICU stays, long-term neurological sequelae, and recurrent inflammatory episodes.

This review consolidates practical, clinician-oriented guidance on recognizing severe disease early, differentiating MOG-E from mimics, and implementing a rational stepwise immunotherapy escalation framework. Through integrating current literature with emerging therapeutic insights, we aim to support pediatric neurologists, intensivists, and multidisciplinary teams in making timely diagnostic and management decisions that optimize outcomes for children affected by this increasingly recognized and potentially devastating autoimmune encephalitis.

Keywords: *Myelin oligodendrocyte glycoprotein antibody–associated disease, Encephalitis*

Introduction

Myelin oligodendrocyte glycoprotein antibody–associated disease (MOGAD) has gained considerable attention over the last decade as a distinct autoimmune demyelinating and neuroinflammatory disorder separate from multiple sclerosis and aquaporin-4–positive neuromyelitis optica spectrum disorder [1]. Although MOGAD affects both adults and children, the pediatric population often presents with a broader and more severe inflammatory phenotype, including acute disseminated encephalomyelitis, optic neuritis, transverse myelitis, and the increasingly recognized entity of MOG antibody–associated encephalitis (MOG-E) [2]. Severe MOG-E may evolve rapidly with profound encephalopathy, refractory seizures, and multifocal neurological deficits requiring ICU-level care, often mimicking infectious or neuronal-surface–antibody encephalitides and complicating early diagnosis [3].

Despite growing international awareness, substantial knowledge gaps remain regarding the mechanisms driving severe encephalitic presentations in pediatric MOGAD and the optimal diagnostic strategy during acute deterioration. Diagnostic confirmation relies heavily on serum MOG-IgG detection using live cell–based assays, yet fluctuations in antibody titers, differing assay cutoffs, and imperfect specificity can introduce diagnostic uncertainty, especially when MRI patterns resemble infectious meningoencephalitis or autoimmune encephalitides such as NMDA receptor antibody encephalitis [4]. Furthermore, no universally accepted severity criteria exist for MOG-E, limiting the ability to consistently identify children at highest risk of neurological decline and long-term sequelae [5].

The aim of this practical review is to synthesize current evidence to guide clinicians in recognizing the clinical and radiological features of severe pediatric MOG-E, the major diagnostic pitfalls and mimics that delay definitive diagnosis, and the therapeutic rationale for timely and stepwise immunotherapy escalation beyond corticosteroids [6]. The research gap addressed by this review centers on the lack of integrated, pediatric-specific frameworks for early severity recognition, interpretation of evolving biomarkers, and evidence-informed escalation of immunotherapy in severe MOG-E—areas where current practice relies largely on observational data and expert consensus rather than standardized protocols [7].

1. Epidemiology and Emerging Recognition of Severe Pediatric MOG-E

Severe MOG antibody–associated encephalitis (MOG-E) in children is increasingly recognized as a distinct phenotype within the broader spectrum of MOGAD, with rising incidence attributed partly to the expanded availability of cell-based antibody assays. Unlike classic demyelinating disorders, pediatric MOG-E often presents with a predominance of cortical and deep gray matter inflammation, leading to more dramatic encephalopathic presentations. Reported prevalence varies among cohorts, but severe encephalitic presentations account for a meaningful proportion of pediatric MOGAD hospitalizations, particularly in tertiary neurology centers. Early epidemiologic studies likely underestimated case numbers due to misclassification as infectious encephalitis. Awareness of this phenotype has contributed to improved recognition, though significant regional variability persists. [8]

2. Immunopathogenic Considerations in Severe Pediatric MOG-E

The immunopathogenesis of MOG-E remains only partially understood, with evidence suggesting both antibody-mediated and T-cell–mediated mechanisms contributing to cortical inflammation. MOG-IgG antibodies, particularly of the IgG1 subclass, are strongly implicated in complement activation and antibody-dependent cytotoxicity in severe disease. Post-infectious immune activation is frequently reported, supporting a para-infectious or molecular mimicry hypothesis in susceptible children. Additionally, enriched microglial activation and cortical demyelination have been observed in biopsy and autopsy studies, suggesting a more aggressive inflammatory cascade in severe encephalitic presentations than in milder MOGAD phenotypes. Understanding these mechanisms may ultimately

refine therapeutic targeting. [9]

3. Clinical Red Flags Suggesting Severe MOG-E

Children with severe MOG-E often present with a constellation of neurologic symptoms that progress more rapidly than in classical demyelinating episodes. Red flags include early-onset encephalopathy, persistent altered mental status, and seizures that may become refractory to standard anti-seizure therapy. Focal deficits such as hemiparesis or aphasia commonly accompany global neurologic decline. Behavioral changes, irritability, and agitation may precede overt neurological collapse. Importantly, systemic features such as fever or mild inflammatory markers may mislead clinicians toward an infectious etiology, delaying recognition of autoimmune encephalitis. The acuity and severity of symptoms should prompt early consideration of MOG-E in differential diagnosis. [10]

4. Seizure Phenotypes and Status Epilepticus in Severe MOG-E

Seizures represent a hallmark of severe MOG-E, ranging from focal seizures with secondary generalization to full status epilepticus. Many children experience prolonged or recurrent seizures early in the disease course, necessitating escalation of anti-seizure medications and ICU involvement. Electroencephalography often reveals diffuse slowing with multifocal epileptiform discharges, reflecting widespread cortical irritation. Notably, seizure burden does not always correlate with MRI lesion load, suggesting that inflammatory cytokines and cortical hyperexcitability contribute to pathogenesis. Prompt recognition of seizure patterns in the context of MOG positivity is essential for guiding both acute neurologic management and immunotherapy timing. [11]

5. MRI Characteristics Suggestive of Severe MOG-E

MRI brain findings in severe MOG-E often include widespread cortical and subcortical T2-FLAIR hyperintensities, deep gray matter involvement, and lesions that may mimic viral encephalitis. Leptomeningeal enhancement can also occur, contributing to misinterpretation as infectious meningitis. In some cases, splenial lesions or extensive thalamic involvement are present, adding further diagnostic complexity. While white matter lesions reminiscent of ADEM are well-known in mild MOGAD, severe MOG-E tends to show more aggressive cortical inflammation. Serial MRI is frequently needed, as early imaging may be deceptively normal or evolve rapidly within days. These dynamic features highlight the importance of repeated imaging in deteriorating patients. [12]

6. Cerebrospinal Fluid Findings and Diagnostic Limitations

CSF analysis in severe MOG-E frequently reveals mild to moderate pleocytosis, elevated protein, and occasionally oligoclonal bands, though the latter are far less common than in multiple sclerosis. The presence of neutrophils or high inflammatory markers may be mistaken for bacterial meningitis, contributing to diagnostic delays. Importantly, CSF MOG-IgG testing is less sensitive than serum testing and is not required for diagnosis. False reassurance from near-normal CSF findings may also occur, reinforcing the need for evaluation of clinical and radiological context. CSF abnormalities are supportive but not definitive, and interpretation must be integrated into a broader diagnostic framework. [13]

7. Diagnostic Pitfalls: Differentiating Severe MOG-E From Infectious Encephalitis

Severe MOG-E can closely resemble viral encephalitis, particularly herpes simplex encephalitis, due to overlapping symptoms such as fever, seizures, and temporal lobe involvement. Negative CSF viral PCR results early in the course may be misleadingly reassuring, prompting repeated testing and empiric antiviral therapy before autoimmune etiologies are considered. Misdiagnosis delays immunotherapy, which may lead to prolonged hospitalization or worse functional outcomes. The presence of bilateral, multifocal, or non–temporal-dominant cortical lesions should raise suspicion for autoimmune rather than viral causes, as should lack of clinical improvement despite adequate antiviral coverage. [14]

8. Diagnostic Pitfalls: Distinguishing From NMDA Receptor Encephalitis

NMDA receptor encephalitis shares several clinical features with MOG-E, including behavioral changes, psychiatric manifestations, and seizures. However, children with NMDA receptor encephalitis often exhibit a more prominent movement disorder and dysautonomia compared with those experiencing severe MOG-E. MRI in NMDA receptor encephalitis is frequently normal or shows subtle changes, while cortical hyperintensities are more characteristic of MOG-E. MOG antibodies may occasionally

coexist with neuronal surface antibodies, adding to diagnostic complexity. Careful interpretation of clinical features, MRI, and antibody profiles is required to avoid misclassification and to ensure appropriate immunotherapy timing. [15]

9. Role of EEG in Early Recognition of Severe Disease

EEG abnormalities in severe MOG-E often consist of diffuse slowing, multifocal epileptiform discharges, and, in some cases, patterns resembling encephalopathy associated with autoimmune inflammation. These findings may precede radiological abnormalities, offering an early diagnostic clue in rapidly deteriorating patients. EEG is particularly valuable in detecting non-convulsive status epilepticus, which is common in severe presentations and contributes significantly to morbidity. While EEG is not specific to MOG-E, persistent diffuse abnormalities, especially in combination with MOG-IgG positivity, support early initiation of immunotherapy. Serial EEG monitoring is often necessary as the disease evolves. [16]

10. Standard First-Line Immunotherapy in Severe Pediatric MOG-E

High-dose intravenous corticosteroids are the cornerstone of initial therapy for severe MOG-E, reflecting the rapid steroid responsiveness observed in many children with MOGAD. Methylprednisolone pulses are typically administered for 3–5 days, followed by an oral taper. However, severe or fulminant cases may show incomplete or transient improvement, signaling the need for escalation. Adjunctive intravenous immunoglobulin (IVIG) is commonly used due to its immunomodulatory effects and favorable safety profile in children. The combination of high-dose steroids and IVIG forms the basis of first-line therapy in many centers, although clinical improvement must be assessed closely over the first several days. [17]

11. Indications for Early Escalation of Immunotherapy

Not all children with severe MOG-E respond adequately to first-line treatment, and delay in escalation can worsen long-term neurological outcomes. Indicators for escalation include persistent encephalopathy, ongoing seizures despite first-line therapy, progression of MRI lesions, and continued CSF inflammation. Biomarkers such as high serum MOG-IgG titers may also correlate with severe or prolonged disease activity. Importantly, decisions must be tailored to the individual clinical trajectory rather than rigid timelines, as some children deteriorate quickly despite treatment. Early recognition of non-response is therefore essential to prevent irreversible injury. [18]

12. Plasma Exchange in Severe or Steroid-Refractory MOG-E

Plasma exchange (PLEX) plays a critical role in severe or steroid-refractory MOG-E by rapidly removing pathogenic antibodies and inflammatory mediators. Children requiring ICU support or mechanical ventilation often benefit from early PLEX as part of a multimodal approach. Studies suggest that PLEX leads to meaningful neurological improvement, particularly when initiated within the first two weeks of symptom onset. Logistical challenges in young children, including line placement and hemodynamic stability, may limit its use, yet its therapeutic value remains substantial for selected cases. PLEX is generally combined with corticosteroids and IVIG in aggressive disease. [19]

13. Rituximab in Refractory or Relapsing Severe MOG-E

Rituximab, a monoclonal antibody targeting CD20-positive B cells, is increasingly used for refractory or recurrent MOG-E. Although MOGAD is not strictly a B-cell–driven disease, rituximab can reduce relapse risk and support recovery in children who fail to improve with first-line therapy. Its benefits appear greater in patients with high or persistent MOG-IgG titers, suggesting a role in modulating autoreactive B-cell populations. Rituximab is generally administered after acute stabilization and may be repeated based on B-cell repopulation or clinical relapse. Safety in pediatric populations is favorable, though monitoring for infection risk is essential. [20]

14. Cyclophosphamide and Other Escalation Options

Cyclophosphamide may be considered in fulminant cases unresponsive to corticosteroids, IVIG, PLEX, and rituximab. Although data are limited, reports indicate potential benefit in suppressing aggressive immune activation in severe encephalitic presentations. Other agents, including mycophenolate mofetil and azathioprine, are typically reserved for long-term maintenance rather than acute escalation.

Clinicians must weigh the risks of cytotoxic therapy against the severity of neurologic compromise, particularly in younger children. Early involvement of multidisciplinary teams is critical in these complex decisions, ensuring that immunotherapy escalation balances efficacy and safety. [21]

15. IL-6 Pathway Inhibition in Severe Treatment-Refractory Disease

Emerging therapies such as tocilizumab, an IL-6 receptor inhibitor, have shown promise in refractory MOGAD, particularly in cases characterized by persistent inflammation and high relapse burden. IL-6 may play a central role in promoting B-cell activation and antibody production, supporting the rationale for targeting this pathway. Case reports and small cohorts demonstrate clinical improvement following tocilizumab in children who previously failed multiple immunotherapies. Although evidence in MOG-E specifically remains preliminary, IL-6 inhibition represents a valuable escalation option for the most severe and treatment-resistant presentations. Ongoing studies may clarify its role in acute encephalitic episodes. [22]

16. Monitoring Treatment Response in Severe MOG-E

Clinical recovery in severe MOG-E must be monitored through a combination of neurological examination, seizure control assessment, serial MRI imaging, and laboratory evaluation. Improvement in mental status and seizure burden often precedes radiological recovery, which may lag weeks behind clinical stabilization. Persistent MRI abnormalities do not necessarily indicate treatment failure but should be contextualized within the child's functional recovery. MOG-IgG titers may decline over months; however, titers alone should not guide acute management. Multidisciplinary monitoring ensures early identification of complications and timely advancement or tapering of therapy. [23]

17. Long-Term Cognitive and Behavioral Outcomes

Children recovering from severe MOG-E may experience lingering cognitive, behavioral, or emotional difficulties. Deficits in attention, working memory, processing speed, or executive functioning are commonly reported following severe encephalitic inflammation. Behavioral dysregulation, anxiety, and mood disturbances may persist months beyond clinical recovery. These outcomes often correlate with seizure severity, lesion burden, and duration of ICU stay. Early neuropsychological evaluation and sustained follow-up are essential components of holistic care, ensuring that academic and social reintegration are adequately supported. Rehabilitation programs may be required for optimal long-term recovery. [24]

18. Relapse Risk and Long-Term Immunotherapy Considerations

Relapse risk in pediatric MOGAD varies, with some children experiencing a monophasic course and others developing recurrent disease. Severe initial presentations may be associated with a higher likelihood of relapse, although findings are inconsistent across studies. Long-term immunotherapy, including rituximab, mycophenolate mofetil, or low-dose IVIG, may be considered for children with recurrent episodes or persistently elevated antibody titers. Decision-making must consider age, side-effect profiles, and the psychosocial impact of chronic therapy. More robust biomarkers are needed to stratify relapse risk accurately and tailor long-term treatment plans. [25]

19. Prognostic Indicators in Severe MOG-E

Predictors of poor outcome in severe MOG-E include prolonged encephalopathy, refractory seizures, extensive cortical involvement, and delayed initiation of immunotherapy. High inflammatory markers, persistent CSF abnormalities, and slow radiological improvement may suggest a more aggressive disease course. Conversely, children who receive timely, targeted immunotherapy—particularly PLEX or rituximab when indicated—often exhibit substantial neurological recovery. Identifying prognostic indicators early can guide intensity of monitoring, need for repeat imaging, and selection of escalation therapies. Evidence remains limited, highlighting the need for multicenter studies. [26]

20. Future Directions and Research Priorities

Future research in severe pediatric MOG-E must address critical knowledge gaps, including the development of validated severity criteria, identification of robust biomarkers predicting treatment response, and controlled trials evaluating escalation strategies. Advances in neuroimaging, cytokine profiling, and antibody characterization may refine diagnostic accuracy and enable earlier therapeutic

intervention. International collaboration will be essential to generate adequately powered pediatric datasets, given the rarity of severe MOG-E. Ultimately, a unified clinical and research framework is required to optimize outcomes and reduce variability in management practices across centers. [27]

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