

# Diagnostic Considerations in Acute Disseminated Encephalomyelitis and the Interface with MOG Antibody

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## Abstract

Acute disseminated encephalomyelitis (ADEM) is a common yet clinically heterogeneous syndrome characterized by encephalopathy, focal neurologic findings, and abnormal neuroimaging. Differentiating ADEM from other demyelinating disorders of childhood can be difficult and appropriate interpretation of the historical, clinical, and neurodiagnostic components of a patient's presentation is critical. Myelin oligodendrocyte glycoprotein (MOG) antibody-associated diseases are a recently recognized set of disorders, which include ADEM presentations, among other phenotypes. This review article discusses the clinical diagnosis, differential diagnosis, interpretation of data, and treatment/prognosis of this unique syndrome with distinctive review of the spectrum of MOG antibodies.

## Keywords

- ▶ ADEM
- ▶ acute disseminated encephalomyelitis
- ▶ diagnosis
- ▶ treatment
- ▶ MOG antibody

## Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated disorder of the central nervous system (CNS), affecting both children and adults. The estimated incidence of ADEM in children ranges between 0.2 and 0.4/100,000 and is without ethnic or racial predilection.<sup>1,2</sup> Studies have identified marginally higher rates of ADEM in males.<sup>3</sup> The majority of cases occur in children of age 9 years or younger and, interestingly, the rates of hospitalization for this disorder have increased over the past decade.<sup>4</sup>

The pathogenesis and pathophysiology of ADEM are not fully understood. The most consistent proposed mechanism of disease is that of autoimmune priming by an environmental antigen (such as a virus or bacteria) which triggers the production of myelin autoantigens that share antigenic determinates with the causative pathogen.<sup>5</sup> Historically, this process has been divided into two phases: the priming/activation phase and the recruitment phase.<sup>6</sup> The former phase is defined by activation and expansion of T cells with spread to the CNS. In the latter phase, production of cytokines and chemokines by

activated T cells recruits additional immune cells to the CNS leading to primary injury of white matter.<sup>7</sup> Although more nuanced than described, for the scope of this review, the authors will focus on the clinical aspects of the disease and its interface with emerging literature on myelin oligodendrocyte glycoprotein (MOG) antibody.

## Clinical Diagnosis

The diagnosis of ADEM is based on historical, clinical, and radiologic findings. There is no single diagnostic test that is considered confirmatory. For this reason, the Pediatric Multiple Sclerosis Study Group generated criteria in 2007 and 2012<sup>8</sup> for the diagnosis of ADEM to aid in the identification of this condition (▶ **Table 1**).

The clinical diagnosis of ADEM can be difficult in that symptoms are often variable and are frequently polyfocal at onset. Encephalopathy (defined as any alteration in mental state or behavior ranging from coma to irritability) is required for the diagnosis. In children, the degree of encephalopathy varies and patients may have more than depressed mental status, in fact,

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**Table 1** ADEM diagnostic criteria<sup>3</sup>

Clinical features (all required)	Characteristics MRI of the brain lesions
A first polyfocal, clinical central nervous system event with presumed inflammatory demyelinating cause	Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter
Encephalopathy that cannot be explained by fever, systemic illness, or postictal symptoms	Deep gray matter lesions (e.g., involving the basal ganglia or thalamus) can be present
No new clinical and MRI findings emerge 3 mo after the onset	T1 hypointense lesions in the white matter are rare
MRI of the brain is abnormal during the acute (3-mo) phase	

Abbreviations: ADEM, acute disseminated encephalomyelitis; MRI, magnetic resonance imaging.

younger children may often present with irritability, aggression, and other active behavioral changes.<sup>3</sup> Additional neurologic features include cerebellar ataxia, cranial neuropathy, hemiparesis/weakness, optic neuritis (ON) (which can include vision loss, pain with eye movement, and/or afferent pupillary defect), pyramidal dysfunction, and spinal cord dysfunction, which may or may not be consistent with a transverse myelitis (TM).<sup>1–3,5</sup> Disturbances of language function, movement disorders, and alterations in sensorium are appreciated with less frequency. Associated nonneurologic findings include fever, meningismus, nausea/vomiting, and generalized weakness. The presence of area postrema syndrome is very rare and may indicate an alternative diagnosis such as neuromyelitis optica spectrum disorders (NMOSDs).

As with other neuroimmunologic disorders, up to 72% of patients will have a non-life-threatening febrile illness days prior to up to 3 weeks prior to neurologic symptom onset.<sup>3,5</sup> Previously reported infections have included mycoplasma, Epstein–Bar's virus, coronavirus, coxsackie virus, hepatitis, herpes simplex virus, human immunodeficiency virus, human herpesvirus, parainfluenza virus, influenzas A and B, as well as measles, mumps, and rubella viruses.<sup>3,5,8–11</sup> A minority of cases (5%) are associated with vaccination, including but not limited to: hepatitis B, influenza, diphtheria/pertussis/tetanus, measles/mumps/rubella, pneumococcus, and polio.<sup>5</sup> These cases are traditionally thought to be less severe and rarely convert to polyphasic disease. The majority of patients diagnosed with ADEM display a monophasic pattern with steady improvement and return to neurologic baseline within 3 months after onset of symptoms.

## Neurodiagnostic Studies and Differential Diagnosis

The differential diagnosis in a child who presents with polyfocal neurologic abnormalities and encephalopathy is broad. Viral and bacterial meningitis/encephalitis must be ruled out, especially in the presence of fever or leukocytosis. Lumbar puncture is valuable in ruling infection in or out on the differential diagnosis. Cell count with differential is helpful for evaluating pleocytosis (>5 white blood cell [WBC]/ $\mu\text{L}$ ), and if present, with a neutrophilic or lymphocytic predominance which can be useful in discriminating most bacterial versus viral infections, respectively. In most cases of ADEM, cerebrospinal fluid (CSF) WBC counts can range from 0 to 268 WBC/ $\mu\text{L}$ , but are rarely reported beyond the latter range with the mean

between 15 and 50 WBC/ $\mu\text{L}$ .<sup>1,3,7,10</sup> Protein counts in the CSF are typically normal or mildly elevated (0.40–0.60 g/L), although the range can be broad, between 0.10 and 2.7 g/L.<sup>1,3,5,10</sup> Glucose levels in the CSF are almost uniformly normal. Gram stain and cultures provide additional specifics for bacterial infections, while specific viral testing can be tailored to the clinical history. Although in its infancy, metagenomic analysis of CSF is becoming increasingly utilized as a means of identifying specific infectious agents; however, turnaround time and contamination of samples remain problematic.<sup>12</sup> While data are limited, there has been report of meningoencephalitis associated with MOG antibodies which can complicate even the earlier interpretation.<sup>13</sup>

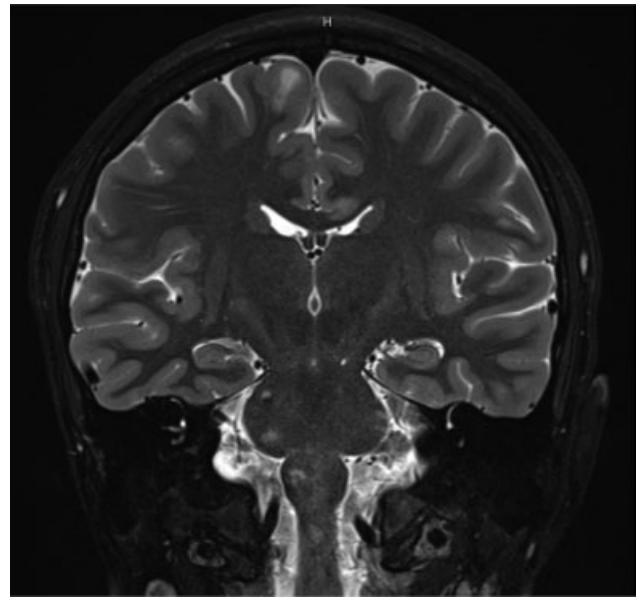
In the setting of noninfectious CSF abnormalities and white matter lesions on MRI of the brain, other inflammatory demyelinating disorders include multiple sclerosis (MS), MOG antibody-associated demyelination, antibody-associated limbic encephalitis, primary angiitis of the CNS, malignancy, mitochondrial disease, and leukodystrophies. The presence of TM and ON may occur concurrently but should be diagnosed in the context of other neurologic findings and radiographic findings.<sup>3</sup> Of note, nearly all demyelinating disorders of childhood, including ADEM, have been linked with the presence of MOG antibodies over the past few years and testing for this from the serum is imperative for diagnostic and therapeutic purposes. Testing for this antibody is not recommended in the CSF which, interestingly, has a lower sensitivity than serum testing and when serum testing is performed.<sup>14,15</sup> In addition, when tested, cell-based assays are recommended.<sup>14,15</sup> Aquaporin-4 (AQP4) antibody is associated with NMOSD and should be tested from the serum as well as therapeutic interventions will vary dramatically in this population. The presence of both MOG and AQP4 antibodies is very rare and should prompt retesting.<sup>14</sup>

Additional diagnostic tools to consider in the CSF are testing of oligoclonal bands (OCB) and immunoglobulin G (IgG) synthesis index. The former is present less frequently in patients with ADEM, although when present, it is associated with relapsing disease<sup>15</sup> and may be an indicator of alternative diagnoses.<sup>15,16</sup> In a longitudinal study of children with ADEM, overall rates of OCB were 3%.<sup>1,10,17</sup> OCBs are not a sensitive indicator of ADEM and may only be transiently present,<sup>17</sup> but when not present in the acute phase, it can be used in the context of other less sensitive indicators such as IgG index, Neopterin, an indiscriminate marker of intrathecal immune

activation, has also been found to be elevated in a variety of inflammatory CNS disorders, although is not specific for ADEM and is of less utility in these cases given established neuroimaging abnormalities which are discussed later.<sup>18</sup>

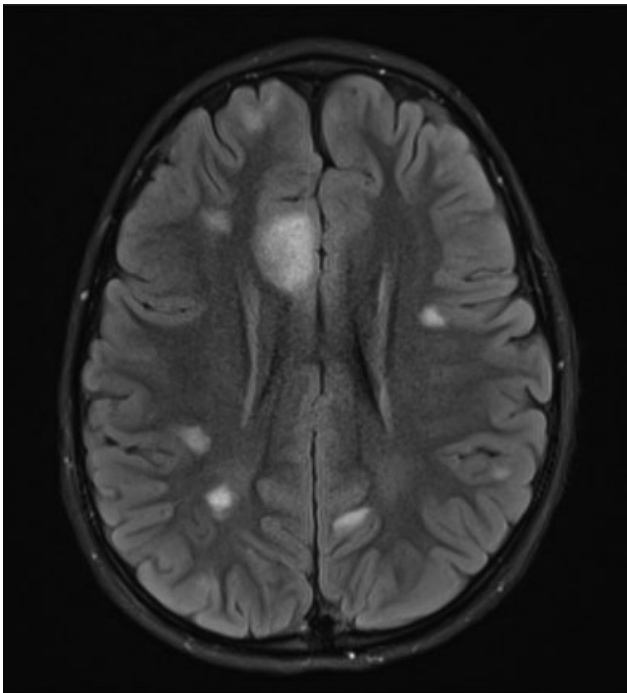
In addition to infectious etiologies, autoimmune and paraneoplastic conditions should be on the differential diagnosis in any clinical presentation with subacute encephalopathy or behavioral dysregulation. Over the past two decades, considerable amounts of antibody-associated limbic encephalitides have been identified, some with clinical overlap with ADEM. The most broadly described entity, anti-NMDA receptor antibody encephalitis, can be differentiated from ADEM by features such as the presence of movement disorders, epilepsy, waxing and waning behavioral and personality changes, autonomic instability, and language disturbances. In addition, the course of this disease is more variable than that of ADEM, presenting over multiple weeks or even months. Other limbic encephalitides to consider are anti-Hu, anti-Ma2, anti-GAD, anti-AMPA, anti-GABA B, anti-GABA A, anti-mGluR5, anti-D2 receptor, anti-LGI1, anti-CASPR2, and anti-DPPX.<sup>19</sup> Imaging in these disorders is variable but can include medial temporal lobe T2 hyperintensities, cortical ribboning, and white matter lesions. For patients presenting with status epilepticus at presentation, antibodies against thyroid peroxidase and thyroglobulin may indicate Hashimoto's encephalopathy (also known as steroid responsive encephalopathy associated with autoimmune thyroiditis) is warranted.

Neuroimaging in ADEM is classically described as diffuse, poorly demarcated, and bilateral lesions involving the cerebral white matter and spine.<sup>20,21</sup> Examples of "typical" ADEM neuroimaging is displayed in ►Figs. 1, 2 to 3. Relapsing and remitting disorders such as MS may initially present with

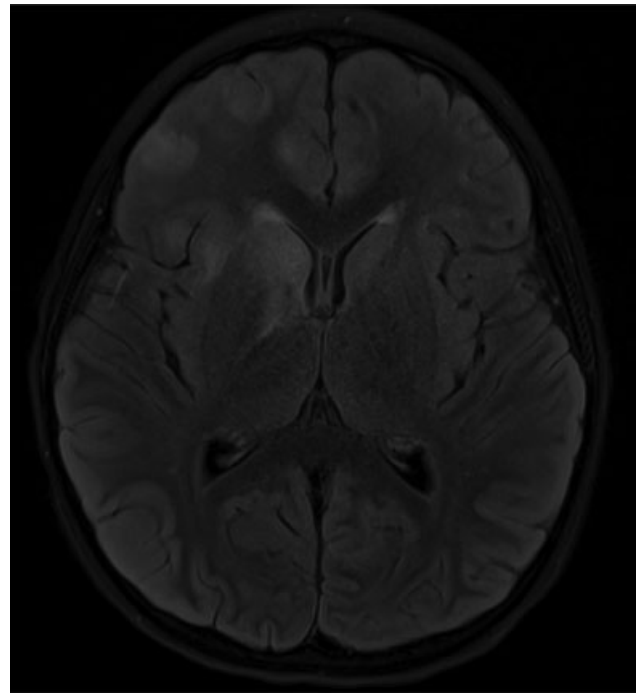


**Fig. 2** Coronal T2 sequence demonstrating multiple, patchy, cortical, brain stem, and cervical cord lesions in a 4-year-old girl with myelin oligodendrocyte glycoprotein antibody-positive acute disseminated encephalomyelitis.

symptoms consistent with ADEM. Distinguishing ADEM from a primary presentation of MS can be challenging. Clinical and neuroimaging features that may indicate a diagnosis ADEM rather than MS include are listed in ►Table 2. In a retrospective study of neuroimaging in pediatric patients diagnosed with ADEM and then MS, Callen et al identified three factors that



**Fig. 1** Axial flair sequence demonstrating multiple, bilateral, T2 signal hyperintensities in the white matter tracks in a 5-year-old boy with myelin oligodendrocyte glycoprotein antibody-negative acute disseminated encephalomyelitis.



**Fig. 3** Axial flair sequence demonstrating poorly circumscribed, patchy, T2 signal prolongation in the right frontal lobe and right deep gray matter in a 6-year-old boy with myelin oligodendrocyte glycoprotein antibody-positive acute disseminated encephalomyelitis.

**Table 2** Indicators of a diagnosis of ADEM rather than MS

Clinical	Neuroimaging
Ataxia (rare in MS)	Multiple, large, confluent lesions in asymmetric distributions throughout the white matter
Fever and meningismus	Lesions are poorly demarcated (MS lesions have more defined margins)
Prodromal viral illness or recent vaccination	Multiple lesions of the same age indicate ADEM rather than MS which can have multiple lesions of various ages (active/inactive lesions)
Encephalopathy or polyfocal neurologic findings	Thalamic and deep gray lesions occur less frequently in MS
Absence of oligoclonal bands in CSF	

Abbreviations: ADEM, acute disseminated encephalomyelitis; CSF, cerebrospinal fluid; MS, multiple sclerosis.

predicted a higher likelihood of developing MS:  $\geq 2$  periventricular lesions, presence of black holes, and absence of diffuse bilateral lesion restricted diffusion.<sup>22</sup> Although less studied, neuroimaging of patients with ADEM and MOG antibodies has also been reported with important differences including more widespread distribution of lesions, increased frequency of longitudinally extensive lesions in the spine ( $>3$  vertebral segments), and a higher likelihood of complete reversal of signal on subsequent scans in patients with MOG antibody compared with idiopathic forms of ADEM.<sup>20</sup> Distinguishing ADEM from MOG-associated ADEM and other demyelinating disorders is essential in guiding therapy and providing prognostic information to patients and families as the interventions for each disorder are increasingly nuanced. Other neuroradiologic mimics of ADEM include hypotensive encephalopathy, hemophagocytic lymphohistiocytosis, primary CNS lymphoma, systemic rheumatologic disorders (systemic lupus erythematosus, Behcet's disease, Sjogren's disease, Wegner's disease, and CNS vasculitis), granulomatous disorders (neurosarcoidosis), genetic disorders, and leukodystrophies, although differentiation can be made on physical examination and clinical history in most cases.

As mentioned previously, the concept of "relapsing" ADEM has become increasingly controversial as relapsing/remitting demyelinating syndromes need to be continually re-evaluated. The authors encourage caution when using this term, especially in the absence of MOG antibodies, and advocate for in-depth exclusion of the alternative diagnoses (such as MS, NMOSD, and ADEM-ON) with each clinical demyelinating event and radiographic change.

## MOG Antibody and ADEM

The presence of MOG antibodies is elevated in pediatric patients with ADEM, although the presence of these antibodies is not specific as they have also been described in MS, TM, ON, NMOSD, and other demyelinating disorders.<sup>23</sup> Children diagnosed with ADEM less than 10 years of age with demyelinating disorders have much higher rates of MOG antibodies, with rates reported as high as 65%, although there appears to be geographic variation in the incidence.<sup>21,24-27</sup> In a large study of children with acquired demyelinating events, there was a higher likelihood of MOG antibody positivity in younger patients (defined as  $<10$  years, but highest in those  $<5$  years), children with an

initial demyelinating event meeting criteria for ADEM, increased CSF cell count, and negative OCBs.<sup>27</sup>

In the context of other MOG antibody spectrum disorders, a diagnosis of MOG-positive ADEM is unique. First, the rates of MOG antibody seropositivity are much higher in cases of ADEM than in cases of NMOSD, CIS, MS, or other less defined demyelinating events such as ON or TM.<sup>27</sup> This same study identified that MOG antibody positivity was a factor in delineating non-MS clinical courses with a specificity of 100% when an antibody titer of 1:1,280 was used.<sup>27</sup> Another study by Hacohen et al (2015) identified that MOG antibody seropositivity had a positive predictive value of 91% for non-MS-related disease.<sup>28</sup> Clinically, patients with MOG antibody seropositive ADEM have a similarly heterogeneous presentation with regard to neurologic disease, although rates of ON are reported to be higher both concurrently and as a relapsing phenotype.<sup>27-29</sup> Although seizures have been reported in patients with ADEM, it appears that MOG antibody-positive patients with ADEM may have increased rates of both seizure at presentation and long-term risk of post-ADEM epilepsy which is another distinguishing characteristic when compared with other MOG antibody spectrum disorders.<sup>30</sup>

Diagnostically, children with MOG antibody-associated ADEM are reported to have an increased rate of large, bilateral, and widespread lesions including the brain and spinal cord.<sup>20,31</sup> Longitudinally extensive TM is also more common in MOG antibody-associated ADEM.<sup>31</sup> Interestingly, following initiation of immunotherapy lesions are more likely to resolve (or significantly decrease in size) on follow-up scans when compared with non-MOG antibody-associated ADEM and other MOG antibody spectrum disorders.<sup>26-29,31,32</sup>

The presence of MOG antibodies in ADEM poses a long-term monitoring challenge in patients, as monophasic and multiphasic forms have been reported. Monophasic illness accounts for the majority of ADEM with MOG antibody-positive cases and has been associated with male gender, younger age at diagnosis ( $<10$  years), and pathology not involving the optic nerves.<sup>27,31</sup> These patients are more likely to seroconvert to negative titers and emerging evidence suggests that these disorders may in fact be easier to treat.

In patients with MOG antibody positivity at their initial diagnosis of ADEM, relapse rates are reported to be as high as 34%.<sup>27</sup> Patients who develop multiphasic disease often have higher anti-MOG antibodies titers, are older at presentation,

and may be more refractory to typical intervention.<sup>26,27,31,32</sup> Clinical phenotypes of relapse vary and can include multiphasic ADEM, ADEM-ON, NMOSD, and relapsing ON.<sup>26,31,32</sup> Interestingly, as additional attacks occur (and age increases), encephalopathy is less frequently appreciated, although new neurologic signs and radiographic lesions are present.<sup>32</sup> Age is not only an important driver of relapse risk but also of phenotype of relapse, with younger patients being noted to have more frequent relapses of multiphasic ADEM as opposed to ADEM-ON, relapsing ON, or NMOSD (collectively referred to as “opticospinal” pathologies).<sup>32,33</sup>

Seroconversion to negative titers has been reported in both monophasic and relapsing disease, although patients with continued seropositivity have been noted to have higher rates of polyphasic disease, up to 88% in children diagnosed with anti-MOG-associated ADEM.<sup>34–36</sup> The concept of seroconversion is attractive, although this has not been linked to less severe clinical courses or monophasic disease at this time.

### Inflammatory Role of MOG Antibodies in Continually Seropositive Patients

The increased rate of relapse seen in persons with continued MOG antibody positivity has provided some insight into the more diffuse and multifaceted inflammatory nature. One large study identified both elevations in ESR (>20 mm/h) and increased CSF neutrophil profiles, indicating a systemic inflammatory process which was independent of age.<sup>37</sup> Similarly, complement cascades are also activated in MOG antibody-driven disease which also has systemic implications on inflammation as well.<sup>38</sup> It remains to be seen what, or if, other organ systems may be affected in persons with longstanding MOG antibody disease over time.

Intrathecal inflammation is also present, with increased Th17-mediated cytokine responses as well as increased intrathecal B cell responses in persons with MOG antibody-positive versus -negative ADEM, respectively.<sup>39</sup> This latter finding is interesting in that it appears MOG antibody insults occur by both antibody-mediated and T cell-mediated mechanisms, possibly explaining the variability in phenotypes, neurodiagnostic studies, and therapeutic responses.<sup>33</sup> Data continues to evolve in MOG antibody-positive disease, but these initial findings have guided current therapeutic practices.

### Treatment

The mainstay treatment of ADEM is intravenous (IV) methylprednisolone, typically administered as 30 mg/kg/d (max. 1,000 mg/d) for 3 to 5 days.<sup>40</sup> Some centers will also provide an oral steroid taper for 4 to 6 weeks, but there are no data to support this practice. For refractory cases, IV immunoglobulin (IVIg) (typically administered as 1 g/kg for 2 days or 0.4 g/kg for 5 days) and plasma exchange have been demonstrated to improve patients' clinical outcomes after failure of glucocorticoids, although the latter is limited to adult data.<sup>41</sup>

Information regarding the treatment of ADEM with anti-MOG antibody is complex and limited both in regard to large-scale studies and long-term follow-up. Patients with anti-MOG

antibody positivity and an acute demyelinating event appear to respond to therapy with glucocorticoids.<sup>26</sup> Interestingly, these patients are vulnerable to relapses with steroid reduction and cessation prompting trials with multiple forms of immunotherapy.<sup>42</sup> For this reason, prolonged and slow steroid tapers are often utilized anecdotally following initial anti-MOG-associated demyelinating events. Anecdotally, the authors have appreciated an increased frequency of relapse in the setting of lower level steroids toward the end of taper as opposed to during initial portions of taper calendars, although these data are unpublished. The risk versus benefit of prolonged steroid tapers in children need to be carefully weighed, and our current practice is to limit prednisone tapers to 4 to 6 weeks. Beyond this point in the face of resurgence of relapse symptoms, IVIg or a disease-modifying drug may be considered. Of note, even with immunotherapy initiation, relapses are common with one group reporting that > 90% of patients had relapses within 13 months after diagnosis and averaged 2.2 relapses in the first 2 years.<sup>27</sup>

Disease-modifying drugs such as interferon  $\beta$  and glatiramer acetate have been evaluated in patients with anti-MOG antibody positivity and are not associated with clinical improvement, resulting in no changes in annualized relapse rates or expanded disability status scale scores over time.<sup>26</sup> Unlike patients with NMOSD, the use of these agents does not appear to worsen the clinical course. Other attempts at maintenance therapy including azathioprine, mycophenolate mofetil, rituximab, and IVIg have been associated with reduction in relapse in patients with relapsing MOG antibody-positive demyelinating disorders, although further large-scale studies are needed.<sup>26,42</sup>

### Prognosis

Prognosis associated with ADEM is good in most cases. In cases that present with ON, this was expectedly a determinant of visual disability. Repeating neuroimaging, even in relatively straightforward cases 3 to 6 months after presentation can be instrumental in risk stratification for patients with regard to developing MS or other polyphasic neuroimmunologic disorders at a later time point.

Although many patients do not have any focal neurologic deficits after recovery, recent data suggest that one of the less appreciated long-term sequelae of ADEM is neurocognitive dysfunction. A two large series identified that up to 44% of children had attention-deficit hyperactivity disorder, 32% with behavioral problems, and 22% with learning disabilities.<sup>43,44</sup> Risk factors for these clinical phenotypes was more severe neurologic involvement at presentation, older age, and male gender, indicating a likely link with their neuroimmunologic disorder. The etiology of these sequelae is unclear, although two studies have demonstrated diminished brain volume in both the cortex and cerebellum in children with demyelinating events.<sup>45,46</sup> It is possible these acute demyelinating attacks may damage the maturation and integrity of the existing white matter at critical brain points in development, causing long-lasting neurocognitive effects.<sup>47</sup>

Interestingly, prognosis in cases of ADEM associated with MOG antibodies appears to be somewhat different with some studies reporting better neurologic outcomes than non-MOG-associated ADEM.<sup>20</sup> However, patients with persistent MOG antibody may be more likely to develop polyphasic disorders which exist on a convoluted spectrum of neuroimmunologic disorders, which include multiphasic ADEM, and ADEM followed by ON, and NMO-SD. Additionally, the potential for post-ADEM epilepsy also seems to be higher in this group, although larger scale longitudinal studies are needed.<sup>30</sup> Several studies are now ongoing to better define the course and treatment of monophasic and multiphasic forms of MOG antibody-associated disease.

## Conclusion

While long characterized, ADEM continues to be a moving target with regard to both diagnostic and therapeutic intervention as more data are gathered about its etiology and pathophysiology. The proliferation of information on MOG antibody-associated ADEM has provided clinicians' additional diagnostic and therapeutic targets in the interim, although much more research is needed for targeted and personalized interventions in the future.

**Conflict of Interest**  
None.

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