Understanding Pediatric Neuroimmune Disorder Conflicts: A Neuroradiologic Approach in the Molecular Era

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Abbreviations: ADEM = acute disseminated encephalomyelitis, ADEM-ON = ADEM followed by ON, ADS = acquired demyelinating syndrome, AQP4 = aquaporin-4, CNS = central nervous system, FLAIR = fluid-attenuated inversion-recovery, IgG = immunoglobulin G, LETM = longitudinally extensive TM, MDEM = multiphasic demyelinating encephalomyelitis, MOG = myelin oligodendrocyte glycoprotein, MS = multiple sclerosis, NMOSD = neuromyelitis optica spectrum disorder, ON = optic neuritis, TM = transverse myelitis

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SA-CME LEARNING OBJECTIVES

After completing this journal-based SA-CME activity, participants will be able to:

- Describe the clinical phenotypes and key imaging findings of MOG antibody–associated disease.
- Differentiate imaging features of MOG antibody–associated disease, AQP4 antibody NMOSD, and MS according to brain, optic nerve, and spinal cord MRI findings.
- Implement the provided algorithmic approach in clinical practice to optimize radiologic diagnosis, clinical management, and therapy.

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Neuroimmune disorders in children are a complex group of inflammatory conditions of the central nervous system with diverse pathophysiologic mechanisms and clinical manifestations. Improvements in antibody analysis, genetics, neuroradiology, and different clinical phenotyping have expanded knowledge of the different neuroimmune disorders. The authors focus on pediatric-onset myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease, which is a new entity in the spectrum of inflammatory demyelinating diseases, distinct from both multiple sclerosis (MS) and anti–aquaporin-4 (AQP4) antibody neuromyelitis optica spectrum disorders (NMOSDs). The authors review the importance of an optimized antibody-detection assay, the frequency of MOG antibodies in children with acquired demyelinating syndrome (ADS), the disease course, the clinical spectrum, proposed diagnostic criteria, and neuroimaging of MOG antibody–associated disease. Also, they outline differential diagnosis from other neuroimmune disorders in children according to the putative primary immune mechanism. Finally, they recommend a diagnostic algorithm for the first manifestation of ADS or relapsing ADS that leads to four demyelinating syndromes: MOG antibody–associated disease, AQP4 antibody NMOSDs, MS, and seronegative relapsing ADS. This diagnostic approach provides a framework for the strategic role of neuroradiology in diagnosis of ADS and decision making, to optimize patient care and treatment outcome in concert with clinicians.

Online supplemental material is available for this article.

Introduction

Pediatric neuroimmune disorders are a heterogeneous group of neurologic conditions predominantly characterized by inflammatory responses in the central nervous system (CNS) (1,2). These neuroimmune disorders of the CNS define a group of diseases with different clinical phenotypes and can be grouped according to the putative primary immune mechanism into antibody-mediated disease, immune cell–mediated disease, infection-associated disease, paraneoplastic neurologic conditions, and genetically driven immune-mediated disease (1).

We will focus on myelin oligodendrocyte glycoprotein (MOG) antibody–associated disease, in which clinical and neuroradiologic interest has become more relevant with use of an optimized assay to detect antibodies, the live cell–based assay, which provides high sensitivity and specificity (3–6). MOG antibody–associated disease is now considered a new entity in the spectrum of inflammatory demyelinating diseases, distinct from both multiple sclerosis (MS) and aquaporin-4 (AQP4) antibody neuromyelitis optica spectrum

TEACHING POINTS

- The clinical phenotype associated with MOG antibodies changes with age, from ADEM-like (ADEM, ADEM-ON, MDEM, encephalitis) in children to opticospinal phenotype (ON, myelitis, NMOSD, brainstem encephalitis) with increasing age.
- MOG antibodies are present in more than 30% of children at first presentation with ADS, approximately 35% of cases following a relapsing course, more than 50% of those presenting with ADEM, 37% of those presenting with ON at onset, 13% of those presenting with TM at onset, 50% of those with NMOSD, and almost all of those with MDEM or ADEM-ON.
- The MRI findings of MOG antibody–associated disease are variable, but the following MRI patterns have been described: *(a)* predominantly multifocal hazy or poorly demarcated lesions involving gray or white matter with both supratentorial and infratentorial lesions; *(b)* predominantly multiple, extensive, confluent, bilateral white matter lesions resembling a leukodystrophy pattern; *(c)* cortical encephalitis with leptomeningeal enhancement; and *(d)* spinal cord (myelitis) or optic nerve (ON) involvement without brain lesions, nonspecific white matter lesions, or in combination with an ADEM-like pattern.
- Bilateral ON and longitudinally extensive lesions with perineural enhancement extending to surrounding orbital tissue are characteristics of MOG antibody–associated ON and have been proposed as a sensitive feature to distinguish MOG antibody–associated ON from AQP4 antibody–associated ON or MS-related ON.
- The diagnostic algorithm—which combines clinical, neuroradiologic, and serologic biomarkers applicable to any episode of CNS demyelination—can provide the radiologist with a framework for the strategic role of radiology in diagnosis, to optimize clinical management and therapy in concert with pediatric neurologists.

disorders (NMOSDs) (4,7,8). MOG antibodies are common in children with acquired demyelinating syndromes (ADSs) with both monophasic and relapsing disease courses (5). The clinical spectrum of MOG antibody–associated disease embraces a broadening range of phenotypes, including acute disseminated encephalomyelitis (ADEM), multiphasic demyelinating encephalomyelitis (MDEM), optic neuritis (ON), ADEM followed by ON (ADEM-ON), recurrent ON, encephalitis, myelitis, and NMOSD (4–6,9,10).

In this article, we discuss the epidemiology of MOG antibodies, their frequency in children with ADS, clinical features, disease course, diagnostic criteria, and neuroimaging findings with emphasis on the different MRI patterns and in relation to the spectrum of clinical phenotypes. Moreover, we discuss differential diagnosis from AQP4 antibody NMOSD, MS, and a variety of other pediatric neuroimmune disorders. Finally, we provide an algorithmic approach to diagnosis of MOG antibody–associated disease, AQP4 antibody NMOSD, MS, and seronegative relapsing ADS.

A Short History of MOG Antibody–associated Disease

MOG is a glycoprotein expressed selectively on oligodendrocytes and has potential as a marker of oligodendrocyte maturation and myelin compaction (8). MOG was first identified as the primary antigenic target of demyelinating antibodies in experimental autoimmune encephalomyelitis (11). The seminal work of O'Connor et al (12) defined the clinical association of MOG antibody with a non-MS demyelinating phenotype. Mader et al (13) showed for the first time that AQP4–immunoglobulin G (IgG) antibody–seronegative patients with an NMOSD phenotype harbor an MOG-IgG–directed immune response.

Recent developments have improved detection of MOG antibodies using the cell-based assay (14), with recommended measurement of levels in the serum (15). Measurement of MOG antibodies in cerebrospinal fluid is not usually required, since MOG-IgG is produced mostly extrathecally, resulting in lower titers (15) (Fig E1).

Diagnostic Criteria

Diagnostic criteria for MOG antibody–associated disease have been proposed by several groups but have not been fully validated (15,16). Jarius et al (15) proposed the following criteria: seropositivity for MOG antibody (by means of a cell-based assay) in patients with monophasic or relapsing ON, transverse myelitis (TM), brainstem encephalitis, encephalitis, or any combination of these syndromes, if MRI or electrophysiologic findings are compatible with CNS demyelination. In another proposal for diagnostic criteria for MOG antibody–associated disorders, López-Chiriboga et al (16) proposed the following criteria: detection of MOG-IgG with clinically validated cell-based assay and presence of one or more of the following clinical manifestations: ADEM, ON, chronic relapsing inflammatory optic neuropathy, TM, brain or brainstem syndrome compatible with demyelination, or any combination of the described manifestations after exclusion of alternative diagnoses.

The international recommendations for MOG antibody testing in patients with acute CNS demyelination of suspected autoimmune origin were first published in 2018 (15). Note that these recommendations are mainly intended for use in adults and adolescents; however, the panel members recommended that indications for MOG antibody testing in young children do not need to be as rigid as in adults and adolescents, because MOG antibody–associated disease is thought to be more common among young children with ADS than among adults.

Recently, Cobo-Calvo et al (17) reported that despite the observed predilection for the optic

nerve and spinal cord, only 19% of patients fulfilled the 2015 criteria for NMOSD (18), based on a large cohort of patients with MOG antibody–associated disease. In another cohort study, the authors reported that of 22 pediatric patients, 13 fulfilled the 2015 criteria for NMOSD (19). This accentuates the complexity of grouping patients by the clinical syndrome rather than defining them on the basis of biologic phenotype (16,17,20). This has led to some debate and disagreement in the field about whether to use syndrome-based (NMOSD) or biomarker-based (AQP4 antibody, MOG antibody) diagnostic criteria. Several authors (16,17,20) have argued in favor of molecular-based diagnostic criteria that allow diagnosis at the initial episode of limited disease without delay.

Epidemiology and Demographics

MOG antibodies have been detected in 30%–50% of children with ADS (5,21,22). These studies have also demonstrated that MOG antibodies are present in children more frequently than AQP4 antibodies (21,22).

Several studies (8,19,21) found that the clinical phenotype associated with MOG antibodies changes with age, from ADEM-like (ADEM, ADEM-ON, MDEM, encephalitis) in children to opticospinal phenotype (ON, myelitis, NMOSD, brainstem encephalitis) with increasing age. Young children most often present with ADEM, whereas ON is the most common feature in children older than 9 years.

Clinical Spectrum of MOG Antibody–associated Disease

MOG antibody–associated disease has been recognized as a distinct disease entity. Some patients have a monophasic course, while others go on to develop relapsing disease. The clinical phenotypes of children with MOG antibody–associated disease include ADEM, MDEM, ADEM-ON, NMOSD, recurrent ON, encephalitis and seizures, brainstem demyelinating episodes, and myelitis (3–5,8).

MOG antibodies are present in more than 30% of children at first presentation with ADS, approximately 35% of cases following a relapsing course, more than 50% of those presenting with ADEM, 37% of those presenting with ON at onset, 13% of those presenting with TM at onset, 50% of those with NMOSD, and almost all of those with MDEM or ADEM-ON (5,21–26). In the following sections, we present the clinical features of the wide spectrum of MOG antibody–associated syndromes in children.

MOG Antibody–associated ADEM

ADEM is a demyelinating disorder of the CNS (27). Between 55% and 86% of pediatric ADEM cases are reported to be preceded by symptoms of systemic viral illness (27,28). The average age at onset of pediatric ADEM is 3.6–7 years (27).

Children with ADEM and MOG antibodies have a monophasic course in the majority of cases and a good outcome (29). These patients are more likely to have undetectable titers of MOG antibody in follow-up samples (21,29). It is important to note that children with ADEM and persistence of MOG antibodies are at high risk of relapse, which leads to phenotypes such as MDEM, ADEM-ON, or NMOSD (8,16,21,22,29–33).

MOG Antibody–associated MDEM

Children with an initial episode of ADEM associated with MOG antibodies can continue to develop further demyelinating episodes characterized by ADEM-like episodes including new MRI lesions (9,29). In the majority of children, the second demyelinating event occurs in the 1st year, and the number of attacks during the first 24 months after the onset ranges from one to six episodes (21).

MOG Antibody–associated ADEM-ON

ADEM followed by a single or recurrent episodes of ON is a MOG antibody–associated relapsing disorder that can have a heterogeneous disease course (9,32). These patients are reported to have frequent ON episodes, occasionally in combination with MDEM (9,29,34).

MOG Antibody–associated NMOSD/NMO-related Phenotypes

Cobo-Calvo et al (4) have proposed the term *NMO-related phenotypes* for MOG antibody–positive patients presenting with ON, TM, or a combination of both to differentiate from AQP4 antibody NMOSD. Children with NMOSD and MOG antibodies can present with simultaneous ON and TM or sequentially show other core clinical characteristics such as brainstem syndrome or longitudinally extensive TM (LETM) (35).

Antibodies against MOG have been found in 15%–40% of AQP4-IgG–seronegative patients with a clinical diagnosis of NMOSD (36,37). Interestingly, Hacohen et al (30) detected MOG antibody in 83.3% of NMOSD patients without AQP4 antibody, much higher than in previously reported adult cohorts (8,38).

MOG Antibody–associated ON.—ON is the dominant clinical phenotype of all MOG antibody–associated disease episodes in both children and adults (39–41). A monophasic course is reported in approximately two-thirds of MOG antibody–positive children (21,39). One-third of affected patients will develop recurrent disease, which is associated with severe cumulative disability (41).

Children with recurrent ON often harbor MOG antibodies at the first episode itself and continue to have high and persisting titers, in contrast to children with a monophasic event (9,21).

In a recent observational case series of patients (mixed adult and child studies) with MOG antibody–associated ON, the authors found that 30% of patients had recurrent ON without other neurologic symptoms, 10% had single ON, 16% had chronic relapsing inflammatory optic neuropathy, and 41% had ON with other neurologic symptoms (NMOSD-like phenotype or ADEM) (42).

MOG Antibody–associated Myelitis.—Myelitis is an early manifestation of MOG antibody–associated disease and may occur in isolation or concurrently with ON or cerebral involvement with an NMOSD or ADEM phenotype (43). MOG antibody–associated myelitis is clinically more severe than MS myelitis but has a better long-term outcome than AQP4 antibody myelitis (43,44). It should also be noted that the clinical manifestation of MOG antibody–associated myelitis may meet clinical criteria of acute flaccid myelitis related to viral infections (43).

MOG Antibody–associated Brainstem Syndrome

Brainstem involvement is the presenting symptom in around 7% of patients with MOG antibodies (4), leading to symptoms like ataxia, dysarthria, facial palsy, and in some cases respiratory insufficiency (45). Brainstem involvement can manifest with isolated brainstem attacks or as part of a severe clinical manifestation involving LETM and ON (6,46). Brainstem phenotype could be related to a poorer prognosis, but this needs to be further corroborated (45).

MOG Antibody–associated Encephalitis

Encephalitis and seizures are observed in patients with MOG antibody and are now a well-recognized clinical phenotype, which may overlap with autoimmune encephalitis or infectious encephalitis (4,47,48). Previous studies found more selective cortical involvement (unilateral or bilateral) with or without white matter involvement compared with ADEM (17,47,49). Recent studies have reported high rates of ON in the setting of the encephalitic episode or later (17,47,49,50). In rare cases, the encephalitic phenotype is associated with rapid death due to intracranial hypertension (17) or respiratory failure (51). MOG antibody encephalitis may coexist either simultaneously or in succession with anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in rare cases (50,52). Of interest, in a recent article, Armangue et al (53) reported that among 64 patients with autoimmune encephalitis, MOG antibodies were more common (34%) than all other neuronal antibodies combined (33%).

It should be taken into account that MOG antibody–associated syndromes are a recent entity and the clinical spectrum is in expansion, including multiple demyelinating or encephalitic syndromes (53). Furthermore, the clinical phenotypes described earlier can occasionally manifest with overlapping features, and change from one to another clinical phenotype is also possible.

Neuroimaging of MOG Antibody–associated Disease

Radiologic studies in MOG antibody patients should include the brain, optic nerves (if visual symptoms are present), and spinal cord (5). The MRI findings of MOG antibody–associated disease are variable, but the following MRI patterns have been described: *(a)* predominantly multifocal hazy or poorly demarcated lesions involving gray or white matter with both supratentorial and infratentorial lesions; *(b)* predominantly multiple, extensive, confluent, bilateral white matter lesions resembling a leukodystrophy pattern; *(c)* cortical encephalitis with leptomeningeal enhancement; and *(d)* spinal cord (myelitis) or optic nerve (ON) involvement without brain lesions, nonspecific white matter lesions, or in combination with an ADEM-like pattern (5,31,39).

The interpreting radiologist must be able to recognize imaging features of MOG antibody–associated disease and distinguish them from AQP4 antibody NMOSD, MS, and other pediatric neuroimmune diseases, being aware of the difficulties that this entails owing to possible overlapping features.

Brain MRI Findings

As mentioned earlier, the clinical phenotype associated with MOG antibodies changes with age from ADEM-like in young children (often <5 years) to opticospinal with increasing age (between 5 years and puberty) (8,9).

In MOG antibody–associated ADEM, the following findings have been described: bilateral, multiple, poorly demarcated and widespread lesions that are hyperintense on T2-weighted and fluid-attenuated inversion-recovery (FLAIR) images with involvement of several regions including the subcortical, periventricular, and deep white matter; cortical gray matter; deep gray matter (most commonly the thalamus); brainstem; and cerebellum (39,54,55). Some studies have detected corpus callosum lesions (39,56,57), contrary to the study by Fernandez-Carbonell et al (23), who reported absence of corpus callosum lesions in MOG-seropositive children. Some children may

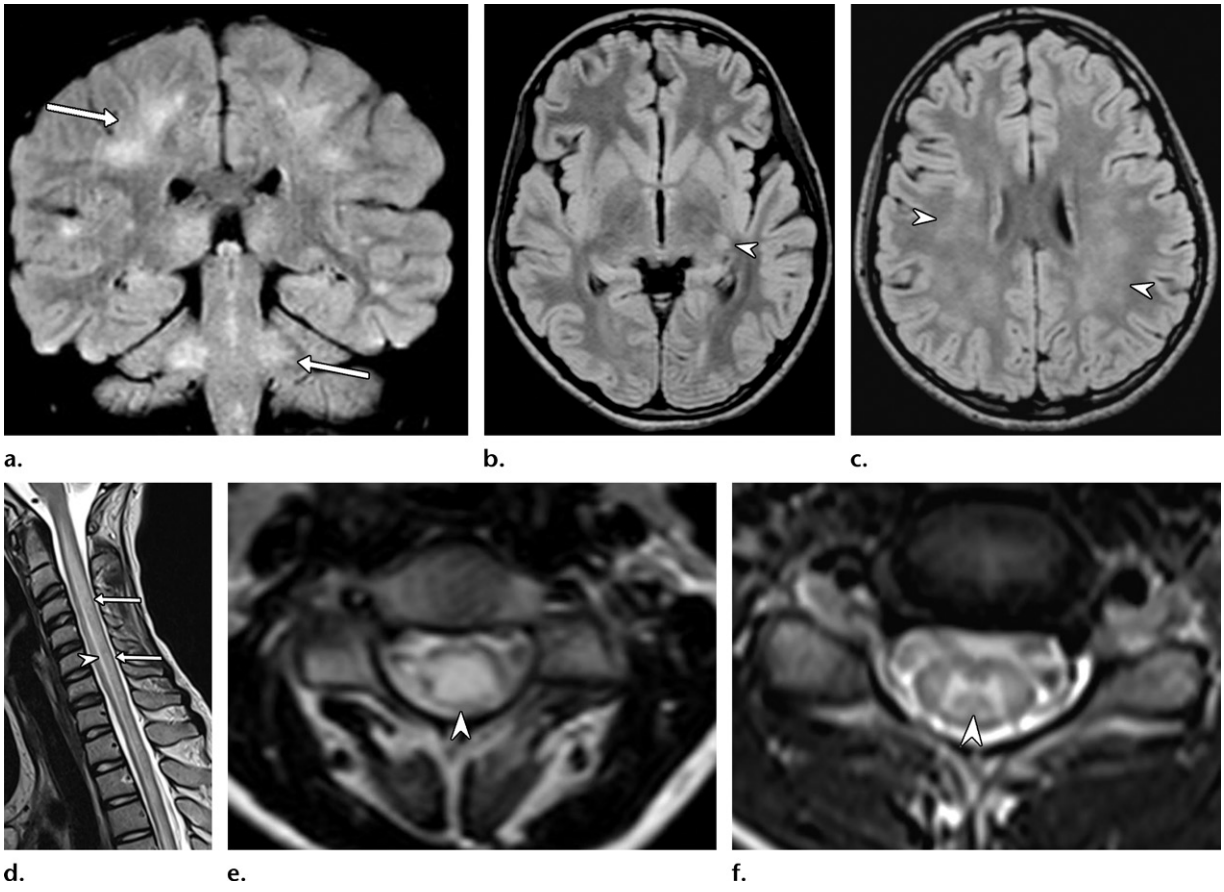


Figure 1. MOG antibody–associated ADEM in a 12-year-old girl with encephalopathy, ataxia, and lower extremity weakness after a viral illness. **(a)** Coronal FLAIR image shows large and blurred hyperintense lesions (arrows) involving both cerebral hemispheres and the cerebellar peduncles. **(b, c)** Axial FLAIR images show hyperintensity in the left thalamus (arrowhead in **b**) and widespread poorly demarcated lesions in the white matter (arrowheads in **c**). **(d)** Sagittal T2-weighted image shows a sagittal hyperintense line (arrowhead) surrounded by hyperintensity (arrows) in the cervical cord extending to the thoracic cord. **(e, f)** Axial T2-weighted images show abnormal hyperintensity that involves both the gray and white matter (arrowhead in **e**) and the central gray matter in an H-type configuration (arrowhead in **f**).

have lesions that enhance after administration of contrast medium (28,29,39). There have also been reported a few cases with restricted diffusion suggestive of cytotoxic edema (39) (Figs 1–4).

Cases of leukodystrophy-like phenotype have been reported in children with MOG antibody–associated disease, and in these cases, MRI showed a pattern of predominantly diffuse, confluent, extensive, bilateral white matter lesions; associated intense contrast-enhancing lesions that may be present even outside of a clinical attack (frequent relapses); and brain atrophy (31) (Fig 5). In cases of MOG antibody–associated encephalitis including seizures, the following findings have been reported: cortical lesions, leptomeningeal enhancement, white matter changes, and brainstem involvement (58). In rare cases, anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis and MOG antibody–associated disease may occur in the same patient (50,52) (Fig 6).

Recently, two clinicoradiologic patterns of poor prognosis have been described: *(a)* ADEM-like relapses progressing to leukodystrophy-like MRI characteristics and *(b)* extensive cortical encephalitis resulting in severe brain atrophy (53).

Optic Nerve MRI Findings

Bilateral optic involvement is reported in more than 80% of patients (37,41,59). Characteristic orbital MRI findings include *(a)* T2 hyperintensity and enhancement of the optic nerve, *(b)* longitudinally extensive lesions with involvement of the anterior optic pathways and relative sparing of the chiasm and optic tracts, and *(c)* perineural enhancement that sometimes extends to surrounding orbital tissue in the acute attack (41,60). Findings are shown in Figures 3e and 6c.

Spinal Cord MRI Findings

MOG antibody–associated myelitis lesions are characterized by the following intramedullary patterns of distribution: *(a)* longitudinally extensive lesions (at least three vertebral body segments), also known as LETM, with T2-hyperintense signal intensity that affects both the gray and white matter (43); *(b)* T2-hyperintense short

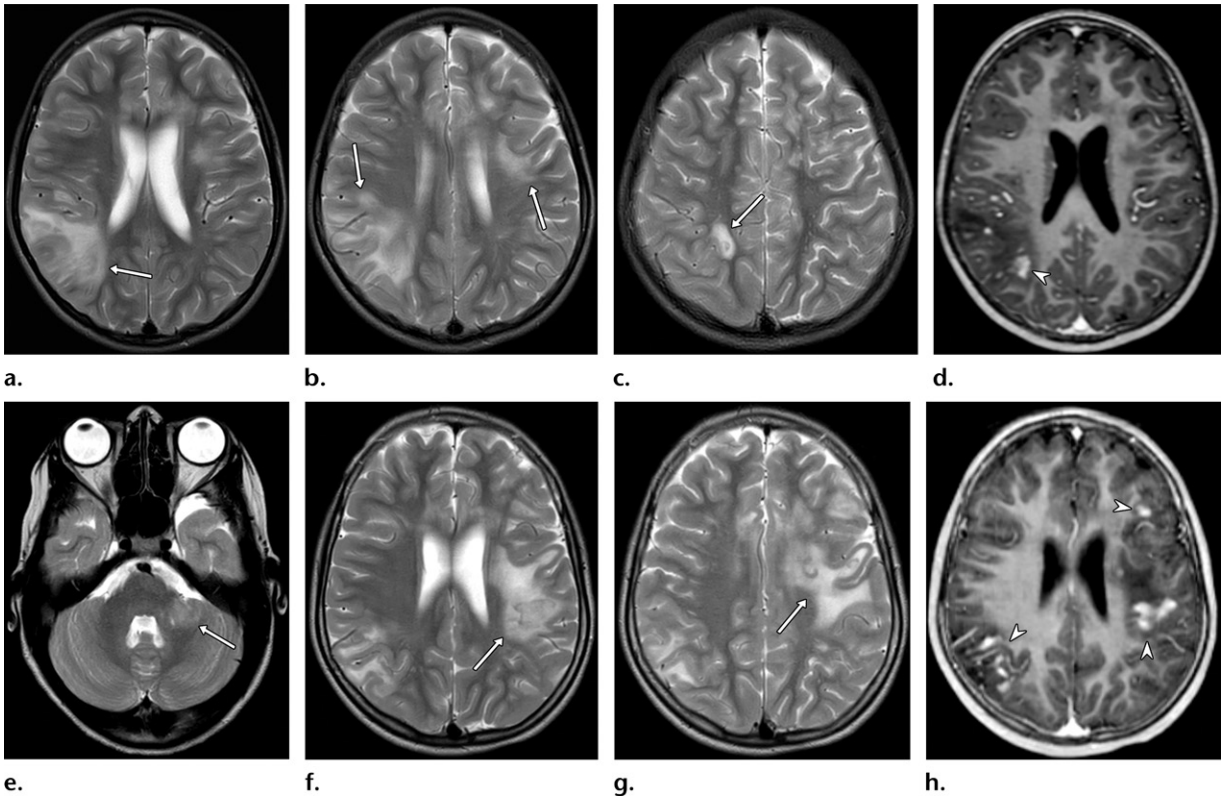


Figure 2. MOG antibody–associated MDEM in a 7-year-old girl with encephalopathy, fluctuating drowsiness, and irritability. She went on to have three relapses over the next 3 years. **(a–c)** Axial T2-weighted images at initial presentation show bilateral cortical and white matter lesions (arrows). **(d)** Axial postcontrast T1-weighted image shows an enhancing cerebral lesion (arrowhead). After 12 months of follow-up, MRI demonstrated near-complete resolution of all lesions (not shown). **(e–g)** Axial T2-weighted images at the first relapse 19 months later show multifocal bilateral but asymmetric white matter lesions including the left cerebellar peduncle (arrow). **(h)** Axial postcontrast T1-weighted image shows several punctate nodular enhancing lesions (arrowheads). Repeat MRI during clinical relapses at 22 months and 32 months revealed new confluent lesions involving the deep and subcortical white matter (not shown).

lesions (less than three vertebral segments), so-called non–longitudinally extensive TM (43,61); and *(c)* T2 hyperintensity confined to gray matter in a sagittal line and forming an H sign on axial images in approximately one-third of patients (43,62) (Figs 1d–1f, 4h, 4i, 7).

Another important finding is the presence of at least two noncontiguous lesions, with the conus often involved (43,44). Contrast enhancement and swelling of the spinal cord can be seen in an acute setting (43,61). In a recent study that included children, the authors found that around 27% had abnormal initial spinal cord MR images, 18% of which showed LETM (57).

Differential Diagnosis from AQP4 Antibody NMOSD and MS

There is some clinical and radiologic overlap among these entities (3,63–65) (Fig 8). The clinical features and imaging findings in the brain, optic nerve, and spinal cord of AQP4 antibody NMOSD and MS will be described to distinguish these entities from the newly recognized MOG antibody–associated disease. We also provide a summary of the demographic and clinical characteristics as well as MRI features that allow distinction of MOG antibody–associated disease from its mimics. This initial clinical and radiologic diagnostic approach is valuable because antibody test results can take several weeks to obtain at many institutions.

Demographic and Clinical Characteristics

The clinical appearance of MOG antibody–associated disease has two cardinal manifestations: ADEM-like and opticospinal phenotypes. The three cardinal manifestations in AQP4 antibody NMOSD are ON, myelitis, and area postrema syndrome. In MS patients, the most common manifestations are ON, myelitis, brainstem or cerebellar syndrome, cognitive dysfunction, fatigue, and myelopathy with progressive MS (6,8,44,65).

MOG antibody–associated disease can affect individuals of any age, but children are more predisposed than adults (8,44). The disease course in MOG antibody–associated disease is monophasic or recurrent, in AQP4 antibody NMOSD is more often recurrent than monophasic, and in MS is relapsing-remitting or chronic progressive (6,8,44,65). Oligoclonal bands are common

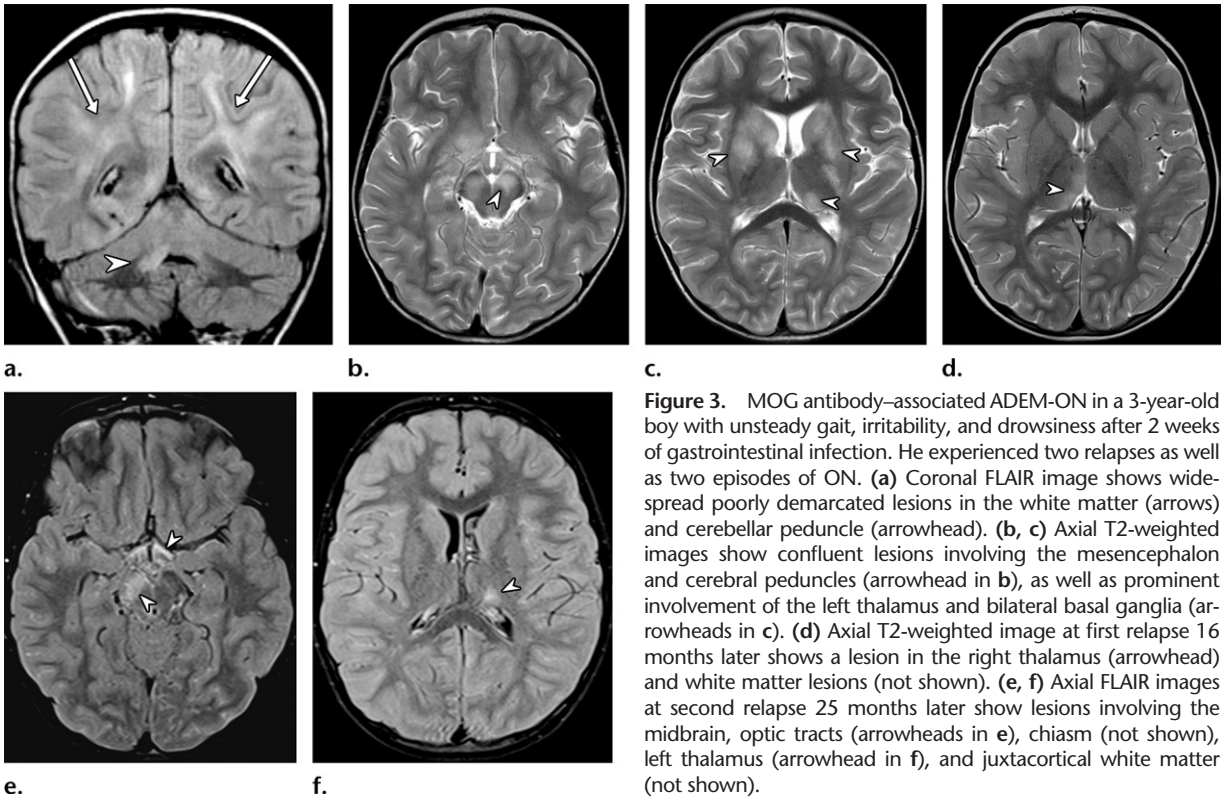


Figure 3. MOG antibody–associated ADEM-ON in a 3-year-old boy with unsteady gait, irritability, and drowsiness after 2 weeks of gastrointestinal infection. He experienced two relapses as well as two episodes of ON. **(a)** Coronal FLAIR image shows widespread poorly demarcated lesions in the white matter (arrows) and cerebellar peduncle (arrowhead). **(b, c)** Axial T2-weighted images show confluent lesions involving the mesencephalon and cerebral peduncles (arrowhead in **b**), as well as prominent involvement of the left thalamus and bilateral basal ganglia (arrowheads in **c**). **(d)** Axial T2-weighted image at first relapse 16 months later shows a lesion in the right thalamus (arrowhead) and white matter lesions (not shown). **(e, f)** Axial FLAIR images at second relapse 25 months later show lesions involving the midbrain, optic tracts (arrowheads in **e**), chiasm (not shown), left thalamus (arrowhead in **f**), and juxtacortical white matter (not shown).

(>90%) in MS patients but rare in the other two entities (8). The demographic and clinical features are summarized in Table 1.

MRI Features

Brain Lesions.—Abnormalities that are considered typical for MS are well-defined multiple ovoid T2- and FLAIR-hyperintense lesions throughout the white matter (66) and callosal lesions perpendicular to the ventricle wall (Fig 9), in contrast to those in AQP4 antibody NMOSD, which are often located adjacent to the lateral ventricles and can exhibit a characteristic "arch bridge pattern" (67). Of interest, children have a higher lesion burden at initial brain MRI than adults (66,68); prepubertal children have larger, confluent, ill-defined border lesions compared with adolescents at initial brain MRI (66); and tumefactive lesions have been described in young children with MS (69). Furthermore, accumulation of silent T2 lesions can occur over time in MS but does not usually occur outside of relapses in AQP4 antibody NMOSD and MOG antibody–associated disease (70). It is also worth noting that substantial resolution of the lesions can be seen at follow-up MRI in children with MOG antibody–associated disease (31,53).

The typical brain lesions of AQP4 antibody NMOSD are found in a minority of patients (71). These lesions are located in areas of high AQP4 expression in the brain (72). One of the most characteristic MRI findings is involvement of the area postrema (71,73). Brainstem lesions can be seen in the cerebral peduncles, cerebellar peduncles, and medulla other than the area postrema (73). Diencephalic lesions and involvement of the corticospinal tract have also been reported as typical MRI findings (73,74) (Fig 10).

Patterns of enhancement such as cloudlike and pencil-thin ependymal enhancement allow distinction of this condition from MS (75,76). Large hemispheric white matter lesions can be seen with a tumefactive, radial, or spindlelike appearance (73,74). The MRI features are presented in Table 2.

Optic Nerve Lesions.—Bilateral ON and longitudinally extensive lesions with perineural enhancement extending to surrounding orbital tissue are characteristics of MOG antibody–associated ON (4,41) and have been proposed as a sensitive feature to distinguish MOG antibody–associated ON from AQP4 antibody–associated ON or MS-related ON (4) (Fig 6c). Perineural enhancement is not seen in AQP4 antibody–associated ON (60). Compared with AQP4 antibody–associated ON and MS-related ON, ON in MOG antibody–associated disease tends to involve the anterior visual pathway, with relative sparing of the chiasm and optic tracts and with associated optic disk edema (41,60). Recurrent ON has been

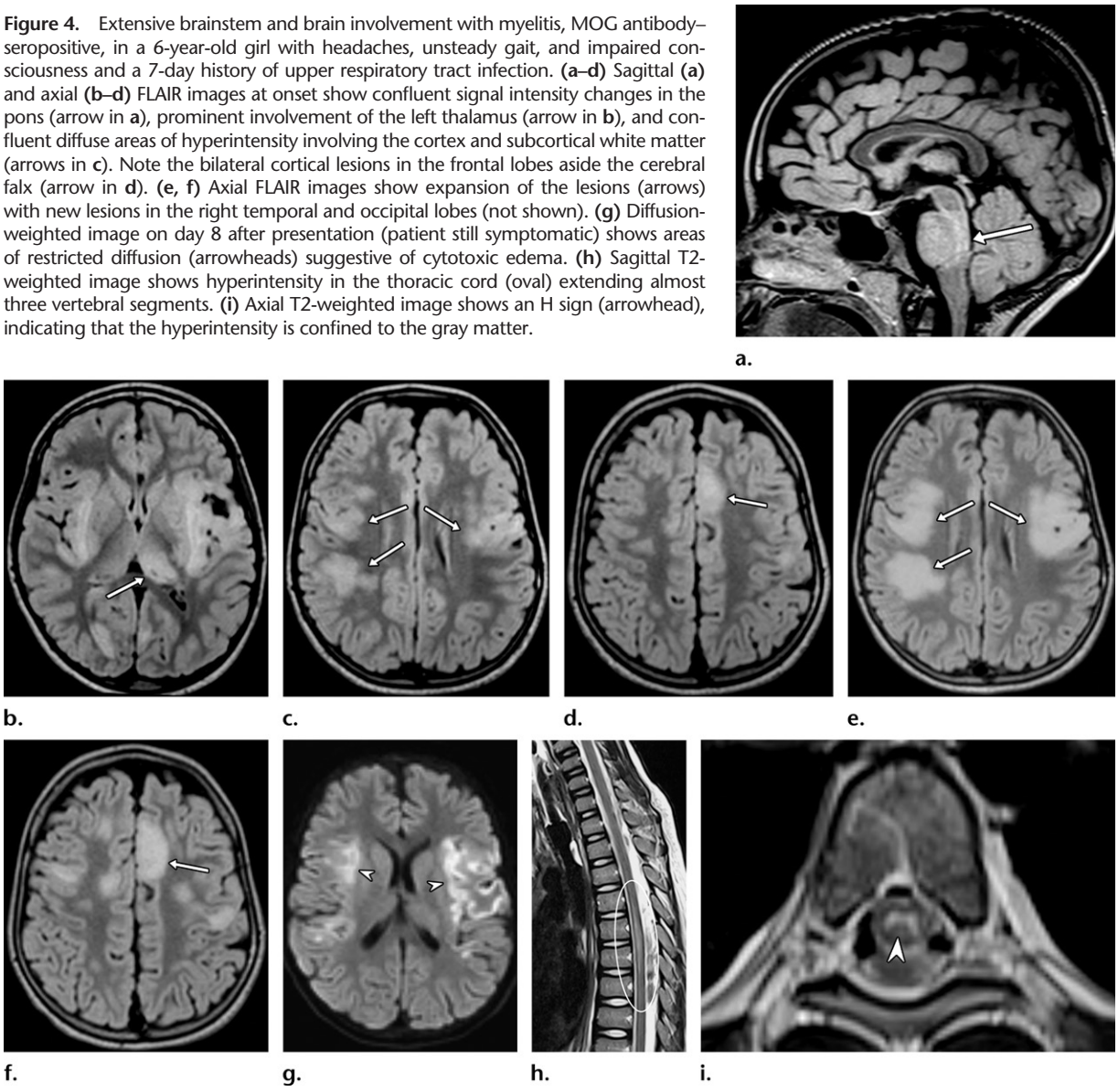


Figure 4. Extensive brainstem and brain involvement with myelitis, MOG antibody–seropositive, in a 6-year-old girl with headaches, unsteady gait, and impaired consciousness and a 7-day history of upper respiratory tract infection. **(a–d)** Sagittal **(a)** and axial **(b–d)** FLAIR images at onset show confluent signal intensity changes in the pons (arrow in **a**), prominent involvement of the left thalamus (arrow in **b**), and confluent diffuse areas of hyperintensity involving the cortex and subcortical white matter (arrows in **c**). Note the bilateral cortical lesions in the frontal lobes aside the cerebral falx (arrow in **d**). **(e, f)** Axial FLAIR images show expansion of the lesions (arrows) with new lesions in the right temporal and occipital lobes (not shown). **(g)** Diffusion-weighted image on day 8 after presentation (patient still symptomatic) shows areas of restricted diffusion (arrowheads) suggestive of cytotoxic edema. **(h)** Sagittal T2-weighted image shows hyperintensity in the thoracic cord (oval) extending almost three vertebral segments. **(i)** Axial T2-weighted image shows an H sign (arrowhead), indicating that the hyperintensity is confined to the gray matter.

identified in 50%–93% of patients with MOG antibody–associated disease (60,77).

In contrast to MS, AQP4 antibody–associated ON is often associated with a long optic nerve lesion (>50% of the nerve length) that tends to involve the posterior segments and optic chiasm (78,79) (Figs 10a, E2a). The combination of optic disk edema, bilateral ON, and recurrent ON is proposed as a feature favoring MOG antibody–associated ON (42,77,80). The MRI features are summarized in Table 3. A case of double-seronegative isolated recurrent ON is shown in Figure E3.

Spinal Cord Lesions.—LETM, a contiguous spinal cord lesion extending over three or more vertebral segments, is a characteristic feature of both MOG antibody–associated myelitis and AQP4 antibody–associated myelitis (36,79) (Figs 1d, 10c, E2b, E2c). On the other hand, shorter-segment lesions are more suggestive of MS-related myelitis (81) (Fig 9d). Nevertheless, it is important to mention that children are more likely to have LETM regardless of cause, thus making the length of the lesion less diagnostically useful in this population (81). Furthermore, short lesions have been described in both MOG antibody–associated myelitis and AQP4 antibody–associated myelitis (61) (Fig 4h).

In MOG antibody–associated myelitis, it has been reported that the T2 hyperintensity can be restricted to the ventral and dorsal horns of the spinal cord gray matter, forming an axial H sign (43) (Figs 1f, 4i, 7); however, this feature is not specific and can be seen in AQP4 antibody–associated myelitis, viral myelitis, and spinal cord infarct (43,62,82). Some studies have reported that bright spotty lesions on T2-weighted images are highly specific for AQP4 antibody–associated myelitis and

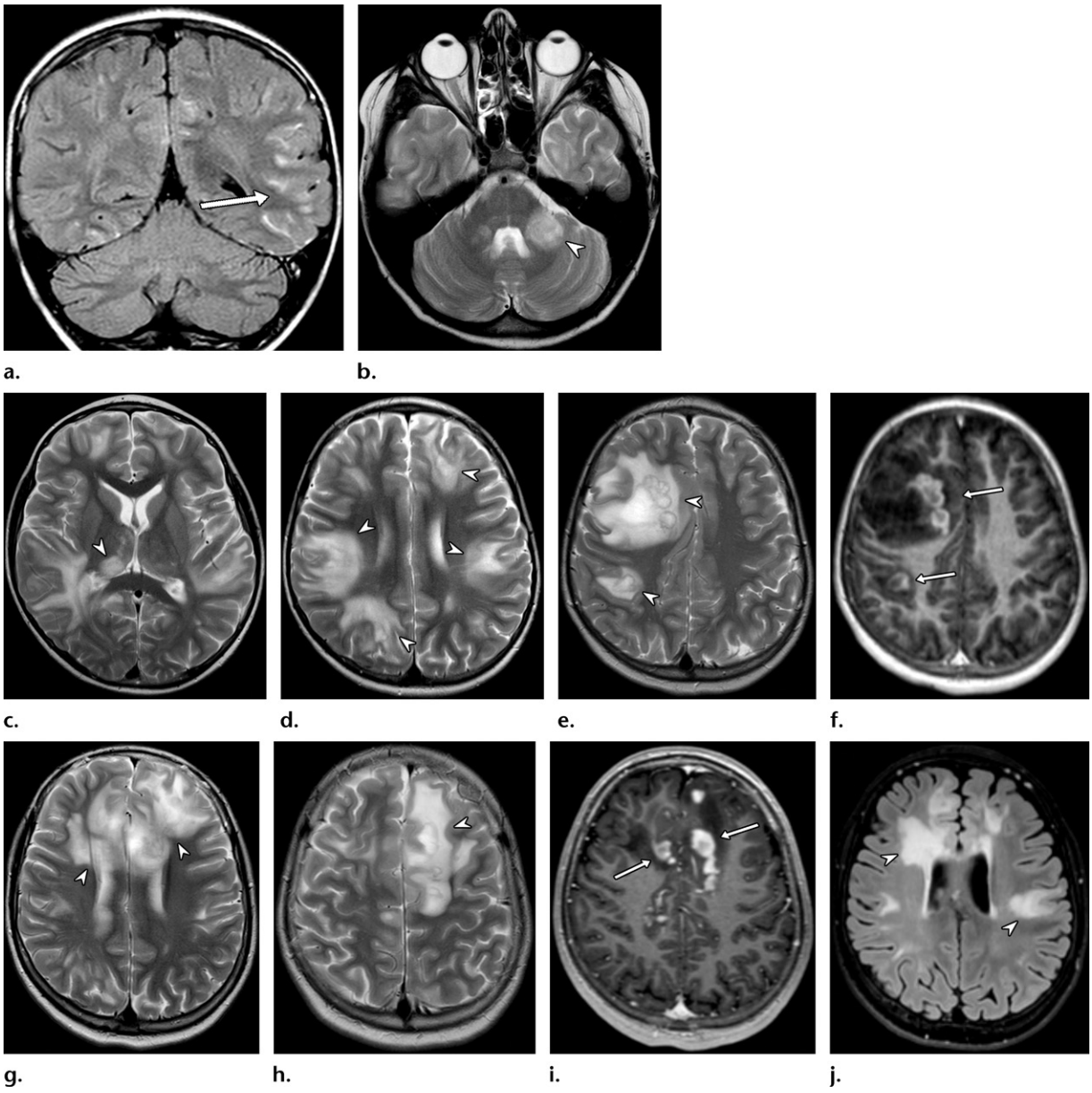
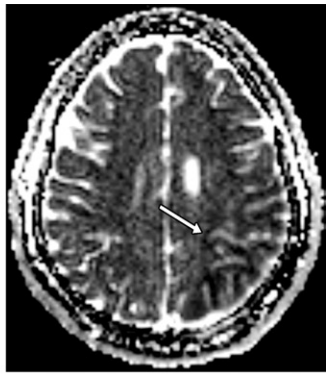


Figure 5. Leukodystrophy-like MRI pattern in a 9-year-old boy with encephalopathy, seizures, right arm weakness, ON, and myelitis at admission and with recurrent ON and multiple relapses later. **(a)** Coronal FLAIR image from initial MRI shows cortical (arrow) and juxtacortical white matter changes. **(b–d)** Axial T2-weighted images at clinical relapse 4 months later show several large confluent white matter lesions (arrowheads in **d**), bilateral temporal lesions (middle arrowheads in **d**), gray matter involvement in the right thalamus (arrowhead in **c**), and changes in the left cerebellar peduncle (arrowhead in **b**). **(e, f)** Axial T2-weighted **(e)** and postcontrast T1-weighted **(f)** images at clinical relapse 6 months later show asymmetric confluent white matter lesions (arrowheads in **e**) with enhancement (arrows in **f**). **(g–i)** Images at clinical relapse 6 years later. **(g, h)** Axial T2-weighted images show extensive confluent white matter and cortical changes in the frontal lobes (arrowheads). **(i)** Axial postcontrast T1-weighted image shows serpentine or twisting enhancement along the cortical lesions. **(j)** Axial FLAIR image at clinical relapse 4 months later shows gradual partial resolution of the initial changes in the frontal lobe. Note the new lesions (arrowheads). Imaging at follow-up 9 years later showed cerebral atrophy (not shown). MRI of the spinal cord showed two noncontiguous lesions involving the cervical and thoracic cord, indicating myelitis (only one episode at onset) (not shown).

can be used to differentiate it from other entities that could manifest as LETM (83,84) (Fig 10d). Compared with the lesions in MOG antibody– or AQP4 antibody–associated myelitis, the spinal cord lesions in MS are peripherally located within the spinal cord white matter (dorsal or lateral column) (44) and are only infrequently seen in the anterior columns or central cord area (85) (Fig 9d).

The presence of enhancement in the spinal cord lesions is less common in MOG antibody–associated myelitis than in MS-associated or AQP4 antibody–associated myelitis. The pattern of enhancement is described as patchy and faint (43). On the other hand, irregular and ring enhancement has been described in patients with AQP4 antibody–associated myelitis in acute phases (86)



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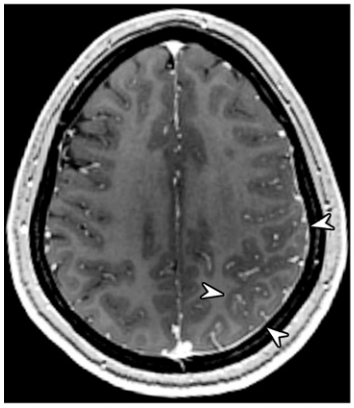

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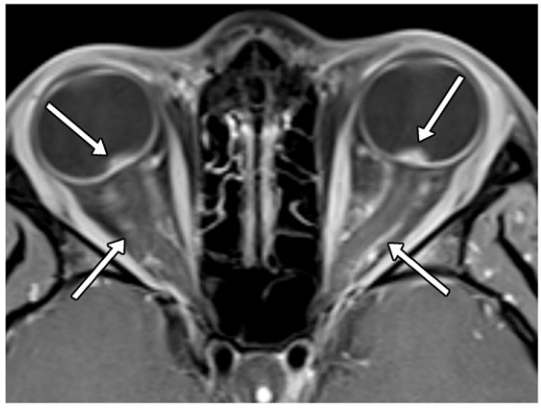

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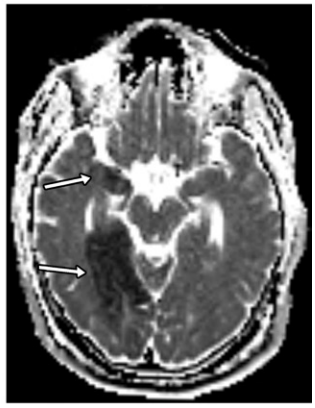
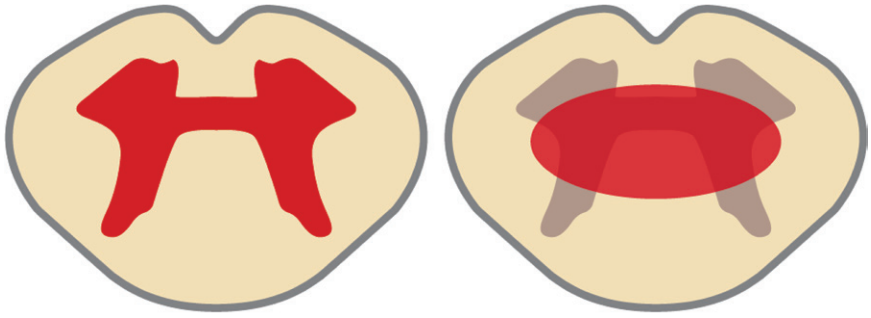


d.

Figure 6. Overlapping of MOG antibody–associated disease and anti–*N*-methyl-D-aspartate receptor (NMDAR) encephalitis in a 15-year-old girl with headache, seizures, speech dysfunction, right arm palsy, and encephalopathy. Clinical relapse occurred 4 weeks later with headache, blurry vision, and diplopia. Three years later, she experienced headache, nausea, hypoventilation and gradually encephalopathy, elevation of lumbar puncture cerebrospinal fluid opening pressure, and seizures. **(a, b)** Axial apparent diffusion coefficient (ADC) map **(a)** and postcontrast T1-weighted image **(b)** at onset show restricted diffusion (arrow in **a**) and leptomeningeal enhancement (arrowheads in **b**) in the left parietal region. **(c)** Axial postcontrast T1-weighted image 4 weeks later shows enhancement of the optic nerve head and perineural optic nerve enhancement and swelling (arrows). **(d)** Axial ADC map 3 years later shows restricted diffusion in the right parahippocampal gyrus, hippocampus (arrows), and thalamus (not shown).



a. b.

Figure 7. Drawings show the typical imaging appearances of MOG antibody–associated myelitis. **(a)** The lesion involves the spinal cord gray matter in an H-type configuration. **(b)** The lesion involves the spinal cord gray and white matter. (Adapted and reprinted, with permission, from reference 62.)

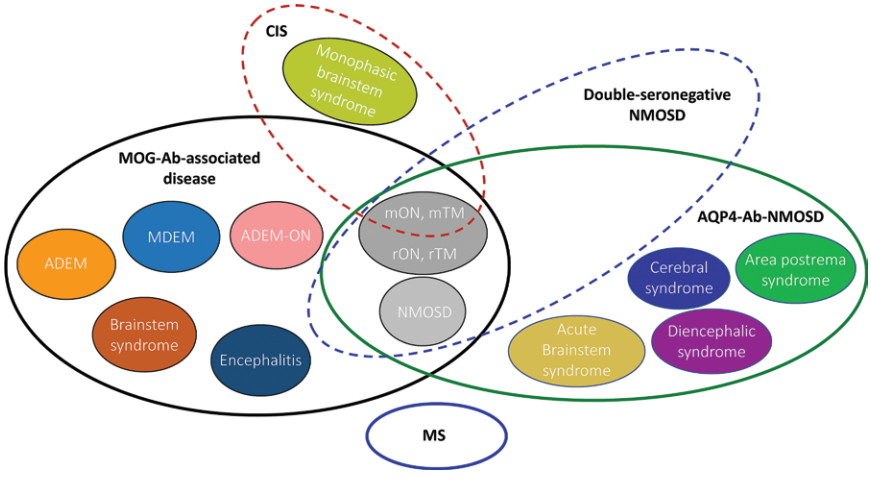


Figure 8. Spectrum of acquired demyelinating diseases in children. Note that the clinical phenotype and neuroradiologic features may be shared, although the autoantibody biomarkers (MOG antibody *[Ab]*, AQP4 antibody) may differ. *CIS* = clinically isolated syndrome, *mON* = monophasic ON, *mTM* = monophasic TM, *rON* = recurrent ON, *rTM* = recurrent TM.

Table 1: Demographic, Clinical, and Pathologic Features of MOG Antibody–associated Disease, AQP4 Antibody NMOSD, and MS

Feature	MOG Antibody–associated Disease	AQP4 Antibody NMOSD	MS
Antecedent infection or vaccination	Common	Rare	Rare
Clinical manifestation	ADEM-like phenotype (ADEM, MDEM, ADEM-ON, encephalitis) or opticospinal phenotype (ON, myelitis, NMOSD, brainstem encephalitis)	ON, LETM, area postrema syndrome, acute brainstem syndrome, acute diencephalic syndrome, symptomatic cerebral syndrome with typical brain lesions	Clinically monofocal event (TM, ON, brainstem syndrome), clinically polyfocal event without encephalopathy, ADEM-like event (encephalopathy and seizures)
Pediatric onset	More common in children than in adults	3%–5% of all cases of NMOSD	3%–4% of all cases of MS
Female-to-male ratio	3:1	3:1	<6 years = 0.8:1, 6–10 years = 1.6:1, >10 years = 2.1:1
Disease course	Monophasic or relapsing	Typically relapsing (>90%)	Relapsing-remitting (>95%)
Type of relapses	Commonly ON	ON, LETM	ON, myelitis, brainstem attacks, cerebral attacks
Cerebrospinal fluid analysis	OCBs <10%, pleocytosis common	OCBs = 30%, pleocytosis common	OCBs >90%, pleocytosis moderate
Serum biomarker	MOG antibody	AQP4 antibody	NA
Prognosis	Good with monophasic disease course, although patients can accumulate disability with recurrent attacks	Attacks and high relapse rate can result in disability	More disability occurs in secondary progressive phase
Neuropathologic features	Oligodendrocytopathy	Astrocytopathy	Demyelination, extensive acute axonal damage at prepubertal age, oligodendrocyte dystrophy or loss

Sources.—References 3, 6, 8, and 44.
Note.—OCBs = oligoclonal bands, NA = not applicable.

Table 2: MRI Characteristics of Brain Lesions in MOG Antibody–associated Disease, AQP4 Antibody NMOSD, and MS

Type of Lesions	MOG Antibody–associated Disease	AQP4 Antibody NMOSD	MS
Brain lesions	Poorly demarcated and widespread lesions involving cortical and deep gray matter (thalamus); juxtacortical, deep, and periventricular white matter; brainstem including cerebellar peduncles; less commonly cortical lesions Leptomeningeal enhancement, intensely enhancing lesions in leukodystrophy-like phenotype	Large (>2 cm) subcortical white matter lesions and lesions within areas of AQP4, such as area postrema, periependymal surface of fourth ventricle/third ventricle (diencephalic region)/lateral ventricles, hypothalamus, corpus callosum, and brainstem More frequently ependymal and leptomeningeal enhancement, cloudlike or perivascular enhancement	Large confluent lesions with poorly defined borders in young children, T1 hypointensity (black holes), brainstem lesions higher in children than in adults, periventricular lesions or lesions perpendicular to long axis of corpus callosum Ring or open-ring enhancement
New lesions at follow-up brain MRI outside of relapse	Rare	Rare	Accumulation of silent T2 lesions over time, new enhancing lesions

Sources.—References 6, 44, 73, 74.

Table 3: MRI Characteristics of Optic Nerve Lesions in MOG Antibody–associated Disease, AQP4 Antibody NMOSD, and MS

Type of Lesions	MOG Antibody–associated Disease	AQP4 Antibody NMOSD	MS
Optic nerve lesions	Bilateral ON frequent Extensive lesions with more involvement of anterior optic pathways Long optic nerve enhancement (more than half) and perineural enhancement extending into surrounding orbital fat Tortuous optic nerve because of swelling In chronic phase, rare optic nerve atrophy	Bilateral ON frequent Extensive lesions involving posterior optic nerve, optic chiasm, or optic tract Long optic nerve enhancement; can involve chiasm Tortuous optic nerve much less common In chronic phase, often long-segment atrophy	Bilateral ON sometimes Short unilateral optic nerve lesions (one-third or less) Short segment of enhancement

Sources.—References 41, 42, 59, 60, 77, and 78.

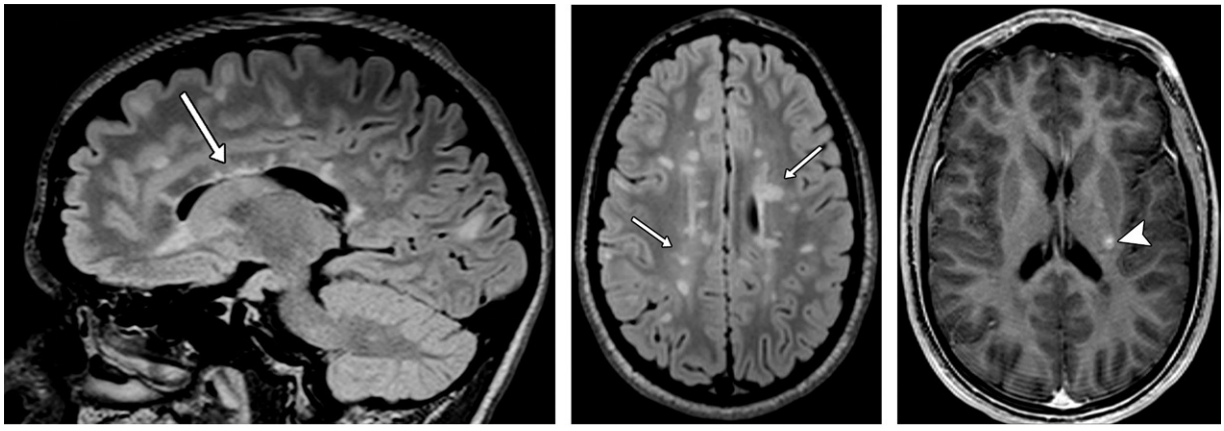
Table 4: Imaging Findings of Myelitis in MOG Antibody-associated Disease, AQP4 Antibody NMOSD, and MS

Spinal Cord MRI Findings	MOG Antibody Myelitis	AQP4 Antibody Myelitis	MS-related Myelitis
Distribution	Cervical and thoracic cord, conus	Cervicomedullary junction, upper thoracic spinal cord9	Cervical region
Resolution of spinal cord lesions	Common	May persist permanently	Enhancement resolves within 8 weeks
LETM lesions*	Common (two-thirds of cases)	Very common, extension to brainstem, area postrema	Sometimes (17%)
Short lesions†	Common; LETM and short lesions may be present simultaneously	Sometimes (15%)	Common
Multiple lesions	Common, two noncontiguous lesions	Rare	Common
H-shaped central gray matter	Common	Less common	Rare
Oval central gray and white matter	Very common	Very common	Rare
Peripheral white matter	Rare	Rare	Very common (lateral or dorsal white matter)
Bright spotty T2 cord lesions	Common	Very common	Very uncommon
T1-hypointense spinal cord lesions	Common	Very common	Very common
Swelling of spinal cord	Less common in acute or early phase, no severe swelling	Very common in acute or early phase, severe swelling	Often in acute lesions
Enhancement	Less common (absent or subtle)	Very common, ring or punctate, irregular	Common, nodular, 20% ring-shaped
Atrophy in chronic stages	Less common	Extensive cord atrophy	Cervical cord atrophy, more pronounced in progressive forms of MS

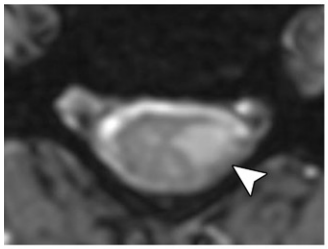
Sources.—References 43, 57, 61, 62, 73, 79, and 87.
*Children are more likely to have LETM regardless of cause.
†The timing of imaging can affect the lesion length.

(Fig E2c). The presence of ring-enhancing lesions seems to be useful for distinguishing NMOSD from other causes of LETM but not for distinguishing NMOSD from MS (86).

Resolution of the abnormal T2 hyperintensity is not typical for lesions associated with AQP4 antibody–associated myelitis but is more commonly seen in patients with MOG antibody–



a. b. c.



d.

Figure 9. MS in a 15-year-old boy with polyfocal deficits without encephalopathy. **(a, b)** Sagittal **(a)** and axial **(b)** FLAIR images show multiple focal hyperintense lesions with well-defined borders and a bilateral distribution involving the white matter. Note the multiple linear and ovoid FLAIR-hyperintense lesions emanating tangentially from the corpus callosum (arrows). **(c)** Axial postcontrast T1-weighted image shows a nodular lesion with enhancement (arrowhead). **(d)** Axial T2-weighted image shows a typical demyelinating lateral lesion (arrowhead) in the cervical cord. There was also a laterodorsal lesion in the thoracic cord (not shown).

associated myelitis (87). Cord atrophy is more pronounced in patients with AQP4 antibody–associated myelitis than in patients with MOG antibody–associated myelitis (87). In Table 4, we present a comparison of the imaging findings in MOG antibody–associated, AQP4 antibody–associated, and MS-associated myelitis.

Differential Diagnosis from Other Neuroimmune CNS Disorders

A wide variety of other neuroimmune disorders that primarily affect the CNS are outlined in a table that summarizes the main neuroradiologic features of these immune cell–mediated or antibody-associated CNS diseases (Table E1). A more in-depth review of this topic is beyond the scope of this article. There are recent articles that provide detailed information including clinical features, biomarkers, pathobiologic mechanisms, differential diagnosis, and treatment options (1,44,54,88).

Diagnostic Algorithmic Approach

In 2017, Hacohen et al (30) approached the issue by proposing a diagnostic algorithm for any episode of CNS demyelination including MOG antibody–associated disease. This algorithmic approach can be applied to the first manifestation of ADS or relapsing ADS in children. The algorithm modified after Hacohen et al (30) is shown in Figure 11 and presented in steps with more details in this section.

First step: clinical evaluation. The clinician (pediatric neurologist) must determine if the clinical manifestation (signs, symptoms, cerebrospinal fluid, or electroencephalography [EEG] results) is suggestive of pediatric ADS.

Second step: neuroimaging. The examination has to include brain and spinal cord MRI and additional orbital MRI in some cases (ON, recurrent ON). The interpreting radiologist must be able to recognize imaging patterns of MOG antibody–associated disease, AQP4 antibody NMOSD, MS, and other pediatric neuroimmune disorders (see Table E1). If MRI findings support the diagnosis of MS, then the International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria for pediatric-onset MS should be applied (the 2012 IPMSSG consensus diagnostic criteria incorporated the 2010 McDonald criteria, and the next update will likely incorporate the McDonald criteria updated in 2017) (89–91).

Third step: investigation of immunopathophysiology. The next key step is to check for serum antibodies in pediatric demyelinating disease (antibodies against AQP4 and MOG) by using a cell-based assay. When clinical and radiologic features suggest NMOSD, the patient should be tested for AQP4 antibody and MOG antibody simultaneously, and MOG antibody testing is primarily recommended in children with features of ADEM.

Fourth step: follow-up. If no diagnosis can be made after the first manifestation of ADS, MRI and testing for MOG and AQP4 antibodies should be repeated at the time of clinical relapse. Alternative diagnoses should be considered in double-seronegative patients.

Finally, this diagnostic algorithm—which includes clinical, neuroradiologic, and serologic biomarkers applicable to any episode of CNS

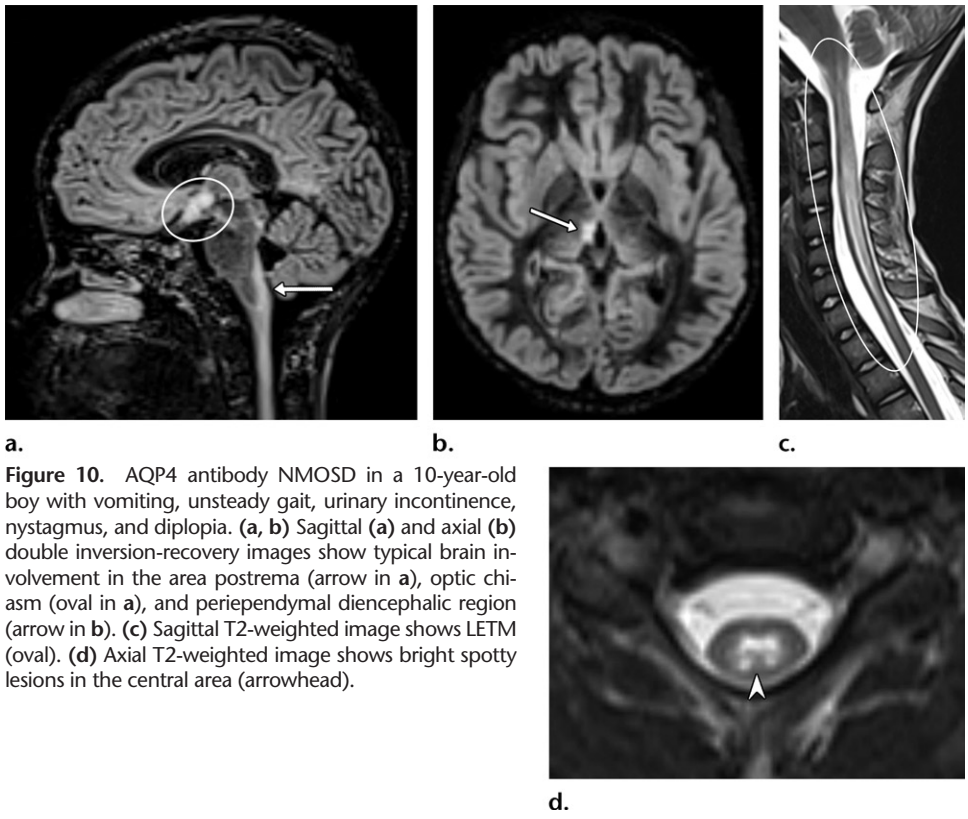


Figure 10. AQP4 antibody NMOSD in a 10-year-old boy with vomiting, unsteady gait, urinary incontinence, nystagmus, and diplopia. **(a, b)** Sagittal **(a)** and axial **(b)** double inversion-recovery images show typical brain involvement in the area postrema (arrow in **a**), optic chiasm (oval in **a**), and periependymal diencephalic region (arrow in **b**). **(c)** Sagittal T2-weighted image shows LETM (oval). **(d)** Axial T2-weighted image shows bright spotty lesions in the central area (arrowhead).

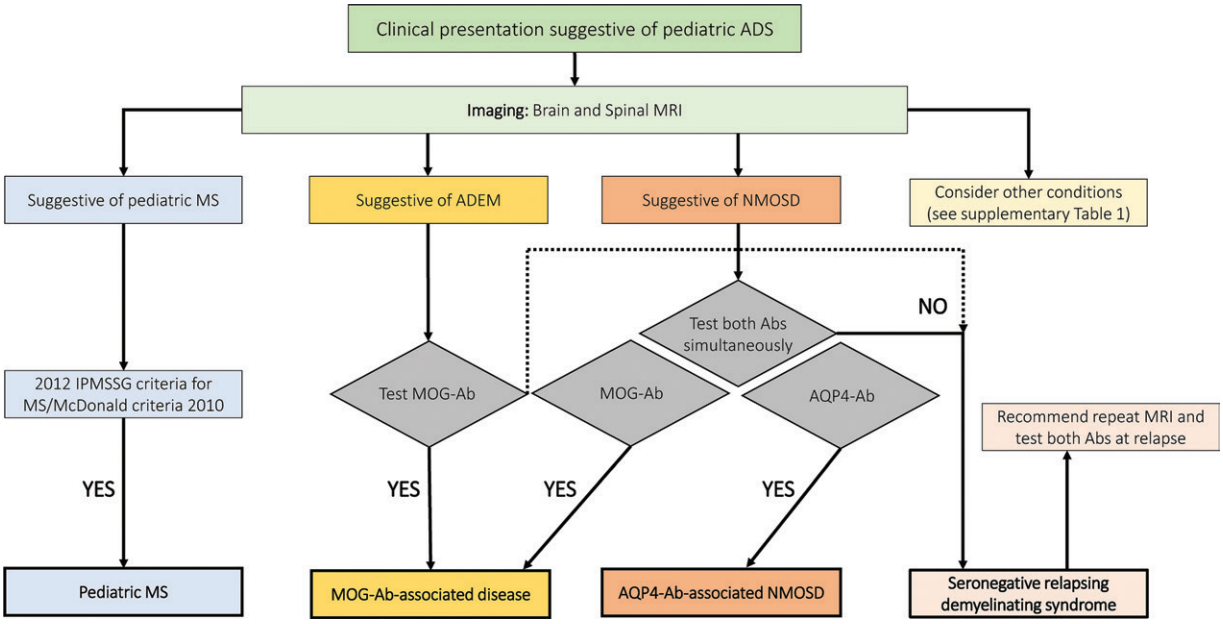


Figure 11. Diagnostic algorithm for children with ADS. *Ab* = antibody, *IPMSSG* = International Pediatric Multiple Sclerosis Study Group. (Adapted and reprinted, with permission, from reference 30.)

demyelination—leads to four principal phenotypes: MOG antibody–associated disease, AQP4 antibody NMOSD, MS, and seronegative relapsing demyelinating syndrome (30,92).

Conclusion

MOG antibody–associated disease is a recently recognized entity in the spectrum of inflammatory demyelinating diseases that includes pediatric demyelinating or encephalitic syndromes, distinct from both MS and AQP4 antibody NMOSD. The clinical manifestation of MOG antibody–associated disease changes with age from ADEM and multiphasic forms of the disease (MDEM, ADEM-ON) in young children to an opticospinal manifestation in children older than 9 years.

Radiologists must be aware of the different imaging patterns in children with MOG antibody–associated disease to narrow the differential diagnosis. Finally, the diagnostic algorithm—which combines clinical, neuroradiologic, and serologic biomarkers applicable to any episode of CNS demyelination—can provide the radiologist with a framework for the strategic role of radiology in diagnosis, to optimize clinical management and therapy in concert with pediatric neurologists.

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