EPIDEMIOLOGY OF ATYPICAL DEMYELINATING DISEASES

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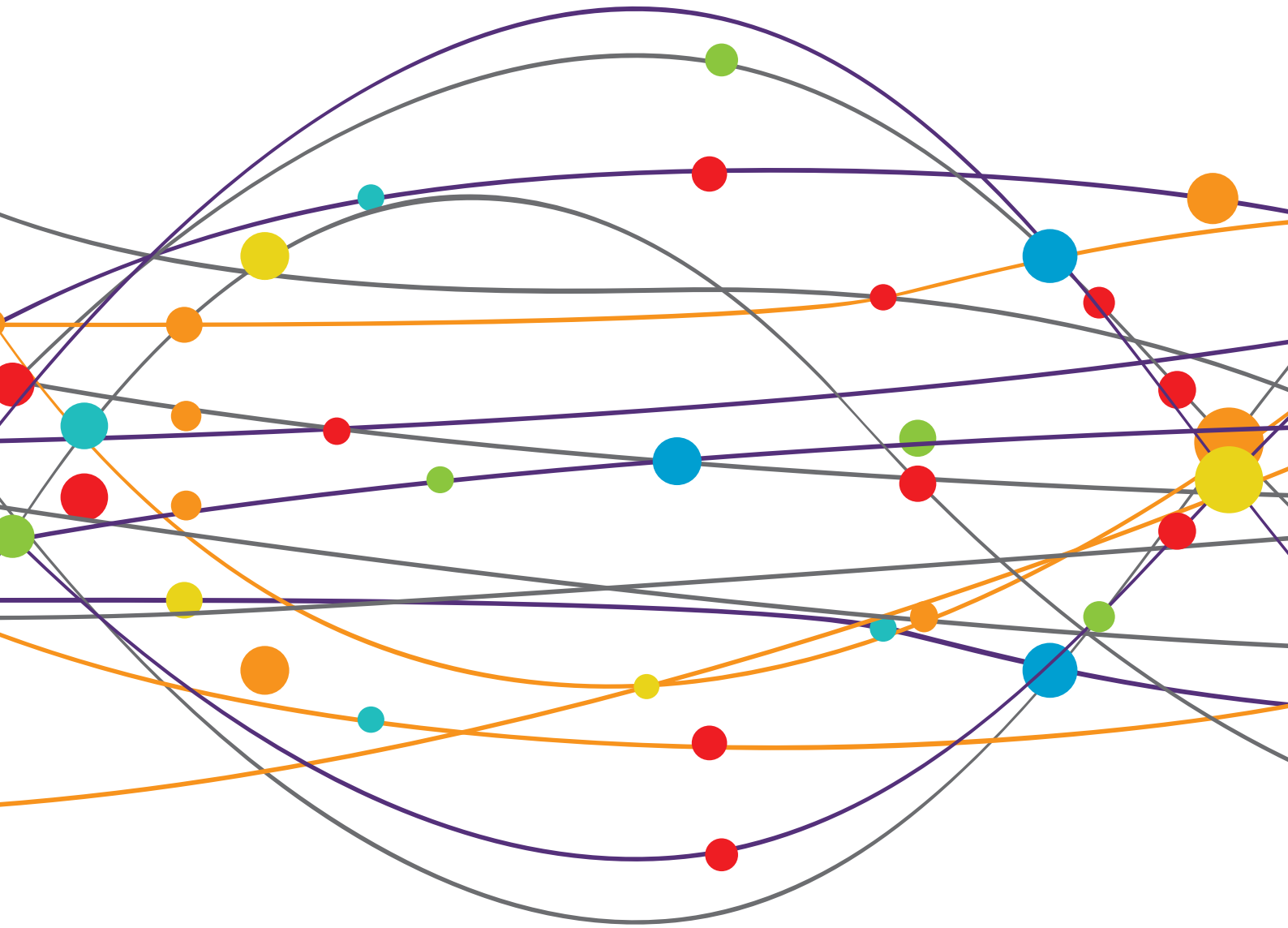

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EPIDEMIOLOGY OF ATYPICAL DEMYELINATING DISEASES

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EDITORIAL
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Editorial: Epidemiology of Atypical Demyelinating Diseases

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Keywords: NMO spectrum disorder, myelin oligodendrocyte glycoprotein antibody, EPI - epidemiology, demyelinating disease, optic neuritis, transverse myelitis

Editorial on the Research Topic

Epidemiology of Atypical Demyelinating Diseases

In Shakespeare a rose by any other name would smell as sweet, but in medicine names are chosen—and revised—to reflect the biologic underpinnings of the diseases they are affixed to. Over the last 15 years categorization of atypical demyelinating diseases has been transformed by the discovery of novel pathogenic antibodies. Identification of aquaporin-4 (AQP4) antibodies in patients with NMOSD has resulted in expansion of clinical phenotype beyond the optic nerve and spinal cord. In 2015, neuromyelitis optica was therefore renamed neuromyelitis optica spectrum disorder (NMOSD) (1). Myelin oligodendrocyte glycoprotein (MOG) antibody has since been observed in association with some seronegative cases of NMOSD, as well as with isolated and recurrent optic neuritis (ON), brainstem syndromes, encephalitis, transverse myelitis (TM), and acute disseminated encephalomyelitis (ADEM) (2). Diagnostic criteria for MOG antibody disease (MOGAD) have yet to be formally defined but current diagnostic schemata such as seronegative NMOSD are insensitive for clinical and radiographic features associated with positive serum MOG antibody testing (3). AQP4 and MOG IgG disease are now known to be marked by distinctive pathophysiology even where clinical phenotypes overlap: a primary astrocytopathy in AQP4+ disease vs. oligodendrocytopathy in MOGAD.

The new disease categorizations represent a seismic shift in the topography of the atypical demyelinating conditions and populations they affect—a shift with profound implications for hallmark demographic and clinical characteristics, prognostic factors, therapeutic algorithms, and approaches to repair.

This research topic focuses on the Epidemiology of Atypical Demyelinating Diseases as we embark on this new epoch. We would like to thank our authors and reviewers for their contributions, time, and insights.

NEW DISEASE DEFINITIONS

Many pieces in this collection address how the new disease definitions have altered descriptive epidemiology of NMOSD, MOGAD, and other atypical demyelinating populations. Most notably, with incorporation of serum AQP4 testing in the 2015 diagnostic criteria, reported prevalence, and incidence of NMOSD have increased substantially in many world regions (Hor et al.). Racial differences in NMOSD prevalence have become more apparent with exclusion of MOG+ cases. Hor et al. report prevalence of NMOSD as ∼1/100,000 in whites, ∼3.5/100,000 in East Asians, and up to 10/100,000 in blacks. Data from a multi-national study (5) suggest that blacks were more likely to

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suffer from severe attacks [visual acuity ≤0.1 in at least one eye or Expanded Disability Status Scale (EDSS) score ≥6.0 at nadir] at onset with a further study from the US observing higher mortality rates in NMOSD patients of African ancestry (4). Further investigation will help guide resource distribution, intensity of therapy, and mitigation of racial inequities. Prevalence and incidence statistics for AQP4+ NMOSD and MOGAD will undergo additional revisions as existing antibody assays are improved, new autoantibodies are discovered, and regional registries are developed.

Testing for AQP4 and MOG antibodies has highlighted mimics previously mislabelled as NMOSD (Lechner et al.; Chhabda et al.). In double seronegative cases, localization and presumptive etiology may offer insights as we move toward targeted biomarker discovery and therapeutic approaches. Blackburn and Greenberg address the need for a new nomenclature for TM with distinction among infectious, para-infectious, idiopathic, and disease-associated inflammatory causes. Oliveira et al. discuss immune checkpoint inhibitors as the trigger for a range of demyelinating attacks, some due to unmasking of pre-existing CNS demyelinating, paraneoplastic, or other inflammatory conditions. Careful work-up including an accurate medical history, CSF studies, and serum antibody panels can help predict risk of recurrent disease.

PROGNOSTICATION

The need for evidence-based prognostic measures for NMOSD has risen to the forefront with our growing array of therapies, with AQP4 and MOG antibodies emerging as important predictors of disease course. In a systematic review and meta-analysis by Filippatou et al. relatively poor visual outcomes were noted in those with isolated ON with AQP4 in contrast to MOG autoantibodies. Risk of relapsing disease is likely lower in MOGAD, but may be higher in adult vs. pediatric patients and depend on duration of follow-up (6). The latter is illustrated in a survival analysis of a retrospective cohort of 21 MOGAD patients in Western Canada; probability of relapse was 0.43 at 1 year, but 0.63 at 4 years (Cross et al.). In another Canadian retrospective series of MOGAD, 7/9 experienced more than one attack, but EDSS scores were relatively favorable at last follow-up (1.0–3.0) (Alsharmrani et al.). The prognostic value of persistent MOG IgG positivity requires further investigation. Children with monophasic disease became negative for serum MOG IgG earlier than in relapsing disease (6), but seroconversion does not seem to wholly preclude the possibility of a subsequent attack (7).

Beyond autoantibodies, clinical, and demographic features may predict disease course and deserve further study. In AQP4+ NMOSD, there is a predilection for relapses to occur in the same location as the previous event (Muir et al.), although this may not be the case in MOGAD (Cross et al.). Age in NMOSD is predictive of attack location with ON being the most common localization prior to age 30 (8), and TM thereafter (Khalilidehkordi et al.). Age in MOGAD is likewise predictive of localization and phenotype with more ADEM attacks seen in children and focal ON or TM in adults (Parrotta and Kister) (6). Area postrema syndrome is extremely rare in MOGAD regardless of age, but a common presentation of AQP4+ NMOSD (Hyun et al.). Females may be at higher risk of relapse in AQP4+ disease (9). Chronic symptoms like pain and fatigue limit quality of life in NMOSD and MOGAD independent of attack frequency; we need to better understand who is at risk and how to treat these common complications (Asseyer et al.). MRI features including cervical cord atrophy (10) and optic nerve (11) and spinal cord lesion length (10) may predict disability outcomes but require validation. Serum biomarkers including glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) are under investigation and may help guide therapy in the future; early data suggest that NfL and GFAP rise with relapses in AQP4+ disease, and NfL correlates with EDSS in MOGAD and AQP4+ NMOSD (12).

THERAPEUTIC STRATEGIES AND POTENTIAL FOR REPAIR

Three therapies with phase III randomized controlled trial evidence for treatment of AQP4+ NMOSD—eculizumab, inebilizumab, and satralizumab—were introduced in 2019–2020. These therapies prolong time to relapse and will likely improve patient outcomes although long-term efficacy and safety are unknown. Expansion in treatment options allows for new opportunities for personalized medicine in NMOSD. Age and gender (e.g., family planning) should be considered in therapy selection. D'Souza et al. review therapies with some evidence for safe use during pregnancy, including corticosteroids, azathioprine, eculizumab, rituximab, and tocilizumab. Future research will help clarify how personal characteristics, such as age, gender, and race, and clinical characteristics predict response and adverse event profiles for each therapy. Lifetime use of certain therapies may not be sustainable given higher risk of opportunistic infection in older individuals and regional resource availability and coverage climate. Development of treatment algorithms in NMOSD should also include evidence-based approaches to treatment de-escalation.

Appropriate therapy for MOGAD and seronegative NMOSD remains under investigation and represents a large unmet need. Recent evidence suggests efficacy of corticosteroids, azathioprine, and mycophenolate in MOGAD; benefits of rituximab have been less clear (13, 14).

The presence of specific target antigens in AQP4+ NMOSD and MOGAD may allow for novel therapeutic strategies through induction or restoration of immune tolerance—and obviate the need for long-term immunosuppression. Such strategies could include oral tolerization approaches as have been used to treat allergies, or a messenger RNA (or other) vaccine as has been explored in experimental autoimmune encephalomyelitis (15). These approaches have not yet proven successful in human autoimmune diseases but deserve further study. However, individual factors such as age, disease stage, and clinical phenotype could prove essential to the potential for repair (16).

What's in a name? For NMOSD and MOGAD, the new categorizations depend on pathogenic autoantibodies, but

also have ushered in a new epidemiology with unique clinical characteristics, prognostic factors, and therapeutic strategies associated with each condition. Further epidemiologic research into these diseases will help refine management and improve outcomes. There remain many seronegative idiopathic demyelinating cases where an epidemiologic approach, with groupings by clinical phenotype, diagnostic test results, demographic features, relapse frequency, and any identified triggers, may focus efforts to identify additional antibodies and other underlying pathogenic mechanisms. For while insights into pathophysiology have led recent advances in treatment, epidemiology may provide the critical bridge to an enhanced, precision approach to the atypical demyelinating diseases.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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CASE REPORT
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Case Series: Myelin Oligodendrocyte Glycoprotein-Immunoglobulin G-Related Disease Spectrum

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Introduction: Myelin oligodendrocyte glycoprotein-immunoglobulin G (MOG-IgG)-related disease was initially described as a subtype of neuromyelitis optica spectrum disorder (NMOSD) with antibodies against MOG. However, it has recently been described as a separate disease entity with clinical and radiological features that overlap those of multiple sclerosis (MS) and NMOSD; the clinical features of this disease phenotype remain undetermined. We herein report the clinical presentation of nine MOG-IgG-positive patients, not all of whom fulfill the NMOSD criteria, in order to highlight the features and challenges of this condition.

Method: We retrospectively reviewed the records of the London (Ontario) MS clinic to identify patients diagnosed with positive MOG antibodies based on the 2015 NMOSD consensus criteria.

Result: Nine patients were identified, all Caucasian. Seven (78%) were female, and the median age of onset was 41 years (range, 28–69 years); the median Expanded Disability Status Scale score at onset was 3.0 (range, 2.0–4.0). A monophasic course was noted in two (22.2%) patients, while the median number of relapse events was 3 (range 2–5) in 77.8% of the patients. Optic neuritis and transverse myelitis contributed equally as initial manifestations in three individuals (33%), while brainstem relapse was reported in two individuals (22%). The brain magnetic resonance imaging findings were compatible with McDonald's 2010 dissemination in space criteria in three cases (33%). Short myelitis and an (H)-sign were each documented in one patient.

Conclusion: The phenotypes of MOG Ab-positive cases exhibited overlapping features with MS and NMOSD. This finding highlights the importance of screening for anti-MOG in individuals with demyelinating symptoms, in consideration of the possibility of false-positive MOG Ab results.

Keywords: myelin oligodendrocyte glycoprotein, optic neuritis, neuromyelitis optica spectrum disorder, multiple sclerosis, transverse myelitis

INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG) is a component of central nervous system (CNS) myelin. Antibodies against MOG have recently been recognized in a clinical syndrome that is likely a CNS demyelinating disorder separate from multiple sclerosis (MS), acute demyelinating encephalomyelitis (ADEM), and neuromyelitis optica spectrum disorder (NMOSD). Although MOG antibodies have been mentioned in the literature for the last 30 years, their role in demyelinating disease has not been fully elucidated and, to date, remains controversial (1, 2). In experimental allergic encephalomyelitis mouse models, MOG is the only CNS myelin autoantigen to cause both an encephalitogenic T cell-mediated inflammatory response and demyelination (3, 4). The significance of this is unclear, and the prevalence of MOG antibodies in MS remains undetermined.

MOG antibodies have recently been linked to seronegative cases of NMOSD. Recent cohort studies have demonstrated that 15–35% of seronegative NMOSD patients will test positive for MOG antibodies (5). The presence of MOG antibodies is not only described in seronegative cases of NMOSD (6); indeed, MOG antibody-positive cases have also been identified within a wider spectrum of demyelinating disorders. Recurrent optic neuritis, myelitis, brainstem encephalitis, and ADEM-like presentation such as encephalomyelitis have all been described in MOG-immunoglobulin (IgG)-positive patients (7–9). However, the clinical features of this disease phenotype remain undetermined. We herein report the clinical presentation of a case series of MOG-IgG-positive patients, not all of whom fulfill the NMOSD criteria, in order to highlight the features and challenges of this condition.

CASE DESCRIPTION

This study was approved by the University of Western Ontario's (Western) Health Science Research Ethics Board and written informed consent was obtained from all patients.

All individuals who tested positive for anti-MOG at the London (Ontario) MS clinic were retrospectively reviewed. Data were obtained for age at onset, sex, first clinical presentation, number of relapses, disease course, and duration. The neurological examination data included the Expanded Disability Status Scale (EDSS) score at the initial and final follow-up and brain and spine magnetic resonance imaging (MRI). In addition, data on serological testing and cerebrospinal fluid (CSF) analysis including oligoclonal bands (OCB) were collected if available. Data on current and disease-modifying therapies (DMTs) were also included. Nine MOG-IgG-positive cases were identified (**Table 1**).

Case A

A 52-year-old male patient was referred due to suspected MS. In 2008, he presented with an episode of vertigo and gait instability, which resolved over a period of 2 months following corticosteroid and plasmapheresis treatment. He remained quiescent until 2017, when he presented with right facio-brachial weakness for 3 weeks. The EDSS score was 1.0 at the final follow-up at the clinic in 2019; brain MRI confirmed McDonald's 2010 dissemination in space (DIS) criteria (**Figure 1**). CSF analysis revealed one distinct band and two faint bands with a normal IgG index. One year later, the patient experienced sensory spinal cord relapse and was started on azathioprine. No spinal cord lesions were identified on 1.5-T MRI at our center.

Case B

A 29-year-old female patient presented in 2008 with double vision, ataxia, nausea, and vomiting. She was presumptively diagnosed with Miller Fisher syndrome or possibly thiamine deficiency; she was treated with intravenous immunoglobulin and thiamine, and her condition returned to normal within 3 months. All serology at that time was unremarkable. CSF analysis was unremarkable without albumin-cytological dissociation during hospitalization.

In 2017, she developed decreased vision and color perception in her left eye; her visual acuity (VA) was 20/20 in the right eye and 20/50 in the left, with left relative afferent pupillary defect (RAPD). She scored 12/16 on the Ishihara color plate on the left eye, and the EDSS score was 2.0. She partially responded to 5 days of intravenous (IV) methylprednisolone treatment. Her brain MRI revealed an enhanced lesion at the anterior aspect of the left optic nerve sheath with unremarkable brain and spine findings. Her CSF examination was negative for OCB, and she had a normal IgG index. She was maintained on mycophenolic acid with no further relapse or new MRI brain lesions to date. At her final follow-up in 2019, her EDSS score was 2.0.

Case C

A 31-year-old female patient was referred to our clinic with a diagnosis of MS following a diagnosis of transverse myelitis in 2014. Her spine MRI revealed short and long myelitis in the cervical and thoracic spinal cord (**Figure 1**). She was treated with IV methylprednisolone for 5 days with no significant improvement. She was subsequently treated with a course of plasma exchange. She exhibited some improvement, but residual mild right-sided weakness remained. The EDSS score improved from 3.0 to 2.0 post-treatment. The patient was maintained on glatiramer acetate. One year later, she presented with optic neuritis. Brain MRI confirmed the DIS criteria. She discontinued glatiramer acetate in 2019 post-MOG testing and preferred not to start any further DMTs. Her disease remained clinically and radiologically inactive. The EDSS score remained steady at 2.0 at her final follow-up in 2019.

Case D

A 19-year-old male patient presented in 2008 with right optic neuritis with residual peripheral visual field defect. In 2017, he presented with another episode of severe right optic neuritis; his VA in that eye was finger counting only. The EDSS score at this time was 4.0. Fundoscopic examination revealed bilateral optic pallor. There was no RAPD. He was treated with a 5-day course of IV methylprednisolone with good recovery; his uncorrected VA was 20/20 on the left and 20/40 on the right. His brain MRI revealed increased signal in his right optic nerve reaching the optic chiasm with mild gadolinium enhancement, with no brain

TABLE 1 | Demographic, clinical, and radiological characteristics of patients.

Case	Age	Sex	Initial symptoms	Relapse #	Initial EDSS	Final visit EDSS	Brain MRI	Spine MRI	CSF OCB	Long-term treatment
A	52	M	Brainstem (vertigo)	3	2	1	Multiple periventricular and deep white matter lesions	N/A*	3 OCB	AZT**
B	29	F	Brainstem (diplopia and ataxia)	2	2	2	Left optic nerve enhancement	Normal	Negative	Mycophenolic acid
C	31	F	Short myelitis	2	3	2	Multiple supratentorial and infratentorial lesions	Multiple cervical and thoracic segment (2-3 vertebral lengths)	N/A	Was on glatiramer acetate, discontinued and received no further treatment
D	28	M	ON***	3	4	2	Right optic nerve hyperintensity up to the chiasma and enhancement	N/A	Negative	Mycophenolic acid
E	43	F	ON	4	4	2	Right optic nerve hyperintensity, no contrast enhancement	Normal	Negative	No treatment
F	58	F	Bladder and ataxia	1	3.5	2	Few subcortical hyperintensities	Normal	Negative	AZT
G	69	F	ON	4	2.5	3	Juxtacortical, periventricular, and deep white matter more pronounced in both occipital lobes	Normal	Negative	No treatment
H	34	F	Transverse myelitis	1	2.5	1	Normal	Longitudinally extensive hyperintensity in the thoracic spinal cord	Negative	No treatment
I	35	F	Longitudinal transverse myelitis	1	3.5	2	Normal	Longitudinally extensive hyperintensity in the cervical spinal cord	Negative	No treatment

**N/A, not available; **AZT, azathioprine; ***ON, optic neuritis; OCB, oligoclonal bands; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; CSF, cerebrospinal fluid.*

or spinal cord lesions. His CSF examination was negative for OCB, and he had a normal IgG index. He was maintained on mycophenolic acid with no further relapses or imaging activity. At the final follow-up in 2018, the EDSS score was 2.0.

Case E

A 43-year-old female patient presented with right optic neuritis since September 2014, with recurrent attacks in July 2015, December 2015, and June 2016. Her VA during each attack was 20/100 in the right eye and 20/20 in the left eye. She received 3 days of IV corticosteroids followed by oral prednisone treatment for her first episode in September 2014, and 1,250 mg of prednisone for 3 days followed by a tapered dose for the 2015 and 2016 relapses. After treatment, her corrected VA was 20/30-2 in the right eye and 20/20-2 in the left eye, with right RAPD. The brain and spine MRI examinations were unremarkable. Her CSF examination was negative for OCB with a normal IgG index. After treatment, her EDSS score improved from 4.0 to 2.0 with no further disease activity and normal brain MRI findings until 2018, despite no DMT upon patient preference.

Case F

A 58-year-old female patient presented in February 2018 with ataxic gait along with bladder and bowel urgency and incontinence. She was initially evaluated by a urologist and received an undetermined diagnosis. Her neurological assessment revealed severe gait and truncal ataxia, and an EDSS score of 3.5. Her brain MRI indicated two foci of increased T2 signal in the subcortical area, and these lesions were non-specific. No lesions were identified in the spinal cord. Her CSF examination was negative for OCB, and she had a normal IgG index. She did not receive any first-line therapy and was maintained on azathioprine with disease stability but a subtle increase in the size of the T2 lesions. The EDSS score at the final follow-up in March 2019 had worsened from 3.5 to 2.0.

Case G

A 69-year-old female patient who experienced two separate relapses of optic neuritis, one in each eye, with partial spontaneous recovery, re-presented in January 2018 with right arm weakness. She received 1,250 mg of prednisone for 3 days,

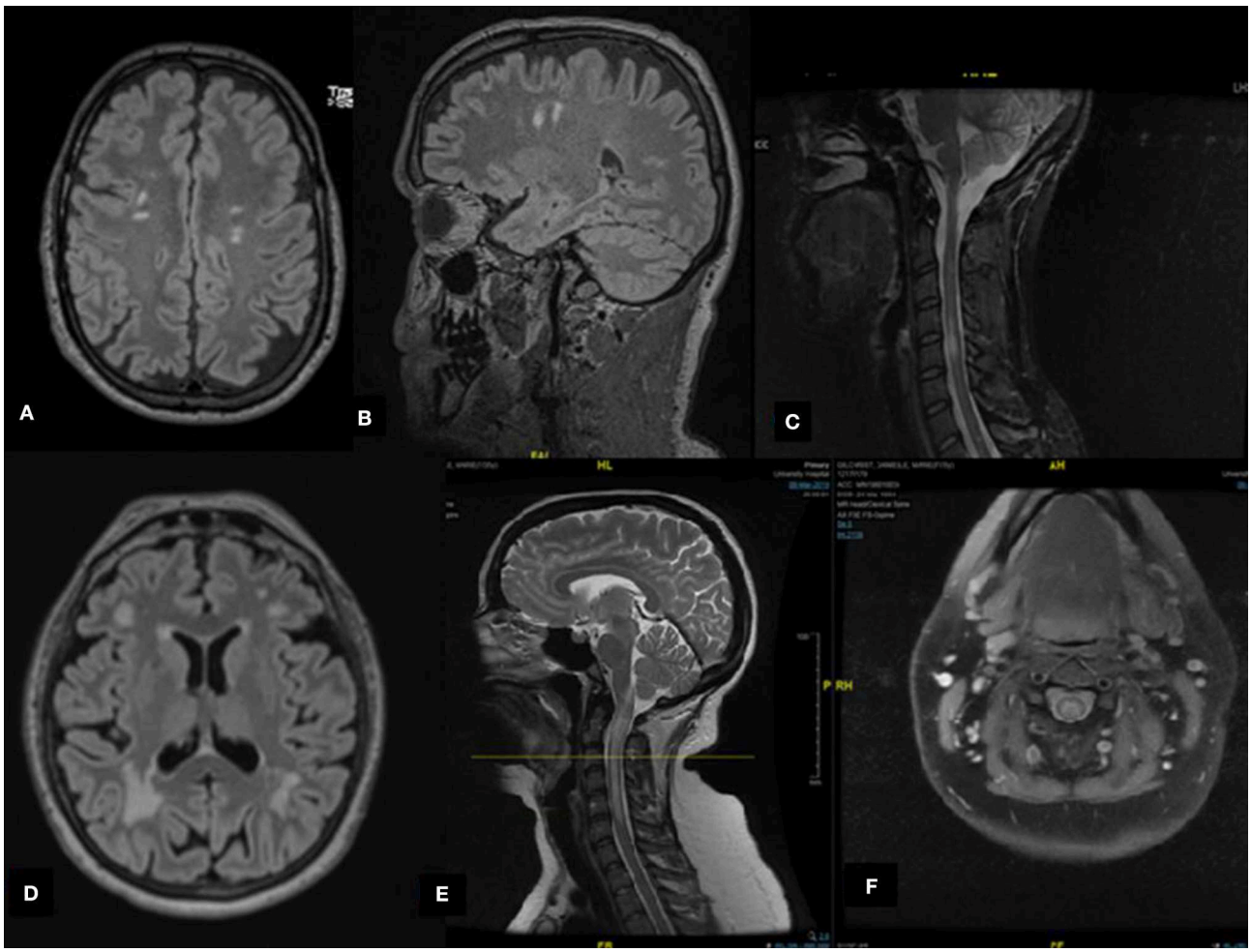

FIGURE 1 | Radiological features of selected cases. **(A,B)** Case A: Axial and sagittal magnetic resonance imaging (MRI) fluid attenuated inversion recovery (FLAIR) revealing multiple subcortical hyperintense lesions. **(C)** Case C: Sagittal MRI short-TI inversion recovery of the cervical spine demonstrates cervical hyperintensities. **(D)** Case G: Axial MRI FLAIR revealing multiple hyperintense lesions involving subcortical and periventricular areas, predominantly in the occipital regions. **(E,F)** Case I: Cervical spine MRI T2 reveals a hyperintense lesion extending from the posterior medulla (area postrema) to the area between C5 and C6 of the spinal cord forming an H sign.

but her right arm strength did not return to baseline. Her EDSS score was 2.5 according to visual and pyramidal findings. Her brain MRI was compatible with the DIS criteria. No cord lesions were identified (**Figure 1**). Her CSF examination was negative for OCB, and she had a normal IgG index. The patient declined to start DMT, despite worsening balance. At her final follow-up in 2018, her EDSS score was 3.0.

Case H

A 34-year-old female patient presented in July 2018 with sensory symptoms, bladder frequency and urgency, along with L'hermitte phenomena. Her EDSS score was 2.5 according to the bladder symptoms and pyramidal findings. Her brain MRI was normal, but longitudinal extension was identified from T2 to T11. Her CSF examination was negative for OCB and she had a normal IgG index and slight increase in CSF proteins. The patient recovered with no treatment within 4 weeks, and her EDSS score improved to 1.0. Repeat MRI revealed subtle lesions at T2 in the spinal cord.

Case I

A 35-year-old female patient presented with left-sided paresthesia and weakness, without bowel or bladder symptoms, that gradually progressed over the course of 2 weeks. There was no history of visual symptoms, nausea, vomiting, hiccups, or change in appetite. Her initial EDSS score was 3.5 according to the severe pyramidal and moderate sensory findings. Her spine MRI revealed an extensive lesion from the dorsal medulla to C6. On the axial T2 view, there was prominent gray matter involvement forming an H sign (**Figure 1**). Her brain MRI was unremarkable. CSF analysis revealed only lymphocytic pleocytosis, with a lack of high protein levels or intrathecal immunoglobulin synthesis. The patient's EDSS score improved to 2.0, with minimal pyramidal disability, 1 week after receiving

5 days of high-dose corticosteroids. Her serum anti-MOG was positive, and she was maintained on oral corticosteroids for 6 months.

DISCUSSION

Currently, there are no published diagnostic criteria for MOG-IgG-related disease. However, there are some recommendations based on expert consensus regarding appropriate testing for MOG antibody as well as some preliminary diagnostic criteria (10). Optic neuritis, either unilateral or bilateral, and myelitis are the most common presentations. Brainstem and supratentorial encephalomyelitis are also recognized presentations. Myelitis and optic neuritis occurred simultaneously in some of our cases (9). Generally, symptoms present as an acute demyelinating attack, while a progressive course seems to be extremely rare (9). Some unusual presentations have been reported in previous studies, for example, bilateral lower limb sensory symptoms with normal spine MRI findings (11) and symptoms suggestive of spinal involvement with no spinal lesions.

In an immune-mediated optic neuritis analysis (12), MOG-IgG1 was identified in 10% of those with single-episode isolated optic neuritis, 25% of those with recurrent isolated optic neuritis (RION), and 25% of those with chronic relapsing inflammatory optic neuropathy (CRION). These proportions were comparable to those in our cohort: 22% had RION, and 11% had CRION.

Area postrema syndrome/lesions have been identified as disease-defining symptoms for AQP4-positive NMOSD (13, 14); however, this syndrome/localization is not specific (14). In Case I, we observed extensive myelitis extending from the dorsal medulla to C6; however, the patient's history was unremarkable for intractable nausea, vomiting, or hiccups. While this is only a single case, it might suggest that the circumventricular body in the fourth ventricle is less impacted in MOG-IgG-related disease, while patients with anti-AQP4 and area postrema involvement may be more clinically unwell.

MOG-IgG-related disease more frequently presents with a relapsing course, although monophasic cases have been described. A monophasic course may be attributed to age and a short follow-up duration in previous studies. In a large cohort of 197 cases reported by Cobo-Calvo et al. (15), the cumulative risk of relapse after 2 and 5 years was 45 and 62%, respectively (15). MOG-IgG-related disease can also mimic MS in the form of recurrent relapsing attacks (9, 16). In our case series, 78% of the patients had a relapsing course; the median number of relapses was 3 (range, 2–5).

No patient has been reported to test positive for MOG-Ab and NMO-Ab simultaneously (4, 17). All of our patients were tested in-house using the Euroimmune commercial biochip immunofluorescence cell-based assay. Although there is a possibility of false-positive results in some of the cases, the risk is low as the Euroimmune cell-based assay has an 82.1% positive predictive value (18, 19).

Misdiagnosis of MOG-IgG-related disease as MS can be common. Among 16 MOG-IgG-related disease patients (20), 6 (37.5%) had MS-like syndromes (opticospinal disease with MS-like features, i.e., short lesions in the spinal cord, good recovery from optic neuritis, progression of disability between relapses), and 2 of these patients met the imaging criteria for MS. One had Dawson's fingers, which was similar to the proportion in our cohort, and 33% were initially diagnosed as MS. Of a total of 104 patients diagnosed with MS based on McDonald's DIS criteria (2010), 5 (4.8%) tested positive for MOG-Ab despite having MRI findings typical of MS and testing positive for OCB (16). It is important to be mindful that these cases were considered to be MOG-Ab positive rather than diagnosed with MS due to the good response to corticosteroid treatment and improved EDSS scores, which is more common in MOG-IgG-related disease than in MS. The poorest EDSS score was 4, which had improved to 2 on subsequent assessment (case E). However, in atypical cases with sustained disability, differential diagnoses should be considered as there is a chance of false positives for MOG-Ab.

Brain MRI findings can vary from a normal MRI to large fluffy lesions. Supratentorial lesions are more common (47%) followed by brainstem (29%) and cerebellar lesions (13%). Orbital MRI findings include unilateral or bilateral optic nerve lesions, which can be longitudinal and involve the optic chiasma. Contrast enhancement is a commonly reported feature in the optic nerve, reported in 80–100% of the cases, in association with optic nerve swelling and perineural enhancement (21–23). The spinal MRI findings in our case series are inconsistent with those of previously reported cases. Longitudinally extensive lesions with a median length of four segments are commonly reported findings in MOG-IgG-related disease (78%) (24). Hyperintense lesions on T2 involve the central gray matter of the spinal cord, producing H-shaped hyperintensity on axial MRI (9, 24–26), which was noted in case I.

Although it may be difficult to distinguish MOG-Ab positive cases from NMO seropositive cases radiologically, it has been proposed that MOG-Ab positive cases can be distinguished radiologically from MS, with high sensitivity and specificity (20). Lesions in the periventricular area, Dawson's fingers, juxtacortical U fibers, and T1 hypointense lesions are typical features of MS. In contrast, large fluffy lesions, few lesions (<3), and lesions around the third ventricle and cerebellar peduncles are more common in MOG and NMO seropositive cases (20, 27); none of our patients exhibited findings similar to these.

The optimal treatment for MOG-IgG-related disease remains controversial. Due to the lack of randomized clinical trials and rarity of the disease, the choice of immunosuppressive therapy depends on the clinical experience of the treating physician. The treatment typically follows the same approach as that for NMOSD. Azathioprine, mycophenolate, rituximab, and a longer corticosteroid taper (6 months) are all possible treatment options (11, 21).

In our case series, the patients did not receive prolonged steroid tapers. Long-term treatment was a shared patient decision; most were started on steroid sparing agents such azathioprine and mycophenolic acid, although two patients preferred not to be on any treatment.

Traditionally, it was thought that MOG-Ab-positive cases carry a benign course and good prognosis. With the expanding

clinical phenotype and accumulating experience, we have learned that disability can occur, and a relapsing course is not uncommon. Patients can have severe disability at presentation, but recovery from the acute relapse may be better than that of NMO seropositive cases. Further, significant residual disability does occur (25, 28). To avoid the risk of relapses or disability, we recommended long-term immunosuppressive treatment. However, the optimal treatment regimen and duration remain unclear at this time.

Our case series provides practical and clinical indications of MOG-Ab-positive cases, which expand our knowledge of this disease. However, there are potential limitations regarding possible false-positive serology results in those with atypical presentation. The short-term follow-up of some cases and variable treatment modalities could be another limitation in this cases series.

CONCLUSION

Our study demonstrates that MOG-Ab-positive cases can have a variable clinical presentation and overlap with seropositive NMO or MS cases. Relapsing courses were more frequent in our case series, and persisting disability was also observed. Distinction of this disease from others such as MS based on clinical and radiological features can be challenging. Anti-MOG testing in all patients with suggestive demyelinating events is recommended, although the possibility of false-positive tests should not be ignored. Randomized controlled trials are needed to determine the optimal treatment option and duration.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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CASE REPORT
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Mirror-Image Lesions in Sequential Relapses of AQP4-Positive Neuromyelitis Optica Spectrum Disorder

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A 25 year-old Nigerian woman with aquaporin-4 antibody-positive neuromyelitis optica spectrum disorder (NMOSD) presented with a 6 week history of nausea, vomiting, and refractory hiccups; as well as progressive lower extremity sensory loss, weakness, saddle anesthesia, and urinary incontinence. She had experienced her first NMOSD relapse seven years prior with bilateral lower extremity weakness and area postrema syndrome. After pulse steroids and plasma exchange she made a complete neurologic recovery and was started on azathioprine. An initial aquaporin-4 (AQP4) antibody ELISA test was positive, but three subsequent tests were negative and repeat MRI brain showed resolution of T2/FLAIR signal abnormalities with the exception of a right thalamic lesion and a left medullary lesion. Azathioprine was discontinued after 1 year and she was lost to follow-up. With her second relapse, she had new lesions in her left thalamus and right medulla—a mirror image of the thalamic and medullary lesions associated with her first relapse. In addition, an MRI spine demonstrated a new longitudinally extensive transverse myelitis from T7 to L1 with edematous expansion of the cord. Her serum AQP4 antibody test using a cell-based assay was strongly positive. NMOSD lesions are typically associated with brain regions with high density of the AQP4 channel. These areas include optic nerves, hypothalamus, and the diencephalic and brainstem tissues that surround the cerebral aqueduct and third and fourth ventricles. Previous studies have demonstrated that those with relapsing NMOSD have a predilection for recurrence in the same neuroanatomical region as their first episode. We hypothesize, using data from prior pathologic and epidemiologic studies, that mirror image lesions, where the same anatomic sites are affected on the contralateral side of the brain or spinal cord, may appear in subsequent attacks due to (i) areas of high remaining AQP4 density and/or (ii) local compromise of astrocyte or blood-brain barrier (BBB) function that persists after the initial inciting attack.

Keywords: neuromyelitis optic spectrum disorder, MRI, astrocytopathy, blood brain barrier (BBB), aquaporin (AQP)-4

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BACKGROUND

Neuromyelitis Optica Spectrum Disorder (NMOSD) is a relapsing inflammatory disease of the central nervous system (CNS). The past few decades have witnessed a rapid evolution in the understanding of the clinical and radiographic manifestations as well as the underlying pathophysiologic mechanisms of NMOSD. NMOSD, previously known as Devic's disease, was first described in the late 19th century as a monophasic illness characterized by optic neuritis and myelitis (1). However, more recently, the discovery of the pathogenic aquaporin-4 (AQP4) antibody has led to an appreciation of the diverse phenotypic expression of this relapsing disease.

Neuroimaging studies have characterized lesion localization and features that help distinguish NMOSD from Multiple Sclerosis (MS). For example, in MS, spinal cord attacks are associated with short segment lesions with partial, predominantly dorsal cord involvement, whereas in NMOSD lesions are typically longitudinally extensive, spanning $\geq$ 3 vertebral bodies in length, and often have complete transverse involvement. For many years, brain lesions were considered atypical of NMOSD, but it is now recognized that they occur in about half of those with NMOSD. In one study, 18.1% had brainstem periventricular/periaqueductal lesions, 32.7% had periependymal lesions along the lateral ventricles, 3.4% had large hemispheric lesions, 6.0% diencephalic lesions, and 4.3% corticospinal tract lesions (2). In contrast, ovoid lesions adjacent to the body of the lateral ventricle as well as Dawson's finger lesions affecting the corpus callosum are commonly observed in MS, and rarely observed in NMOSD (2, 3). The presence of (i) periependymal lesions along lateral ventricles and (ii) longitudinally extensive transverse myelitis (LETM), coupled with the absence of juxtacortical/cortical lesions, periventricular lesions, and Dawson's fingers was 92% sensitive and 91% specific for NMOSD (2). Furthermore, diencephalic lesions in one study were not present in any case of MS and were therefore 100% specific to NMOSD (2). In another NMOSD study, patients with brain lesions in regions of high AQP4 expression that were also considered to be classic brain lesions for NMOSD experienced more extensive myelitis compared to those without (4).

The brain and spinal cord regions typically affected in NMOSD and visualized on MRI have been shown to have the greatest AQP4 channel density (5). The AQP4 channel is the predominant water channel in the brain and has an important role in the development and homeostatic regulation of the interfaces between brain and blood, as well as between brain and cerebrospinal fluid (CSF) (5). Immunohistochemistry studies highlight an abundant concentration of the AQP4 channel at: astrocytic end feet of the blood-brain barrier (BBB); the glial lamellae of the supraoptic nucleus of the hypothalamus, and the basolateral membranes of ependymal cells along periventricular and periaqueductal areas (5–7). AQP4 channels have also been described in the amygdala, midbrain raphe nuclei, reticular formation, red nucleus, and tegmentum of the pons (4). In the spinal cord, AQP4 channels are present to a greater extent in the central gray matter compared to white matter (7). Pathologic analysis of those with NMOSD has revealed a stage independent and targeted loss of AQP4 immunostaining from early active lesions right through to chronic lesions (7). In early active inflammatory perivascular lesions, in addition to AQP4 channel loss, there is vasculocentric immune complement activation and deposition which may drive astrocytic dysfunction and necrosis (7, 8).

These observations beg the question of whether individual variability in regions of greatest AQP4 density in the CNS may explain the regional predilection for subsequent relapses in NMOSD. In this report, we highlight a case of a patient with AQP4-IgG positive NMOSD with a second relapse affecting regions known to have high AQP4 density and mirroring the lesion locations of the first attack.

CASE

Our patient, originally from Nigeria, first presented to an outside community hospital in 2012, when she was 17 years of age, after experiencing a witnessed generalized tonic-clonic seizure in the context of a 3 week history of progressive headaches, fever, nausea, refractory hiccups, and neck-stiffness, but without any cognitive or behavioral aberrancies. She had a lumbar puncture performed which revealed a white blood cell count of 250 cells/mL (91% lymphocytes), but bacterial culture and viral PCR studies were negative. Oligoclonal bands were not sent. She was initially started on acyclovir for presumed aseptic meningitis, however, she began to develop bilateral leg weakness and gait instability while in hospital. A brain MRI demonstrated T2/FLAIR signal hyperintensities in the right anterior thalamus, left posterior thalamus, left medial occipital lobe, and left dorsal medulla. A spine MRI revealed a short segment transverse myelitis at the T10/T11 vertebral levels. These images are depicted in **Figure 1**. Post-gadolinium T1 sequences did not reveal evidence of enhancement although, notably, the MRI was acquired after her course of intravenous methylprednisolone one gram daily for 5 days, followed by 100 mg daily of prednisone orally. Infectious causes were excluded prior to initiation of methylprednisolone. She had no improvement in her leg weakness. She was then transferred to our institution for consideration of plasma exchange. Repeated MRI brain and spine were unchanged and she received plasma exchange for 5 days under the presumption that she either had a demyelinating illness or Acute Disseminated Encephalomyelitis (ADEM). After seven cycles of plasma exchange, she gradually improved and slowly regained her ability to ambulate independently. An initial AQP4 antibody ELISA test performed at the outside hospital was verbally reported as positive (titer unavailable). She was subsequently started on azathioprine 150 mg daily. She made an excellent recovery and eventually resumed full activities as a student.

During the following year, three subsequent AQP4 antibody ELISA tests returned negative and repeat MRI demonstrated resolution of her occipital lesions and improvement of diencephalic lesions. With three negative ELISA tests and only a verbally reported positive initial AQP4 antibody ELISA test, her treating neurologist came to favor a diagnosis of

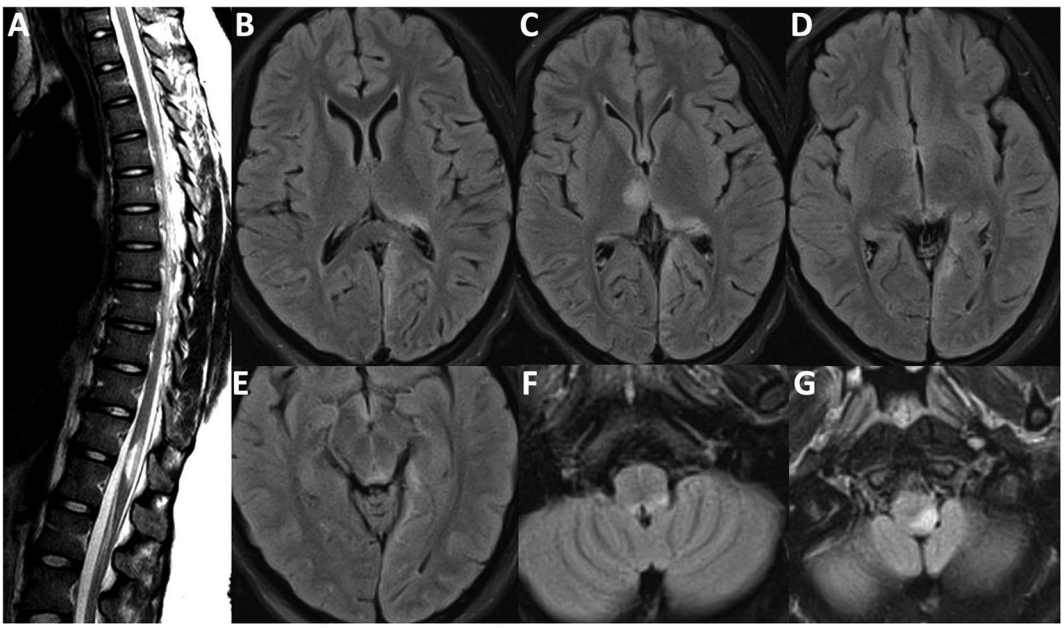

FIGURE 1 | MRI Brain-FLAIR sequence from first attack in 2012. **(A)** Short segment transverse myelitis at T11/T12 vertebral segment with mild cord expansion. Lesions depicted affecting the **(B)** left posterior thalamus and the subcortical/juxtacortical white matter of the left medial occipital lobe; **(C)** right anterior thalamus and pulvinar region of the left thalamus; **(D)** highlighting left medial occipital lobe involvement; **(E)** periaqueductal gray matter hyperintensity; **(F)** left dorsal medullary hyperintensity also depicted in **(G)**.

ADEM and discontinued azathioprine a year after the initial presentation without further use of immunosuppressive or immunomodulatory agents.

Seven years later, at the age of 25 years, she presented to hospital with 6 weeks of progressive neurologic decline, which started with hiccups, nausea, and vomiting. Two weeks after onset, while still experiencing hiccups and nausea, she developed tingling and burning of the complete right leg, as well as lumbar and buttock pain. Four weeks after her initial symptoms started, she developed right leg weakness and subsequently left leg weakness. By the 5th and 6th weeks after onset she was unable to ambulate independently and developed saddle anesthesia, urinary incontinence. She presented to the emergency room for urgent medical attention.

At presentation, refractory hiccups were noted and bladder scan indicated retention of 750 mL of urine. Mental status was appropriate. Cranial nerve examination was unremarkable with preserved visual acuity, no evidence of red color desaturation, relative afferent pupillary defect, internuclear ophthalmoplegia, or nystagmus. Fundoscopy did not reveal any optic disc pallor or atrophy. Motor exam revealed full power in the upper extremities, but she had grade four-weakness in a pyramidal pattern in the bilateral lower extremities. While reflexes were preserved in the upper extremities, they were absent in the lower extremities. There was an extensor plantar response on the right and equivocal response on the left. She had near-absent pinprick and vibration sensation in the bilateral lower extremities with a discernable spinal level at the umbilicus. Sensation was entirely preserved in the upper extremities.

Her MRI brain demonstrated new FLAIR hyperintense lesions in her left thalamus and right dorsal medulla. Old lesions were visualized in the right thalamus and left dorsal medulla. MRI of the whole spine revealed a longitudinally extensive T2 hyperintensity in the thoracic and lumbar regions from T7 to L1 with associated edematous expansion of the cord. These images are depicted in **Figure 2**. Unfortunately, gadolinium-enhanced sequences were not performed. Her serum AQP4-IgG test using a cell-based assay returned strongly positive with a titer of 4+. Myelin oligodendrocyte glycoprotein antibody was negative. CSF testing was not repeated. After her MRI, she received a 5 day course of intravenous methylprednisolone at one gram daily without clinical improvement. Plasma exchange was then initiated for seven cycles and over the course of 2 weeks the patient regained leg strength and sensation in her lower extremities, and, furthermore, her saddle anesthesia, urinary retention, and incontinence improved as well. She was started on mycophenolate 1 g twice daily in hospital and was ultimately discharged to a neuro-rehabilitation center. Rituximab, an anti-CD20 monoclonal antibody therapy, was also considered for maintenance therapy, but access to and funding for rituximab for treatment of NMOSD are severely restricted in Ontario, Canada. Three months after her discharge she was seen in follow up with repeat spine and brain MRI which demonstrated interval stability of her CNS disease.

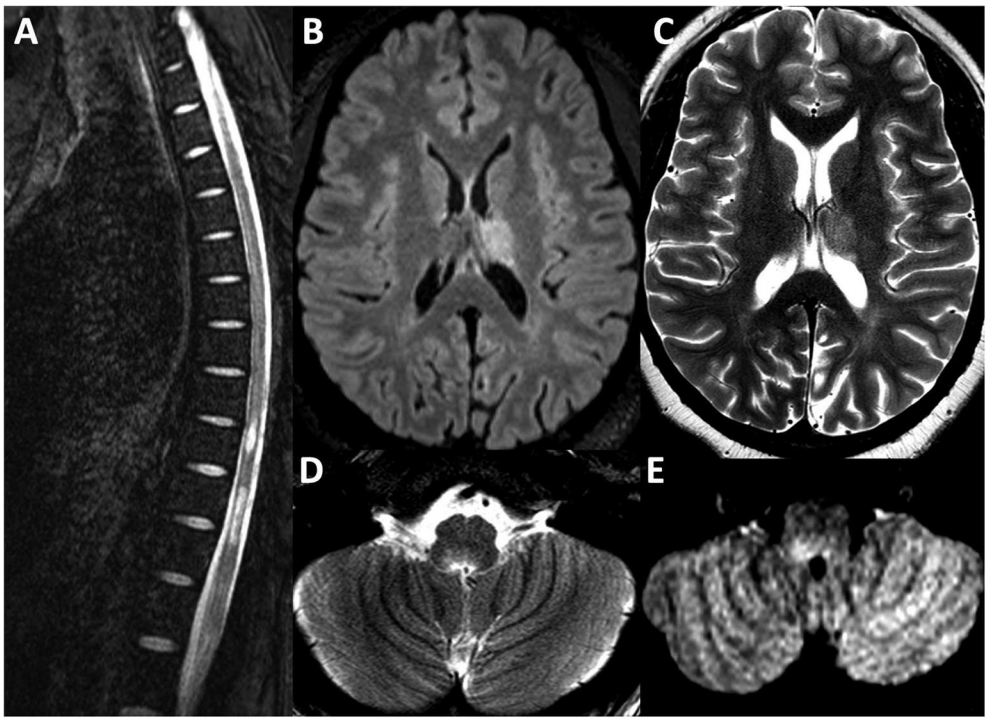

FIGURE 2 | MRI Brain sequence from the second attack in 2019. **(A)** T2 weighted sequence depicting longitudinally extensive transverse myelitis from T7 to L1, associated with mild cord expansion. Lesions depicted affecting the left thalamus are depicted in the T2-FLAIR sequence in **(B)** and the T2 weighted sequence in **(C)**. A new right ponto-medullary lesion is visualized on the T2 weighted sequence in **(D)** and T2-FLAIR sequence in **(E)**.

DISCUSSION

The typical locations affected by the inflammatory lesions of NMOSD have a high density of the AQP4 channel (9). These areas include the optic nerves, hypothalamus, and the astrocytic end feet that abut capillaries and pia in the brain—namely diencephalic and brainstem tissues that surround the cerebral aqueduct, third, and fourth ventricles (1, 2, 5). There is also an abundance of AQP4 channels in the gray matter of the spinal cord.

In our report, we describe a patient with relapsing NMOSD whose inflammatory lesions mirrored those of her first attack. Mirror lesions occur in the same anatomic region on the contralateral side of the brain or spinal cord. Often one lesion may be directly adjacent to the other. Other times, as with the contralateral thalamic lesions observed in this case, lesions may surround the same ventricular space. Our patient's brain MRI demonstrated new lesions in the previously unaffected left thalamus and right dorsal medulla—creating a mirror image of her first diencephalic and brainstem lesions.

In a study of 164 patients with relapsing NMOSD, recurrent attacks were more likely to present with clinical features localizing to the same anatomic site(s) as the initial episode (10). This observation encompasses attacks that occurred in the same anatomic region on the contralateral side of the brain or spinal cord. For example, an increased odds of a second attack occurring in the initial event location were seen in all localizations, with the greatest odds of regional recurrence noted in the brain and brainstem (10). Furthermore, with a first attack of myelitis, there was a statistically significant 74% reduced odds of a second attack presenting as optic neuritis. It is interesting to note that our patient, despite extensive diencephalic, brainstem, and spinal cord lesions had never experienced an episode of optic neuritis. Even among those with established NMOSD there may be regional variability in AQP4 density and vulnerability to AQP4 antibodies associated with a predilection for relapses at anatomic sites similar to the initial event.

In addition to greater density of AQP4 in affected regions, a second theory to explain this regional predilection is that astrocytes and/or the BBB could be compromised at the sites of previous inflammation, making these regions or adjacent regions more likely to be affected in subsequent relapses. It is unknown exactly how AQP4-IgG initially crosses the BBB and gains access to the AQP4 antigen. Complement dependent and/or antibody mediated astrocyte cytotoxicity in NMOSD may further compromise the integrity of the BBB or lining of circumventricular organs leading to a kindling effect (7). Pathologic studies in NMOSD have demonstrated, consistently, the persistent loss of AQP4 immunohistochemistry within inflammatory lesions at all stages, but in the surrounding peri-plaque white matter there is a similar degree of AQP4 staining as normal regionally matched controls (8). This is in contrast to MS where AQP4 immunostaining is temporarily diminished in actively demyelinating lesions, but in remyelinating MS lesions,

AQP4 immunoreactivity is diffusely increased in active astrocytes (8). In NMOSD, a glial astrocytopathy, AQP4 immunoreactivity remains low even during the recovery phase. Furthermore, the loss of glial repair mechanisms in NMOSD may confer an additional propensity for recurrence in adjacent regions or periventricular locations (7). It is possible that recently observed clusters of attacks soon after NMOSD presentation, with iterative attacks presenting with similar clinical manifestations, could be a reflection of regionally compromised repair mechanisms (11). However, future studies would be needed to test this hypothesis.

Interestingly, more extensive myelitis has been observed in patients with NMOSD whose lesions occur with greater frequency in typical AQP4 dense brain regions compared to those with NMOSD without AQP4 regionally typical lesions (4). This finding suggests that the topography of lesions in NMOSD may have pathophysiologic significance on the clinical course of NMOSD. In this case, our patient had a large LETM spanning seven vertebral segments. One can postulate whether the propensity of our patient's lesions to occur and recur in areas with greatest AQP4 channel density may have some relationship to the magnitude of her LETM.

With our patient's initial presentation in 2012, the diagnosis of ADEM was strongly considered. Her initial AQP4 antibody ELISA test was apparently positive, which would argue against ADEM, but three subsequent tests were negative which led the treating neurologist at the time to believe that the initial ELISA could have been a false verbal report or false positive test result. Particularly in the past when AQP4 and MOG serologic testing was less reliable, it could be difficult at times to distinguish the first episode of NMOSD from ADEM, as ADEM can also present with LETM, large hemispheric lesions, as well as diencephalic and brainstem lesions. In one study, thalamic and internal capsule involvement were found to occur more frequently in ADEM than in NMOSD (12). Our patient's initial presentation with thalamic lesions, meningismus, fevers, and a seizure led the treating neurologist to favor a diagnosis of ADEM after the first attack. This case highlights overlapping clinical features in ADEM and NMOSD, particularly in pediatric cohorts, and emphasizes the need for repeat AQP4 cell-based assay testing when there is a strong index of clinical suspicion for NMOSD.

The implications of this report are limited by the fact that this is a single case. Although we did not find any other cases in the literature of mirror-image lesions reported in association with AQP4 positive NMOSD, a recent international study supported the tendency of sequential NMO relapses to have similar localizing features (13). One reason why we may be the first to report this phenomenon is that it is difficult to discern mirror-image lesions in NMOSD in locations other than the brain. Myelitis and optic neuritis are much more common relapse types in NMOSD. Spinal cord lesions are often bilateral obviating the opportunity to observe mirror-image lesions. With respect to optic neuritis, bilateral simultaneous optic neuritis is a hallmark feature of NMOSD, and itself could be considered an example of mirror-image lesions.

In summary, our report highlights a case of relapsing NMOSD with recurrent lesions occurring in the same region, but contralateral to the lesions implicated in the first attack. Mirror-image lesions may be due to effects of the pathogenic antibody on areas of high remaining AQP4 density and individual variability in the most dense AQP4 regions. We hypothesize, using data from previous pathologic and epidemiologic studies, that regions mirroring the prior attack site may be vulnerable to recurrent attacks due to (i) patterns of high AQP4 antigen density in the CNS and/or (ii) local compromise of astrocyte and/or BBB functions.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent for the publication of this case report.

AUTHOR CONTRIBUTIONS

RM: study conception and design, manuscript preparation. AB: study conception and design, manuscript preparation, and neuroimaging figure preparation. DR: study conception and design, manuscript preparation, acquisition of data, and final approval of manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Epidemiology of Pediatric NMOSD in Germany and Austria

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Background: Neuromyelitis optica spectrum disorders (NMOSD) are severe inflammatory demyelinating disorders of the central nervous system mainly characterized by recurrent episodes of uni- or bilateral optic neuritis (ON), transverse myelitis (TM) and brainstem syndromes (BS). The majority of adult patients has serum antibodies directed against the water channel protein aquaporin 4 (AQP4-abs). In pediatric patients, AQP4-abs are less, while antibodies against myelin oligodendrocyte glycoprotein (MOG-abs) are more frequently detectable than in adults. Some children with NMOSD have neither AQP4- nor MOG-ab (double-seronegative).

Objective: Evaluation of epidemiological data regarding incidence and prevalence of pediatric NMOSD in Germany and Austria.

Methods: We recruited pediatric NMOSD patients between 1 March 2017 and 28 February 2019 with five different tools: (1) ESPED (Surveillance Unit for Rare Pediatric Disorders in Germany), (2) ESNEK (Surveillance for Rare Neurological Disorders during Childhood), (3) pediatric neurology working group within the Austrian Society of Pediatrics and Adolescent Medicine, (4) BIOMARKER Study and (5) NEMOS (Neuromyelitis optica Study Group). We requested data regarding clinical symptoms, antibody status, therapy regimen and response via a standardized questionnaire.

Results: During the 2-year recruitment period, 46 (both incidental and prevalent) patients with a suspected diagnosis of NMOSD were brought to our attention. Twenty-two of these patients did not fulfill the inclusion criteria. Of the remaining 24 children, 22 had a median age at onset of 11 (range 3–17) years and 16/22 were female (72.7%) (no data in two patients). Sixteen of 24 patients were AQP4-ab positive (67%), 4/24 MOG-ab positive (16.7%), three children were double-seronegative and in one patient no antibody testing was done. We calculated an incidence rate of 0.022 per 100,000 person-years for Germany, while there was no incidental case in Austria during the recruitment period. The prevalence rate was 0.147 and 0.267 per 100,000 persons in Germany and Austria, respectively.

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Conclusion: Pediatric NMOSD, with and without associated antibodies, are very rare even considering the different limitations of our study. An unexpected finding was that a considerable proportion of patients was tested neither for AQP4- nor MOG-abs during diagnostic work-up, which should prompt to establish and disseminate appropriate guidelines.

Keywords: NMOSD, AQP4-antibodies, MOG-antibodies, transverse myelitis, optic neuritis, brainstem syndrome

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are severe inflammatory demyelinating disorders of the central nervous system mainly characterized by simultaneous or sequential episodes of uni- or bilateral optic neuritis (ON), transverse myelitis (TM) and brainstem syndromes (BS) (1, 2). The discovery of a specific autoantibody in NMO patients, targeted against the water channel protein aquaporin 4 (AQP4) located in high density in astrocytic processes at the blood-brain barrier, in 2004 supported the differentiation between NMO and MS (3). In the following, multiple studies could show that AQP4-antibodies (AQP4-abs) are detectable in up to 80% of adult patients diagnosed with NMO (4–6). This led to a modification of the diagnostic criteria for NMO by adding the presence of AQP4-abs as a supportive criterion (7–10). Increasing AQP4-abs assay quality and reliability as well as further publications showing the connection between AQP4-abs and different clinical phenotypes other than ON and TM, resulted in another revision of the diagnostic criteria and led to the extension of NMO utilizing the umbrella term NMOSD (11–13).

Up to 20% of adult NMOSD patients remain AQP4-antibody (ab) negative (14–18) and a certain proportion of these AQP4-ab negative patients show antibodies against myelin oligodendrocyte glycoprotein (MOG-abs) (19–23). Recent studies showed that pediatric and adult NMOSD patients with MOG-abs can also have recurrent disease courses (24–28). The reported prevalence of MOG-abs in AQP4-ab negative pediatric patients shows a wide range between different working groups, possibly due to different inclusion criteria and unreported MOG-ab status. Consequently, in some studies the majority of NMOSD patients show MOG-abs while others report similar frequencies of AQP4-abs in pediatric as in adult patients (23, 29–32).

NMOSD is, by definition of WHO and EU, considered a rare disease with 1 (or fewer) in 2,000 individuals affected. Several population-based studies, focussing primarily on adult patients, showed incidence rates of 0.053 to 0.4 per 100,000 person-years and prevalence rates of 0.52 to 4.4 per 100,000 people (33–39). However, none of these studies applied the revised diagnostic criteria of 2015 and thus it remains unknown if (and how much) the incidence and prevalence rates were affected by the broadening of the spectrum. So far, Sepúlveda et al. 2015 criteria increased incidence and prevalence by 1.5 times (18). Hyun et al. even reported a 1.85-fold increase (40).

There are only a few studies focusing on the frequency of acquired demyelinating syndromes (ADS), among them NMOSD, in children (41–43). Very recently Boesen et al. specifically undertook a population-based, multicentre cohort study to estimate the incidence of pediatric NMOSD in Denmark, which was 0.031 per 100,000 person-years (44). An Australian single-center retrospective study could show that five of 67 (7.5%) pediatric patients presenting with ADS between 2007 and 2014 were diagnosed with NMOSD (43).

The aim of our study was to ascertain the incidence and prevalence of pediatric NMOSD in Germany and Austria, using the 2015 criteria. Subsequently, we evaluated if these patients would also fulfill the 2006 criteria and calculated the respective incidence and prevalence rates.

MATERIALS AND METHODS

Setting

Germany and Austria are two geographically and politically defined countries located in Western and Middle Europe, respectively, with a combined area of 441,265 km^2. Austria has 8,851,417 (30 October 2018 census) and Germany 83,019,213 (31 December 2018 census) inhabitants, resulting in a total of 91,870,630 people. By information of the Federal Offices of Statistics (Statistik Austria and Statistisches Bundesamt Deutschland) 1,535,958 and 13,597,428 respectively (combined 15,133,386), of these 91,870,630 inhabitants are underage (16.5%). Both countries have a majority of Caucasian ethnicity, however to our knowledge the official census institutions do not collect the population's ethnicities. Health care in Austria and Germany is provided by an open access public health care system with a network of pediatric neurologists specializing on demyelinating disorders.

Case Ascertainment Tools and Study Populations

For this clinic- and questionnaire-based multicentre pro- and retrospective study we used the following tools to estimate the incidence and prevalence of pediatric NMOSD between 1 March 2017 and 28 February 2019:

Abbreviations: ab, antibody; abs, antibodies; ADS, acquired demyelinating syndrome; APS, area postrema syndrome; AQP4-abs, antibodies against aquaporin 4; AZA, azathioprine; bilON, bilateral optic neuritis; BS, brainstem syndromes; DMF, dimethyl fumarate; DMT, disease-modifying therapy; ESNEK, Rare paediatric neurological disease registry Germany; ESPED, Surveillance Unit for Rare Paediatric Disorders in Germany; GLAT, glatiramer acetate; IVIG, intravenous immunoglobulins; IVMP, intravenous methylprednisolone; LETM, longitudinally extensive transverse myelitis; MMF, mycophenolate mofetil; MOG-ab, antibodies against myelin oligodendrocyte glycoprotein; NMOSD, neuromyelitis optica spectrum disorders; OCB, oligoclonal bands; ÖGKJ, Austrian Society of Paediatrics and Adolescent Medicine; ON, optic neuritis; PLEX, plasma exchange; pos, positive; RTX, rituximab; TM, transverse myelitis; unilON, unilateral optic neuritis.

1) We initiated a prospective epidemiological study via ESPED (Surveillance Unit for Rare Pediatric Disorders in Germany, in German "Erhebungseinheit für Seltene Pädiatrische Erkrankungen in Deutschland"; based in Dusseldorf) and included incidental cases of pediatric NMOSD diagnosed during the investigation period. Every pediatric department in Germany has one responsible colleague designated to report patients with newly-diagnosed rare diseases to the different ongoing ESPED studies.

2) Furthermore, we used ESNEK (Surveillance for Rare Neurological Disorders during Childhood, in German "Erhebung seltener neurologischer Erkrankungen im Kindesalter"; based in Göttingen) as an e-mail-based recruitment tool once a year during our recruitment period. Via ESNEK, we contacted all ∼1,200 members of the Society for Neuropediatrics (Gesellschaft für Neuropädiatrie) and by this the majority of all Germany- and Austria-based pediatric neurologists and asked to report pediatric NMOSD patients, diagnosed and/or under their care during the recruitment period.

3) By using the e-mail distribution list of the pediatric neurology working group within the Austrian Society of Pediatrics and Adolescent Medicine, we contacted about 170 (and thereby most) Austria-based pediatric neurologists and asked to support our epidemiological study by referring pediatric NMOSD patients using our standardized questionnaire. As the majority of these colleagues are also part of the Society for Neuropediatrics, they received our e-mails twice each time.

4) Additionally, we included all pediatric NMOSD patients who were referred to our BIOMARKER study (based in Innsbruck and Datteln) between March 2017 and February 2019. This is an ongoing prospective, multicentre study started in 2009 with currently more than 900 included children and teenagers presenting with the first event of an ADS. We also included all previously referred children with ongoing follow-ups who fulfilled the inclusion criteria and were still <18 years old.

5) Finally, we contacted the adult NMO Study Group, called NEMOS, currently with representatives in 45 neurology clinics in Germany and asked how many pediatric (both incidental and prevalent) NMOSD patients had been brought to their attention between March 2017 and February 2019 and had been included in their patient registry. Representatives from about 25 German universities founded NEMOS in 2008 to improve the care of NMOSD patients (45).

Study Population and Diagnostic Criteria

Patients included in this study had to meet the following inclusion criteria: (1) diagnosis of NMOSD fulfilling the 2015 International Panel for NMO Diagnosis criteria (12), (2) age below 18 years at disease onset, and (3) written informed consent. Exclusion criteria included the diagnosis of another type of ADS like MS or an infectious, metabolic, vascular, or neoplastic CNS disease.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the Ethics Committee of the Medical University of Innsbruck, Austria (Study number AN4059) and by the Ethics Committee of the Witten/Herdecke University, Germany (Study number 10/2017). All patients and/or their caregivers provided written informed consent.

Antibody Assays

Serum samples were analyzed for the presence of MOG- and AQP4-abs by live cell-based immunofluorescence assays as previously described (46, 47).

Using the above-mentioned case ascertainment tools, not all serum samples were tested in Innsbruck. Serum of patients recruited via ESPED was not referred to our lab in Innsbruck and thus screened for MOG- and AQP4-abs by unknown assays. However, it is very likely that AQP4-ab testing was either done with a live cell-based assay (CBA) or with the well-evaluated Euroimmun kit (13). MOG-ab testing is possible with an Euroimmun kit as well, though the sensitivity and specificity are not as high as established live CBAs (47). Treating doctors might have sent serum samples to neuroimmunology labs in Heidelberg (S. Jarius) or in Kiel (F. Leypoldt), which both use the above-mentioned live CBAs.

Statistical Methods

All of the 95% confidence intervals (95% CI) were calculated for the prevalence and incidence rate estimates using the modified Wald method. Quantitative variables were described using median and range. Statistical analysis was performed using IBM SPSS, release V.24.0 (IBM Corporation).

RESULTS

With the above-mentioned ascertainment tools, a total of 46 pediatric patients with a suspected diagnosis of (both incidental and prevalent) NMOSD were brought to our attention. In 40/46 children we had enough clinical information necessary to evaluate the patients' diagnoses using the 2015 criteria. We identified 22 patients who did not fulfill the inclusion criteria and were thus excluded from this study (see **Figure 1**). None of the excluded patients fulfilled the 2006 criteria. All of these excluded patients were recruited via ESPED, meaning they were referred anonymously. Therefore, the type of antibody assay, used in 18/22 patients, was unknown. The remaining four patients were not tested for MOG- and AQP4-abs at all.

Of the remaining 24 children, 22 had a median age at onset of 11 (range 3–17) years and 16/22 were female (72.7%) (no data in two patients). In 18/24 patients, ethnicity was reported: 13/18 were Caucasian (72%), 3/18 (16.7%) were from the Near or Middle East or Egypt, 1/18 (6%) was African and 1/18 (6%) from South Asia.

Sixteen of 24 patients were AQP4-ab positive (67%), 4/24 MOG-ab positive (16.7%), three children were MOG- and AQP4-ab negative (double-seronegative) and in one patient no antibody testing was done. None of these patients were positive for both

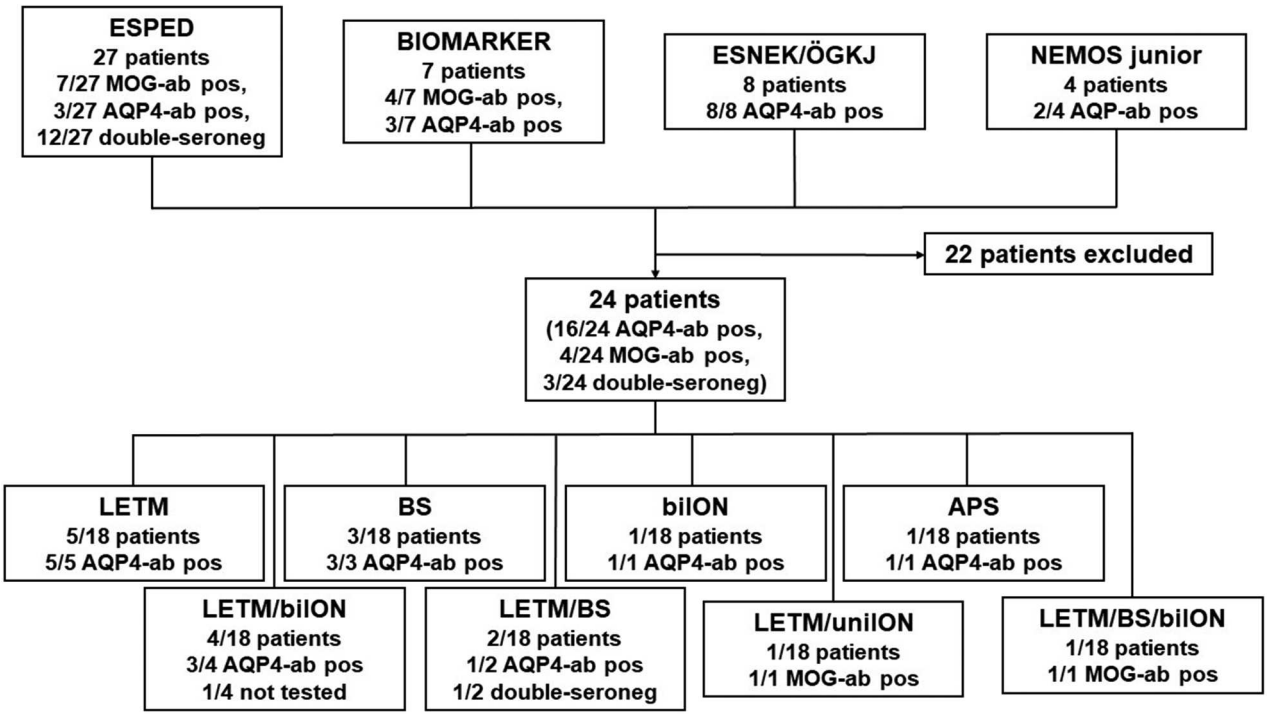

FIGURE 1 | Flow chart study profile. APS, area postrema syndrome; AQP4-ab, antibodies against aquaporin 4; bilON, bilateral optic neuritis; BS, brainstem syndromes, ESNEK, Surveillance for Rare Neurological Disorders during Childhood; ESPED, Surveillance Unit for Rare Paediatric Disorders in Germany; LETM, longitudinally extensive transverse myelitis; MOG-ab, antibodies against myelin oligodendrocyte glycoprotein; ÖGKJ, Austrian Society of Paediatrics and Adolescent Medicine; unilON, unilateral optic neuritis.

MOG- and AQP4-abs. In 19/23 patients, antibody testing was done with a live CBA. Thirteen of these 19 patients were screened in Innsbruck. The remaining four patients were recruited via ESPED and due to its anonymous referral method, we could not ask treating doctors which assay was used. However, as described above, it is very likely that well-established assays or kits were used.

Detailed clinical data was available for 18/24 patients (see **Figure 1** and **Supplementary Table 1**). All 18 patients received intravenous methylprednisolone (IVMP) as acute therapy. Additional treatments at onset included intravenous immunoglobulins (IVIG; $n = 7$; 4/7 AQP4-ab pos, 1/7 MOG-ab pos, 1/7 double-seronegative, 1/7 not tested), plasma exchange (PLEX; $n = 7$; 5/7 AQP4-ab pos, 1/7 double-seronegative, 1/7 not tested) and rituximab (RTX; $n = 2$; 2/2 AQP4-ab pos). 14/18 pediatric patients were subsequently started on long-term treatments: RTX ($n = 8$; 1/8 after relapses on azathioprine; 7/8 AQP4-ab pos, 1/8 double-seronegative), azathioprine (AZA; $n = 4$; 4/4 AQP4-ab pos), tocilizumab ($n = 2$; after relapses on RTX; 2/2 AQP4-ab pos), mycophenolate mofetil (MMF; $n = 1$; not tested for autoantibodies), IVIG ($n = 1$) and cyclophosphamide ($n = 1$; after relapses on RTX; 1/1 AQP4-ab pos). We had no information about the type of DMT in one patient.

Of the remaining six patients without clinical information, four were referred via NEMOS with a confirmed diagnosis of NMOSD. Two of these four patients were AQP4-ab positive. The other two patients (not referred via NEMOS), both AQP4-ab positive, were brought to our attention as NMOSD without further details.

Further demographic and clinical details of these patients are summarized in **Table 1** and **Supplementary Table 1**.

Study Populations

ESPED

During our observation period, a total of 27 pediatric patients were referred via ESPED with a diagnosis of NMOSD. However, 22 of these 27 patients (81.5%) with a median age at diagnosis of 14 (range 2–17) years, did not meet the diagnostic criteria (neither the 2006 nor the 2015): Seven of these 22 patients showed MOG-abs, 11 were tested negative for AQP4- and MOG-abs and in four no antibody testing was done. Clinically, 11 presented with ON, six with TM, three with LETM, and two with simultaneous TM (meaning less than three involved segments on spinal MRI) and ON. All these 22 pediatric patients were excluded.

The remaining five patients fulfilled the inclusion criteria. AQP4-abs were detected in 3/5 children (3 males, median age 7 [range 4–11] years), while one 13 year-old male patient was double-seronegative (patient 14) and in one 9 year-old female patient no antibody testing was done as she had already received IVIG prior to sample collection (patient 3). The cumulative median age was nine (range 4–13) years, 4/5 patients were male.

TABLE 1 | Demographic and clinical characteristics of the included patients.

	Patients ($n = 24$)
Female sex, n (%)	16/22 (72.7%)
Ratio female:male	2.67:1
Ethnicity, n (%)	
Caucasian	13/18 (72%)
Near or Middle East or Egypt	3/18 (16.7%)
African	1/18 (6%)
South Asia	1/18 (6%)
Antibody status, n (%)	
AQP4-abs	16/24 (67%)
MOG-abs	4/24 (16.7%)
Double-seronegative	3/24 (12.5%)
Not tested	1/24 (4.2%)
Age at onset (years), median (range)	11 (3-17)
Clinical attack at onset, n (%)	
Longitudinally extensive transverse myelitis	5/18 (27.8%)
Bilateral optic neuritis + LETM	4/18 (22.2%)
Brainstem syndrome	3/18 (16.7%)
LETM + brainstem syndrome	2/18 (11.1%)
Bilateral optic neuritis	1/18 (5.6%)
Unilateral optic neuritis + LETM	1/18 (5.6%)
Area postrema syndrome	1/18 (5.6%)
Bilateral ON + LETM + BS	1/18 (5.6%)
Cerebral MRI, n (%)*	
Normal	5/18 (27.8%)
Non-specific WM lesions	6/18 (33.3%)
Brainstem involvement	5/18 (27.8%)
Optic nerves involvement	2/18 (11.1%)
Spinal MRI, n (%)*	
Normal	5/18 (27.8%)
LETM	13/18 (72.2%)
TM	0/18 (0%)
Acute therapy, n (%)	
Intravenous methylprednisolone	18/18 (100%)
Add-on therapy (IVIG, etc.)	8/18 (44.4%)
Long-term therapy, n (%)	14/18 (77.8%)

**The minimum requirements to re-evaluate the referred MRI results were available imaging data with (contrast-enhanced) T1 and T2 for the spinal MRI and (contrast-enhanced) T1, T2, and FLAIR for the cerebral MRI. These criteria were fulfilled by 12/24 patients.*

Clinically, one AQP4-ab positive patient presented with an area postrema syndrome (patient 1), two with a simultaneous LETM and bilON (1 AQP4-ab positive patient and patient 3) and two with a simultaneous LETM and BS (1 AQP4-ab positive patient and patient 14).

Four of five patients did not only receive IVMP as acute treatment, but also at least one of the following: PLEX ($n = 4$), IVIG ($n = 3$) and RTX ($n = 2$). These four children were also put on long-term treatments: RTX ($n = 3$) and MMF ($n = 1$).

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By contacting the majority of the Germany- and Austria-based pediatric neurologists via e-mail, seven so far unknown patients were brought to our attention. Another patient was already part of our BIOMARKER Study but reported again via ESNEK.

All these eight patients were AQP4-ab positive. Two patients were referred only stating their antibody status and without further demographic or clinical details. The remaining six patients had a median age of 13 (range 10–17) years and all of them were females. Interestingly, 5/6 patients initially presented with LETM. The remaining patient (patient 29) had a BS.

All patients were given IVMP, 3/6 additionally received IVIG and PLEX. Regarding the long-term treatment, we had no information about one patient (patient 39). Two of the remaining five children received the IL-6-receptor antagonist tocilizumab (after relapses on RTX), 1/5 azathioprine (AZA), 1/5 RTX and one patient did not respond to RTX and was changed to cyclophosphamide.

BIOMARKER Study

Since 2009, more than 900 children with a first (suspected) event of ADS were referred to our BIOMARKER Study and tested for MOG- and AQP4-abs. Within this cohort, seven patients fulfilled the diagnostic criteria and were still underage at the beginning of our observation period.

Four of seven patients were MOG-ab positive, 3/7 AQP4-ab positive. Their median age was 9 (range 3–14) years, 5/7 patients were female. One AQP4-ab positive, female patient (patient 33) had an ON as onset attack, the other two AQP4-ab positive children presented with a BS. The remaining four MOG-ab positive patients had simultaneous ON and LETM.

Every patient was treated with IVMP during the clinical event. Only one female, MOG-ab positive teenager (patient 43) additionally received IVIG. The three AQP4-ab positive patients were started on AZA and one was changed to RTX due to insufficient therapy response. Among the MOG-ab positive patients, only one received IVIG as long-term treatment (patient 44).

NEMOS

By contacting NEMOS and asking to report NMOSD patients who were underage at the beginning of our observation period, we could include four additional patients into this study, who have not been identified with one of the other tools.

Two of these patients were AQP4-ab positive and the other two AQP4-ab negative. In the latter two MOG-ab status was unknown. The median age was 11 (range 6–16) years, all four patients were females. One AQP4-ab negative patient (patient 34) was newly-diagnosed during our observation period and was added to the incidental cases. Besides age, sex and antibody status we did not receive any further demographic or clinical details.

Incidence and Prevalence

Overall, six Germany-based patients were newly-diagnosed with NMOSD during our observation period and thus considered as incidental cases. Within our 2-year recruitment period, no child was newly-diagnosed with NMOSD in Austria. The remaining 18 children had already been diagnosed prior to our recruitment period and were therefore categorized as prevalent cases.

Considering a total of 13,597,428 minors in Germany, we estimated an incidence rate of 0.022 (95% CI 0.005–0.066) per 100,000 person-years. If we included only the three AQP4-ab positive patients, the estimated incidence rate was 0.011 (95% CI 0.002–0.033) per 100,000 person-years. For Austria, lacking an incidental case, we could not calculate the incidence rate.

With 20 pediatric NMOSD patients, the estimated prevalence rate in Germany was 0.147 (95% CI 0.096–0.217) per 100,000 persons, considering only the 12 AQP4-ab positive patients, it was 0.088 per 100,000 (95% CI 0.0456–0.154). Double-seronegative pediatric NMOSD ($n = 3$) had a prevalence of 0.022 (95% CI 0.005–0.066) per 100,000, and the four MOG-ab positive patients, fulfilling the diagnostic criteria for NMOSD, 0.029 (95% CI 0.009–0.076) per 100,000. One of these 20 patients was not tested for MOG- or AQP4-abs (patient 3).

In Austria, considering a total of 1,535,958 minors and four reported pediatric AQP4-ab positive NMOSD patients, the prevalence rate was 0.267 (95% CI 0.105 to 0.524) per 100,000 persons.

If we apply the 2006 criteria, only four of the above mentioned, Germany-based six patients would count as incidental cases, with one of them being AQP4-ab positive. Respectively, the incidence rate would be 0.015 (95% CI 0.001 to 0.055) cases per 100,000 person-years, resulting in an ∼1.5-fold increase if the 2015 criteria are used.

The prevalence rates would decrease to 0.118 (95% CI 0.073–0.184) per 100,000 persons in Germany and to 0.200 (95% CI 0.064–0.460) per 100,000 persons in Austria.

DISCUSSION

Using different case ascertainment tools to assess and calculate the incidence and prevalence rate of pediatric NMOSD in Germany and Austria, we detected only 24 pediatric patients who fulfilled the 2015 criteria of NMOSD during our 2-year observation period. Nevertheless, the estimated incidence rate of 0.022 per 100,000 person-years (95% CI: 0.0081–0.048) is comparable to the systematic registry-based incidence rate of 0.031 per 100,000 person-years (95% CI: 0.011–0.082) calculated in the study by Boesen et al. (44) with both confidence intervals overlapping.

We could further show that a significant number of referred cases did not fulfill the 2015 NMOSD criteria, indicating that pediatric neurologists without special expertise in pediatric neuroimmunology are not familiar with the recently revised criteria.

In total, 22/27 pediatric patients (81.5%) referred via ESPED were incorrectly classified as NMOSD. Our ESPED inquiry also revealed that in five patients (4/5 were excluded from this study) no antibody testing was done at all. As antibody status could have had important diagnostic and therapeutic implications considering the disabling potential of relapses in AQP4-ab positive NMOSD, we strongly encourage pediatric neurologists to screen for MOG- and AQP4-abs in pediatric patients with ADS (32, 48). Furthermore, this lack of information should lead to the creation of better guidelines, facilitating diagnosis and therapy of pediatric ADS patients, which should be disseminated among physicians caring for children in particular with NMOSD.

Theoretically, it could have been possible that treating doctors referred their patients to us not only via ESPED, but also via ESNEK. As ESPED patients are reported anonymously, there is a chance that we counted double-referred patients twice and by this, created a falsely increased prevalence rate. However, postcodes of all ESPED reported patients were available and were double-checked with the patients referred via ESNEK or the BIOMARKER Study. The same issue arose with the four patients who were included via NEMOS. For these patients, we compared available data (age and antibody status) with the remaining patients and could thereby exclude that they had already been brought to our attention by another ascertainment tool.

Using both the 2006 and 2015 criteria, we could demonstrate that implementing the 2015 criteria has increased the incidence rate in Germany by 1.5 times. Similar increases of the incidence rate were also shown in recent studies [1.5 times in Sepulveda et al. (18), 1.85 times in Hyun et al. (40)].

Another important issue is the heterogeneity of NMOSD in the subgroup of AQP4-ab negative patients either harboring MOG-abs or being double-seronegative, which we included both in this epidemiological study. However, considering for example the different pathogenic mechanisms in AQP4-ab positive NMOSD (astrocytopathy) and MOG-ab associated disease (MOG-AD; oligodendrocytopathy), we calculated the prevalence both for AQP4- and MOG-ab positive patients separately fulfilling the 2015 criteria for NMOSD (0.088 vs. 0.029 per 100,000 persons, respectively). Appreciating the pathophysiological, clinical and radiological differences between AQP4-ab positive NMOSD and MOG-AD (also MOG-ab disease, MOG-encephalomyelitis, MOG spectrum disorders) it seems reasonable in the future to not include MOG-ab positive patients with a clinical phenotype of NMOSD, but to consider them as a separate disease entity (17, 20, 21, 25, 28, 49–56). While the pathophysiology of the double-seronegative NMOSD patients is still not understood, the clinical management remains the same, so we kept these patients in our calculation.

Sixteen of 24 (67%) pediatric patients showed AQP4-abs, while only four patients had MOG-abs. These results are partly supported by the literature (29–31, 57–59). An explanation for the large proportion of AQP4-ab positive patients in our study might be the fact that awareness among physicians for NMOSD is especially high when their patients are tested positive for AQP4-abs. Still, children clinically presenting with ADS rather show MOG- than AQP4-abs (60). However, more than half of all MOG-ab positive patients remain monophasic and are thus unlikely to fulfill the 2015 diagnostic criteria for NMOSD (27, 61). MOG-ab positive patients fulfilling these criteria may not have been referred to our study due to the treating physicians' decision to classify these patients as MOG-AD.

Our study has the following strengths: (1) first study addressing the epidemiology of pediatric NMOSD in Germany and Austria, (2) usage of multiple ascertainment tools, and (3) available clinical data for 18/24 patients (despite focussing on epidemiological data).

However, several limitations need to be addressed: Specific registries, using medical data provided by insurances or the health care system, for pediatric NMOSD patients exist neither in Germany nor Austria. Accordingly, population-based studies are currently not possible in these countries. However, by using various tools to recruit patients, we tried to compensate for this limitation as much as possible.

We are aware of the fact that this study still has a certain selection bias as the referring colleagues do not represent the majority of all pediatric neurologists in Germany or Austria. For example, there is not a single patient referred from Berlin- or Hamburg-based tertiary care children's hospitals, which is very unlikely considering that these are the two biggest cities in Germany. Therefore, we assume that there is a certain proportion of pediatric patients with NMOSD who were not reported to one of our ascertainment tools.

Another limitation is that we are not aware of the type of assay used in four patients referred via ESPED and in 18/22 excluded patients. However, it is very likely that well-established live CBA or commercially available Euroimmun kits were used to screen for MOG- and AQP4-abs.

In 6/24 included patients, we did not have sufficient clinical data to verify the referral diagnosis NMOSD. However, 4/6 patients were AQP4-ab positive making the diagnosis rather easy, and the two AQP4-ab negative patients were referred by an NMOSD expert consortium convincing us of the diagnosis.

CONCLUSION

Pediatric NMOSD, both with and without associated antibodies, are very rare disease entities. An unexpected finding was that a considerable proportion of patients was tested neither for AQP4- nor MOG-abs during diagnostic work-up, which should prompt to create and disseminate commonly available and easy-to-follow guidelines. Finally, we are convinced that multicentric studies with higher patient numbers are needed to evaluate the true epidemiology, long-term outcome and prognosis of pediatric patients with AQP4-ab positive and double-seronegative NMOSD as well as MOG-AD.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Medical University of Innsbruck, Austria Ethics Committee of the Witten/Herdecke University, Germany. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin. Written informed consent was obtained from the minor(s)' legal guardian/next of kin for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

CL and KR created concept and design of the study, jointly acquired, and analyzed the data. CL drafted the manuscript. MR supported the data analysis. MBr, E-MW, MBa, BK, KS, and MR acquired the data and critically reviewed the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00415/full#supplementary-material

Supplementary Table 1 | Demographic, serologic, clinical, radiologic and therapeutic characteristics of the included patients.

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Value of Area Postrema Syndrome in Differentiating Adults With AQP4 vs. MOG Antibodies

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Objectives: To compare the frequency of area postrema syndrome (APS) in adults with anti-aquaporin-4 (AQP4) and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies.

Methods: APS is defined as acute or subacute, single or combined, episodic or constant nausea, vomiting, or hiccups, persisting for at least 48 h, which cannot be attributed to any other etiology. The presence of APS was investigated in 274 adults with AQP4 antibodies and 107 adults with MOG antibodies from 10 hospitals.

Results: The study population comprised Korean adults (≥18 years). At the time of disease onset, 14.9% (41/274) adults with AQP4 antibodies had APS, while none of the participants with MOG antibodies developed APS ($p < 0.001$). During the course of the disease, 17.2% (47/274) adults with AQP4 antibodies had APS in contrast to 1.9% (2/107) adults with MOG antibodies with APS ($p < 0.001$).

Conclusions: APS, one of the core clinical characteristics of individuals with AQP4 antibodies, is an extremely rare manifestation in Korean adults with MOG antibodies.

Keywords: area postrema syndrome, aquaporin-4 antibody, MOG antibody, neuromyelitis optica spectrum disorder, diagnosis

INTRODUCTION

Individuals with anti-aquaporin-4 (AQP4) antibodies and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies were previously grouped under the umbrella term neuromyelitis optica spectrum disorder (NMOSD), as they shared two cardinal clinical manifestations, optic neuritis and longitudinally extensive transverse myelitis. However, the two conditions are now considered distinct entities based on differences in histopathology, plausible underlying pathogenic mechanisms, clinical courses, treatment responses, and some distinguishing clinical manifestations (1–3).

Area postrema syndrome (APS), one of the core clinical characteristics described in the 2015 diagnostic criteria for NMOSD, is defined as intractable nausea, vomiting, or hiccups, which persist for at least 48 h (4, 5). Area postrema is located in the dorsal tegmentum of the medulla, an AQP4-rich region, which is often affected in individuals with AQP4 antibodies (6–8). In contrast to the preferential expression of AQP4 in certain regions of the central nervous system (CNS) (9), MOG is expressed throughout the CNS. As such, APS is not particularly expected in individuals with MOG antibodies, unlike those with AQP4 antibodies. This study evaluated the value of APS as a clinical characteristic in differentiating individuals with AQP4 antibodies from those with MOG antibodies in a large Korean cohort.

METHODS

The study included 298 participants with AQP4 antibodies from National Cancer Center (NCC) NMOSD cohort and 124 participants with MOG antibodies from 10 referral hospitals between 2005 and 2019. Four non-Koreans and 37 participants (21 with AQP4 antibodies and 16 with MOG antibodies) with the age of onset below 18 years were excluded. Finally, the frequency of APS was evaluated in 274 participants with AQP4 antibodies and 107 participants with MOG antibodies, by retrospective reviewing of the medical records based on physicians' active questioning regarding APS. APS was defined as per the following recently proposed criteria: (1) acute or subacute, single or combined, episodic or constant nausea, vomiting, or hiccups, (2) persistent for at least 48 h, (3) without a known etiology (5). The serostatus of AQP4 and MOG antibodies was assessed using live cell-based assays performed at the NCC and Seoul National University Hospital (10–12).

Fisher's exact test was used to compare the presence of APS between the two groups. The study protocol was approved by the institutional review boards of the NCC.

RESULTS

Demographics

The female-to-male ratio was 7.1:1 and 1.1:1 in participants with AQP4 antibodies and MOG antibodies, respectively. All the participants enrolled in this study were Korean. The mean age at disease onset was 37 years (range, 18–80 years) and 36 years (range, 18–72 years) for participants with AQP4 and MOG antibodies, respectively. The mean disease duration was 11 years (range, 1–36 years) and 7 years (range, 1–30 years) in participants with AQP4 and MOG antibodies, respectively. The mean follow-up period was 6 years (range, 1–14 years) and 4 years (range, 1–16 years) in individuals with AQP4 and MOG antibodies, respectively. The mean total number of attacks was 6 (range, 1–36) and 3 (range, 1–12) in participants with AQP4 and MOG antibodies, respectively.

Presence of APS

The initial manifestations of APS were observed in 41 (14.9%) of 274 participants with AQP4 antibodies, while none were observed in participants with MOG antibodies ($p < 0.001$). During the course of the disease, APS occurred in 47 of 274 participants (17.2%) with AQP4 antibodies, while only 2 of 107 participants (1.9%) with MOG antibodies experienced APS ($p < 0.001$). After considering the number of attacks, the significant difference in frequency of APS remained [2.8% (47/1686) vs. 0.6% (2/310), number of APS/total attacks, $p = 0.026$]. One of the two participants with MOG antibodies reported a 1-week history of constant nausea associated with acute disseminated encephalomyelitis (ADEM)-like lesions in the bilateral cerebral hemispheres and poorly demarcated dorsal midbrain and pontine lesions around the fourth ventricle (**Figure 1**). The other one with MOG antibody had episodic nausea and vomiting for 2 days with ADEM-like patch lesions in the left frontal lobe, basal ganglia, thalamus, and right external capsule (**Figure 2**). Four other patients with MOG antibodies presented with episodic or constant nausea/vomiting ($n = 3$), or hiccups ($n = 1$), but their symptoms did not persist for at least 48 h. Of six participants with AQP4 antibodies who developed APS after their initial presentation, four showed isolated APS as main phenotype of relapse (two of four with brain MRI at the time of relapse had no or only non-specific brain lesion except area postrema lesion). The remaining two participants with AQP4 antibodies experienced APS with optic neuritis ($n = 1$) or myelitis ($n = 1$) at the time of relapse.

Discussions

In contrast to AQP4 antibody-positive NMOSD, APS was rarely observed in Korean adults with MOG antibodies: none at onset and only 1.9% during the course of the disease. As the first manifestation, APS was exclusively observed in Korean adults with AQP4 antibodies while two adults with MOG antibodies had APS in the context of ADEM in their subsequent attacks. None of the participants with MOG antibodies had APS with area postrema lesion.

Two previous studies conducted in Western countries reported similar findings in both children and adults; APS at disease onset was rare in children with MOG antibodies (3.8%, 1/26) compared to those with AQP4 antibodies (50%, 4/8) (13), and APS presented only as a subsequent attack (2%, 1/50) in adults with MOG antibodies (14). Most recent article published after the completion of our study reported that the frequency of APS in the context of ADEM was 8.5% (10/117), while APS associated with area postrema lesion was extremely rare (0.9%, 1/117) in adults with MOG antibodies (15). Another recent study focused on magnetic resonance imaging findings also showed that area postrema lesions were uncommon in individuals with MOG antibodies (7%, 1/14) compared to those with AQP4 antibodies (50%, 8/16) (16). However, one study reported a relatively high frequency of APS (14.6%, 11/75) in a Caucasian and adult predominant cohort with MOG antibodies (17). Of note, the duration of patients' symptoms suggestive of APS in this study is uncertain and may have not persisted for at least 48 h, as defined by the criteria (5, 17).

Owing to the retrospective design of the current study based on a cohort of referral hospitals, inevitable potential recall and selection bias in the evaluation of APS might be present; larger prospective population-based studies are warranted to confirm our findings.

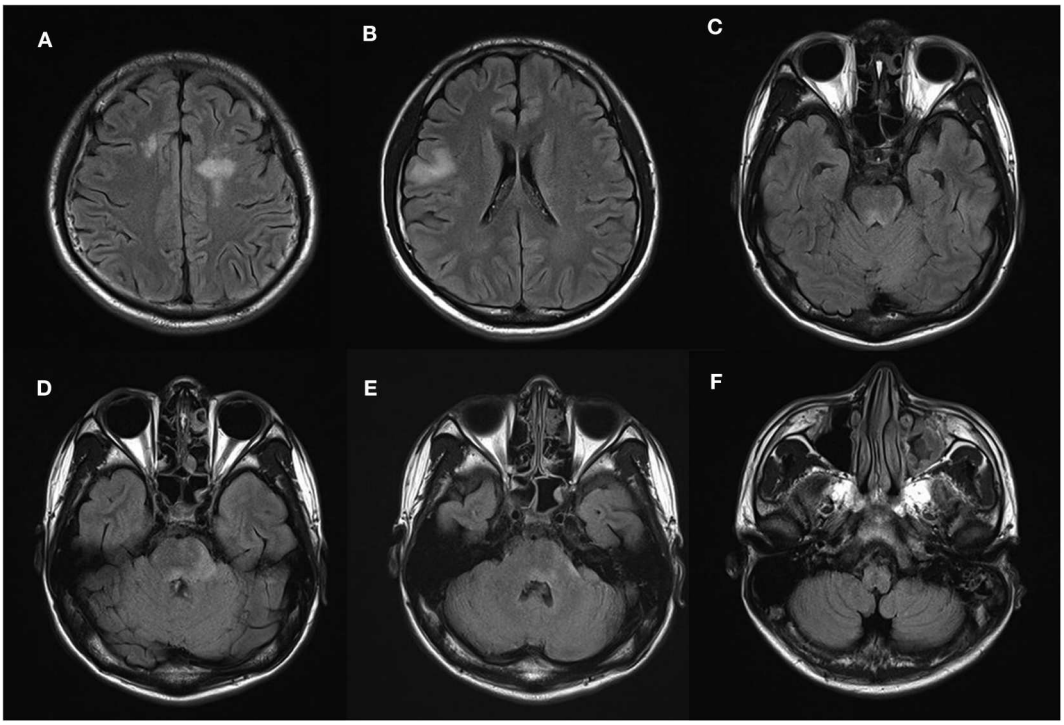

FIGURE 1 | Participant 1 shows high fluid-attenuated inversion recovery (FLAIR) signal abnormalities in **(A,B)** bilateral cerebral hemispheres, **(C)** poorly demarcated dorsal midbrain, and **(D,E)** pontine lesions around the fourth ventricle. **(F)** No area postrema lesion is observed.

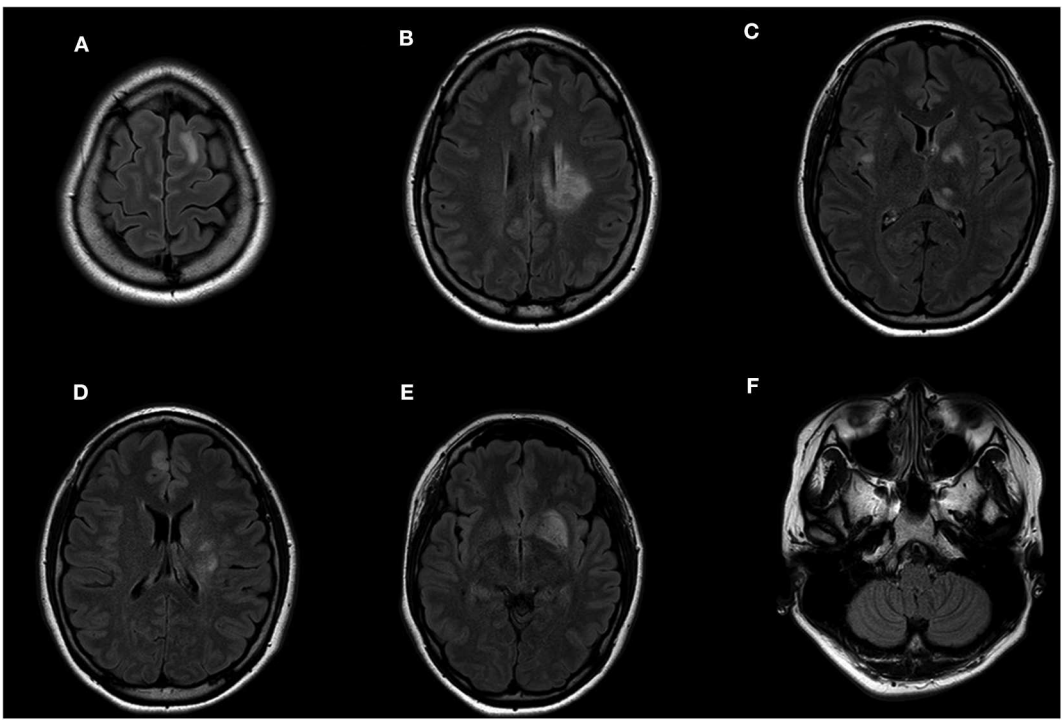

FIGURE 2 | Participant 2 had high FLAIR signal abnormalities in the **(A)** left frontal lobe, **(B–E)** basal ganglia, **(C)** thalamus, right external capsule, and **(D)** right frontal lobe. **(F)** No area postrema lesion is observed.

In conclusion, APS is a rare clinical feature in Korean adults with MOG antibodies and a reliable core clinical characteristic in those with AQP4 antibodies. Our findings suggest that a comprehensive evaluation of APS could be helpful in distinguishing individuals with AQP4 antibodies from those with MOG antibodies.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/supplementary material.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Cancer Center. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

J-WH and HK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, study concept and design and drafting of the manuscript. All authors: acquisition, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content.

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Relapse Patterns in NMOSD: Evidence for Earlier Occurrence of Optic Neuritis and Possible Seasonal Variation

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Neuromyelitis optica spectrum disorders (NMOSD) and multiple sclerosis (MS) show overlap in their clinical features. We performed an analysis of relapses with the aim of determining differences between the two conditions. Cases of NMOSD and age- and sex-matched MS controls were collected from across Australia and New Zealand. Demographic and clinical information, including relapse histories, were recorded using a standard questionnaire. There were 75 cases of NMOSD and 101 MS controls. There were 328 relapses in the NMOSD cases and 375 in MS controls. Spinal cord and optic neuritis attacks were the most common relapses in both NMOSD and MS. Optic neuritis ($p < 0.001$) and area postrema relapses ($P = 0.002$) were more common in NMOSD and other brainstem attacks were more common in MS ($p < 0.001$). Prior to age 30 years, attacks of optic neuritis were more common in NMOSD than transverse myelitis. After 30 this pattern was reversed. Relapses in NMOSD were more likely to be treated with acute immunotherapies and were less likely to recover completely. Analysis by month of relapse in NMOSD showed a trend toward reduced risk of relapse in February to April compared to a peak in November to January ($P = 0.065$). Optic neuritis and transverse myelitis are the most common types of relapse in NMOSD and MS. Optic neuritis tends to occur more frequently in NMOSD prior to the age of 30, with transverse myelitis being more common thereafter. Relapses in NMOSD were more severe. A seasonal bias for relapses in spring-summer may exist in NMOSD.

Keywords: neuromyelitis optica, multiple sclerosis, aquaporin, epidemiology, relapse, seasonality

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) have been recognized as having a distinct clinical and radiological phenotype which helps to differentiate these patients from those with multiple sclerosis (MS) (1). Early studies had indicated that the pathology of these two disorders was quite distinct, with NMOSD being more destructive (2). The identification of antibodies to the water channel aquaporin-4 (AQP4) in a significant proportion of patients with NMOSD (3) has greatly aided the diagnosis and treatment of this condition. The response to both acute relapse treatments and long-term preventive therapies are quite different for NMOSD and MS.

We have previously reported on the incidence and prevalence (4), AQP4 antibody assay findings (5) and clinical features (6) of a sizeable cohort of NMOSD cases meeting the 2015 International Panel for NMO Diagnosis (IPND) diagnostic criteria (1) collected from Australia and New Zealand. Here we analyze the specific details of relapse patterns, use of acute therapies and temporal patterns both in relation to the calendar year and across the lifespan of the disease. These data are compared with an age- and sex-matched cohort of MS cases collected from the same region with the aim of identifying distinct patterns of relapse that might further assist in the early identification of cases of NMOSD and provide information about potential trigger factors.

METHODS

Case Ascertainment

This was a retrospective case-control study of NMOSD cases and MS controls. Cases of suspected NMOSD and MS were referred by a network of 23 clinical centres in Australia and New Zealand specializing in the assessment of patients with inflammatory diseases of the central nervous system in both adult and pediatric populations as previously described (4, 6). Cases of NMOSD were defined according to the 2015 IPND criteria (1). Testing for AQP4 antibodies was undertaken using either a tissue-based immunofluorescence technique or positivity on a least two cell-based assays (fixed, Euroimmun® or live, Oxford) as previously described (5). Testing for MOG antibodies was conducted using a live cell-based assay as previously described (5). Age- and sex-matched MS cases were identified from each centre with the diagnosis of MS being confirmed according to the 2010 McDonald criteria (7) with the added requirements of having no clinical features suspicious for NMOSD and being negative for AQP4 antibodies. Basic demographic and clinical features were recorded for all cases and controls as per a standardized data collection questionnaire as previously described (6). All participants provided written informed consent and the study was approved by the human research ethics committee of all participating institutions.

Relapse Definitions

For relapses, data regarding the date of onset, symptoms experienced, presumed lesion location, treatment (intravenous steroids, plasma exchange, or intravenous gammaglobulin), maximal expanded disability status scale (EDSS), visual acuity, extent of recovery (full, partial or none), laterality (unilateral, bilateral or multicentric) was recorded for each relapse. Details of symptoms were provided by the participants and where available corroborated by reference to contemporaneous medical records and MR imaging findings. The precision for the date of onset

was recorded as being either the day (date confirmed by medical records or patient diary reference), month (patient recollection or indirect medical records) or year (patient recollection). Lesion locations were based on symptomatology according to the following conventions. Motor, sensory, bladder, and pain symptoms in the limbs were attributed to a lesion of the spinal cord, unless there were additional brainstem or cerebral signs, or there was evidence of an active lesion elsewhere on MR imaging that could account for the symptoms in the absence of a relevant lesion in the spinal cord. Symptoms in the limbs with either ataxia, vestibular symptoms or cranial nerve signs were deemed to be a lesion of the brainstem/cerebellum. Hemi-motor or sensory symptoms were attributed to a lesion of the cerebral hemisphere where there was involvement of the face, cortical signs or a relevant hemispheric lesion. Blurring of vision in one or both eyes was deemed to be due to a lesion of the optic nerve, chiasm or tracts, unless there were additional brainstem signs. If symptoms could not be attributed to a single lesion site or if there was evidence of multiple active lesions on MR imaging, then lesions were deemed to be multifocal and assigned to the smallest number of regions required to explain all the symptoms. Episodes of hiccoughs, nausea and vomiting with a lesion of the area postrema evident on MR imaging were counted as area postrema relapses. Encephalitic presentations were defined as focal hemispheric symptoms or a focal hemispheric lesion associated with seizures, headache or clouding of consciousness. Classical Devic presentations were defined as the simultaneous or sequential onset (within 3 months) of optic neuritis and transverse myelitis (8).

Statistical Analysis

Frequencies are expressed as n/N (%) and continuous data are presented as median (range) if not normally distributed or mean (SD) if normally distributed. Comparisons between NMOSD and MS have been made using appropriate parametric or non-parametric tests. For categorical variables, Fisher's exact test was used when the number of patients in any cell was less than five. No correction for multiple testing was undertaken. These statistical tests were performed using Statistical Package for Social Science (SPSS®) v25 (IBM®; Chicago, US). Auto regressive integrated moving average time series method was used to analyze the effect of month and seasons in the time series to predict the occurrence of relapse in MS. Relapse counts were analyzed by month using a Poisson regression model with the median month of relapse used as the reference, as has been used previously in MS (9). These analyses were performed using the STATA® statistical package v14 (StataCorp®; College Station, Texas, US).

RESULTS

NMOSD Cases and MS Controls

There were 75 cases of NMOSD with full clinical data that met the 2015 IPND criteria (1), of which 68 (91%) were positive for AQP4 antibodies. There were 101 controls with MS who were all negative for AQP4 antibodies and met the 2010 McDonald criteria (7). Testing for MOG antibodies was conducted on 42/75 (56%) of NMOSD cases, including all of the seronegative cases and 52/101 (51%) of MS controls, and all were negative (5). The demographic and clinical features of the NMOSD cases and MS controls have been previously reported (6) and show that they were well matched for age and sex, but differ in a number of predictable clinical features as summarized in **Table 1**. Age of onset in MS cases was younger and consequently disease duration was longer. Despite this the number of relapses seen in NMOSD was greater, although not significantly, and the annualized relapse rate was approximately double that of MS controls ($p < 0.001$). The distribution of numbers of relapses in the two groups is illustrated in **Figure 1**. The level of disability at last review was greater in NMOSD compared to MS (median EDSS 4.0 vs. 2.0; $p < 0.001$). Secondary progressive disease was only seen in two cases of NMOSD and primary progressive NMOSD was not seen. The proportion of cases with monophasic disease was similar for NMOSD and MS although the extent of follow up for the MS cases was greater. The proportion of NMOSD cases experiencing a classical Devic presentation showed a trend toward being higher than in MS and these presentations were more likely to involve bilateral optic neuritis or be sequential in NMOSD, but were more commonly recurrent in MS. However, none of these differences were statistically significant due to the small numbers.

TABLE 1 | Comparison of clinical features of NMOSD and MS.

Clinical feature	NMOSD	MS	*p*-value
N	75	101	
Age (Years)–median (range)	47 (19–85)	46 (16–73)	ns
Gender (Female)–*n*/*N* (%)	68/75 (91)	86/101 (85)	ns
Age at Onset (Years)–median (range)	40 (13–85)	32 (6–59)	0.001
Disease Duration (Years)–median (range)	4.1 (0.1–43.1)	12.3 (0.5–43.3)	<0.001
Relapses–median (range)	4 (1–16)	3 (0–11)	ns
Annualized relapse rate–median (range)	0.77 (0.13–3.33)	0.33 (0.06–3.78)	<0.001
EDSS–median (range)	4 (0–9)	2 (0–9)	<0.001
Clinical Course–*n* (%)			ns
Monophasic (CIS)	10 (13)	12 (12)	
Relapsing remitting	63 (84)	73 (72)	
Secondary progressive	2 (3)	13 (13)	
Primary progressive	0 (0)	3 (3)	
Classical Devic presentation–*n* (%)	12 (16)	9 (9)	ns
With bilateral optic neuritis	4/12 (33)	2/9 (22)	ns
Sequential (≤3 months)	6/12 (50)	1/9 (11)	ns
Recurrent	2/12 (17)	3/9 (33)	
Initial MR brain imaging normal–*n*/*N* (%)	12/70 (17)	3/100 (3)	0.001
LESCL on MR spine imaging–*n*/*N* (%)	48/71 (68)	1/89 (1)	<0.001

NMOSD, neuromyelitis optica; MS, multiple sclerosis; LESCL, longitudinally extensive spinal cord lesion; CIS, clinically isolated syndrome; SD, standard deviation; EDSS, expanded disability status scale; ns, non-significant.

Types of Relapse

The frequency of different relapse types and lesion locations is summarized in **Table 2**. The proportions of relapse locations

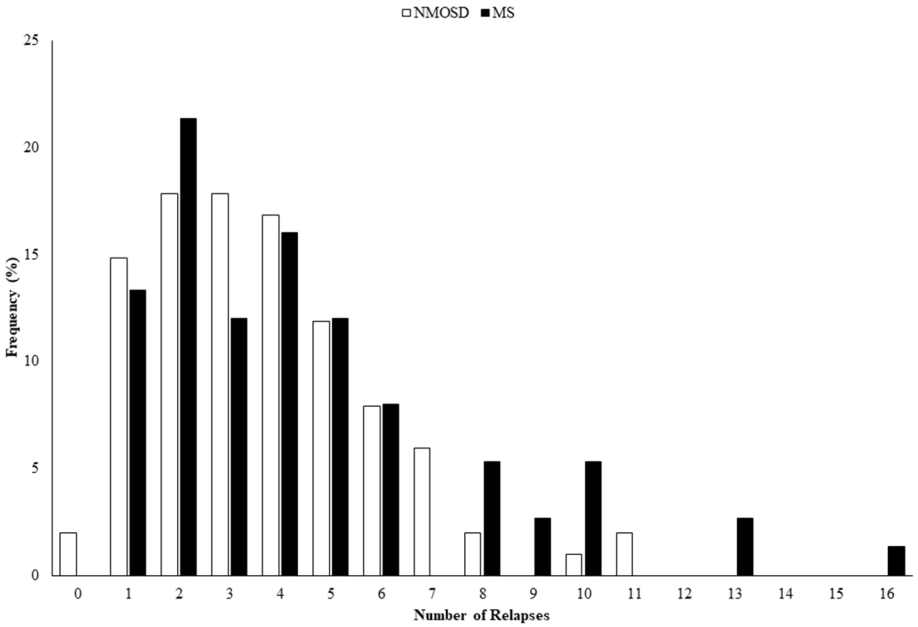

FIGURE 1 | Histogram showing distribution of numbers of relapses seen in NMOSD and MS. NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis.

TABLE 2 | Frequency of relapse locations in NMOSD and MS.

Relapse syndrome	First relapse			All relapses		
	NMOSD	MS	*p*-value	NMOSD	MS	*p*-value
n	75	101		329	375	
Transverse myelitis	33 (44)	51 (50)	ns	159 (48)	165 (44)	ns
Optic neuritis	29 (38)	12 (12)	<0.001	131 (40)	62 (16)	<0.001
Area postrema syndrome	7 (9)	0 (0)	0.009	11 (3)	0 (0)	0.002
Other brainstem syndrome	3 (4)	25 (25)	<0.001	16 (5)	90 (24)	<0.001
Optic neuritis and transverse myelitis	2 (2)	3 (3)	ns	7 (2)	14 (4)	ns
Cerebral syndrome	0 (0)	5 (5)	ns	2 (1)	15 (4)	ns
Optic neuritis and brainstem syndrome	0 (0)	2 (2)	ns	2 (1)	9 (2)	ns
Brainstem syndrome and transverse myelitis	1 (1)	0 (0)	ns	1 (0.3)	0 (0)	ns

NMOSD, neuromyelitis optica; MS, multiple sclerosis; ns, non-significant.

at first relapse and for all relapses were similar within the two cohorts (**Table 2**). However, there was a difference between NMOSD cases and MS controls in the frequency of optic neuritis ($p < 0.001$) and brainstem lesions ($p < 0.001$). Optic neuritis and area postrema lesions were more common in NMOSD and other brainstem lesions were more common in MS. Cerebral syndromes were rare in NMOSD and there was a trend toward these being more common in MS, but the overall numbers were lower, and this difference was not significant. There was only one encephalitis presentation seen in NMOSD. Area postrema syndromes were more common as a first relapse (9%) compared to all relapses (3%). There were no cases of NMOSD that presented with hypothermia, drowsiness or syndrome of inappropriate anti-diuretic hormone syndrome. When analyzed by sex and serostatus there were no significant differences in the pattern of relapse in NMOSD (data not shown).

The frequency of lesion location in NMOSD according to age at the time of relapse for all relapses is shown in **Figure 2** and indicates that episodes of optic neuritis predominate at a younger age with a peak age at 20–29 years, whilst attacks of transverse myelitis predominate later with a peak incidence at 40–49 years. Relapses of all types were seen across a broad range of ages (10–69 years).

Relapse Features, Treatment and Outcomes

The principal features, treatment and outcomes for all relapses in NMOSD and MS are given in **Table 3**. The time between relapses was shorter in NMOSD (10.6 months) compared with MS (18.0

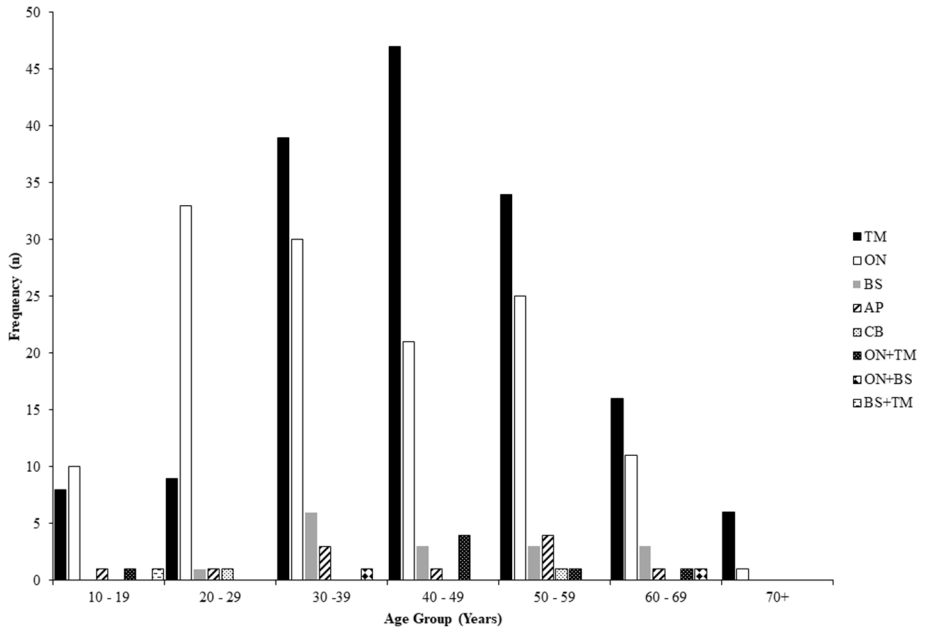

FIGURE 2 | Frequency of relapse lesion locations according to age at the time of relapse in NMOSD. NMOSD, neuromyelitis optica spectrum disorder; TM, transverse myelitis; ON, optic neuritis; BS, brainstem/cerebellar; AP, area postrema; CB, cerebral.

months). There was no difference in the proportion of optic neuritis attacks that were bilateral in NMOSD and MS, but the absolute frequency was higher in NMOSD (21 vs. 8). Spinal cord relapses were more commonly partial in MS. Relapse duration and maximal disability level were greater in NMOSD. NMOSD cases were more likely to be treated with high dose intravenous or oral steroids, plasma exchange and intravenous immunoglobulin. Complete recovery from a relapse was more common ($p < 0.001$) in MS (56%) than NMOSD (29%).

Seasonal Variation in Relapses

The seasonal pattern of relapses in NMOSD is shown in **Figure 3**. The auto regressive integrated moving average analysis indicated a marginal significance of month on number of relapses per month with coefficient = 0.531 C95% CI−0.678 – 1.13, $P = 0.082$) and adjusted coefficient = 3.677 (95% CI 2.034–5.320, $P < 0.001$). Poisson regression analysis indicated that no individual month significantly deviated from the median (**Figure 3**). Analysis of 3-month époques indicated a trend toward fewer relapses in February to April compared to November to January ($P = 0.065$). This corresponds to a potential peak risk of relapse in mid-spring and summer in the Southern Hemisphere and is similar to the pattern seen in MS for this part of the world (10) which has been attributed to a 1–2 month lag in relapses after the nadir of vitamin D levels (September in the Southern Hemisphere) (10).

TABLE 3 | Comparison of relapse features, treatment and outcomes in NMOSD and MS.

Relapse feature	NMOSD	MS	*p*-value
N	328	375	
Time between relapses (months)–median (range)	10.6 (0.3–336.0)	18.0 (0.5–408.4)	<0.001
Bilateral optic neuritis–*n*/*N* (%)	21/116 (18)	8/55 (15)	ns
Partial cord syndrome– *n*/*N* (%)	55/134 (41)	80/148 (54)	0.03
Relapse duration (days)–mean* (range)	68 (2–666)	50 (1−365)	<0.001
Maximal EDSS–median (range)	4 (1–10)	3 (1–8)	<0.001
Treated with IVMP–*n* (%)	193 (59)	149 (40)	<0.0001
Treated with PLEX–*n* (%)	41 (13)	0 (0)	<0.0001
Treated with IVIg–*n* (%)	20 (6)	2 (1)	<0.0001
Outcome– *n*/*N* (%)			<0.0001
Complete recovery	78/271 (29)	165/295 (56)	
Partial recovery	170/271 (63)	109/295 (37)	
No improvement	23/271 (8)	21/295 (7)	

**Mean is given in place of median which was 30 days (1 month) for both NMOSD and MS. NMOSD, neuromyelitis optica spectrum disorder; MS, multiple sclerosis; EDSS, expanded disability status scale; IVMP, intravenous methylprednisolone or very high dose oral steroids; PLEX, plasma exchange; IVIg, intravenous immunoglobulin; ns, non-significant.*

DISCUSSION

The present data indicate that the commonest relapse types seen in NMOSD are transverse myelitis and optic neuritis and that optic neuritis attacks, particularly as first attacks, are more common in NMOSD than MS. Area postrema presentations were exclusively seen in NMOSD and accounted for 9% of first relapses and 3% of all relapses. Attacks of optic neuritis were seen more frequently at a younger age in NMOSD with episodes of transverse myelitis occurring more frequently later. Relapse frequency, duration and severity, together with the requirement

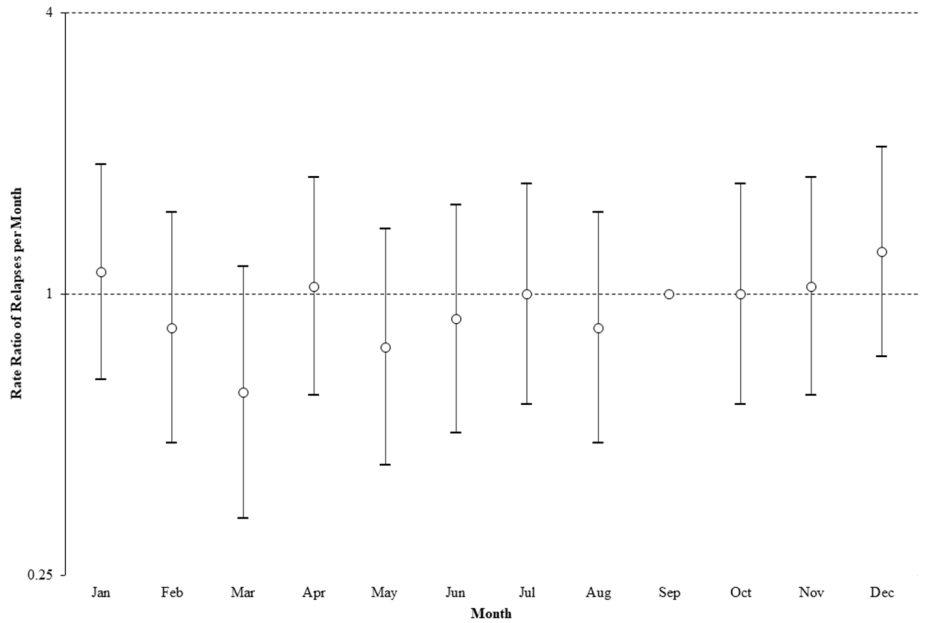

FIGURE 3 | Rate ratio of relapses per month, using median of 29 relapses per month (September). Error bars show 95% confidence intervals (Poisson regression analysis). Y-axis plotted on logarithmic scale.

for acute immunotherapies, were all greater in NMOSD than MS. In the situation where the diagnosis of NMOSD had been established there would be a potential bias toward the use of acute immunotherapies.

As with previous studies the most frequent form of relapse in NMOSD was a lesion of the spinal cord and the frequency observed in the present study (48%) falls in the middle of previous observations (36–63%) (11–15). The frequencies of other relapse types were similar to these prior studies. As with previous studies relapses with encephalitic or other cerebral features were uncommon in NMOSD. Area postrema lesions as an initial presenting feature was seen in (9%) which was similar to prior studies (15). We found that area postrema relapses were more common at first presentation than with subsequent relapses. This finding is contrary to a recent larger study of several international cohorts (16). However, we note the definition for area postrema syndrome used in that study was broader than the definition used in the present study. No relapses involving hypothermia (17) or syndrome of inappropriate anti-diuretic hormone syndrome (18) were seen in our cohort.

Despite being an inclusion criterion for suspected NMOSD in our original clinical survey, there were eight optic neuritis attacks in our MS cohort that were bilateral. These were historical attacks and the lesion location was based on symptomatology which can be prone to error. For example, bilateral visual blurring can arise as a result of mild diplopia from a brainstem lesion or a homonymous field deficit due to a cerebral lesion. These cases otherwise had features typical for MS and were therefore not reclassified. Classical Devic presentations with either simultaneous or sequential optic neuritis and transverse myelitis were only marginally more common in NMOSD than MS and this was not a significant difference. Classical Devic presentations were seen in 16% of NMOSD cases. The exclusion from the MS controls of cases with features suspicious for NMOSD could potentially introduce a bias in the relapse features reported here. However, we would note that the number of cases referred with NMOSD-like features that did not meet 2015 IPND criteria was similar to the number of confirmed NMOSD cases in our original survey (6), thus representing no more than 1% of all MS cases. This is unlikely to introduce any significant bias. Recall bias is always a potential issue with retrospectively collected relapse data. However, the methods used in this study were identical for the NMOSD cases and MS controls.

The frequency with which high dose steroids were administered for attacks of NMOSD (58%) was higher than in MS and was similar to previous studies (65–84%) (12, 13). The frequency of complete recovery was lower in NMOSD than MS and was in a range similar to that observed previously (13).

Two novel findings in the present study are the observation that attacks of optic neuritis predominate in younger patients with NMOSD whilst transverse myelitis is more common later in life and that there is a seasonal variation in the frequency of attacks. An earlier study has noted the predominance of optic neuritis in first presentations prior to the age of 30 years, with transverse myelitis being more common above 30 (19). We are not aware of prior data looking at seasonal variability of relapses in NMOSD. A trend toward fewer relapses from February to April compared to a peak from November to January is similar to the pattern seen in MS both in the Northern and Southern Hemisphere (9, 10). This finding is somewhat surprising considering the absence of a latitudinal gradient seen in two national studies of NMOSD prevalence (4, 20). This suggests that relative vitamin D deficiency or decreased ultraviolet

B radiation exposure are not significant factors in the risk of developing NMOSD but may be factors influencing the likelihood of relapses. These findings require confirmation in further studies.

In conclusion, we have confirmed the findings of prior studies with regard to the pattern of relapses and clinical features seen in NMOSD. We have shown that this pattern differs significantly from MS in a number of areas. There was no difference in the frequency of classical Devic presentations between NMOSD and MS, but there was a trend toward sequential and bilateral optic neuritis Devic's presentations being more common in NMOSD. The finding of optic neuritis attacks occurring more commonly at a younger age is interesting and as with the sequential optic nerve involvement with later spinal cord disease seen in classical Devic's syndrome suggests a specific vulnerability of the optic nerve early in the disease course. The increased risk of NMOSD relapse during the spring-summer suggests a seasonally dependent environmental risk factor influencing the timing of relapses in NMOSD.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was reviewed and approved by Griffith University Human Research Ethics Committee (MED2009/646) and had local Governance Approval at each participating site. All participants gave written informed consent.

AUTHOR CONTRIBUTIONS

DA, MHB, SBh, SBl, MBo, KB, BB, SAB, MBr, WBr, HB, WC, CC, AC, RD, CD, DG, SHa, RH, AH, SHo, AGK, TJK, JK, CK, JL-S, CL, RM, MM, DM, PM, CO'G, JPa, JPe, JDP, KP, SWR, CS, MS, JSp, JSu, IS, BT, AV, SV, MWa, PW, EW, and RCW conceived and designed the study. EK, SAB, WBu, CB, LC, JSu, MF-P, DG, SHe, SJ, M-WL, KP, RS, JSt, BT, PW, MWo, and EY conducted the analyses. EK, WBu, and LC prepared the initial draft. AC, BB, FB, HB, RD, MF-P, SHa, SHo, JK, AJK, JL-S, PM, RM, SWR, JSi, BT, AV, SV, and PW contributed to revisions. All authors approved the final draft.

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Conflict of Interest: MHB has received honoraria for participation in advisory boards and travel sponsorship from Novartis, BioCSL, Genzyme and Biogen Idec. MBo has received travel sponsorship and honoraria from Sanofi-Genzyme, Teva, Novartis, Biogen Idec and Roche. BB has received honoraria as a board member for GlaxoSmithKline, Biogen Idec, ViiV Healthcare and Merck Serono, has received speaker honoraria from ViiV Healthcare, Boehringer Ingelheim, Abbott, Abbvie, and Biogen Idec; has received travel sponsorship from Abbott and Viiv Healthcare, and has received research support funding from EI Lilly, GlaxoSmithKline, ViiV Healthcare and Merck Serono. SAB has received honoraria for attendance at advisory boards and travel sponsorship from Bayer-Scherring, Biogen-Idec, Merck-Serono, Novartis, and Sanofi-Genzyme, has received speakers honoraria from Biogen-Idec and Genzyme, is an investigator in clinical trials sponsored by Biogen Idec, Novartis and Genzyme, and was the recipient of an unencumbered research grant from Biogen-Idec. HB has received honoraria for serving on scientific advisory boards for Biogen Idec, Novartis and Sanofi-Genzyme, has received conference travel sponsorship from Novartis and Biogen Idec, has received honoraria for speaking and acting as Chair at educational events organized by Novartis, Biogen Idec, Medscape and Merck Serono, serves on steering committees for trials conducted by Biogen Idec and Novartis, is chair (honorary) of the MSBase Foundation, which has received research support from Merck Serono, Novartis, Biogen Idec, Genzyme Sanofi and CSL Biopharma and has received research support form Merck Serono. WMC has been the recipient of travel sponsorship from, and provided advice to, Bayer Schering Pharma, Biogen-Idec, Novartis, Genzyme, Sanofi-Aventis, BioCSL, and Merck-Serono. 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Epidemiology of Neuromyelitis Optica Spectrum Disorder and Its Prevalence and Incidence Worldwide

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Neuromyelitis optica spectrum disorder (NMOSD) is an uncommon inflammatory disease of the central nervous system, manifesting clinically as optic neuritis, myelitis, and certain brain and brainstem syndromes. Cases clinically diagnosed as NMOSD may include aquaporin 4 (AQP4)-antibody-seropositive autoimmune astrocytopathic disease, myelin oligodendrocyte glycoprotein (MOG)-antibody-seropositive inflammatory demyelinating disease, and double-seronegative disease. AQP4-antibody disease has a high female-to-male ratio (up to 9:1), and its mean age at onset of ∼40 years is later than that seen in multiple sclerosis. For MOG-antibody disease, its gender ratio is closer to 1:1, and it is more common in children than in adults. Its clinical phenotypes differ but overlap with those of AQP4-antibody disease and include acute disseminated encephalomyelitis, brainstem and cerebral cortical encephalitis, as well as optic neuritis and myelitis. Double-seronegative disease requires further research and clarification. Population-based studies over the past two decades report the prevalence and incidence of NMOSD in different populations worldwide. One relevant finding is the varying prevalence observed in different racial groups. Consistently, the prevalence of NMOSD among Whites is ∼1/100,000 population, with an annual incidence of <1/million population.

Among East Asians, the prevalence is higher, at ∼3.5/100,000 population, while the prevalence in Blacks may be up to 10/100,000 population. For MOG-antibody disease, hospital-based studies largely do not observe any significant racial preponderance so far. This disorder comprises a significant proportion of NMOSD cases that are AQP4-antibody-seronegative. A recent Dutch nationwide study reported the annual incidence of MOG-antibody disease as 1.6/million population (adult: 1.3/million, children: 3.1/million). Clinical and radiological differences between AQP4-antibody and MOG-antibody associated diseases have led to interest in the revisions of NMOSD definition and expanded stratification based on detection of a specific autoantibody biomarker. More population-based studies in different geographical regions and racial groups will be useful to further inform the prevalence and incidence of NMOSD and their antibody-specific subgroups. Accessibility to AQP4-antibody and MOG-antibody testing, which is limited in many centers, is a challenge to overcome. Environmental and genetic studies will be useful accompaniments to identify other potential pathogenetic factors and specific biomarkers in NMOSD.

Keywords: neuromyelitis optica spectrum disorder, NMOSD, AQP4, MOG, prevalence, incidence, population study, epidemiology

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an uncommon inflammatory disease of the central nervous system, with clinical features of optic neuritis, myelitis, and certain brain, and brainstem syndromes. Although it had long been debated whether NMOSD is a severe variant of multiple sclerosis (MS), the discovery of NMOSD-specific aquaporin 4 (AQP4) antibody, and the subsequent clinical, immunological, and pathological data have established that NMOSD is indeed a distinct entity (1–3). Currently, cases clinically diagnosed as NMOSD may include AQP4-antibody-seropositive autoimmune astrocytopathic disease, myelin oligodendrocyte glycoprotein (MOG)-antibody-seropositive inflammatory demyelinating disease, and double-seronegative disease (4).

AQP4-antibody-seropositive NMOSD has a high female-to-male ratio (up to 9:1) (5), and its mean age at onset is around 40 years (6, 7), older than in MS. Pathologically, it is primarily an astrocytopathic disease rather than a demyelinating disease (3, 8). For MOG-antibody disease, the sex ratio is close to 1:1, and it is more common in children than in adults (9, 10). Its clinical manifestations overlap with those of AQP4-antibody disease but there are differences about which there is emerging consensus. Besides optic neuritis and myelitis, its clinical phenotypes also include acute or multiphasic disseminated encephalomyelitis (ADEM/MDEM), brainstem and cerebral cortical encephalitis, and cranial nerve involvement (11–14). Double (AQP4- and MOG-antibodies)-seronegative disease is enigmatic at present and requires further clinical and laboratory research for specific classification.

There have been several editions of the diagnostic criteria for NMOSD since 1999 (15, 16), with the latest being the 2015 International Panel on NMO Diagnosis (IPND) criteria (17). In the meantime, laboratory assays for AQP4 antibody and MOG antibody have also improved over time, with increased sensitivity and specificity (18, 19). These factors have contributed to the improvement in the accuracy of the diagnosis of NMOSD cases.

In this article, we review current data on the worldwide epidemiology of NMOSD, specifically on the population-based studies of NMOSD to determine its prevalence and incidence among different populations and racial groups. We emphasize that the field of NMOSD is undergoing a rapid evolution, making epidemiological estimates tentative. Additionally, different levels of diagnostic rigor to exclude NMOSD mimics and access to medical care in study populations can bias the epidemiological survey results in the disease, which makes the interpretation and comparison of the findings in and across the studies difficult. Nonetheless, the best known of current knowledge is being presented.

Search Strategy and Selection Criteria

The PubMed database was searched for population-based studies on NMOSD with prevalence data, from 1st January 2000 till 11th March 2020. A combination of the following search terms was used: "neuromyelitis optica," "NMO," "NMOSD," "aquaporin 4," "AQP4," "myelin oligodendrocyte glycoprotein," "MOG," "optico-spinal multiple sclerosis," "OSMS," "idiopathic inflammatory demyelinating disease," "IIDD," "epidemiology," "prevalence," "population," and "demographic." The reference lists in published articles on NMOSD were also queried to identify further studies. Additionally, recent conference proceedings of major neurology and MS congresses, including the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS) and the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis (PACTRIMS), were searched for relevant abstracts where the full studies are not yet published. Population-based studies with information on the prevalence of NMOSD in English language were reviewed.

The final list of publications was selected on the basis of relevance to the topic.

Prevalence of NMOSD

The prevalence range of NMOSD is ∼0.5–4/100,000, and may be up to 10/100,000 in certain racial groups. Nevertheless, this prevalence range is rather small relative to that of MS, which ranges from 1–2/100,000 in the equatorial region, to 150–200/100,000 in Canada and northern part of Europe (20, 21).

Over the past two decades, population-based studies of NMOSD have provided important insights into its prevalence. The earliest population-based studies were conducted in French West Indies (Martinique) (22, 23), Cuba (24), Denmark (25), and Tokachi Province on Hokkaido Island in Japan (26). Interestingly, the majority of these early studies were conducted on island populations, which facilitate population-based studies by providing well-delimited boundaries of the study area. Two of the studies (Martinique and Hokkaido) (22, 23, 26) have since been updated by the original groups of researchers.

Since 2017, several new population-based studies were published, expanding knowledge of NMOSD in diverse populations around the world. Inter-racial variation in prevalence, as summarized in **Table 1**, is notable and consistent across geographical regions. More recently, the Australia/New Zealand group has also re-analyzed the data from their 2017 study (47) to provide further information with regards to the prevalence among different racial groups in their large continent (46). **Figure 1** is a map showing population-based prevalence studies of NMOSD around the world.

East Asians

East Asians (Japanese, Chinese, and Koreans) appear to have a higher prevalence of NMOSD (around 3.5/100,000) as compared to Whites and other Asian racial groups. The study in Hokkaido, Japan recorded a prevalence of 4.1/100,000 (36), while the Japanese nationwide survey estimated a prevalence of 3.42/100,000 (40). Meanwhile, a study conducted in the multi-racial population in Penang Island, Malaysia showed that the prevalence among Chinese was 3.31/100,000 (39). These results were in line with the genetic studies that showed that Japanese and Chinese share the same HLA risk genes for NMOSD, namely, HLA-DPB1*05:01 and HLA-DRB1*16:02 (49–51). In a very recent study from South Korea, by using a nationwide health insurance research dataset, it was calculated that the prevalence among Koreans was 3.56/100,000 in 2017 (48). More studies, especially from China, Taiwan, and Hong Kong will be useful to further inform the prevalence of NMOSD among the East Asians.

Blacks

In 1971, a study conducted in a single hospital in the sub-Saharan African city of Ibadan (Nigeria) reported 95 cases of NMO, 22 cases of acute transverse myelitis, 11 cases of bilateral retrobulbar neuritis, and only two cases of MS over 12 years of hospital admissions (1957–1969) (52). During the same period, there were nine cases of non-Nigerians with MS (in eight Europeans and one Indian). It estimated that NMO cases made up 0.43/1000 (or 430/100,000) of the hospital population.

Population-based studies over the past two decades showed that Blacks also have a higher NMOSD prevalence than Whites. A study conducted in Liverpool, UK reported a prevalence rate of 1.8/100,000 among Blacks (29). The Australia/New Zealand study estimated a prevalence rate of 1.84/100,000 in those with African ancestry (46). The study conducted in the French Martinique Island in the Caribbean reported a very high prevalence of 11.5/100,000 among its Black population (34), and this was the highest prevalence reported so far. In population-based studies, within the same localities, prevalence among Blacks is always higher than in Whites, as seen in Cuba (24), Liverpool (UK) (29), Olmsted county (USA) (34), Martinique Island (34), and Australia/New Zealand (46).

As Blacks are genetically diverse, more data from different geographical regions are needed, and especially those from the African continent. Although no population-based studies of NMOSD have been published from Africa, recently there have been reports of NMOSD cases from various African countries that are to be compiled and reported elsewhere.

Whites/Caucasians

In recent nationwide and region-wide studies, the prevalence of NMOSD among Whites has consistently been ∼1/100,000. The prevalence was 0.55/100,000 in Australia and New Zealand (46, 47), 0.89/100,000 in Catalonia (38), 1.09/100,000 in Denmark (42), and 1.04/100,000 in Sweden (43). Also recently, a re-analysis of the data of an earlier study from South Denmark has reported the prevalence of AQP4-antibody-positive NMOSD as 1.68/100,000, and the prevalence of the total clinical phenotype including AQP4-antibody-negative and MOG-antibody-positive subsets was 4.4/100,000 (25, 27).

Interestingly, the prevalence among Hungarians was slightly higher, at 1.91/100,000 (45). This has brought up the notion of whether there are some admixtures of Asian genes (from North East Asia) among the Hungarians (53). Furthermore, there is scarcity of prevalence data from Central Asia, and such data from this region will be informative.

Other Asians

South Indians

If the 2015 IPND criteria were applied, the prevalence among South Indians in Mangalore was 0.72/100,000 (31). No cases were found among the 10% South Indian population in Penang Island, Malaysia (39), suggesting a low prevalence.

Austronesian Peoples

The Austronesian peoples reside in the Philippines, Malaysia, Indonesia, the Pacific Islands (Polynesia, Micronesia, and Hawaii), down to New Zealand, and also to the west in Madagascar. The study conducted in the multi-racial Penang Island, Malaysia (39) found that the prevalence of an Austronesian group, the Malays, was ∼0.80/100,000 (this was revised from 0.43/100,000 as reported earlier, after a new case was diagnosed). The prevalence data from another Austronesian group was available recently, namely, the Māoris in New Zealand, with an estimated prevalence of 1.50/100,000 (46). Nevertheless, in the same study, no cases of NMOSD were found among

TABLE 1 | Population-based prevalence and incidence studies of NMOSD.

Population-based study	Geographical location	Prevalence of NMOSD (per 100,000 population), as according to racial groups				Incidence (per million population)	AQP4-ab testing methods	AQP4-ab positivity	Female-to-male ratio
		Whites/ Caucasians	Blacks	East Asians	Other Asians/Other Races				
Cabrera-Gomez et al. (2009) (24)	Cuba	0.43	0.80			0.53	Not tested	Not tested	7.3:1
Asgari et al. (2011) (25) (re-analyzed 2019) (27)	South Denmark	1.68*				1.5	CBA	62%	5.3:1
Cossburn et al. (2012) (28)	South East Wales	1.96				NR	NR	71%	6:1
Jacob et al. (2013) (29)	Merseyside, England	0.66*	1.8*			0.8	Oxford CBA	88%	3:1
Aboul-Enein et al. (2013) (30)	Austria	0.77				0.54	Innsbruck CBA	100%	7:1
Pandit and Kundapur (2014) (31)	Mangalore, India				South Indians: 2.6 (0.72 if using 2015 IPND criteria)	NR	NR	27%	1.2:1
Etemadifar et al. (2014) (32)	Isfahan, Iran	1.9				NR	NR	66%	2.3:1
Kashipazha et al. (2015) (33)	Khuzestan, Iran	1.1				NR	NR	54%	7.5:1
Flanagan et al. (2016) (34)	Olmsted county, USA	4.0	13.0			0.7	Mayo CBA	83%	5:1
	French Martinique Island	6.1 (single case, AQP4-ab negative)	11.5			7.3	Mayo CBA	79%	8.8:1
van Pelt et al. (2016) (35)	Netherlands	—				0.9	CBA	NA	4.9:1
Houzen et al. (2017) (36)	Tokachi, Hokkaido, Japan			Japanese: 4.1		NR	Sendai CBA	79%	6:1
Eskandarieh et al. (2017) (37)	Tehran, Iran	0.86				NR	ELISA	47%	5.1:1
Sepúlveda et al. (2018) (38)	Catalonia	0.89				0.63	Mainly CBA (96%)	73%	3.1:1

(Continued)

TABLE 1 | Continued

Population-based study	Geographical location	Prevalence of NMOSD (per 100,000 population), as according to racial groups				Incidence (per million population)	AQP4-ab testing methods	AQP4-ab positivity	Female-to-male ratio
		Whites/ Caucasians	Blacks	East Asians	Other Asians/Other Races				
Hor et al. (2018) (39)	Penang Island, Malaysia			Chinese: 3.31	Malays: 0.80 (revised)	NR	Euroimmun CBA	100%	14:1
Miyamoto et al. (2018) (40)	Japan (nationwide estimate)			Japanese: 3.42		NR	NA	NA	6.4:1
Holroyd et al. (2018) (41)	Abu Dhabi, UAE				Arabs: 1.09	1.16	NR	83%	All females
Papp et al. (2018) (42)	De nmark	1.09*				0.70	Various, incl. CBA	70%	4.5:1
Jonsson et al. (2019) (43)	Sweden	1.04				0.79	Immunoblot and CBA	NR	2.8:1
Kim et al. (2019) (44)	South Korea			Koreans: 2.56		7.3	CBA	NA	2.37:1
Papp et al. (2020) (45)	Hungary	Hungarians: 1.91*				1.32	CBA	83%	8.8:1
Bukhari et al. (PACTRIMS 2019) (46) (updated from 2017 study) (47)	Australia and New Zealand	0.55	1.84		Asians: 1.57 Māoris: 1.50 Australian Aborigines: 0.38	0.37	IF tissue assay, some also ELISA and CBAs	>90%	6:1
Lee et al. (2020) (48)	South Korea			Koreans: 3.56		4.1–6.5	NA	NA	4.7:1

**Only consider adult population. (As AQP4-antibody-positive NMOSD is rare in children, thus, if full population is considered, the prevalence will be slightly lower).*
NMOSD, neuromyelitis optica spectrum disorder; AQP4-ab, aquaporin 4-antibody; CBA, cell-based assay; IF, immunofluorescence; NA, not applicable; NR, not reported.

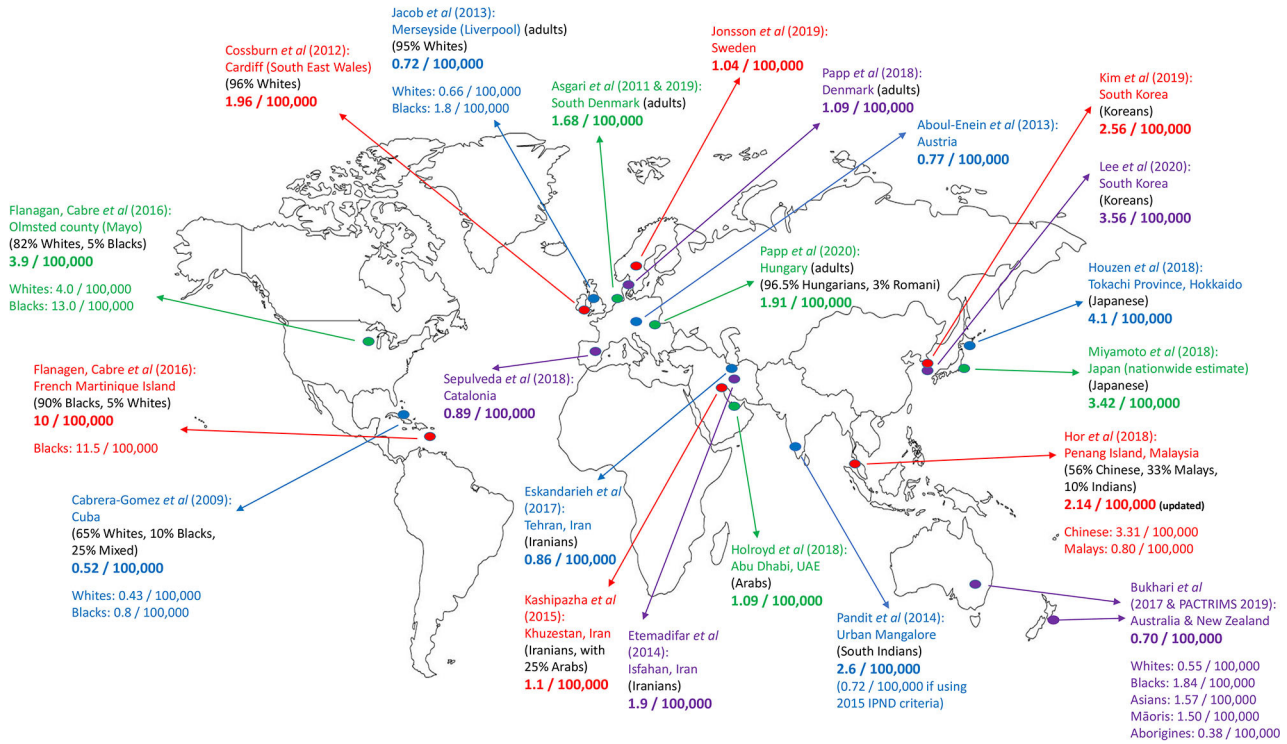

FIGURE 1 | Map showing population-based prevalence studies of NMOSD around the world. There were eight studies in Europe, 10 in Asia, one in Oceania, and two in the Americas (one in Cuba and one joint study in the USA and Martinique Island). Numbers given were prevalence per 100,000 population. In certain studies, the prevalence according to racial groups was given. Adults, only adult population was studied.

the ∼295,000 Pacific Islanders (Pasifika) (46). More data from other Austronesian groups in other localities will be useful to clarify this.

Arabs

A study from Abu Dhabi, United Arab Emirates reported six cases of NMOSD among its citizens, consistent with a prevalence of 1.09/100,000 (AQP4-antibody seropositivity: 83%, all six cases were females) (41). If only adult citizens aged ≥20 years were considered (a total of five cases), the prevalence is higher at 1.76/100,000. Data on Arabs in other regions of Middle East and North Africa will be very informative.

Australian Aborigines

The Australian Aborigines are one of the oldest populations in the world, with their ancestors having migrated to Australia around 50,000 years ago. There is evidence of some admixture of Denisovan genes in the Aborigines (Denisovans are an extinct species or subspecies of humans of the genus *Homo*). It is interesting to note that MS rarely exists in the Aborigines (54, 55). Recent data showed that NMOSD is also rare among the Aborigines, with a prevalence of 0.38/100,000 (46). However, the paper cautioned whether inequality in health care access may lead to this low figure.

Native Americans

MS is less common among Native Americans than in Whites in North America. Prior to AQP4-antibody discovery, a study conducted among the Native Canadians in Manitoba (56) found seven cases of "MS," of which five cases were of NMO phenotypes, while the other two had brainstem involvement. Autopsy of one patient showed eosinophil infiltration in the cervical cord lesion, and retrospectively, this pathological finding suggests that this case was likely to be NMOSD. Genetically, Native Americans may be more closely related to early East Asians, and thus they may also have a higher prevalence than Whites. A re-look at these native populations will be helpful to confirm the results, though may be practically difficult.

Latin America

After the arrival of Europeans in the 1500's, the indigenous populations of Latin American had dwindled rapidly. Today, along with the indigenous peoples, there is a large proportion of Whites, Blacks, and mixed races in Latin America.

In an earlier study from a tertiary hospital in Mexico City (57), using 1999 Wingerchuk criteria, a total of 34 cases of NMO were identified, with all patients being Mestizos (mixed race). By calculating the ratio of MS and NMO in the hospital, and by using the estimated MS prevalence in the country at that time, it was extrapolated that the prevalence of NMO among Mexican Mestizos was around 1.3/100,000. With the availability of AQP4-antibody assays, and the newer diagnostic criteria that include NMOSD cases, this prevalence rate is likely to be higher.

From the preliminary findings of a recent study involving seven general hospitals in Venezuela presented at a conference (58), it was estimated that the prevalence of NMOSD in Venezuela was 2.2/100,000, with a female-to-male ratio of 4:1, and again Mestizos formed the majority of those patients.

Studies from other representative populations will be useful to further inform the prevalence of NMOSD in Latin America.

North Africa

The populations of North Africa consist mainly of Amazighs (Berbers) and Arabs. As in Whites/Caucasian populations, there appear to be much higher number of MS than NMOSD cases in North Africa (59, 60). There have been no population-based studies on NMOSD in North Africa so far. There is only one population-based study on Arabs in the Middle East (Abu Dhabi) (41), and the prevalence data among Amazighs are awaited.

Incidence of NMOSD

Table 1 summarizes the incidence reported in the available population-based studies. Among Whites, the annual incidence of NMOSD is generally reported to be around 0.5–0.8/million (30, 38, 42, 43). In populations with a higher prevalence, the incidence is also higher. For instance, Blacks in Martinique have a high prevalence of 11.5/100,000, and its incidence was also reported to be high, at 7.3/million (34). Recently, the data from South Korea also showed a high incidence, ranging from 4.1 to 7.3/million for the period 2013–2017 (44, 48). Other populations with a prevalence higher than 1/100,000 also reported an incidence higher than 1/million [for example, 1.16/million in Arabs (41), and 1.32/million in Hungarians (45)].

A limitation regarding incidence calculation is that, if a new antibody test becomes available in the study region, or when there is increased awareness among clinicians, then the number of newly diagnosed cases in that particular year will be higher, leading to a higher incidence rate, even though the disease could have started many years earlier in some cases. Nevertheless, if researchers are able to calculate the incidence rates over the past few years (e.g., past 5 years) and average them, it is likely to be more accurate.

For pediatric NMOSD, there were two recent nationwide/region-wide studies that reported on its incidence. In the Danish study, the incidence of pediatric NMOSD was calculated as 0.31/million (61). In the Taiwanese study using the national health insurance research database, over the period from 2011 to 2015, the average annual incidence was reported as 1.1/million (62). Again, this higher incidence in Taiwan as compared to Denmark is not surprising as NMOSD is more prevalent among East Asians than Whites.

Age and Racial Differences in the Clinical Features and Severity of NMOSD

Some studies have analyzed how the clinical features and disability are affected by onset age and racial differences. Patients with young-onset NMOSD were more likely to have optic neuritis as onset attack, while older-onset patients often developed myelitis as the initial presentation (63). Furthermore, young-onset patients with optic neuritis were more likely to develop not only recurrent optic neuritis but also higher likelihood of developing blindness, as compared to older-onset patients with optic neuritis (63, 64). Conversely, older-onset patients with myelitis often had poor recovery, while most young-onset patients with myelitis recovered well without permanent motor disability (63, 64).

There also appears to be some differences in the clinical features of NMOSD among different races. Blacks and Asians tended to have lower mean ages at onset than Whites (Blacks: around 28–33 years, Asians: 35–40 years, vs. Whites: 44 years) (63, 65). Black and Asian patients were more likely to have brain and brainstem attacks and abnormalities on brain MRI as compared to Whites (64, 65). Overall, the risk of relapse was lowest in Japanese than in Whites and Blacks (63, 64).

Blacks were found to have a greater likelihood of developing visual disability with time than Whites and Japanese (63, 64). On the other hand, Whites had a higher probability of developing severe motor disability or wheelchair dependence as compared to Japanese (63). Severe attacks were more frequent in Blacks than in Asians and Whites, and therefore Blacks were at a higher risk of severe disability in the early course of the disease (65). In a study from the USA, patients with African ancestry were also found to have a higher mortality rate (15.4%) as compared to the overall mortality rate (7.0%) (66). Nonetheless, while race affected the clinical phenotype, age at onset, and severity of attacks, the overall outcomes were mostly dependent on early and effective immunosuppressive treatment (65).

MOG-Antibody-Associated Disease: Prevalence and Incidence

After the discovery of the AQP4 antibody, a majority of NMO cases have been found positive for this antibody. Nevertheless, there is still a proportion of cases with an NMO phenotype that are persistently tested negative for AQP4 antibody, despite using the most sensitive cell-based assays available. It was later realized that some of these AQP4-antibody-negative NMOSD cases were in fact seropositive for MOG antibody. This so-called MOG-antibody-associated disease consists of a significant proportion of NMOSD cases that are AQP4-antibody seronegative, ranging from 7 to 42% (7, 67–70).

Interestingly, for MOG-antibody-associated disease, besides NMO phenotype, optic neuritis, and myelitis, some of these MOG-antibody-positive cases also have clinical phenotypes beyond the current NMOSD spectrum, such as ADEM/MDEM-like presentation (71), cerebral cortical encephalitis (12), and cranial nerve involvement (14). Pathologically, MOG-antibody-associated disease is a type of demyelinating disease, as opposed

to astrocytopathic disease seen in AQP4-antibody-positive NMOSD (72, 73).

A recent Dutch nationwide study reported the incidence of MOG-antibody-associated disease as 1.6/million, with 1.3/million in adults, and a higher incidence of 3.1/million in children (74). It should be noted that this incidence rate of 1.6/million is higher than the incidence rate of 0.5–0.8/million in NMOSD (mostly AQP4-antibody-positive) among Whites.

So far, hospital-based studies largely did not observe any significant racial preponderance for MOG-antibody-associated disease. For instance, in the UK cohort, the racial breakdown was as expected in the general population (9). Nevertheless, from the annual report of the Oxford NMO Service, there were 145 patients with AQP4-antibody-positive NMOSD, 111 patients with MOG-antibody disease, and 28 patients who were double-seronegative. The proportion of MOG-antibody disease within the NMOSD spectrum was rather significant (75). Additionally, a study from Mayo Clinic on AQP4- and MOG-antibody testing for 15,598 patients showed higher positivity rate for MOG antibody (1291 patients, 8.3%) than for AQP4 antibody (387 patients, 2.3%). Of the adults, 6.5% were MOG-antibody positive vs. 2.6% for AQP4 antibody, while in children, 21.1% were positive for MOG antibody as compared to 1.9% for AQP4 antibody (76). Similarly, one study in Sri Lanka, in collaboration with the Mayo Clinic, also reported more MOG-antibody-positive cases (126 patients) than AQP4-antibody-positive cases (36 patients) (77). On the other hand, MOG-antibody-associated disease was relatively uncommon in the non-Caucasian population in Rio de Janeiro (Brazil) (70).

The preliminary findings of a population-based prevalence study of MOG-antibody-associated disease, jointly conducted at

TABLE 2 | Epidemiological and clinical comparison between AQP4-antibody-seropositive NMOSD, MOG-antibody disease, and MS.

	AQP4-antibody disease	MOG-antibody disease	MS
Mean age at onset	40 years	More common in children than in adults	30 years
Female:male ratio	9:1	Around 1:1	2–4:1
North–South gradient	No increased prevalence with increasing latitude	No data	Increased prevalence with increasing latitude from the equator (either toward North or South)
Prevalence	East Asians: 3.5/100,000 Whites: 1/100,000 Blacks: range from 1.8 to 10/100,000	More common in children than in adults	Up to 100–200/100,000 in White populations, but <5–50/100,000 in many Asian and African countries Rising in most parts of the world
Annual incidence	Around 0.5–0.8/million in Whites Higher annual incidence in non-White populations	Dutch nationwide study: 1.6/million; adults: 1.3/million; children: 3.1/million More data are needed	Up to 100/million in White populations, but was low in many equatorial countries
Disease course	Relapsing	Monophasic or relapsing	Relapsing, with the majority eventually converting to a secondary progressive disease Up to 15% are primary progressive in Whites
Clinical manifestations	Optic neuritis Myelitis Area postrema syndrome Other brain syndromes	Optic neuritis Myelitis ADEM/MDEM Brainstem/cerebral cortical encephalitis Cranial nerve involvement	Optic neuritis Myelitis Brain syndromes
Optic neuritis	Unilateral/chiasmal, long (>1/2 of optic nerve)	Unilateral/simultaneous bilateral, long; frequent optic disc swelling (papillitis)	Unilateral, short
Myelitis	Long (>3 vertebral segments) in 85%; centrally located; affects cervical or thoracic cord	Often long, but may be <3 vertebral segments; gadolinium enhancement less common than AQP4-antibody disease; relatively more common in the lumbosacral region	Non-transverse, short; peripheral/dorsolateral
Attack severity	Moderate to severe	Mild to moderate	Mild to moderate
Recovery	Variable, but commonly poor	Fair to good	Fair to good
Disability	Attack-related	Attack-related	Mainly due to progression
Pathology	Astrocytopathy	Demyelination	Demyelination
Treatment	Immunosuppressants; some MS drugs may be harmful	Consider immunosuppressants if recurrent; some MS drugs may be ineffective	MS disease-modifying drugs

ADEM/MDEM, acute disseminated encephalomyelitis/multiphasic disseminated encephalomyelitis; AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorder.

Olmsted county (USA) and Martinique Island, were recently presented at a conference (ECTRIMS 2019) (78). In Olmsted county, the prevalence was calculated to be 3.42/100,000, with an incidence of 2.39/million, while at Martinique, the prevalence was 1.6/100,000, with an incidence of 1.12/million.

In the Catalonia NMOSD prevalence study, 12% of cases were MOG-antibody-positive (38). However, the cases in this study were required to strictly fulfill the 2015 IPND criteria, and thus only those with an NMO phenotype were analyzed (The prevalence of MOG-antibody-positive NMO was calculated to be 0.11/100,000.). Needless to say, if MOG-antibody-positive cases with optic neuritis alone or myelitis alone and those with ADEM-like presentation are included, the prevalence of MOG-antibody disease is likely to be higher.

More data from different geographical areas are clearly in need to further inform about the prevalence and incidence of MOG-antibody-associated disease.

Some demographic and epidemiological data and clinical features of AQP4-antibody-positive NMOSD and MOG-antibody-associated disease in comparison with MS are shown in **Table 2**.

CONCLUSION

There appears to be varying prevalence rates of NMOSD, most cases of which are AQP4-antibody-positive cases, among the different racial groups worldwide, with East Asians and Blacks having a higher prevalence than Whites. In most regions, these prevalence rates are lower than that of MS. In AQP4-antibody-positive NMOSD, female preponderance is definite (up to 90%) and the majority of the cases are adults. Moreover, the clinical features of NMOSD and disability accrual may be influenced by onset age and race. The data suggest that certain genetic and environmental factors associated with race may be involved in the pathogenesis of NMOSD. More well-designed population-based and longitudinal studies in different geographical areas and racial groups will be useful to clarify the issue, and to shed new lights onto this unique neuroinflammatory disease. Among AQP4-antibody-negative NMOSD, some patients are MOG-antibody-positive, and unlike AQP4-antibody-positive NMOSD, males, and females are equally affected by MOG-antibody-associated disease and the prevalence may be higher in children than in adults. However, the prevalence data of MOG-antibody-associated disease including the ones with an NMOSD phenotype are still insufficient and being accumulated. Accessibility to AQP4-antibody and MOG-antibody testing, which is currently limited in many regions, is a challenge to overcome.

AUTHOR CONTRIBUTIONS

JH conceived and designed the study, drafted the manuscript, contributed to data acquisition, and critically revised the manuscript for intellectual content. NA, IN, SB, ML, NK, AJ, RM, BW, FP, SP, JP, DW, JB, and MY made substantial contribution to the intellectual content, contributed to data acquisition, and critically revised the manuscript for intellectual content. KF supervised the study, conceived and designed the study, drafted the manuscript, contributed to data acquisition, and critically revised the manuscript for intellectual content. All authors approved the final manuscript.

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Relapsing Demyelinating Syndromes in Children: A Practical Review of Neuroradiological Mimics

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Relapsing demyelinating syndromes (RDS) in children encompass a diverse spectrum of entities including multiple sclerosis (MS) acute disseminated encephalomyelitis (ADEM), aquaporin-4 antibody associated neuromyelitis optica spectrum disorder (AQP4-NMOSD) and myelin oligodendrocyte glycoprotein antibody disease (MOG-AD). In addition to these, there are "antibody-negative" demyelinating syndromes which are yet to be fully characterized and defined. The paucity of specific biomarkers and overlap in clinical presentations makes the distinction between these disease entities difficult at initial presentation and, as such, there is a heavy reliance on magnetic resonance imaging (MRI) findings to satisfy the criteria for treatment initiation and optimization. Misdiagnosis is not uncommon and is usually related to the inaccurate application of criteria or failure to identify potential clinical and radiological mimics. It is also notable that there are instances where AQP4 and MOG antibody testing may be falsely negative during initial clinical episodes, further complicating the issue. This article illustrates the typical clinico-radiological phenotypes associated with the known pediatric RDS at presentation and describes the neuroimaging mimics of these using a pattern-based approach in the brain, optic nerves, and spinal cord. Practical guidance on key distinguishing features in the form of clinical and radiological red flags are incorporated. A subsection on clinical mimics with characteristic imaging patterns that assist in establishing alternative diagnoses is also included.

Keywords: demyelimating disease, pediatric, multiple scleorsis, ADEM, MS, MOG, AQP4, mimics

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WHAT ARE THE TYPICAL RADIOLOGICAL FEATURES OF RELAPSING INFLAMMATORY DEMYELINATING DISORDERS IN CHILDREN?

Multiple Sclerosis (MS)

MS is the most common RDS in children. The diagnosis of MS is based on the revised 2017 McDonald criteria which integrates clinical, radiological, and laboratory findings (1). The McDonald criteria perform well in identifying pediatric patients with MS (2), however they are not validated in patients under 11 years (1). Additionally, these criteria

should only be applied when alternative causes have been excluded by clinical assessment and laboratory testing.

The radiological appearances of pediatric MS are largely similar to those observed in adult cohorts (3). Some unique imaging findings have however been described in pediatric MS, such as a higher lesion burden at presentation when compared to adults, particularly involving the brainstem and cerebellum. In prepubertal children demyelinating lesions are usually larger, confluent, have ill-defined borders and show a higher predilection for deep gray matter structures. Tumefactive (>2 cm) lesions are also more common in children (4–8).

In typical cases, MS lesions are small, well-defined, round or ovoid in shape and located in the periventricular white matter, juxta/intracortical regions, brainstem, and cerebellum, and/or in the spinal cord (9). The periventricular lesions abut the lateral ventricular margin with no normal white matter interspersed in between. They are orientated perpendicular to the ventricular margin along the deep medullary veins and have been termed "Dawson's fingers." Likewise, the juxta/intracortical lesions should abut the cortex or be present within the cortex.

Contrast enhancement is common and variable and may be nodular, or demonstrate an open or closed ring-like morphology. Enhancement may persist for up to 2–8 weeks (9).

Spinal cord lesions are typically short segment (usually less than two vertebral heights), peripheral (or eccentric) on axial imaging, and cover less than half the cord circumference. A predilection for the cervical and thoracic cord has been noted (3).

Unlike in adults, optic nerve involvement in children, especially in those under 10 years of age tends to be more commonly bilateral with severe loss of visual acuity (10, 11). However, some studies dispute this (12). Bilateral involvement and white matter lesions on MRI at presentation, irrespective of the number, are associated with a significant risk of development of MS subsequently (11, 12). On MRI, there is T2 signal hyperintensity, with or without swelling or contrast enhancement. Optic nerve atrophy can be seen in the chronic phase.

Aquaporin-4 Antibody Neuromyelitis Optica Spectrum Disorder (AQP4-NMOSD)

Aquaporin-4 (AQP4) is a membrane protein that assists with the transfer of water molecules across cell membranes. NMO-IgG targets the water channel AQP4 and is positive by serology in up to 70% of NMOSD patients. The diagnosis of AQP4-NMOSD is based on the 2015 international consensus criteria which comprises of core clinical characteristics, AQP4 antibody status, and MRI features (13). These criteria are applicable to both children and adults (14).

Specific to neuroimaging, the absence of juxtacortical/cortical lesions, absence of periventricular lesions, absence of Dawson's fingers, presence of longitudinally extensive transverse myelitis and presence of periependymal lesions along lateral ventricles supports the diagnosis of AQP4-NMOSD (15).

Other regions typically involved in the disease process, and on imaging are regions of high AQP4 expressivity and are located in the periependymal region surrounding the 3rd ventricle and cerebral aqueduct, dorsal brainstem adjacent to the 4th ventricle including the area postrema and nucleus tractus solitaries (9, 16).

The classically described findings are present in ∼50% of cases. Other brain imaging patterns in AQP4-NMOSD include large hemispheric lesions, longitudinally extensive lesions along white matter tracts specifically corticospinal tracts, and, at times, even normal appearances.

Spinal cord involvement is usually in the form of longitudinally extensive transverse myelitis (LETM) involving more than three vertebral segments. The lesions often span >50% of the cross-section of the cord and demonstrate a central-predominant cord distribution. Short segment involvement has, however, also been described in a third of cases (15).

Optic nerve involvement is most commonly longitudinally extensive and bilateral, with a propensity for intracranial segments including the optic chiasm (17).

Myelin Oligodendrocyte Glycoprotein Antibody Disease (MOG-AD)

MOG-AD represents a group of inflammatory demyelinating disorders united by the presence of IgG antibodies to myelin oligodendrocyte glycoprotein. MOG tends to affect younger children who presenting clinically with an ADEM-like picture. Older patients (>9 years) are more likely to present with optic neuritis or an AQP4-NMOSD-like picture (18).

The clinical presentations in MOG-AD are heterogeneous. Seizures have been described as a presenting clinical feature in MOG-AD with a higher frequency when compared to other RDS, namely AQP4-NMOSD and MS. Hypothesized theories for seizures associated with MOG-AD are cortical involvement by an encephalitic process, and also the co-existence of anti N-Methyl D-Aspartate antibodies (19).

The brain lesions on imaging are often large, ill-defined, and involve the white matter. There is variable deep gray matter involvement, with a predilection for the thalamus (18). Cortical involvement with or without meningeal enhancement has been described as a rare but distinct pattern in MOG-AD, and is characterized on imaging as FLAIR hyperintensity and swelling with reduced diffusivity (17, 20–22).

Spinal cord lesions are typically longitudinally extensive. Unlike other RDS, there is a predilection for the conus medullaris (23).

Optic neuritis with MOG-AD has distinct features, such as bilateral optic nerve involvement, anterior optic pathway predilection with optic disc swelling, and rapid visual impairment (24). Relapses with isolated optic neuritis are common.

Figure 1 summarizes the typical brain and spine imaging patterns in pediatric RDS as described in the text. These are also tabulated for reference in **Table 1**.

The key radiological patterns that emerge in the spectrum of pediatric relapsing demyelinating syndromes are listed below.

An understanding of these patterns will help one approach the imaging mimics in a structured fashion.

Optic Neuritis (ON) in RDS

The specific imaging patterns of ON in MS, AQP4-NMOSD, and MOG-AD have been described in the relevant sections. ON may be the first presentation of a systemic RDS in up to 23% of children (25) and may occur in isolation as a monophasic event (such as seen in acute disseminated encephalomyelitis—optic neuritis), recurrent event (chronic relapsing inflammatory optic neuritis) or in association with systemic RDS. On follow-up, up to 36% of children presenting with ON are eventually diagnosed with MS (26).

Brain	• Discrete white matter (WM) lesions: periventricular (MS), juxtacortical (MS), cortical (MS and MOG-AD) • Confluent WM lesions: cortical-subcortical (MOG-AD), periventricular (MS) • Para-median WM lesions (AQP4-NMOSD) • Deep gray matter involvement (MS, MOG-AD)
Spine	• Focal/short segment lesions: AQP4-NMOSD (central), MS (eccentric) • Longitudinally extensive lesions: MOG-AD, AQP4-NMOSD
Optic nerves	• Focal/short segment lesions (unilateral): MS • Long segment lesions (bilateral): MOG-AD, AQP4-NMOSD • Relative sparing of the optic chiasm: MOG-AD

In addition to the previously described RDS, there is a wide differential diagnoses for ON in the pediatric age group. Systemic inflammatory and rheumatological disorders, vasculitis and other granulomatous disorders including sarcoidosis also need consideration and exclusion. Whilst MRI is not strictly necessary for confirmation of the diagnosis of ON, it can be helpful for assessing the pattern of optic nerve involvement and in cases where there are atypical clinical features such as insidious symptom onset, severe optic nerve pallor or acute visual loss (11).

In addition to conventional MRI, there are clinical and further imaging modalities such as spectral domain optical coherence tomography (S-OCT) that can help differentiate between the possible underlying etiology of ON with a high degree of specificity. In a recent Italian cohort study of 22 pediatric patients

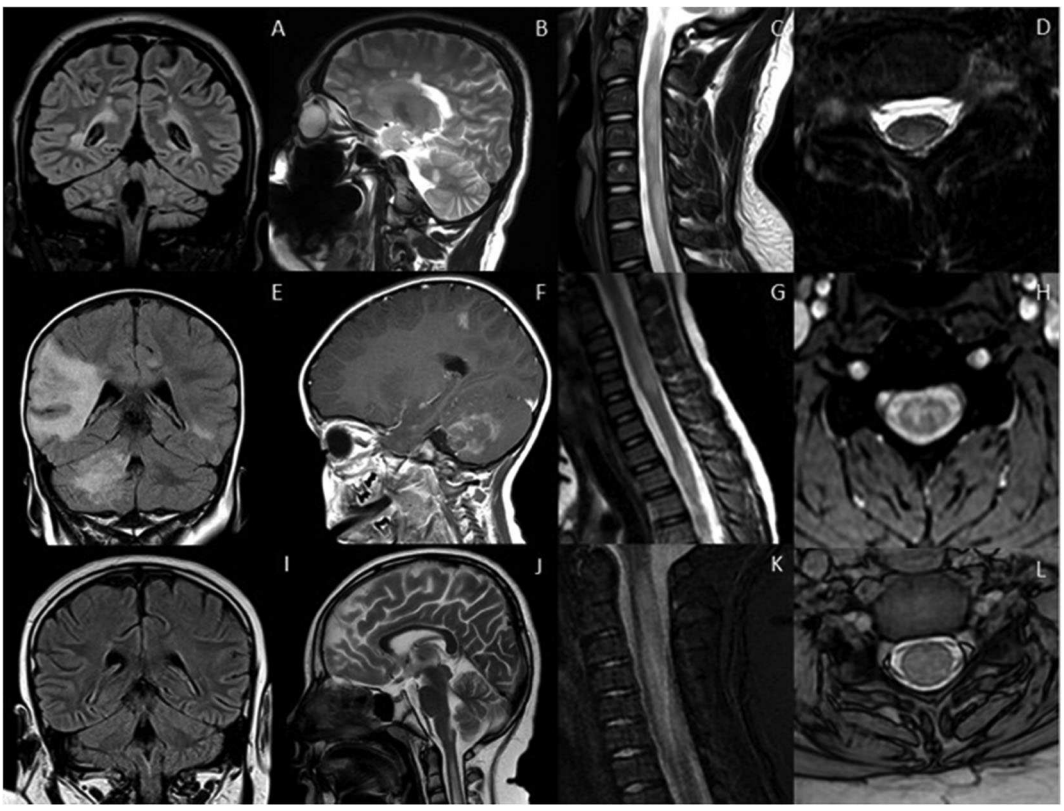


FIGURE 1 | Typical appearances of RDS in children. MS—top row **(A–D)** Juxtacortical, periventricular and infratentorial brain lesions are readily appreciated on coronal T2-FLAIR **(A)** and sagittal T2-weighted images **(B)**. In the spine there are short segment eccentric lesions appreciated on sagittal and axial T2-weighted images (**C,D**, respectively). MOG-AD—middle row **(E–H)** Large confluent lesions with ill-defined enhancement are demonstrated within the brain on coronal T2-FLAIR **(E)** and contrast-enhanced sagittal T1-weighted images **(F)**. In the spine, there are lesions involving gray and white matter on sagittal and axial T2-weighted images (**G,H**, respectively). AQP4-NMOSD—bottom row **(I–L)** Brain lesions are present in areas of AQP4 expressivity. For example, in this case there is involvement of the area postrema on coronal T2-FLAIR **(I)** and sagittal T2-weighted images **(J)**. A lesion is also present in the upper spinal cord. In the spine there is longitudinally extensive transverse myelitis on sagittal and axial T2-weighted images (**K,L**, respectively).

TABLE 1 | Imaging features of relapsing demyelinating syndromes.

Features	MS	NMOSD	MOG-AD	ADEM
Brain	• Discrete ovoid lesions • Size: 3 mm–2 cm • Location: Supratentorial lesions are typically periventricular (perpendicular to ventricles), juxtacortical, and cortical in location. Infratentorial lesions typically involve the brainstem, cerebellar peduncle and deep white matter paramedian medulla, peripheral location in pons, and trigeminal root entry zone • Enhancement: Typically 4 weeks but may last anywhere between 2–8 weeks. • T1 hypointensity is common and an important criterion to distinguish from monophasic illness • Course: Variable - may remain stable, enlarge or resolve. • Advances: Central vein sign, subpial demyelination and smoldering lesions	• Typical periventricular locations in periaqueductal, area postrema (often contiguous with cord), hypothalamus, thalamus. • Periventricular lesions surrounding lateral ventricles paralleling the ependymal surface unlike MS • Corpus callosum lesions paralleling long axis • Large confluent hemispheric white matter lesions • Longitudinally extensive lesions along corticospinal tracts • Non-specific white matter lesions are common • Usually no enhancement can show cloud like patchy enhancement in up to 56% • Course: Cystic changes and corresponding higher disability is common	• Multifocal deep white matter lesions with hazy boundaries • Tumefactive, poorly demarcated lesions • Cortical gray/juxtacortical white matter • Pons cerebellum, midbrain, medulla corpus callosum-focal, discrete and nodular without a specific orientation around the ventricles. A leukodystrophy-like pattern may be present. • Nodular, incomplete ring and leptomeningeal enhancement • Normal MRI despite symptoms • Non-enhancing scattered and punctate • Course is favorable in most cases with significant resolution	• Multifocal large hazy whitematter lesions • Deep gray and cortical involvement • Variable enhancement • Atypical features with MS like lesions and T1 hypointense lesions are also described • Course is less favorable than MOG positive cohort with 50% showing significant residual changes
Spinal cord	• Discrete, multiple • Cigar shaped on sagittal with short craniocaudal length (Usually <2 vertebral heights) • >3 mm • Peripheral and wedge shaped on axial images covering less than half the circumference of cord, typically along lateral and dorsal columns • Cervical >Thoracic • T1 hypointense • Enhancement less common than brain lesions nodular > incomplete ring like	• Longitudinally Extensive Transverse Myelitis (LETM) extending craniocaudally >3 vertebral heights • Central cord involvement • >50–75% cord circumference is usually involved	• LETM >short segment myelitis • Conus involvement is common. Regional cord involvement variable in different studies. • Normalization of signal on follow up is common • Variable central and peripheral cord involvement, >50% circumference involved in 60% • Enhancement in 60%	• Cord involvement is less common than MOG positive cohort. LETM is the predominant pattern
Optic nerve	• Short length, orbital segment, unilateral	• Bilateral long segment with posterior predominance, Intracranial and Chiasmal involvement common	• Longitudinally extensive or short segment bilateral or unilateral • Anterior predominant, optic disc involvement common	• Less common than MOG positive cohort

MS, Multiple sclerosis; NMOSD, Neuromyelitis optic spectrum disorders; MOG, Myelin oligodendrocyte glycoprotein related disorders; ADEM, Acute demyelinating encephalomyelitis; LETM, Longitudinally extensive transverse myelitis.

with ON, MOG antibody positivity was strongly associated with optic disc swelling, increased retinal nerve fiber layer (RNFL) thickness on S-OCT and better recovery (24).

WHAT ARE THE NEURORADIOLOGICAL MIMICS OF THE RELAPSING DEMYELINATING SYNDROMES?

Prior to a more detailed discussion on disorders that may mimic pediatric demyelinating disease, it is important to note that there are several important clinical red flags that should raise concern for a mimic prior to performing any imaging (**Table 2**). Specifically, a relevant family history, history of drug use, fever at the onset of symptoms, multi-system involvement, or sudden onset of severe symptoms raise the suspicion of alternative pathologies. Additionally, clinical signs like deafness, psychosis, cranial neuropathy and presence of cutaneous manifestations should also prompt consideration of a mimic.

Intracranial Mimics

Discrete white matter lesions of the brain can be seen as incidental or "non-specific" findings in many conditions and are, at times, erroneously reported as "possible inflammatory demyelinating" lesions (**Figure 2**). Increased prevalence of such

TABLE 2 | Clinical red flags in the diagnosis of demyelinating disorders.

Systemic features	
Persistent fever	Infection, autoimmune disorders
Weight loss	Infections, autoimmune disorders, secondary neoplasms
Anemia, nutritional deficiencies	Vitamin B12 deficiency, copper deficiency
Sicca symptoms (dry eyes, dry mouth)	Sjogren's syndrome
Neuro cutaneous markers	Hypomelanosis of Ito, Sturge Weber syndrome, pigmentary mosaicisms
Slivery hair	Griscelli syndrome
Alopecia, rash, conjunctivitis	Biotinidase deficiency
Rash, joint pain, hair loss, oral ulcers	Systemic lupus erythematosus
Paranasal sinus involvement	Granulomatosis with polyangiitis
Lung involvement	Granulomatosis with polyangiitis, sarcoidosis
Heart: Cardiomyopathy, conduction blocks	Mitochondrial disorders, sarcoidosis, infarcts
Heart : Congenital heart disease	Infarcts, cerebral abscess
Gastrointestinal symptoms	MNGIE, nutritional deficiencies secondary to malabsorption, Whipple disease, porphyria, celiac disease
Renal involvement	Mitochondrial disorders, SLE, fabry disease, systemic vasculitis
Genital ulcers	Behcet's disease
Recurrent miscarriages	SLE, anti-phospholipid antibody syndrome
Bone lesions	Erdheim chester disease, histiocytosis
Tendon xanthomas	Cerebrotendinous xanthomatosis
Antecedent trauma	Arterial dissections with stroke, neurological decompensation in leukodystrophies like Vanishing white matter disease, mitochondrial disorders
Immuno-compromised status	Parasitic and fungal infections, Human Immunodeficiency virus, Progressive multifocal leukoencephalopathy, malignancies, lymphoma
Known diagnosis of malignancy	Secondary tumors in brain, infiltration in hematological malignancies, paraneoplastic syndromes
Multisystem involvement	Mitochondrial disorders
Drugs, toxins, chemotherapy	Toxic leukoencephalopathy
Positive family history	Leukodystrophies, HSP, SCA
Optic nerve	
Sudden onset visual loss	CRAO, CRVO, vitreous hemorrhage, retinal detachment, acute angle closure glaucoma, cardiac emboli
Insidious onset and chronic progressive visual decline	Toxic, nutritional deficiency, retinitis pigmentosa, open angle glaucoma, mitochondrial disorders
Persistent complete loss of vision	CRAO, CRVO, vitreous hemorrhage, retinal detachment
Absence of RAPD	Retinitis, retinal detachment, vitreous hemorrhage, LHON
Severe eye pain	Uveitis, acute angle closure glaucoma, infiltrative disorders
Uveitis	Autoimmune disorders, infections
Exophthalmos	Mass lesions, thyroid ophthalmopathy, orbital pseudotumour
Brain	
Insidious onset and steadily progressive focal symptoms	Neoplasms
Slowly progressive course with generalized involvement	Leukodystrophies, HSP
Stroke/stroke like symptoms	CNS angitis, mitochondrial disorders (MELAS, pol Y), congenital disorders of glycosylation, transient ischemic attacks, CADASIL, fabry disease, migraine, seizures, cardiac emboli, moya moya disease, cerebral hemorrhage
Status epilepticus	Meningoencephalitis, autoimmune encephalitis, mitochondrial disorders (pol Y), CNS angitis
Dystonia, parkinsonism	Anti NMDAR encephalitis, infectious encephalitis, Wilson disease
Early cognitive decline, dysarthria	Neurodegenerative disorders like MSA
Cranial neuropathy	Lyme disease, sarcoidosis
Bilateral non-fatigable ptosis, total ophthalmoplegia	Mitochondrial disorders
Somnolence, diabetes insipidus	Sarcoidosis, lyme disease, chronic meningitis
Psychosis	Anti NMDAR encephalitis, SLE, CNS angitis, Huntington's disease, Wilson disease
Meningeal signs	Meningoencephalitis, SLE, CNS angitis, sarcoidosis
Headache	Hemiplegic migraine, CNS angitis, mitochondrial disorders, SLE, sarcoidosis, meningoencephalitis, cerebral venous sinus thrombosis, Susac syndrome
Deafness	Mitochondrial disorders, Susac syndrome
Polyradiculopathy, peripheral neuropathy	SLE, lyme disease, B12 deficiency, leukodystrophies, HMSN, Guillain Barre syndrome
Amyotrophy	HMSN, lyme disease, ALS, syringomyelia, mitochondrial disorders
Spine	
Hyper-acute onset of symptoms over minutes	Infarct, hemorrhage
Insidious onset and gradually progressive myelopathy	HTLV myelopathy, HSP, AMN, vitamin B12 deficiency, copper deficiency
Recurrent symptoms occurring at the same level	Vascular malformations
Complete transverse myelitis	Infarct, trauma, bleeds, compressive lesions
Severe back pain	Vascular malformation, epidural abscess, bleeds, intervertebral disc compression

AMN, Adrenomyeloneuropathy; ALS, Amyotrophic lateral sclerosis; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CRAO, Central retinal artery occlusion; CRVO, Central retinal vein occlusion; HMSN, Hereditary motor sensory neuropathy; HSP, Hereditary spastic paraparesis; HTLV, Human T-cell lymphotropic virus; LHON, Leber hereditary optic neuropathy; MELAS, Mitochondrial encephalopathy lactic acidosis stroke like episodes; MNGIE, Mitochondrial neurogastrointestinal encephalomyopathy; MSA, Multi system atrophy; SCA, Spinocerebellar atrophy; SLE, Systemic lupus erythematosus.

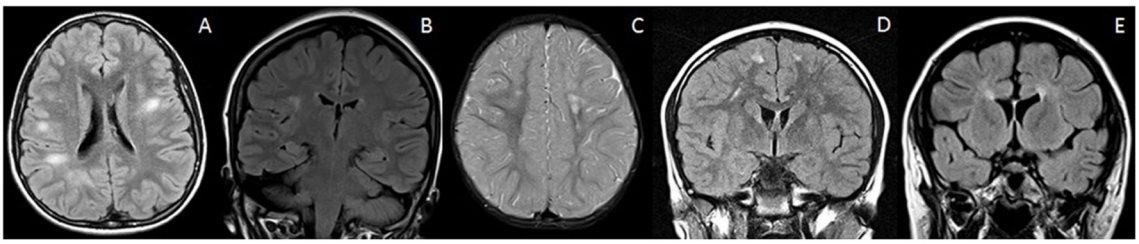


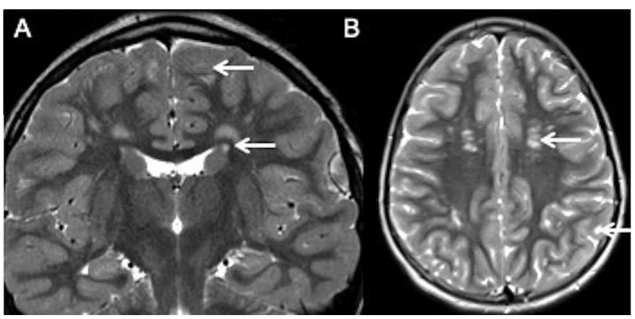
FIGURE 2 | Mimics of RDS with discrete brain lesions. All these lesions on first glance could mimic RDS on the basis of imaging alone. However, the lesions do not strictly satisfy the McDonald criteria. Clinical history and follow up is therefore also vital in reaching a correct diagnosis. **(A)** NOTCH3 mutation: Axial T2-FLAIR imaging demonstrates small discrete lesions in the white matter of both cerebral hemispheres. **(B)** Leber's hereditary optic neuropathy: Coronal T2-FLAIR imaging reveals a discrete brain lesion in the right hemispheric white matter. The optic nerves were also atrophic (not shown). **(C)** Incontinentia pigmenti: Axial T2-weighted images demonstrate white matter lesions in the centrum semiovale bilaterally. There is also volume loss within the left frontal lobe. **(D)** Migraine: Coronal T2-FLAIR imaging demonstrates small discrete lesions in the frontal white matter bilaterally. These were stable on follow up and there were no clinical features of demyelination. **(E)** Hereditary spastic paraparesis: Coronal T2-FLAIR demonstrates thinning of the anterior corpus callosum and periventricular signal abnormality—"ears of the lynx" sign. There were no juxtacortical lesions.

Case Vignette 1—PRRT2 mutation

A young patient presented with a history of bilateral hemifacial spasms. There were no demonstrable neurological deficits on clinical examination.

Her MRI showed multiple scattered white matter hyperintensities bilaterally. Note the rim of normal-appearing white matter separating the lesions from both the ventricular surface and cortex. Thus, her lesions did not satisfy the McDonald criteria for MS.

Because of significant clinical symptoms, genetic testing was undertaken and revealed pathogenic variations in the *PRRT-2* gene, which is a leading cause for a spectrum of paroxysmal diseases. This case illustrates how appropriate image interpretation prevents misdiagnosis even with overlapping or non-specific clinical phenotypes.



T2 coronal **(A)** and T2 axial **(B)** images show hyperintense lesions in deep and subcortical whitematter (white arrows in **B**). Note the presence of normal white matter between the lesions and ventricular surface and cortex (white arrows in **A**).

"MS-like lesions" has been described in association with a diverse list of entities, including migraine, vasculitis, infections/para-infectious conditions, sarcoidosis, certain leukodystrophies, and even hemophagocytic lymphohistiocytosis (HLH) (27).

On closer inspection, however, the morphology and location of these lesions most often do not satisfy the McDonald criteria of being "periventricular" or "juxtacortical," and such lesions are typically deep and subcortical in location. Often, a rim of normal-appearing white matter separates these lesions from the ventricular margin and cortex, respectively.

A typical example of such a mimic with discrete white matter lesions is illustrated in **Case Vignette 1** of a child presenting with bilateral hemifacial spasms due to proline-rich transmembrane protein-2 (*PRRT-2*) gene mutation. *PRRT-2* gene mutations result in a truncated defective proline-rich transmembrane protein-2 in presynaptic terminals leading to an impaired neurotransmitter release. Presentation is in the form of distinct clinical syndromes which can vary with age, can overlap, and even evolve into other defined syndromes. These include benign familial infantile epilepsy (BFIE), paroxysmal kinesigenic dyskinesia (PKD), and PKD/BFIE overlap syndromes, namely infantile convulsions with choreoathetosis (ICCA) and hemiplegic migraine (HM). Scattered white matter hyperintensities may be present in imaging and can be mistaken for demyelinating lesions (28).

Intracranial lesions can also be confluent in a variety of disease states, mimicking primary or secondary progressive MS when in the posterior periventricular regions, or MOG-AD when more cortical-subcortical in location (**Figure 3**). These include the encephalitides, leukodystrophies, and even periventricular

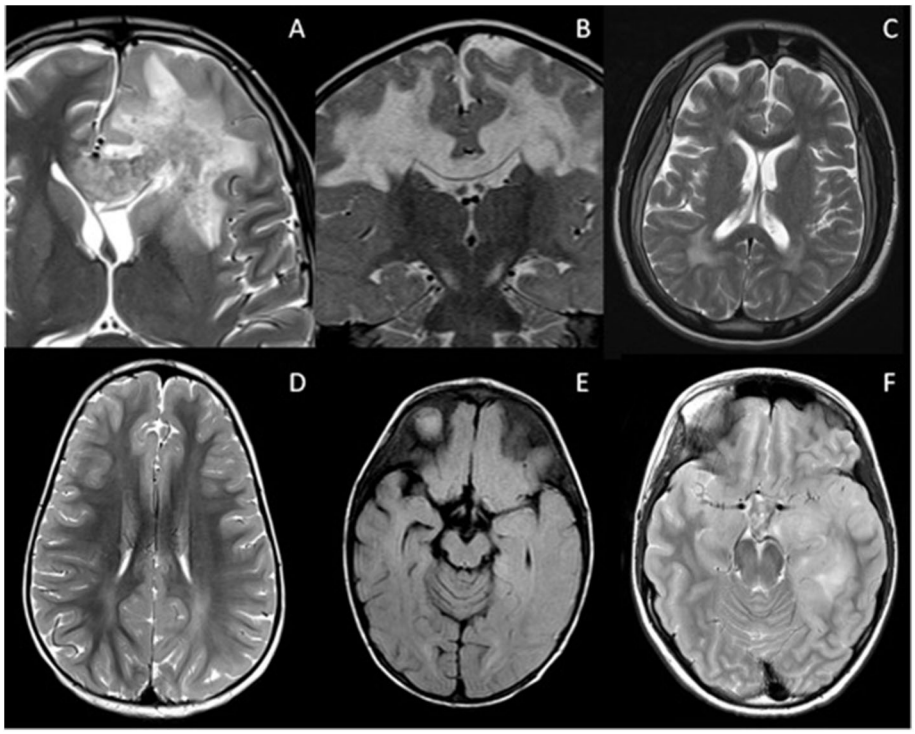


FIGURE 3 | Mimics of RDS with confluent brain lesions. **(A)** Acute haemorrhagic leukoencephalopathy: Confluent white matter lesion in the left frontal lobe with intralesional hemorrhage extending into the corpus callosum. There was patchy enhancement of this lesion (not shown). Salmonella infection was confirmed on serology. **(B)** Complex 1 deficiency mitochondriopathy: Confluent white matter lesions of both cerebral hemispheres which demonstrated cavitation and restricted diffusion (not shown). **(C)** Giant axonal neuropathy due to exon 1 deletion of GAN gene: Axial T2-weighted image illustrates signal abnormality within the frontoparietal white matter and parenchymal volume loss. **(D)** Subacute sclerosing panencephalitis: White matter signal abnormality is noted within the parietal lobes bilaterally, but is more extensive in the left cerebral hemisphere where there is blurring of the gray-white matter margin. **(E)** Anti NMDA receptor antibody encephalitis: Axial FLAIR imaging demonstrates signal abnormality within the caudate nuclei bilaterally, the right putamen and left globus pallidus. There is also involvement of the right sided subinsular white matter and posterior limb of the internal capsule. The appearances could be mistaken for ADEM. **(F)** Glioma: Axial T2-weighted image demonstrates white matter signal change in the left temporal lobe with swelling of the cortex. This was followed up, and subsequently biopsied due to growth and enhancement.

leukomalacia (PVL) in the context of white matter injury of prematurity.

When these lesions occur infratentorially, such as in the case of rhombencephalitis or Alexander disease, they may be confused for AQP4-NMOSD, particularly if there is involvement of the area postrema, as shown in **Case Vignette 2**.

Alexander disease (AD) is a glial fibrillary acidic protein (GFAP) related astrocytopathy characterized by an abundance of Rosenthal fibers in astrocytes, particularly in subpial and subependymal locations. The distribution of lesion in AD is reminiscent of AQP-4 NMOSD (29). Juvenile and adult forms of AD preferentially involve the brainstem and cerebellum. Periventricular, periependymal, midbrain, and brainstem lesions often associated with patchy areas of enhancement can be misinterpreted as AQP4-NMOSD (29).

Infections and Para-infectious Disorders

Infections account for a large group of potential MS mimics. Isolated, multifocal, or confluent lesions of the white and gray matter are often seen in infections, presenting in a rather non-specific manner (30). Clinical and laboratory findings play an important role in distinguishing infectious/para-infectious diseases from demyelinating disorders (31, 32).

Imaging red flags concerning for infectious mimics of RDS include meningeal enhancement (meningitis), complete ring enhancement with restricted diffusion (abscess), venous sinus thrombosis, calcification as in neurocysticercosis and toxoplasmosis, and bilateral striatal and thalamic involvement as commonly in viral encephalitis. Acute haemorrhagic leukoencephalitis (AHLE) is thought to be another post-infectious phenomenon presenting with white matter demyelination. It can occur after viral or bacterial infections.

Borrelia burgdorferi causing Lyme disease deserves special mention as the CNS imaging demonstrates "MS-like" subcortical and periventricular white matter lesions, including the callososeptal interface (32). The presence of cranial and spinal nerve enhancement, as well as meningeal enhancement, are important distinguishing features of Lyme disease on neuroimaging.

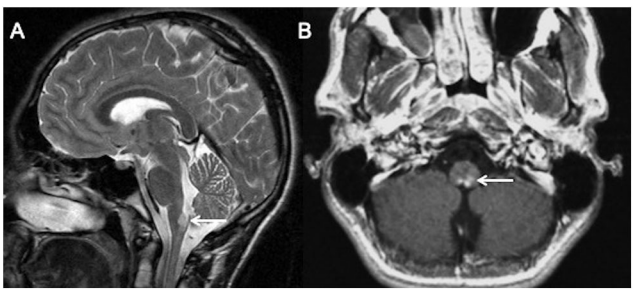
Epstein Barr virus (EBV) encephalitis also presents with multiple lesions in the cerebral cortex/subcortical white matter,

Case Vignette 2—Juvenile Alexander disease

A teenager presented with severe vomiting. His premorbid health was normal except for mild intellectual disability.

His MRI imaging showed focal hyperintensity and swelling of the area postrema with intense enhancement. CSF studies showed no oligoclonal bands. Both AQP4 and MOG antibodies were negative in serum and CSF. He was subsequently diagnosed with juvenile Alexander disease.

This case illustrates that many diseases can have common areas of selective vulnerability. *Homogenous intense enhancement and absence of AQP4 antibodies* were the features that led to further investigation and alternate diagnosis.



T2 sagittal **(A)** and T1 post contrast axial **(B)** images show hyperintensity and swelling of area postrema with intense nearly homogenous enhancement (white arrows).

thalami, basal ganglia, and, sometimes, brainstem or cerebellum. Rarely, it can cause optic neuritis, further confounding the diagnosis (33).

Cytomegalovirus (CMV) has a predilection for the ependymal, germinal matrix, and capillary endothelial cells. The pattern of involvement may mimic MS with a periventricular distribution of lesions (30).

Multifocal lesions, usually related to a microvascular etiology can also be observed in viral diseases such as HTLV-1 and HIV (34). The lack of contrast enhancement distinguishes them from demyelination. Calcification of the basal ganglia or frontal white matter is also a useful discriminator of HIV (35, 36).

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection caused by the JC polyomavirus (JCV). Supratentorial white matter lesions are typically multifocal, asymmetric, bilateral, and at times with confluent lobar involvement. PML can affect the deep gray nuclei also involve the brainstem and cerebellum. Generally, there is no enhancement or mass effect (34).

Acute disseminated encephalomyelitis (ADEM), an autoimmune-mediated white matter disorder that often follows a viral upper respiratory tract infection (EBV, influenza A, coronavirus), can appear very similar to MS. It is characterized by multifocal lesions of the deep and juxtacortical white matter, sometimes involving the cortex, as well as thalami, basal ganglia and also the brainstem and cerebellum. A history of recent upper respiratory infection or vaccination is often present and should be actively sought.

"Open ring" or incomplete peripheral enhancement deemed specific for demyelinating lesions, particularly MS, is useful for differentiating between demyelination and other space-occupying lesions like neoplasm or an abscess. However, CNS infections such as neurocysticercosis and occasionally tuberculosis, as well as ADEM can also be associated with MS-like "open ring" enhancement (32).

Subacute Sclerosing Panencephalitis (SSPE)

SSPE is a progressive measles virus mediated encephalitis that may present with brain MRI findings similar to a demyelinating disease. It is believed to be associated with an immature immune system and is seen in children with the onset of the primary infection in the first two years of life (37). On imaging, multifocal, bilateral but asymmetric lesions of the cortex and subcortical white matter are seen. As the disease progresses, there is usually involvement of the parietal and temporal lobes and the lesions extend into the periventricular white matter and corpus callosum. Mass effect and contrast enhancement may be present during this phase (38, 39).

While there may be some overlap on imaging between SSPE and demyelination, the clinical examination is very specific, characterized by insidious onset of behavioral changes followed by mental deterioration. Seizures, myoclonus, dementia, and inexorable progression to death occur.

Pathological findings include predominant involvement of the gray matter with white matter demyelination, perivascular lymphocytic cuffing, intracellular viral inclusions, neuronophagia, and gliosis (37).

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES may rarely be confused as demyelination mimic on imaging, especially when the lesions are discretely distributed in the white matter, or when there is considerable cortical-subcortical involvement. With PRES however the clinical context is extremely relevant. Usually, there is an apparent predisposing factor such as chemotherapy, hypertension or an underlying

systemic condition. The clinical presentation may however partly overlap with RDS, particularly MOG-AD with features such as encephalopathy and seizures (40).

The exact pathophysiology of PRES remains unclear however it is hypothesized to relate to cerebral vascular auto-regulatory and endothelial dysfunction. PRES itself may be considered a misnomer as the lesions are not always located posteriorly, nor are they always reversible (41). The topographical patterns of PRES in children differ slightly from adults, with frontal lesions being more common than the parieto-occipital pattern, the dominant pattern in adults (42–44). Increased incidence of cerebellar involvement and contrast enhancement has also been noted (42) however this has been disputed by others (43, 45). In addition, involvement of the gray-matter structures, corpus callosum, and brainstem has also been described. Hemorrhage, enhancement and abnormality on diffusion weighted imaging is a less common feature (46).

Genetic Leukodystrophies

Leukodystrophies can share similarities with demyelinating disorders on imaging. In addition, demyelinating disorders have been shown to co-exist in patients with mitochondriopathies. It remains unclear whether the mutations underpin an autoimmune trigger for demyelination or if these cases are indeed unusual presentations of mitochondrial disorders (47). Clinical indicators of a mitochondrial etiology include the presence of ataxia and myopathy, external ophthalmoplegia, refractory optic neuropathy/neuritis, seizures, pigmentary retinopathy, peripheral neuropathy, or cardiomyopathy/cardiac conduction defects.

Leber's hereditary optic neuropathy (LHON), a mtDNA mutation disorder with specific point mutations in complex 1, occurs in patients with MS at a frequency ∼50 times greater than in the general population (48). Another mitochondrial disorder with progressive optic atrophy is optic atrophy type 1. MS-like white matter hyperintensities involving the brain and cord have been described as a feature in both these disorders, although enhancement has never been described (49).

POLG includes a set of nuclear genes with the function of maintaining the mtDNA pool through mtDNA duplication. POLG related disorders have vastly overlapping clinical phenotypes of varying severity. Unusually, a relapsing-remitting illness with MS-like lesions and ADEM like white matter lesions has been described (47, 50, 51).

Certain leukodystrophies manifest as small vessel disease and therefore can mimic inflammatory demyelination. CADASIL (NOTCH3), CARASIL (HTRA1), 6p25 deletion syndrome, cerebral small-vessel diseases (FOXC1 and PITX2) are the typical entities within this group. Whilst most of these disorders have an onset after the 3rd decade, pediatric-onset disease has been rarely described.

NOTCH3 encodes a transmembrane protein expressed in vascular smooth muscles and heterozygous mutations leading to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). The clinical features include recurrent subcortical ischaemic strokes with cognitive decline. Patchy multifocal white matter abnormalities involving the deep and periventricular white matter are common in the described pediatric cases (52–54).

Fabry's disease, a lysosomal disorder with large and small vessel microangiopathy, is another MS-mimic with many patients described as previously wrongly labeled as definite-MS based on revised McDonald criteria (55).

Vasculitis

CNS vasculitis can be classified into primary angiitis and secondary vasculitis. Primary angiitis of the CNS (PACNS) is inflammation limited to the arteries of the CNS (56). Secondary CNS vasculitis is associated with multiple etiologies, such as systemic infectious or inflammatory disease, collagen vascular diseases, malignancy, drugs, and substance abuse.

Imaging, although variable and sometimes transient, shows multiple small/punctate lesions or even tumefactive enhancing lesions in the subcortical white matter and gray matter, more often affecting the anterior than posterior circulation. Basal ganglia involvement is frequently noted. Diffuse leptomeningeal enhancement may also be seen (57).

Additional findings include microhemorrhages and multifocal infarction (58). Systemic involvement may help make the diagnosis but a brain biopsy may be eventually needed.

Hemophagocytic Lymphohistiocytosis (HLH)

HLH is severe systemic hyperinflammatory syndrome of a dysfunctional immune response characterized by unchecked proliferation of natural killer cells and T-lymphocytes (59). While an underlying genetic defect is responsible for the primary form, the secondary form usually follows infectious, malignant or autoimmune triggers (59). Primary and secondary HLH are further classified based on the genetic defect and the resulting disrupted immune process, and the inciting trigger (60). The familial forms can also be associated with immune deficiency syndromes (Chédiak-Higashi syndrome 1, Griscelli syndrome 2, and X-linked lymphoproliferative syndrome) in which HLH can develop sporadically during the disease course (59).

CNS involvement is common in both inherited and acquired forms of HLH. The most common imaging pattern is asymmetric confluent white matter lesions with subcortical and deep white matter distribution (61). Cerebellar and deep gray nuclear involvement is also common and these features closely mimic MOG related and antibody-negative demyelinating syndromes.

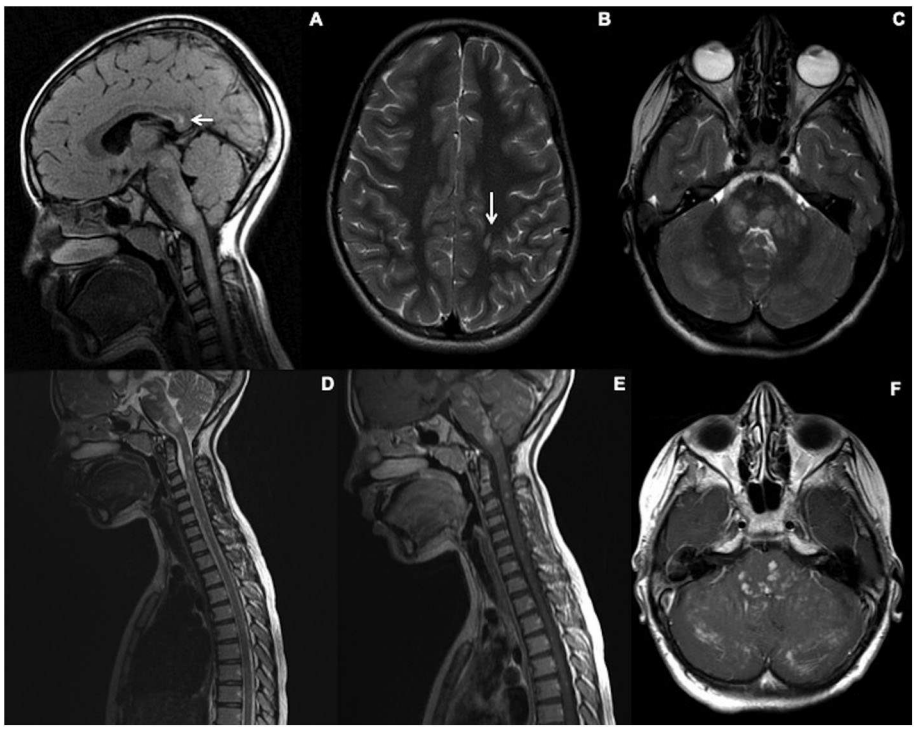
A nodular perivascular pattern of enhancement, which is often seen, may help in differentiation. Very occasionally more focal well-circumscribed lesions may be present mimicking MS lesions. Some of these cases were previously incorrectly labeled as CLIPPERS (chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids).

Case Vignette 3 demonstrates the typical clinico-radiological picture of HLH in the setting of Griscelli syndrome Type 2, a primary HLH associated syndrome with immunodeficiency and hypopigmentation caused by dysfunction in T-cell vesicle docking due to *RAB27A* mutations (59).

Case Vignette 3—Griscelli type 2 syndrome (HLH) An adolescent presented to the neurology services with a long history of recurrent episodes of blurred vision and ataxia. Clinically the patient was diagnosed as demyelination.

CSF analysis showed normal protein with no cells or organisms. Genetic testing subsequently confirmed Griscelli type 2 syndrome. The suspicion was also raised on the grounds of the clinical picture which included abnormal hair pigmentation.

Although MOG-AD can also present with large fluffy ill-defined white matter lesions and show a predilection to cerebellar peduncles, the pattern of enhancement seen here is quite atypical. Nodular intense enhancement in a perivascular distribution is more characteristic of the inflammatory and vasculitis spectrum of disorders. HLH also demonstrates a pontine and cerebellar peduncle predominant distribution.



Top row **(A–C)**: Initial imaging at age 12. **(A)** Sagittal T2 FLAIR-weighted imaging through the brain demonstrates evidence of signal hyperintensity within the calloso-septal interface, callosal splenium (white arrow), dorsal brainstem, and cervical spine. **(B,C)** Axial T2-weighted sequences of the brain show a juxtacortical lesion in the left perirolandic region (arrow) and ill-defined areas of abnormal signal in the pons and cerebellar hemispheres bilaterally (R>L).
Bottom row **(D–F)**—Initial imaging at age 12. **(A,B)** Sagittal T2 and post-contrast T1-weighted sequences show the extent of signal abnormality within the brainstem and spinal cord. All the T2 hyperintense parenchymal lesions show enhancement. F-Axial post-contrast T1 Weighted sequence through the posterior fossa shows enhancement corresponding to the T2 hyperintense areas of abnormal signal in the pons and cerebellar hemispheres bilaterally (R>L). In addition, there is folial enhancement suggesting pial involvement.

Anti N-Methyl D-Aspartate Receptor Encephalitis (Anti-NMDARE)

Anti-NMDARE presents with a characteristic clinical spectrum of abnormal behavior, speech dysfunction, memory/cognitive disturbance, seizures, movement disorder, and even decreased level of consciousness and autonomic dysfunction (62). CSF may show pleocytosis and presence of oligoclonal bands (63).

Knowing that there is an overlap between anti-NMDARE and demyelinating disease (AQP4-NMOSD and MOG-AD) is important as patients may present clinically with concurrent or separate episodes of demyelination and/or atypical psychomotor features. The presence of different antibodies has implications for treatment and prognosis. Testing for anti-NMDA, AQP4 and MOG antibodies may therefore be warranted in such cases (64).

There is a higher prevalence of anti-NMDARE in children with herpes simplex virus (HSV) 1 IgG antibodies, including those without clinically evident encephalitis (65). Although less common in children, there is a strong association of ovarian teratomas in young women (46–70%) with anti-NMDARE (62, 66).

MR imaging is often normal at initial presentation, but when abnormal shows non-specific cortical and subcortical lesions with no clear localization. Optic neuritis can also be a feature (62). Striatal necrosis, hippocampal, or global atrophy is present in progressive stages (67).

Neurosarcoidosis (NS)

Neurosarcoidosis is a disorder of unknown etiology, characterized by non-caseating granulomas histologically.

It is rare in the pediatric population. NS can affect any part of the nervous system. Uveitis, optic neuropathy, hypothalamic dysfunction, mass-like brain lesions, and encephalopathy are features seen in pediatric NS (68). The most common neurological complication of sarcoidosis is cranial neuropathy, with a distinct predilection for cranial nerves II, III, and VII. Facial nerve palsy may be bilateral. Optic neuritis, often bilateral, has been observed as an initial disease presentation in up to 35% of cases (69).

Imaging in children with neurosarcoidosis more commonly shows enhancing parenchymal lesions than its adult counterpart. Discrete to confluent white matter and cerebellar hyperintensities with punctate or discrete enhancing lesions are noted. Leptomeningeal, pituitary stalk or cranial nerve enhancement are additional features (70, 71).

Rare Disorders With White Matter Lesions

Neurocutaneous and microangiopathic disorders with asymmetrical CNS white matter involvement can also mimic pediatric demyelinating disorders on imaging and should be borne in mind.

Incontinentia Pigmenti (IP)

IP, an X-linked dominant disorder, is caused by mutations in nuclear factor (NF)-*k*-B *e*ssential m*o*dulator (NEMO) gene (72). Clinically, affected neonates present with inflammatory skin abnormalities, encephalopathy, and seizures (73). Imaging in neonates shows asymmetrical lobar or hemispheric cortical and white matter oedema with diffusion restriction, often labeled as an encephalitis. On follow-up, atrophy, scattered white matter hyperintensities, cortical laminar necrosis and ex-vacuo ventriculomegaly are usually present and can be mistaken as seqeulae of PVL (72, 74).

Hypomelanosis of Ito

Hypomelanosis of Ito, a disorder of chromosomal mosaicism, with several underlying genetic defects has typical hypopigmented skin lesions along the lines of Blaschko. White matter involvement in the form of asymmetrical deep and periventricular white matter hyperintensities can be present, often with dilated cystic or perivascular spaces (74).

Hereditary Spastic Paraparesis (HSP)

Whilst periventricular hyperintensities may be present on imaging in HSP, the clinical phenotype of progressive spastic paraparesis with a relevant family history serve as useful differentiators (75). Additional neuroimaging clues may also be present, such as thinning of the corpus callosum.

Susac Syndrome (SS)

SS is another rare condition in the pediatric age group. It is an autoimmune microangiopathic disorder resulting in occlusion of the branch retinal arteries and microinfarction of the central nervous system and cochlea. The onset of all three characteristic features at presentation is seen in only a minority of patients, reported as low as 13% (76, 77). Although primarily a disease affecting young women between the age of 20 and 40 years, SS has been reported in patients aged 7–70 years (78). The characteristic finding on MRI is the involvement of the middle layers of the corpus callosum with T2 hyperintense punched out lesions referred to as "snowball" lesions. Acute lesions demonstrate punctate enhancement. Leptomeningeal enhancement occurs in 30% of patients (79).

OPTIC NERVE MIMICS

Optic nerve involvement with swelling, T2- hyperintensity and enhancement is not specific for demyelinating disorders and can be seen in other inflammatory, infective, ischemic, toxic, and neoplastic conditions (**Figure 4**). That said, discrete brain lesions, as seen in MS, are not demonstrated in many of these mimics. Given the non-specific nature of optic neuritis, the morphology of coexisting brain and spinal cord lesions is often the most helpful feature in diagnosis.

Extra-neural involvement of other orbital structures is also a good indicator that one is not dealing with a primary demyelinating disorder, but rather a granulomatous, infectious or neoplastic cause. In addition, abnormal dural and leptomeningeal enhancement should also raise the suspicion of granulomatous disease, particularly sarcoidosis (68, 80).

Viral infections can present with optic neuritis. Specifically, EBV and Lyme disease should be considered. In such cases, there may be additional intracranial imaging findings which should be carefully sought (81, 82).

Tumors are typically less challenging to differentiate. Optic nerve glioma can be distinguished by expansion, relatively lessT2 hyperintensity and paucity of enhancement of the nerve, whereas optic nerve sheath meningiomas are characterized by enhancing expansion of the optic nerve sheath complex along with tram-track calcification, usually better shown on CT (83).

SPINAL CORD MIMICS

For practical purposes, the spinal mimics of relapsing demyelinating disorders can be subdivided into diseases with short segment cord involvement (**Figure 5**), and those with a longitudinally extensive involvement (LETM) (**Figure 6**).

SHORT SEGMENT SPINAL CORD INVOLVEMENT

Foci of Abnormal Signal Intensity (FASI) in Neurofibromatosis Type 1 (NF1)

FASI's have been described within the spinal cord of children with NF1. Short segment, non-enhancing intramedullary lesions demonstrating stability or regression on follow-up have been described (84). These are almost never found in isolation and the classic brain and orbit findings will help make the diagnosis.

Vasculitis

CNS vasculitis with spinal involvement may occur as a part of a systemic vasculitic process such as Bechet disease, systemic lupus erythematosus or granulomatosis with polyangiitis. Primacy CNS vasculitis involving the spinal cord only is a rare entity (85). The

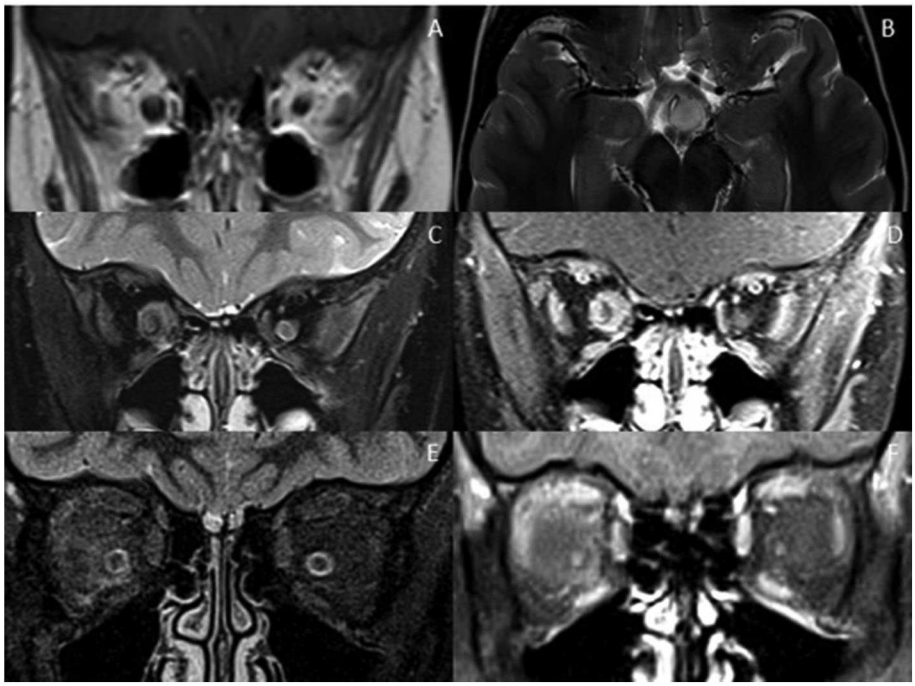


FIGURE 4 | Optic nerve mimics of RDS. **(A,B)** Optic pathway glioma: The coronal T1-weighted image with contrast shows an expanded intra-orbital right optic nerve. The optic chiasm is expanded on T2-weighted axial imaging **(B)**. **(C,D)** Optic nerve sheath meningioma: On coronal STIR **(C)** and coronal T1-weighted image with contrast **(D)** there is thickening and enhancement of the right optic nerve sheath complex. **(E,F)** Orbital sarcoidosis: On coronal STIR **(E)** and coronal T1-weighted image with contrast **(F)** there is stranding of the intraconal fat, minimal perineural thickening and enhancement.

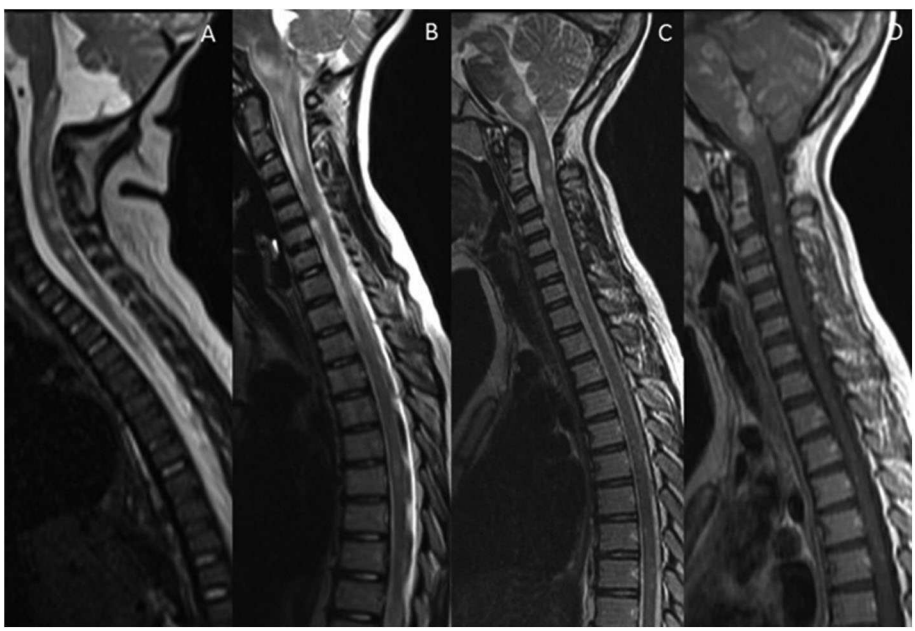


FIGURE 5 | Mimics in the spine—short segment spinal lesions. **(A)** Infectious myelitis secondary to cytomegalovirus: Multifocal short segment T2 hyperintense lesions are noted in the cervical and upper thoracic cord. **(B)** Neurofibromatosis 1: Intramedullary foci of abnormal signal intensity (FASI). **(C,D)** Hemophagocytic Lymphohistiocytosis: Short segment enhancing lesions. These have a more punctate morphology.

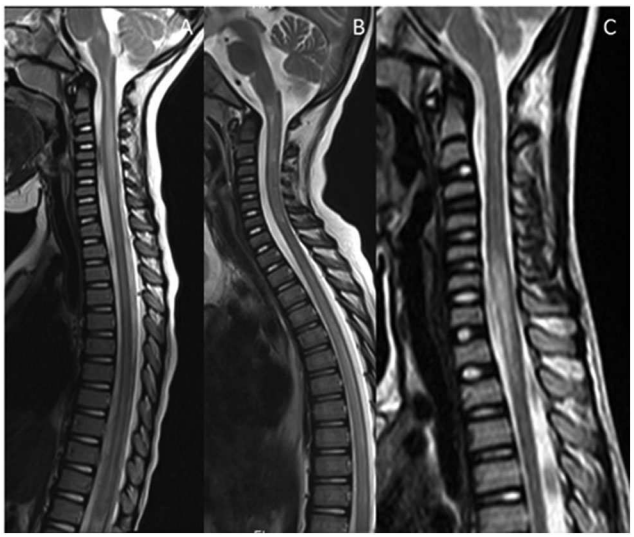


FIGURE 6 | Mimics in the spine—longitudinally extensive spinal lesions. **(A)** Rhombencephalomyelitis: This was confirmed as mycoplasma on serological testing. **(B)** Biotinidase deficiency: Confirmed on genetic and enzymatic testing in a child with skin rash, seizures and alopecia. The appearances are similar to those seen on the RDS spectrum LETM however the clinical features are not typical of RDS. **(C)** Fibrocartilaginous embolism: Note the signal abnormality in the cord as a result of infarction. There was restricted diffusion within the lesion (not shown). The likely source was the C3/4 intervertebral disc which demonstrates a reduction in signal (white arrow).

imaging features of spinal vasculitis are non-specific and include intrinsic T2 hyperintense lesions which may or may not enhance after contrast (86).

Intramedullary Tumors

Intramedullary spinal tumors represent 4–10% of all central nervous system tumors. They are predominantly of glial origin and account for up to 35% of all intradural tumors in children (87). The imaging features of intramedullary spinal tumors can overlap with inflammatory conditions. Location wise, intrinsic cord tumors can be located centrally or eccentrically within the cord, as typically in the case of ependymomas and astrocytomas, respectively. T2 signal hyperintensity may be present and cord expansion can be a variable feature. They may be short or long in terms of segmental involvement. The tumors may enhance, be associated with hemorrhage, tumoral cysts, and syringohydromyelia (88). Mass effect and enhancement, when present can sometimes be helpful in distinguishing from a demyelinating process.

LONGITUDINALLY EXTENSIVE CORD INVOLVEMENT

Longitudinally extensive transverse myelitis (LETM) presents clinically with a bilateral, symmetric or asymmetric sensorimotor and autonomic spinal cord dysfunction. Typically, there is a clearly defined sensory level and a progression to the nadir of clinical deficits between 4 h and 21 days after symptom onset. The primary mimics of spinal demyelination with a longitudinally extensive pattern include tumors (covered above), sarcoidosis, infections, vascular abnormalities, nutritional deficiencies such as vitamin B12 or copper deficiency, and rarely, certain metabolic entities such as biotinidase deficiency, and mitochondriopathies.

Sarcoidosis

Spinal disease may occur in the absence of intracranial disease. Myelopathy associated with sarcoidosis is typically in the form of longitudinally extensive spinal cord lesions affecting the dorsal part of the cord, extending laterally at times as a crescent, but also less commonly the anterior aspect of the cord (89). Occasionally, central canal enhancement may be present. Long linear sub-pial enhancement, and persistence of enhancement for months despite pulsed and oral corticosteroid treatment, is highly suggestive of spinal cord sarcoidosis.

Infectious and Para-infectious Disorders

Clinically, infective myelitis can present in a similar fashion to idiopathic myelitis with constitutional symptoms and fever. The pathogenic cause may be viral, bacterial, fungal or parasitic. Certain findings on MRI may help point toward a particular infectious pathogen.

In Lyme disease, MRI shows early enhancement of the pial region followed by non-specific T2 hyperintensities and enhancement of the cord parenchyma (33, 90).

CMV is associated with thickening, clumping, and enhancement of nerve roots and leptomeninges along the conus medullaris, often with associated long-segment T2 high signal of the cord (30).

Herpesviruses, including types 1, 2, 6, and 7 are most frequently associated with myelitis and share an overlapping imaging presentation, characterized by long-segment T2 high signal with variable enhancement (91).

In varicella-zoster myelitis, when a concomitant skin lesion is present (in 33% of patients), the dorsal root and posterior horns of the spinal cord are affected and usually correspond to the affected dermatome (92). Additionally, the MRI may show single or multiple lesions, with or without enhancement, associated with marked edema (93).

Another presentation of viral diseases, characterized by a poliomyelitis-like syndrome is seen in the picornavirus family (enterovirus 71, poliovirus, and, less commonly, coxsackievirus A and B) and in some flaviviruses, including Dengue and West Nile viruses. Imaging demonstrates unilateral or bilateral high signal on T2 sequences in the anterior horns of the spinal cord across multiple segments with variable enhancement (91).

Spinal cord presentation in HTLV-1 usually reflects involvement of the dorsolateral columns, with T2 high signal long-segment involvement of the lateral columns, less commonly extending to the dorsal columns, occasionally with enhancement (32, 91). HIV is another possible differential diagnosis for imaging abnormalities along the dorsolateral medullary column (91).

Mycoplasma is one of the most common bacterial infections resulting in post-infectious transverse myelitis. The imaging

findings are not specific and a high index of suspicion is needed to exclude it as best as possible (93).

Neurocysticercosis and occasionally tuberculosis, in some stages, are associated with MS-like "open ring" enhancing lesions as mentioned previously (32).

Vascular Abnormalities

Acute spinal cord infarction results in a sudden onset anterior spinal artery syndrome, with loss of function of the ventral two-thirds of the spinal cord, pain, and characteristic dissociative sensory disturbance. There is usually a cardiovascular risk factor for the development of cord infarction (94). On MRI, there is preferential involvement of the gray matter. The appearances may mimic LETM, though the cord lesion typically demonstrates a characteristic appearance of "owl eyes or snake eyes" on axial images, due to involvement of the gray matter of the anterior horns of the spinal cord. The presence of restricted diffusion in such cases can be helpful (94).

Fibrocartilage embolism should be considered when there is an additional finding of altered signal in the disc or in the posterior aspect of the vertebral body (95).

Spinal vascular malformations is an umbrella term encompassing a number of entities which include arterio-venous malformations (AVM), dural arterio-venous fistula (dAVF), cavernous malformations, and capillary telangiectasias. A spinal vascular malformation should be included in the differential diagnosis for any child who presents with slowly progressive or acute symptoms of radiculopathy or myelopathy.

Nutritional Deficiencies

Nutritional deficiencies can cause appearances in the spinal cord that can mimic findings similar to those of transverse myelitis.

The characteristic clinical triad of subacute combined degeneration caused by vitamin B12 deficiency includes symmetric diminished vibration sense, pyramidal signs, and peripheral neuropathy (96, 97).

Symmetric T2 signal hyperintensity with a general lack of enhancement in the lateral and dorsal columns has been reported to be the characteristic neuroimaging finding (94). In such cases, the brain should also be imaged, as brain lesions in vitamin B12 deficiency resemble that of MS with T2 hyperintensities in the periventricular white matter.

A myelopathy similar to that seen in vitamin B12 deficiency with the involvement of the dorsal column and corticospinal tracts also may be seen in copper deficiency myelopathy (54, 98).

CONCLUSION

RDS in children encompass a diverse spectrum of entities. There are a multitude of acquired and genetic disorders that can mimic RDS in children both clinically and radiologically. Furthermore, false negative test results for antibodies associated with RDS, as well as overlap with other syndromes such as anti-NMDARE can make the process of reaching an accurate diagnosis challenging.

A knowledge of the specific and distinct MRI patterns and clinical red-flags can help differentiate between the relapsing demyelinating syndrome subtypes and their clinical and radiological mimics.

AUTHOR CONTRIBUTIONS

PM and NR: compilation of manuscript. SC: contribution to manuscript, final manuscript review, and compilation of images. KMa: project oversee, final manuscript reviews, and corrections. SS: manuscript outlay and proof reads. KMu: neurology input and tables. All authors contributed to the article and approved the submitted version.

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REVIEW
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Pain in NMOSD and MOGAD: A Systematic Literature Review of Pathophysiology, Symptoms, and Current Treatment Strategies

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Neuromyelitis optica spectrum disorders (NMOSDs) and myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD) are autoimmune inflammatory disorders of the central nervous system (CNS). Pain is highly prevalent and debilitating in NMOSD and MOGAD with a severe impact on quality of life, and there is a critical need for further studies to successfully treat and manage pain in these rare disorders. In NMOSD, pain has a prevalence of over 80%, and pain syndromes include neuropathic, nociceptive, and mixed pain, which can emerge in acute relapse or become chronic during the disease course. The impact of pain in MOGAD has only recently received increased attention, with an estimated prevalence of over 70%. These patients typically experience not only severe headache, retrobulbar pain, and/or pain on eye movement in optic neuritis but also neuropathic and nociceptive pain. Given the high relevance of pain in MOGAD and NMOSD, this article provides a systematic review of the current literature pertaining to pain in both disorders, focusing on the etiology of their respective pain syndromes and their pathophysiological background. Acknowledging the challenge and complexity of diagnosing pain, we also provide a mechanism-based classification of NMOSD- and MOGAD-related pain syndromes and summarize current treatment strategies.

Keywords: aquaporin 4, headache, myelin oligodendrocyte glycoprotein-antibody-associated disease, neuromyelitis optica spectrum disorders, neuropathic pain, pain, painful tonic spasms

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INTRODUCTION

In 1894, Eugène Devic (1858–1930) and his doctoral student Fernand Gault (1873–1936) reported a historical case on a patient with optic neuritis (ON) and myelitis and proposed the name "neuro-myélite optique" for this syndrome. The patient, a 45-year-old woman, was admitted for suspected "neurasthenia," suffering from disturbed sleep, gastrointestinal symptoms, neuromuscular asthenia, palpitations, and, especially, headache: "*The pain occurs in attacks, both during the day and night. Pain attacks may be long or short, affecting one side of the face and the head, sometimes the right side, mostly the left, but the highest intensity is always at the occipital region: the neck and eyeballs. The pain is sometimes so strong that it causes the patient to cry.*"

One month after admission, the patient suddenly developed acute complete paraparesis and visual loss. It is currently a matter of debate whether the patient suffered from a neuromyelitis optica spectrum disorder (NMOSD) or a myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD) (1). Terrible, agonizing, and unbearable pain can arise as an acute or chronic symptom in both pathologies (2–4) (**Table 1**).

Neuromyelitis optica spectrum disorders (NMOSDs) are rare and, in most cases, relapsing inflammatory diseases of the central nervous system (CNS) (10). In the majority of cases, NMOSDs are associated with serum immunoglobulin G (IgG) autoantibodies (Abs) targeting the astrocyte aquaporin-4 (AQP4) water channel (11, 12). Patients typically suffer from recurrent attacks of severe optic neuritis and/or myelitis (13, 14) and, less frequently, brainstem or brain involvement (15, 16), leading to a diverse range of symptoms, of which severe pain is one of the most frequent and disabling (2, 17–26). Chronic pain occurs in NMOSD with an estimated prevalence between 72 and 86% (2, 18, 27, 28). Over 50% of NMOSD (82% APQ4-Ab positive) patients recalled an increase in pain intensity as the first indicator of a relapse (26) and 25% of patients with NMOSD (82% AQP4-Ab positive) reported pain as their worst symptom, despite also experiencing severe weakness and bladder or bowel dysfunction (26). Neuropathic pain is the most common type of chronic pain with a prevalence of up to over 80% (2, 26), and painful tonic spasms occur with a prevalence of 25–40% (29–32).

MOGAD is another inflammatory autoimmune condition of the CNS, defined by IgG antibodies against conformationally intact myelin oligodendrocyte glycoprotein (MOG) localized on the surface of the myelin sheaths (13, 33, 34). Although there is some phenotypic overlap with AQP4-Ab-positive NMOSD, most researchers consider MOGAD to be a distinct disease entity (35–37). Affected patients may develop any combination of acute disseminated encephalomyelitis, transverse myelitis (long or short), optic neuritis (ON, typically anterior, often bilateral), brainstem pathology often affecting cerebellar peduncles, cranial nerve involvement, and, less frequently, brainstem encephalitis, encephalitis mimicking small vessel CNS vasculitis, and cortical disease with seizures (33, 38–44). Pain is also becoming increasingly recognized as a common and debilitating symptom in MOGAD. However, data in pain in MOGAD are scarce and have to be verified in larger studies: mild chronic pain has a reported prevalence of 86% (2), and severe acute pain in the context of attacks has a prevalence of 70% (38). Furthermore, in addition to the typical retrobulbar pain and/or pain on eye movement, severe and sometimes migraine-like headache can precede visual loss in MOG-Ab-related ON (45, 46), the most-common clinical feature at onset and subsequent relapse (33, 37, 38, 47, 48).

Pain is a very common feature of both diseases and has a higher prevalence and severity compared to multiple sclerosis (MS), where estimates of pain prevalence are ∼50% (18, 27, 49). It also has a severe impact on the quality of life of affected patients (2, 18, 26, 27), interfering with physical, emotional, and cognitive aspects of well-being (2, 27, 50), as well as activities of daily life in NMOSD (60–83% AQP4-Ab positive) and MOGAD (2, 18, 26, 27). The higher the pain intensity, the worse the physical and emotional quality of life (2, 51).

The alleviation of pain through careful management and treatment should lead to significant improvement in the quality of life of patients with NMOSD and MOGAD. However, successfully controlling pain is highly challenging in these disorders (2, 26–28), and there is relatively little published literature on therapeutic intervention or treatment of pain as a primary outcome in these patient groups. In order to highlight this and facilitate future research in this critical area, we conduct a systematic review of the current literature on different pain syndromes in NMOSD and MOGAD. Based on this, we propose a mechanism-based classification of NMOSD- and MOGAD-related pain and additionally evaluate current treatment strategies.

TABLE 1 | Characteristics of different pain types.

Pain	Pain is defined as an "unpleasant sensory experience associated with actual or potential tissue damage or described in terms of such damage" (5).
Nociceptive pain	Nociceptive pain occurs as an appropriate encoding of noxious or potentially noxious stimuli. It represents a physiological response that the patient becomes conscious of when nociceptors in bone, muscle, or any body tissue are activated, warning the organism of tissue damage. In response, coordinated reflexes and behavioral responses are elicited (5, 6).
Neuropathic pain	Pain caused by a lesion in, or disease of, the somatosensory nervous system (7).
Acute pain	Physiological response to an acute disease-related damage (8, 9), here NMOSD- or MOGAD-attack related.
Chronic pain	Pain that persists or recurs for more than 3 months (9), (https://www.iasp-pain.org/).

METHODS

We performed a search of PubMed (last updated on June 09, 2020), combining neuromyelitis optica or neuromyelitis optica spectrum disorders AND pain, as well as myelin oligodendrocyte glycoprotein AND pain. Additional searches were performed combining neuromyelitis optica and myelin oligodendrocyte glycoprotein, respectively, AND headache or dysesthesia or dystonia or Lhermitte's sign or neuralgia or spasms or spasticity. This search was limited to English language publications and yielded a total of ∼200 articles including case reports, original clinical studies, and reviews, which were reviewed by title and abstract for potential relevance to this topic. When the title and abstract did not clearly indicate the degree of relevance to the topic, the article itself was reviewed. Bibliographies of topic-relevant articles were also examined to discover additional references not identified in the primary search. Finally, the authors' personal knowledge of the literature as well as congress contributions to ECTRIMS 2019 were used to supplement the above references.

As the impact of pain in patients with AQP4-Ab-positive and Ab-negative NMOSD is similar, we document both disease types

together and report the percentage of AQP4-positive NMOSD patients whenever available. We note that some MOG-Ab-positive patients may have been included in former NMOSD studies. However, the percentage of MOG-Ab-positive patients within groups of Ab-negative NMOSD patients should be low.

RESULTS

We identified 18 studies evaluating pain in NMOSD ($n = 17$) and MOGAD ($n = 2$, one overlapping with NMOSD) (**Table 2**).

The studies focused on pain without diagnostic specification (18, 25, 51), neuropathic pain (26, 28, 49, 50, 53, 55, 56), one study on neuropathic pruritus (52), painful tonic spasms (29–32), ON-related headache (54), and a description of diverse pain types (2, 27). One randomized single blind sham-controlled trial studied the effect of Scrambler therapy in NMOSD patients with central neuropathic pain (55). All other studies ($n = 17$) were descriptive and non-interventional. Two reviews on pain in NMOSD are available, one focusing on potential mechanisms underlying the pathogenesis of pain in NMOSD and another focusing on the impact of neuropathic pain medication on patients' quality of life (3, 57). Moreover, we included 12 case reports describing pain as part of the patients' symptom complex (4, 58–68). We additionally reviewed studies ($n = 131$) in NMOSD that included pain but where it was not the primary outcome. Where available, we provide the information on the percentage of AQP4-Ab-positive patients of the respective NMOSD cohort. Our review is the first to provide an overview of (1) disease-associated lesion locations in relation to different pain syndromes, (2) different types of NMOSD- and MOGAD-related pain, (3) possibilities to classify acute and chronic pain in NMOSD and MOGAD, and (4) the impact of the currently available immunotherapy on pain.

PATHOPHYSIOLOGICAL BACKGROUND OF PAIN IN NMOSD AND MOGAD

Inflammatory attacks in the CNS occur in both NMOSD and MOGAD and can lead to acute pain via the release of pronociceptive brain-derived neurotropic factor (BDNF), cytokines and chemokines [interleukin (IL)-1ß, IL-6, IL-17, and tumor necrosis factor (TNF)] (3, 69–71). Cytokine release enhances glutamatergic signaling, the main pronociceptive neurotransmitter in the spinal dorsal horn (3).

Pathological Substrates of Pain in NMOSD

Under healthy conditions, AQP4 is coexpressed with the excitatory amino acid transporter 2, which enables glutamate uptake by astrocytes. Loss of AQP4 in AQP4-Ab-positive NMOSD may lead to an excessive accumulation of glutamate in the extracellular space. In the context of neuroinflammation and dysregulation of sensory neurons, persistent excessive BDNF, and glutamate concentrations affect vulnerable inhibitory alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and gamma-aminobutyric acid (GABA) neurons, respectively (72, 73). The resulting imbalance between excitation and inhibition can then facilitate the development of chronic pain (3, 74, 75). In addition, astrocytes release endocannabinoid 2-arachidonoylglycerol (2-AG), which strongly enhances GABAergic inhibition. Loss of astrocytes in NMOSD leads to 2-AG reduction, likely leading to nociceptive pain and hyperalgesia (28).

Structural cerebral alterations may also affect chronic pain perception in NMOSD. Recently, a study on subcortical abnormalities in female NMOSD patients showed smaller hippocampus and pallidum volumes in patients with neuropathic pain compared to patients without neuropathic pain, as well as a negative correlation between pain intensity and volumes of the accumbens nucleus and thalamus (56). A study on pain-related morphological abnormalities in AQP4-Ab-positive NMOSD described an association of the ventral posterior nucleus (VPN) volume with several measures of pain intensity (76). Both studies suggest that subcortical structures are substantially involved in cognitive, emotional, and modulatory pain processing in AQP4-Ab-positive NMOSD (56, 76).

Pathological Substrates of Pain in MOGAD

While AQP4-Abs target astrocytes, MOG-Abs bind to myelin-forming oligodendrocytes. Therefore, inflammation in MOGAD primarily causes demyelination with a loss of the microtubule cytoskeleton of oligodendrocytes (13, 77–79). Under healthy conditions, the neuropeptide nerve growth factor (NGF) has a high affinity to bind MOG. Moreover, NGF is part of the nociceptive system: It binds tropomyosin receptor kinase A (TrkA). TrkA is expressed on unmyelinated nociceptive axons of the spinal cord and regulates synaptic strength and plasticity of sensory neurons. Thus, the loss of MOG by antibody-mediated destruction in MOGAD may cause abundant NGF concentrations in the CNS, leading to aberrant sprouting of unmyelinated nociceptive fibers in the posterolateral tract of the spinal cord and hence nociceptive pain (80).

Lesion Location and Pain in NMOSD

Spinal cord lesions in NMOSD are typically extensive and occur predominantly in the cervical and thoracic spinal cord (17, 81–83). As AQP4 is mainly expressed in the gray matter, lesions concentrate around the central canal, and the adjacent gray matter in the dorsal and ventral horns, as well as in the dorsal root entry zone (84). Ascendant and descendent white matter tracts, including the spinothalamic tract (STT) (52, 85, 86), are affected by severe lesions (87). Tackley et al. report a significant relationship between persistent thoracic myelitis lesions and the severity of neuropathic pain. The presence of cervical lesions, in contrast, were predictive of lower pain scores (53).

In the brainstem, the dorsal medulla oblongata and area postrema have the highest distribution of AQP4 (74, 88). It has been shown that 27% of NMOSD patients with cervical longitudinally extensive transverse myelitis (LETM) showed lesions involving the brainstem (89). Such a distribution could include trigeminal nucleus or periaqueductal gray (PAG) pathology, causing headaches in affected patients (74). The PAG is considered to be a migraine generator and a modulator of headache in NMOSD. Moreover, the hypothalamospinal tract, localized in the dorsolateral medulla, activates the hypothalamus,

TABLE 2 | Original publications on pain in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD) (listed in chronological order).

References	Patient sample	Portion of AQP4-IgG seropositive patients	Pain and QoL assessment	Imaging data	Pain type	Pain medication	Main findings
Kanamori et al. (18)	42 NMOSD vs. 51 MS	35/42	SF-BPI SF-36	N.A.	N.A.	N.A.	First study on pain in NMOSD: Pain in NMOSD is more frequent and severe than in MS and has a severe impact on the patients' QoL
Qian et al. (27)	29 NMOSD vs. 66 MS	24/29	MPQ 10-point NRS Interview SF-36	Spinal cord MRI	Retroorbital pain Dysesthetic pain Girdle pain Lhermitte's sign Painful tonic spasms	Tricyclic antidepressants Duloxetine Gabapentin Pregabalin Carbamazepine Lamotrigine Phenytoin Sodium valproate Baclofen Cyclobenzaprine Tizanidine Fentanyl citrate Hydrocodone Hydromorphone Methadone Oxycodone Hydromorphone	First study mentioning specific pain syndromes, including spinal cord MRI and examining medication use: Pain in NMOSD is more frequent and severe than in MS, even after controlling for disability and number of involved spinal cord segments. Pain in NMOSD appears insufficiently controlled by pharmacological interventions
Kim et al. (29)	40 NMOSD vs. 35 MS vs. 42 iATM	34/40	N.A.	Spinal cord MRI	Painful tonic spasms	Carbamazepine Gabapentin Phenytoin	First study on PTS in NMOSD: PTS are a common and relatively specific myelitis-related symptom in NMOSD. PTS most commonly occur during recovery from the first myelitis episode
Usmani et al. (31)	57 NMOSD	1/57	Clinical history	Spinal cord MRI	Painful tonic spasms	Carbamazepine	14% of NMOSD patients had documented typical tonic spasms
Elsone et al. (52)	45 NMOSD	45/45	Clinical history	Spinal cord MRI	Neuropathic pruritus	N.A.	First study on neuropathic pruritus in NMOSD: Neuropathic pruritus seems to be a common but underrecognized symptom of myelitis associated with NMOSD
Pellkofer et al. (28)	11 NMOSD vs. 11 HC	11/11	Interview DN4 NRS QST	MRI	Neuropathic pain	N.A.	First study on NP in NMOSD, evaluating endocannabinoid levels in the serum and somatosensory abnormalities by QST: A total of 91% of the patients suffered from NP within the previous 3 months and 72% reported ongoing pain and decreased QoL at the time of assessment. Plasma levels of 2-AG were

(Continued)

TABLE 2 | Continued

References	Patient sample	Portion of AQP4-IgG seropositive patients	Pain and QoL assessment	Imaging data	Pain type	Pain medication	Main findings
							higher in NMOSD patients than in HC, suggesting its relevance for central sensitization. QST revealed pronounced mechanical and thermal sensory loss, strongly correlated to ongoing pain suggesting the presence of deafferentiation-induced pain
Zhao et al. (26)	50 NMOSD	41/50	DN4 BPI SF-36	MRI reports	Neuropathic pain	Amitriptyline Duloxetine Gabapentin Pregabalin Carbamazepine Lamotrigine Baclofen Cannabinoids Paracetamol Opiates	Specific exploration of NP and its effect on the QoL. NP was identified in 62% of patients, affecting ADLs. Pain was associated with significant reduction in the SF-36 mental composite score
Mutch et al. (50)	15 NMOSD	9/15	Semistructured interview	N.A.	Neuropathic pain	N.A.	First qualitative study to explore QoL, including pain in NMOSD: NMOSD is a difficult condition to live with due to the unpredictability of relapses and severe disability of visual or spinal symptoms. Poor vision, reduced mobility, bladder dysfunction, and pain affected participants' independence and experience of living with NMOSD
Carnero Contentti et al. (30)	15 NMOSD	15/15	Clinical history	MRI	Painful tonic spasms	Carbamazepine Gabapentin	PTS occur frequently in patients with NMOSD. PTS generally appear a month after a myelitis attack and are associated with extensive cervicothoracic lesions in MRI
Kong et al. (51)	44 NMOSD	29/44	BPI HADS SF-36	N.A:	Pain (not specified)	Codeine Ibuprofen Paracetamol Amitriptyline Duloxetine Diazepam Clonazepam Gabapentin Pregabalin Carbamazepine Oxcarbazepine Baclofen	Pain correlated strongly with quality of life SF-36 physical composite score. Depression highly correlated with pain severity. Pain severity was the most important factor for QoL

(Continued)

TABLE 2 | Continued

References	Patient sample	Portion of AQP4-IgG seropositive patients	Pain and QoL assessment	Imaging data	Pain type	Pain medication	Main findings
Eaneff et al. (25)	522 self-reported NMOSD	N.A.	PatientsLikeMe online questionnaire	N.A.	Pain (not specified)	Duloxetine Gabapentin Pregabalin Baclofen	Moderate to severe fatigue, pain, stiffness, and spasticity limit activities of over 50% of NMOSD patients
Tackley et al. (53)	76 NMOSD	76/76	BPI	MRI	Neuropathic pain	N.A.	Persistent, thoracic cord lesions in AQP4-Ab positive NMOSD is associated with high postmyelitis chronic pain scores, irrespective of number of myelitis relapses, lesion length, and lesion burden
Asseyer et al. (2)	35 NMOSD vs. 14 MOGAD	29/35	painDETECT MPQ SF-36 BDI-II	MRI	Neuropathic pain Headache/neck pain Musculoskeletal pain Spasticity	NSAID Antidepressants Anticonvulsants Opioids	First study exploring pain in MOGAD: Pain is a frequent symptom of patients with MOGAD and has a severe impact on the patients' QoL in NMOSD and MOGAD. Pain is insufficiently alleviated by medication
Liu et al. (32)	230 NMOSD	181/230	Medical records Prospective interviews	MRI	Painful tonic spasms	Carbamazepine Oxcarbazepine Gabapentin Pregabalin Baclofen	22.6% of NMOSD patients experience PTS. Patients with NMOSD and PTS have a higher age at disease onset, higher ARR, and a tendency to experience pruritus. Sodium channel blocking antiepileptic drugs like carbamazepine and oxcarbazepine have higher efficacy than gabapentin in the treatment of PTS
Asseyer et al. (54)	129 MOGAD	No NMOSD	Medical records	MRI	Optic neuritis related headache and orbital/periorbital pain	N.A.	First study on severe headache preceding visual loss in MOG-Ab-related optic neuritis. Florid intraorbital and perioptic inflammation was likely to involve meninges and nociceptive fibers
Hyun et al. (49)	252 NNOSD vs. 248 MS	91/99 who completed PainDetect	PainDetect SF-BPI BDI-II FSS	N.A.	Pain (not specified) Neuropathic pain	N.A.	60% of the NMOSD patients and 34% of the MS patients suffered from current pain. Neuropathic pain was more severe and pain-related interference in daily life was greater in NMOSD patients than in MS patients
Mealy et al. (55)	22 NMOSD	22/22	Self-reported NP attributable to an inflammatory spinal cord lesion NRS	Details n.a.	Neuropathic pain	Antidepressants Anticonvulsants Opioids	First randomized single-blind, sham-controlled trial in NMOSD patients with central neuropathic pain using Scrambler therapy. The median baseline NRS decreased after 10 days of treatment, whereas the median NRS score did not significantly decrease in the sham arm

(Continued)

TABLE 2 | Continued

References	Patient sample	Portion of AQP4-IgG seropositive patients	Pain and QoL assessment	Imaging data	Pain type	Pain medication	Main findings
Wang et al. (56)	38 NMOSD	38/38	BPI	MRI	Neuropathic pain, but not clearly specified	N.A.	First investigation of subcortical structural abnormalities in female NMOSD patients with NP shows significantly smaller hippocampus and pallidum volumes in the patients with NP compared to patients without NP and a significant negative correlation between pain intensity and volumes of the accumbens nucleus and thalamus in patients with NP

2-AG, 2-arachidonoylglycerol; ADL, activities of daily living; AQP4-IgG, aquaporin 4 immunoglobulin G; ARR, annualized relapse rate; BDI-II, Beck Depression Inventory II; BPI, Brief Pain Inventory; DN4, Douleur neuropathique 4; FSS, Fatigue Severity Scale; HADS, Hospital Anxiety and Depression Scale; HC, healthy control; iATM, idiopathic acute transverse myelitis; MOG-Ab, myelin oligodendrocyte glycoprotein antibody; MOGAD, myelin oligodendrocyte glycoprotein-associated disease; MPQ, McGill Pain Questionnaire; MRI, magnet resonance imaging; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders; NP, neuropathic pain; NRS, numeric rating scale; PTS, painful tonic spasms; QoL, quality of life; QST, quantitative sensory testing; SF-36, 36 item short form health survey; SF-BPI, short form Brief Pain Inventory.

and the trigeminovascular system. Both regions are considered to be involved in the pathogenesis of headache (90, 91).

Dorsal lesions of the medulla oblongata lead to substance P release, a transmitter that can cause and maintain nociceptive activation of the trigeminal tract nucleus (92). Besides headache, neuropathic pain was also reported more frequently in NMOSD patients with medulla oblongata lesions (85.7% AQP4-Ab positive) than in patients without such lesions (31.8 vs. 11.1% and 65.9 vs. 29.4%) (93). Increased neuropathic pain frequency could be explained by the severe and extensive spinal cord involvement associated with the medulla oblongata (93).

Moreover, AQP4-Ab-positive NMOSD has a predilection to affect the optic nerve (94–96). Astrocytes surrounding the optic nerve express high levels of AQP4, but the unmyelinated optic nerve head also expresses AQP4. Moreover, a high density of retinal astrocytic Müller cells, expressing AQP4, are located in the parafoveal area (97–101).

For a further and more detailed pathophysiological background of possible mechanisms explaining pain in NMOSD, we refer to a review by Bradl et al. (3).

Lesion Location and Pain in MOGAD

Spinal cord lesions in MOG-Ab-positive myelitis are not always longitudinal and extensive but can still cause sensory symptoms like pain and dysesthesia (38). The axial lesion extension may be crucial for the risk of pain. Depending on the level of the lesion, aberrant nerve fiber sprouting could lead to occipital neuralgia or to more distal neuropathic pain syndromes. Moreover, it has been shown that central neuropathic pain can be induced by oligodendrocyte death and axonal pathology in the spinothalamic tract (102).

The brainstem is a critical region in the pathophysiology of headache. Brainstem lesions are present in up to one-third of patients suffering from MOGAD and could promote the risk for migraine and trigeminal neuralgia (103, 104).

MOG is highly expressed by oligodendrocytes myelinating the optic nerve (105) and is consequently a predominant target in MOG-Ab-related ON. ON-related pain is particularly severe in MOGAD and can present as a migraine-like headache (54). In these cases, severe edema may lead to irritation of the meningeal nerve sheath, which surrounds the optic nerve and contains nociceptive fibers of trigeminal origin (106–108). The trigeminal nerve provides sensory innervation to the ocular and periocular area, and its recurrent branches innervate the intracranial dura, venous sinuses, and cerebral vessels, likely leading to headache (109, 110).

TYPES OF PAIN IN NMOSD AND MOGAD

Pain can occur during acute attacks and be an indicator of current damage, or it can become a chronic syndrome over the course of the disease. The main pain syndromes in NMOSD and MOGAD comprise ON-related pain, headache, neuropathic pain, and musculoskeletal pain including spasticity, painful tonic spasms, and back pain. We discuss these symptoms in the context of NMOSD and MOGAD below, highlighting any differences between the two diseases where information is available.

Optic Neuritis-Associated Pain

Optic neuritis is an inflammation of the optic nerve characterized by severe visual loss or blindness associated with ocular pain (111) and occurs in the context of many inflammatory diseases (112–116). ON-related eye pain and pain on eye movement is more common in MOGAD, with reports ranging from 65 to 86% (46, 117, 118), compared to AQP4-Ab-positive ON (28.6–50%) (46, 117) and idiopathic Ab-negative ON (10–46%) (117, 119).

AQP4-Ab-positive ON is typically accompanied by retrobulbar pain often worsened by eye movement (2, 27, 46).

MOGAD-related ON pain seems to be particularly severe, sometimes accompanied by migraine-like headaches that precede the visual deficit (54, 120).

Headache

Headache is an unspecific but common symptom in NMOSD (2, 74) and has also been described in MOGAD, here mainly associated with optic neuritis (2, 38, 54). It can occur as a first symptom or persist during the disease course (2, 38, 74). NMOSD-related headache can occur as a cervicogenic-like headache (2, 58, 74), neck pain (60, 68), paroxysmal hemicrania (62), or in the context of meningoencephalitis (74, 121). It is typically a mixed pain condition with neuropathic and nociceptive components (74).

Cervicogenic-Like Headache

Cervicogenic-like headache is caused by a lesion in or disorder of the cervical spine or soft tissues of the neck. While a few cases presenting with cervicogenic-like headache following myelitis have been mentioned in NMOSD and MOGAD (2, 58, 74), only a single case report has described it in detail: The patient had a left occipital headache spreading to the posterior neck associated with numbness and aching. Response to occipital nerve block was slight, and the headache progressed. MRI revealed an extensive myelitis from the medulla oblongata to the C5 level, a bilateral ocular or prechiasmatic lesion, and suspicious bilateral upper brainstem lesion. Symptoms and MRI pathology improved with steroid treatment (58).

Note that we suggest avoiding the diagnosis of cervicogenic headache in NMOSD and MOGAD in favor of the term cervicogenic-like headache or headache attributed to non-infectious inflammatory diseases (106). Classical cervicogenic headache, in contrast, is caused by a disorder of the cervical spine and its component bony disk and/or soft tissue elements (106).

Paroxysmal Hemicrania

Paroxysmal hemicrania is characterized by severe unilateral pain attacks, affecting orbital, supraorbital, and/or temporal regions. The attacks are mostly associated with autonomic features (ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, forehead and facial sweating, miosis, ptosis, and/or eyelid edema) (106). We are aware of one case report, describing a patient presenting with paroxysmal hemicrania as first symptom of an AQP4-Ab-positive NMOSD. MRI revealed a lesion extending from the lower medulla oblongata to the cervical cord (C4), possibly involving the spinal nucleus of the trigeminal nerve (62). As in primary paroxysmal hemicrania, indomethacin has been effective in the case of AQP4-Ab-positive NMOSD-related paroxysmal hemicrania (62), but evidence is limited. No reports of paroxysmal hemicrania in MOGAD were identified.

Encephalitis-Associated Headache

Meningoencephalitis-like pathology with fever, severe headache, and pleocytosis in the cerebrospinal fluid (CSF) has been reported in both disease complexes, NMOSD and MOGAD (74, 121), most likely due to meningeal inflammation (122, 123).

Neuropathic Pain

Neuropathic pain is particularly severe (2, 53) and patients typically characterize neuropathic pain as agonizing, shooting, and distressing (57). Neuropathic pain occurs more frequently in NMOSD (83% AQP4-Ab positive) than in MOGAD (80 vs. 40%) (2, 27). It can occur as an early myelitis-related symptom or develop during the disease course (3, 50, 53). Medication is currently not sufficient to control neuropathic pain (2, 27), particularly in patients with AQP4-Ab-positive NMOSD (51). A higher dosage of pain medication was not associated with being free of pain but rather with greater cognitive dysfunction and fatigue (27).

Neuropathic pain can be permanent or intermittent like Lhermitte's sign (27, 81, 124) and is localized either on the extremities or on the trunk, the latter often defined as a girdle sensation (18, 26, 28, 124, 125).

Lhermitte's sign is often painful and occurs in 35–60% of AQP4-Ab-positive NMOSD patients (27, 81, 124). It is defined as a brief, electric-shock-like sensation that runs from the back of the head down the spine, provoked by inclining the neck forward (124). It has been proposed that Lhermitte's sign occurs because demyelinated sensory fibers are hyperexcitable to percussion or elongation (124).

The girdle sensation describes an often burning sensation on the skin, localized with an extension of three or four dermatomes between T3 and T11 (124). It has been reported in 45.8–69% of NMOSD (83% AQP4-Ab positive) patients and can sometimes be misdiagnosed as acute abdomen (27, 124). Schöberl et al. describe an AQP4-Ab-positive NMOSD patient presenting with typical area postrema syndrome who developed an unusual painful segmental erythema resulting from a dorsolateral spinal cord lesion at C6/7 level. A dysregulated A-beta-fiber-evoked vasodilation has been discussed as a possible underlying pathophysiological mechanism (126). Pelvic pain has been reported to occur as an unusual presentation of AQP4-Ab-positive NMOSD, following a lesion of the conus medullaris (61).

Brainstem pathology can also cause neuropathic pain syndromes like trigeminal (2, 16, 74, 127) and occipital neuralgia (2, 128) in NMOSD and MOGAD. Trigeminal neuralgia is defined by pain in the area of the trigeminal innervation (usually V3 and/or V3 division). It is typically characterized by paroxysmal, sudden attacks of short severe stimulus-triggered and electric-like pain episodes (74). Interestingly, NMOSD patients with trigeminal neuralgia rarely show MRI pathology affecting the trigeminal root entry zone (129). It has been discussed whether or not a dual mechanism including pontine plaques and consecutive neurovascular compression

may contribute to the pathophysiology (74). Neuropathic pruritus has also been described following brainstem and spinal cord lesions (52). Pruritus is defined as "an unpleasant cutaneous sensation provoking the desire to scratch." Neuropathic pruritus is caused by affected pruritogenic neurons in the absence of a pruritogenic substance (52). Neuropathic pruritus associated with myelitis has been observed in 27.3% of ACQP4-Ab-positive NMOSD patients, either as a first symptom or a few days after the onset of other myelitis-related symptoms. It has a sudden onset of high intensity with a duration from seconds to minutes, associated with superficial sensory deficits and/or pain. It can occur on the trunk, the extremities, or the occipital region of the head (52). An inflammation-related demyelination involving second-order itch neurons in the dorsal horn of the spinal cord has been discussed as an underlying pathophysiological mechanism. The role of brainstem lesions affecting the spinal nucleus of the trigeminal nerve or periaqueductal pathways has also been discussed (52, 130).

Very few studies have focused on neuropathic pain in MOGAD. Lhermitte's sign (38, 45), band-like girdle sensations (131), trigeminal and occipital neuralgia, and neuropathic extremity pain (2, 38) have been mentioned but have so far not been studied in detail. Myelitis in MOGAD may have a better tendency to recover (83) and therefore cause less severe central neuropathic pain syndromes than in NMOSD.

Peripheral Nervous System-Related Neuropathic Pain

Some cases of possible peripheral nervous system (PNS) involvement in NMOSD have been published. Painful, flaccid paralysis (63), lumbosacral myelitis (132), clinical and electrophysiological second motor neuron involvement (133), and peripheral neuropathy (134, 135) have been described, and radicular pain has been reported to occur in up to 33% (81, 136). Recently, a few cases with PNS involvement in MOGAD have been described. Cranial nerve involvement, brachial neuritis, multifocal neuropathy, migratory paresthesia, myeloradicular symptoms, recurrent limb paresthesia, and pain have been mentioned (41, 64, 137, 138). As described above, the inflammatory process in the CNS could trigger an immune cascade targeting myelin-specific antigens in the nerve roots. Alternatively, low quantities of MOG may be expressed in the human peripheral myelin and the Schwann cells, as previously described in rodents and primates (64, 138, 139). However, current data are too scarce for pathophysiological conclusions. At present, we can only infer that PNS involvement should not prevent clinicians from investigating the presence of MOG- and AQP4-IgG Abs.

Spasticity and Painful Tonic Spasms

Spasticity is defined as "disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles." At the patient level, it can be defined as an "unusual tightening of muscles that feels like leg stiffness, jumping of legs, a repetitive bouncing of the foot, muscle cramping in the legs or arms, legs going out tight and straight or drawing up" (140). More than 50% of NMOSD patients are reported to suffer from moderate to severe spasticity (25), but very little is known about spasticity in MOGAD (1, 38).

Painful tonic spasms are defined as paroxysmal, recurrent muscle spasms in one or more limbs and/or the trunk, lasting seconds to minutes, accompanied by intense pain and dystonia (29, 30, 65). Several case reports and small series describe PTS in NMOSD (18, 29, 29–31, 65–67, 136, 141–144), but no reports were identified mentioning PTS in MOGAD. Abboud et al. reported that all patients with tonic spasms had associated neuropathic pain (145). PTS and pain occur more frequently in NMOSD than in MS (18, 29), and PTS-associated myelitis in AQP4-Ab-positive NMOSD has been described with a specificity of 98.7% compared to MS (143). Kim et al. showed that transverse myelitis at disease onset, but not optic neuritis, was predictive of future occurrence of PTS. PTS develop mainly during recovery from the first myelitis attack within a mean of 48 days without occurrence of new MRI lesions (3, 29, 30). A spinal cord syndrome with paroxysmal tonic spasms may be particularly suggestive for NMOSD (29, 81). PTS may occur following the loss of inhibitory motor neurons in the central gray matter of the spinal cord (142). Abnormal demyelination can cause ephaptic transmission between the tracts causing spasms (65). As nerve damage does not affect somatosensory pathways, PTS are not considered to be of neuropathic origin (146).

Back Pain

Like headache, back pain is an unspecific syndrome but occurs frequently in NMOSD and MOGAD (1, 38, 131, 147, 148). It can emerge in the context of myelitis following radiculitis as described above but is often a mixed syndrome including central and peripheral neuropathic as well as nociceptive pain components. Malposition and axial instability following paresis or spasticity, reduced mobility with wheelchair dependence, or long-term corticoid therapy leading to osteoporosis are important secondary aspects to consider in these disorders and can enhance pain, especially back pain (5).

Comorbidity-Related Pain

Up to 45% of patients with NMOSD and ∼10% of patients with MOGAD suffer from autoimmune comorbidities (13), including connective tissue disease, dermatomyositis, rheumatoid arthritis, Sjoegren's syndrome, systemic lupus erythematodes, vasculitis, and myasthenia gravis (2, 51, 148–155), which can themselves be associated with pain (156). A careful diagnostic workup is necessary to detect potentially overlapping pathologies.

ADDITIONAL FACTORS ASSOCIATED WITH PAIN IN NMOSD AND MOGAD

Women are more often affected by autoimmune diseases than men, with a female/male ratio of up to 10:1 in NMOSD and, depending on the geographic region, between 1.1:1 and 3:1 in MOGAD (13, 157). However, no sex differences have been found concerning pain prevalence or intensity (26). Mixed results have been found regarding the correlation between pain intensity and age (18, 26). Severe overall disability, measured by the expanded disability status scale (EDSS), has been identified as a risk

TABLE 3 | Classification of pain in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein-antibody-associated disease (MOGAD).

Pain condition	Examples
Acute pain	
ON-related pain	Retro- or periorbital pain, increased by eye movement. In MOGAD: associated headache possible.
Headache	Cervicogenic-like headache, paroxysmal hemicrania, encephalitis-related headache
Neuropathic pain	Myelitis-related neuropathic pain: dysesthetic extremity pain, neuropathic pruritus, girdle sensation, pelvic pain
Chronic pain	
Intermittent neuropathic pain	Lhermitte's sign, trigeminal neuralgia, occipital neuralgia
Permanent neuropathic pain	Dysesthetic extremity pain, neuropathic pruritus, girdle sensation, pelvic pain
Spasticity-related pain	Leg stiffness, muscle cramping in the legs or arms
Painful tonic spasms	Paroxysmal, recurrent muscle spasms in one or more limbs and/or the trunk
Back pain	Multifactorial pathology including nociceptive and neuropathic aspects, e.g., following spasticity

factor for more severe pain (27) and increasing disability scores correlated with pain intensity in NMOSD (83 and 66% AQP4-Ab positive) (27, 51). Moreover, an association of depression, fatigue, and NMOSD (66–83% AQP4-Ab positive) as well as MOGAD has been shown in several studies (2, 19, 27, 51, 158). Depression and pain are known to interact, and one cannot be certain whether depression enhances pain, occurs in response to pain, or both (159).

CLASSIFICATION OF PAIN IN NMOSD AND MOGAD

The International Association for the Study of Pain (IASP) defines pain as an "unpleasant sensory experience associated with actual or potential tissue damage or described in terms of such damage" (https://www.iasp-pain.org/). We propose a classification for pain in NMOSD and MOGAD (**Table 3**), which is similar to a previously provided MS-related pain classification (146). Our aim is to present a structure providing

1) the time course of pain development, to distinguish
   a. pain as a warning signal of acute damage
   b. pain as a self-sustaining chronic syndrome
2) the underlying pathophysiological mechanisms, to distinguish
   a. ON-related pain
   b. headache
   c. neuropathic pain
      i. intermittent (episodic), e.g., trigeminal and occipital neuralgia, Lhermitte's sign
      ii. permanent (continuous), e.g., pain in the extremities
   d. spasticity and painful tonic spasms
   e. mixed pain, e.g., back pain
   f. comorbidity-related pain
3) a reference for specific treatment strategies
4) a framework to generate future research hypotheses.

Of note, acute and chronic pain syndromes can overlap. For efficacious treatment, a detailed medical history is necessary.

TREATMENT OF PAIN IN NMOSD AND MOGAD

Despite the use of multiple medications, pain is currently not sufficiently managed in NMOSD or MOGAD (2, 26–28), and there is relatively little published literature on therapeutic intervention or treatment of pain as a primary outcome in these patient groups. Three studies on immunosuppressive treatment in AQP4-Ab-positive NMOSD have shown promising results when examining pain as a secondary outcome: two in patients treated with the humanized monoclonal IL-6 antibody tocilizumab (125, 160, 161) and one in patients treated with low-dose mycophenolate mofetil (MMF) (162). One study on the positive effect of Scrambler therapy for the treatment of neuropathic pain in NMOSD was identified (55). No studies were found investigating pain treatment in MOGAD. We provide an overview of current strategies for relapse-related treatments and effects of immunosuppressive treatment focusing on acute and chronic pain, respectively. We additionally give a general overview on the management of chronic neuropathic pain, spasticity-related pain, and painful tonic spasms, although these are not specific to NMOSD or MOGAD.

Attack-Related Treatment

Attack-related treatment aims to reduce pain by reducing the destruction of the CNS. In NMOSD, as well as in MOGAD, acute attacks are usually treated with 1,000 mg intravenous methylprednisolone (IVMP) for 3–5 days (163). Prompt treatment initiation should also be considered in patients who present with pain as their only symptom, in order to avoid rapid progression and attack-related disability (148). Of note, attack-related disability can cause the development of secondary pain, e.g., paresis- and malposition-related pain, reflecting attack-independent disease progression. Rapid corticoid therapy showed prompt recovery from pain in NMOSD (120), and Jarius et al. showed nearly complete recovery in 50% of IVMP-treated MOG-Ab-related attacks (38). In cases of poor outcome, IVMP therapy can be increased to 2,000 mg/day. Such a high-dose IVMP therapy, however, seems to be less effective than plasma exchange or immunoadsorption (13, 164–166). Especially in isolated myelitis, it has been shown that clinical response to immediate plasma exchange (PLEX) was better compared to high-dose steroid therapy (166). This could be of relevance in the treatment of patients presenting with neuropathic pain.

Bradl et al. suggest a multidrug treatment at an early disease stage to limit the previously discussed complex interactions of proinflammatory and pronociceptive molecules in order to avoid pain instauration. They propose an approach similar to the treatment for traumatic brain injury, involving minocycline, peroxisome proliferator-activated receptor agonists, cell cycle inhibitors, statins, and progesterone (3). However, currently, there are no data on possible preventive effects on pain development in NMOSD or MOGAD in this regard.

Effect of Immunomodulatory Treatment on Pain in NMOSD and MOGAD

Immunosuppressive therapy is essential to reduce disease activity and to avoid relapses in NMOSD and MOGAD, again with the aim to reduce the risk of future CNS damage. Up to now, although recommendations for treatment of NMOSD are available, these are not based on a high level of evidence (163, 167, 168). It is strongly recommended that patients suffering from AQP4-ab-positive NMOSD should receive immunotherapy after the first attack. Currently used preventative treatments in NMOSD include prednisone, azathioprine, rituximab, MMF, intravenous immunoglobulins (IVIGs), eculizumab, and methotrexate (163, 168, 169). Data on the efficacy of IVIG, however, are scarce (13). Of note, in Canada, the USA, and Europe, Eculizumab is currently the only approved therapy for the treatment of NMOSD, and all other medications are used off-label and empirically. In clinical trials, the positive effects on relapse rates of inebelizumab and satralizumab NMOSD have been described (13, 160, 169–173). Satralizumab has shown no benefit on pain intensity in two phase III studies (171, 174), and no data on pain are available for eculizumab and inebilizumab (169, 170, 173). As mentioned above, tocilizumab and MMF in contrast have shown positive effects on pain in AQP4-Ab-positive NMOSD. Still, evidence has to be proven in prospective studies focusing on pain as a primary outcome.

Tocilizumab is an antibody against IL-6, a major cytokine involved in NMOSD pathophysiology (175). It has been shown that NMO-IgG binding to AQP4 on astrocytes selectively induces internalization of AQP4 and production of IL-6 (70), which is thought to enhance the survival time of plasmablasts, which generate anti-AQP4 antibodies (71). IL-6 is a pronociceptive cytokine, which plays an important role in the development of neuropathic pain (176). Treatment with tocilizumab leads to reduced immunological activity, as well as neuropathic pain reduction (59, 125, 160), and should therefore be considered in patients at risk for neuropathic pain.

MMF is an immunosuppressant inhibiting the inosine monophosphate dehydrogenase. Consequently, the synthesis of guanosine nucleotide is reduced, which leads to an inhibition of B- and T-lymphocyte proliferation. MMF can be administered in both NMOSD and MOGAD, in the latter preferably in combination with steroids (13, 162). MMF reduces immunological activity and has a positive effect on pain intensity in AQP4-Ab-positive NMOSD patients (162). Unfortunately, the type of pain was not defined in this study.

Of note, pain can occur as a side effect of some immunosuppressive therapy. Eculizumab, inebilizumab, MMF, and rituximab can lead to headache, MMF can cause abdominal pain (13, 120, 170), and inebilizumab can cause back pain, extremity pain, and chest pain (173).

It has to be kept in mind that NMOSD and MOGAD are distinct nosologic entities regarding their underlying pathogenesis (36). In MOGAD, long-term immunotherapy is often considered and recommended only after a second attack in light of the presumably high proportion of monophasic cases and the overall good recovery. Empirical data suggest oral steroids as mainstay of treatment, and slow tapering is crucial to avoid recurrence of disease activity (33, 177, 178). In contrast to NMOSD, the efficacy of rituximab in MOGAD is controversial. Two recent studies showed that up to 45% of the patients under rituximab treatment still relapsed, despite an effective biological effect of rituximab. Consequently, memory B-cell depletion seems to be unable to prevent relapses in a subset of patients suffering from MOGAD (179, 180). Currently, a long-term treatment with intravenous immunoglobulins, or in some cases with methotrexate, may be preferred (13, 38). Like in NMOSD, treatment of MOGAD with classical MS drugs should be avoided, as they can worsen the disease course (181). Up to now, no treatment guidelines with high grade evidence are available for the treatment of MOGAD, and all medications are used off-label and empirically. Of note, none of the immunotherapies have been studied with regard to a potential effect on pain in MOGAD.

Symptomatic Pain Treatment

Symptomatic therapies aim to treat pain. Of note, the efficacy of the following treatment strategies have not been specifically demonstrated in NMOSD or MOGAD-related pain.

Neuropathic Pain

Based on the pathophysiological course of neuropathic pain development and the mechanisms of action, Bradl et al. suggest inducing pharmacological inhibition of glutamatergic signal transduction early in the disease course, e.g., by *N*-methyl-D-aspartate (NMDA)-receptor blockade with low-dose ketamine or memantine. In patients with established lesions and reduced antinociceptive inhibition in advanced disease stages, Bradl et al. propose medication with GABA agonists, e.g., baclofen, and monoamine reuptake inhibitors (3). However, evidence on its effects is limited, and none of these agents are routinely used clinically (3, 182).

Regarding the current state of pain research, multidisciplinary care in combination with tricyclic antidepressants (TCAs), serotonin norepinephrine reuptake inhibitors (SNRIs), gabapentanoids, and tramadol are the most effective options to treat central neuropathic pain (7, 183–185). Depending on the type of medication, a 3–8-week trial is recommended to evaluate its effect. If no significant pain relief can be achieved,

the dosage should be adjusted if the medication is tolerated by the patient. In a second step, alternative medication, combination therapy, or evaluation for neurostimulation may be considered (182, 186).

For the effect of medical neuropathic pain treatment on the patients' self-reported quality of life, we recommend the review by Mealy et al. (57).

First-line therapy

Tricyclic antidepressants like nortriptyline and amitriptyline show pain-relieving effects by inhibiting serotonin and noradrenaline reuptake (5, 182, 183, 187–189). Nortriptyline and amitriptyline should be started with a daily dose of 10–25 mg per os (p.o.) and increased to a maximal daily dose of 150 mg. Side effects comprise falls, cardiac arrhythmias, orthostatic dysregulation, urinary retention, and dry mouth, and occur especially in elderly people (182, 184, 187, 190, 191).

Serotonin and norepinephrine reuptake inhibitors (SNRIs) like duloxetine and venlafaxine enhance monoamine neurotransmission in the descending inhibitory spinal pathways, resulting in decreased sensation of pain (183–185, 187–189). SNRIs showed positive effects on neuropathic pain in MS but without a corresponding positive effect on the patients' quality of life. Duloxetine should be started with a daily dose of 30 mg p.o. and increased to a maximal daily dose of 60 mg. Venlafaxine should be prescribed with an initial daily dose of 37.5 mg p.o. and escalated to a maximal daily dose of 200 mg. Side effects include mainly renal and liver pathology (7, 57, 182–185, 187, 191).

Gabapentanoids are anticonvulsant drugs, including gabapentin and pregabalin. These drugs inhibit neurotransmitter release in the dorsal horn of the spinal cord by blocking presynaptic alpha-2-delta calcium channels, leading to pain relief. Gabapentin has been shown to effectively decrease pain intensity and improve quality of life of patients suffering from neuropathic pain after spinal cord injury. Gabapentin dosage should also be increased slowly, starting with a daily dose up to 600 mg p.o., and escalating to a maximum daily dose of 3,600 mg. Pregabalin should be initiated with a daily dose of 150 mg p.o. and escalated to a maximal daily dose of 600 mg. Effective pain release by gabapentanoids should be evaluated after a 4–6-week period with 2 weeks at the maximum tolerated dose. Side effects include mainly renal pathology (57, 182–184, 187–190, 192, 193).

For the treatment of trigeminal neuralgia, carbamazepine is considered to be a first-line therapy (184). Carbamazepine can be induced with a daily dose of 200–400 mg. Slowly increasing the dosage by 50 mg/day can be continued up to 600–1,200 mg/day. Especially in elderly people, the tolerance of dosages above 600 mg/day is often poor with important motor and sedative side effects. Apart from the treatment of trigeminal neuralgia, carbamazepine is considered a third-line therapy for neuropathic pain (5, 194, 195).

Medication of first-line treatment should be trialed over an average time period of 4–6 weeks. If sufficient pain relief is not achieved, progression to the next medication or next line of treatment should occur (182, 184, 187, 189, 191).

Second-line therapy, including tramadol and combination therapy

Most guidelines consider tramadol as a second-line therapy (182, 189–191, 196). However, for acute neuropathic pain and intermittent exacerbations of neuropathic pain, it is considered first-line medication (182, 189, 191). Tramadol primarily acts as a weak μ-opioid agonist and inhibits serotonin and norepinephrine reuptake. One study on neuropathic pain after spinal cord injury showed a positive effect of tramadol, in addition to stable regimen (57).

Tramadol should be started with a daily dose of 50 mg p.o. and escalated to a maximal daily dose of 400 mg. Side effects comprise seizure disorder and renal impairment, notably in the elderly (182).

Combination therapy is common in the treatment of neuropathic pain. The patient should be closely observed due to an increased risk for side effects (182, 187).

Cannabinoids have shown a positive impact on pain, sometimes additionally improving quality of life (5, 57). Cannabinoids bind to the presynaptic cannabinoid receptor, reducing calcium influx from voltage-gated calcium channels, and hyperpolarization. Consequently, cellular excitability decreases. However, cannabinoids are currently only licensed in Canada, Israel, and New Zealand for the treatment of neuropathic pain and the safety profile remains a matter of debate (5, 57).

Third-line therapy

For patients who do not tolerate first- or second-line therapy or do not benefit from adequate pain relief, medication with serotonin-specific reuptake inhibitors (SSRIs), anticonvulsants such as lamotrigine, carbamazepine, topiramate, sodium valproate, and NMDA antagonists, as well as tapentadol, can be considered in a specialized setting. Tapentadol is a newer weak μ-opioid agonist, and strong norepinephrine reuptake inhibitor that does not affect serotonin reuptake. Due to its increased potency compared to tramadol, it is currently considered third- or fourth-line treatment. Evidence grades of third-line treatments are currently relatively low (182, 184, 187–189, 191).

Fourth-line therapy

Neuromodulation, including intracranial stimulation, spinal cord stimulation, high-frequency and burst spinal cord stimulation, and dorsal root ganglion stimulation, is considered to be fourth-line treatment before starting medication with long-term opioids (55, 182). As mentioned above, one phase II study has shown a positive effect of Scrambler therapy for the treatment of neuropathic pain in 22 AQP4-positive NMOSD patients (55). Scrambler therapy is non-invasive technology with Food and Drug Administration (FDA) 510(k) approval for acute, chronic, and postoperative pain. Scrambler is a transcutaneous electric nerve stimulation (TENS) technique that stimulates ascending peripheral C-fibers. It aims to modify nociceptive pain by reorganizing maladaptive signaling pathways in the sensory cortex (197). The trial showed pain reduction from a median baseline numeric rating scale (NRS) pain score of 5.0–1.5 after 10 days of treatment. The median NRS score did not significantly

decrease in the sham arm (55). Currently, the lack of clear guidelines regarding the frequency and stimulation amplitude necessary to achieve sufficient pain reduction currently limits the use of TENS (57, 198, 199). A phase III study would be necessary to prove the effect of Scrambler therapy on pain, reduction in analgesic medication, and QoL in a larger NMOSD cohort (57, 198, 199).

Fifth-line therapy

Low-dose opioid medication to treat permanent neuropathic pain is currently considered as fourth- and fifth-line treatment, if appropriate conservative pharmacological and interventional management (neurostimulation) has failed (182). Opioids bind to an opioid receptor, inhibit adenylyl-cyclase, lead to neuronal hyperpolarization, and decrease neuronal excitability. However, opioids are considered to have a limited efficacy on neuropathic pain, and safety concerns require strict monitoring (7). Combination therapy of gabapentin and opioids provided better neuropathic pain relief than gabapentin or opioids alone but was associated with increased levels of adverse events (182).

Other pharmacological options

Baclofen has shown a positive effect on myelitis-related neuropathic pain in MS patients after intrathecal administration (5–1,200 μg/day). However, baclofen is currently not licensed for the treatment of neuropathic pain but rather indicated for medical treatment of spasticity (5, 146). Some patients may benefit from its positive overlapping effects.

Spasticity-Related Pain

Spasticity can cause discomfort and stiffness and lead to pain, e.g., back pain (194). Management should be patient focused and target function rather than aiming to reduce the degree of spasticity. Effectively reduced spasticity can accentuate profound underlying weakness, which contributes to the disability and potential complications of malposition. To avoid complications like pain, early treatment of spasticity should emphasize self-management strategies, education, and physiotherapy (200).

Oral pharmacological agents most commonly used to treat spasticity are baclofen, tizanidine, benzodiazepines, dantrolene, and gabapentin (3, 200). If oral medication does not reach the sufficient effect, antispastic agents such as botulinum toxin, intrathecal baclofen, phenol, and cannabinoids can be administered (200, 201). A positive effect on both spasticity and pain has been shown for baclofen, gabapentin, botulinum toxin, and cannabinoids (194, 202).

Oral baclofen

Baclofen is a derivate of ɤ-aminobutyric acid (GABA), which can cross the blood–brain barrier to a limited extent. GABA is a major inhibiting CNS transmitter of impulse transmission, and baclofen is thought have an antispastic effect through the inhibition of reflex neurological transmissions in the spinal cord. Baclofen should be administered starting with a daily dose of three times 5 mg p.o. and increased to a maximal daily dose of 80–100 mg. Common side effects include drowsiness, weakness, paresthesia, and dry mouth (194).

Intrathecal baclofen

As oral baclofen crosses the blood–brain barrier only to a small extent, the administration of baclofen directly to the site of antispastic action into the spinal canal improves efficacy and reduces potential side effects. A programmable infusion pump allows a continuous supply of the drug. Dosage has to be titrated over time. Long-term dosage used in MS-related spasticity ranged from 21 to 648 μg/day (194).

Botulinum toxin

The effect of botulinum toxin (botox, dysport) is to inhibit acetylcholine release at the neuromuscular junction. Despite permanent blockade, the clinical effect of botulinum toxin injections is reversible because of nerve sprouting and muscle reinnervation (200). The total dosage of botox should be ≤200 units and the dosage at one site ≤50 units. Dysport should be started with a total dosage of 500 units per patient. Depending on the clinical response, the dosage of dysport can range from 250 to 1,000 units (200).

Gabapentin

Gabapentin is increasingly used as first-line treatment for spasticity, most particularly since it is licensed for neuropathic pain. Its mode of action, administration, and side effects are described in the section of first-line neuropathic pain treatment.

Cannabinoids

The medical use of cannabinoids remains controversial. The two most studied cannabinoids in cannabis are tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the most psychoactive substance and CBD is the major non-psychotropic substance in cannabis. Two cannabinoid receptors, CB1 and CB2, have been identified. CB1 receptors are located in the CNS and on peripheral nerves. CB2 receptors are found on the cells of the immune system. Evidence for successful treatment of both spasticity and pain in MS is available for nabiximols (trade mark: sativex oral spray), oral cannabis extract (OCE) (trade mark: cannador), and synthetic THC (trade mark: dronabinol, nabilone). OCE and THC, however, show only patient-reported spasticity reduction but were not found to be effective to reduce objective measures of spasticity (201, 202).

Nabiximols is a natural cannabis extract with a 1:1 ratio of THC and CBD activating CB1 and CB2 receptors. Nabiximols is available as oromucosal spray with 2.7 mg of THC and 2.5 mg of CBD per actuation (202). Nabiximols has also shown good efficacy for painful tonic spasms (202).

Cannador is a natural cannabis extract with 2.5 mg of THC and 1.25 mg of CBD per capsule and is currently only available in a research setting in Europe. Dronabinol and nabilone are currently not licensed for the treatment of spasticity and pain (202).

Painful tonic spasms

In addition to physiotherapy, most frequent medications used to treat PTS are sodium-channel-blocking antiepileptic agents such as carbamazepine, oxcarbazepine, gabapentin, clonazepam, and phenytoin sodium, as well as benzodiazepines, barbiturates,

baclofen, and cannabinoids (3, 5, 31, 202, 203). It has been reported that topiramate at a daily dose of 400 mg can lead to the alleviation of PTS in AQP4-Ab-positive NMOSD (67) and one AQP4-Ab-positive NMOSD case with a favorable response to levetiracetam has been described (142). The highest efficacy for NMOSD-related PTS has been reported for carbamazepine, oxcarbazepine, and gabapentin (29, 32), with carbamazepine and oxcarbazepine outperforming gabapentin (32). These recommendations refer to a daily dose of 600–1,200 mg of oxcarbazepine and 100 mg three times a day of carbamazepine compared to 300 or 600 mg three times a day of gabapentin (32). Carbamazepine and oxcarbazepine act as voltage-gated sodium channel blockers and decrease neuronal excitability (32). Considering the emergence of important side effects of carbamazepine, oxcarbazepine has been recommended as a first-line treatment, preferably in combination with antispastic medication or antidepressants such as baclofen, pregabalin, or duloxetine (32).

Side effects of carbamazepine comprise ataxia, dizziness, somnolence, leukopenia, Steven–Johnson syndrome, and hyponatremia (204). In MS, carbamazepine can lead to a reversible exacerbation of neurological symptoms (205). Oxcarbazepine is better tolerated and safer than carbamazepine, especially with respect to CNS secondary side effects (ataxia, somnolence, and dizziness) and interaction with other medications (206). Side effects are often resolved after the titration period or with dosage adjustment. Frequently reported adverse effects include dizziness, headache, nausea, somnolence, fatigue, vomiting, back pain, diarrhea, tremor, skin rash, and blurred vision (206).

Non-pharmacological Treatment

Pain is more than just an unpleasant physical sensation. It can comprise emotional, social, and spiritual suffering. Therefore, treatment strategies should not only directly target pain relief. Besides psychotherapy or behavioral therapy, exercise programs for physical reconditioning, relaxation techniques, and patient education should be considered to target functional, affective, social, and spiritual consequences affecting the patients' quality of life (182, 207, 208). Currently, pain syndromes in NMOSD and MOGAD are insufficiently controlled by medication, and multidrug therapy has been associated with worse fatigue and depression (2, 27, 209). Therefore, future studies should explore the efficacy of a multimodal and multidisciplinary approach of pain management (27).

SUMMARY

Pain is a very frequent symptom in NMOSD and MOGAD and has a prevalence of over 80% with a severe impact on the quality of life of affected patients. Pain syndromes differ between NMOSD and MOGAD and can be an indicator for the respective disease type. Acute pain syndromes like retro-orbital pain, headache, or dysesthetic pain can be indicative for a first disease-related attack or a relapse of MOGAD-related optic neuritis, or NMOSD-related myelitis, brainstem, or cerebral affection. Chronic pain syndromes occur during the disease course and comprise primarily neuropathic pain and painful tonic spasms but also spasticity-related pain, back pain, and treatment-associated pain like osteoporosis. Acute ON-related pain seems to be particularly severe in MOGAD, while chronic neuropathic pain is more severe in NMOSD. Symptomatic treatment is currently insufficient to reduce pain intensity and improve the patients' quality of life. However, disease preventative immunosuppressive agents like tocilizumab and mycophenolate mofetil have shown a positive effect on pain reduction and should be further investigated. Patient care and future research should concentrate on a multidisciplinary approach of pain management, focusing on the respective pain type.

AUTHOR CONTRIBUTIONS

All authors contributed equally to the submitted work, analyzed the literature, wrote the manuscript, critically reviewed and revised the manuscript, and approved the final manuscript.

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OPINION
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The Expanding Clinical Spectrum of Myelin Oligodendrocyte Glycoprotein (MOG) Antibody Associated Disease in Children and Adults

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INTRODUCTION

The ability of MOG antibody (MOG-Ab) to induce autoimmune disease in animals has been known for decades (1), but it is only recently since the cell-based assay for MOG-Ab IgG_1 has been developed and commercialized, that it became possible to characterize clinical syndromes associated with MOG-Ab in humans. Early reports of MOG Associated Disease (MOGAD) emphasized its similarity to Neuromyeliits Optica Spectrum Disorder (NMOSD) (2–4). Indeed, a minority of patients with Aquaporin-4 antibody (AQ4-ab)-seronegative NMOSD—42% in one series–test positive for MOG-Ab (5). However, because the spectrum of MOGAD encompasses many NMOSD-atypical presentations, and because of differences in pathophysiology–AQ4-ab-positive NMOSD being an astrocytopathy and MOGAD being an oligodendrocytopathy—there is an increasing tendency to recognize AQ4-Ab-positive NMOSD and MOGAD as distinct entities (6–10).

In this review, we organize the clinical presentations of MOGAD by neuroanatomic compartments, while emphasizing the wide range of reported presentations. While this organization is useful for didactic purposes, it should be borne in mind that MOGAD may involve multiple regions of the CNS simultaneously– much more often than other CNS inflammatory diseases, and that half of MOGAD patients have active lesions in more than one location at the time of initial presentation (11–14) .

While no phenotype is restricted to any specific age group, some generalizations about clinical presentations of MOGAD in children and adults are possible. In children under the age of 11, ADEM-like phenotypes (encephalopathy, multifocal neurologic deficits and "fluffy" supratentorial cerebral lesions in a bilateral distribution) predominate, while in adolescents and adults, focal syndromes of optic neuritis or longitudinally extensive myelitis are more common (11, 15, 16) . Unlike Multiple Sclerosis (MS), where relapse rates are higher in children and decline with older age, in MOGAD the majority of children are not prone to frequent relapses, with 80% of having a monophasic course (17). However, the high rate of monophasic disease may be an overestimate due short follow up (right censoring) as recent case reports documented disease reemergence years and even decades after the initial episode in childhood (18, 19). Given the important differences in pediatric and adult MOGAD, we will qualify discussion of specific syndromes with reference to the respective

age group (with the caveat that the clinical distinctions across age groups are only generalizations).

OPTIC NEURITIS AND OTHER VISUAL PATHWAY PRESENTATIONS

Optic neuritis (ON) is the most common initial presentation of MOGAD in adolescence and adulthood, and a frequent presentation in pediatric patients (11, 16, 20). It is associated with a higher risk of subsequent relapse compared to other clinical presentations (11–13, 18). At the onset, vision loss is often severe and up to 80% of patients have bilateral optic nerve involvement, which is highly unusual in MS (12, 14, 21–24). Despite the severity of vision loss in the acute phase, recovery is usually good, especially in children: 89–98% of children had visual acuity to 20/25 or better at 6 months (14, 25). In adults, 6–14% of patients had permanent loss of vision ($\leq$20/200) in the affected eye (11, 13, 24).

Optic disc edema is rare in MS or NMOSD but is present in up to 86% of patients with MOGAD-ON (13, 21, 22, 24, 26, 27). Rarely, bilateral ON with disc edema can be mistaken for idiopathic intracranial hypertension especially if the patient also complains of headache and has elevated opening pressure on lumbar puncture; however lymphocytic pleocytosis in CSF and enhancement of optic nerve on orbital MRI point toward an inflammatory etiology and should prompt testing for MOG-Ab (28). Fulminant disc edema with peripapillary hemorrhages and "macular star" have been described in MOGAD-ON (29–31). Both of these findings are considered highly atypical for other inflammatory-demyelinating diseases and are more often associated with infectious and ischemic etiologies (29, 30).

Up to 50% of adults with MOG-ON have a recurrence of optic neuritis (11–13, 18) , which may be the only manifestations of MOGAD. Two rare previously described phenotypes, chronic relapsing inflammatory optic neuropathy (CRION)– a rare condition characterized by relapsing, steroid-dependent optic neuritis (32), and relapsing isolated optic neuritis (RION), have been associated with MOG-Ab in some cases (33, 34).

MRI of the orbits during acute MOG-ON typically shows longitudinally extensive optic nerve enhancement with a predilection for the anterior portion of optic nerves; the chiasm and optic tracts are less frequently affected (21, 31). "Optic perineuritis," characterized by inflammation of the optic nerve sheath and surrounding structures on MRI (35), is seen in up to 50% of cases of MOGAD-ON (**Figure 1A**) (13, 21, 25, 36, 37). Perineural enhancement is a feature that can help differentiate MOGAD from NMOSD or MS (13, 21, 25, 36, 37). Isolated cases of MOGAD perineuritis, involving the nerve sheath and surrounding structures but not the optic nerve, have also been reported (38, 39) . Rarely, uveitis and keratitis can occur simultaneously or subsequently to MOG-ON (38).

TRANSVERSE MYELITIS

MOG-Ab associated acute transverse myelitis is a relatively common presentation of MOGAD in adults, and can be seen in children as well (11). In some cases of MOG-TM, there is an antecedent history of infection or vaccination, but in most patients, no such history can be elicited (11, 18, 40). While MOG-TM is typically steroid-responsive with favorable long-term recovery, around 9% of patients have poor recovery (11). Recurrent myelitis, without any other syndromes of MOGAD, is reported in up to 5% of patients (41).

MOG-TM can affect any segments of the spinal cord but has a greater predilection for conus medullaris–reported in 11–41% patients–than other CNS inflammatory-demyelinating diseases (11, 18, 40, 42) . The involvement of the conus (**Figure 1D**) may explain the high incidence of neurogenic bowel and bladder symptoms (83%), and erectile dysfunction (54%) during acute phase (40), as well as in the long-term (11). There are also reports of a steroid-dependent myeloradiculitis in MOGAD with a longitudinally extensive transverse lesion from T12 to the conus with sacral nerve root enhancement (43).

Radiographically, MOG-TM is usually associated with a longitudinally extensive lesion spanning 3-4 vertebral segments (**Figure 1B**) (2, 18, 40, 44). In this respect, MOG-TM is similar to NMO-TM, but there are several radiographic differences between the two diseases. First, cord lesion of MOG-TM during the acute phase are much less likely to demonstrate gadolinium enhancement than in NMOSD: only 26% of MOG patients show enhancement vs. 78% of AQ4-ab-seropositive NMOSD (40). Secondly, spinal cord lesions in MOGAD can be multifocal: 62% of patients had $\geq$2 non-contiguous spinal cord lesions (40). The radiographic multifocality is in line with the notion that MOGAD has a tendency to affect multiple areas of CNS simultaneously.

MOG-TM affects both gray and white matter of the cord. The involvement of gray matter can manifest as linear hyperintensity of the central spinal canal ("pseudo-dilation," **Figure 1C**) (44), or as H-shaped T2-hyperintensity that outlines the anterior and posterior horns ("H-sign," **Figure 1F**) (2, 18, 40). The "H-sign" is suggestive, but not specific for MOGAD, reported in 29% of patients with MOG-TM and 8% of patients with NMO-TM (40). The predilection for the gray matter may explain why MOG-TM sometimes presents as acute flaccid paralysis (AFM) (45): in one series 10 out of 47 MOGAD patients (21%) met clinical criteria for AFM (40).

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM) AND OTHER CEREBRAL PRESENTATIONS

In young children, MOGAD frequently presents as ADEM or an ADEM-like syndrome (ADEM with optic neuritis, multiphasic disseminated encephalomyelitis) (16, 46–49). MRI of the brain typically shows large, ill-defined bilateral lesions frequently involving cortical and deep gray matter structures (**Figure 1G**) (50). Lesions may also involve subcortical white matter and corpus callosum as seen in **Figure 1E**. Optic nerves and spinal cord may be involved concurrently with brain (51). Recurrent ADEM or ADEM associated with recurrent optic neuritis (52, 53) are especially suggestive of MOGAD. Importantly, in children with clinical syndrome of encephalitis, MOGAD

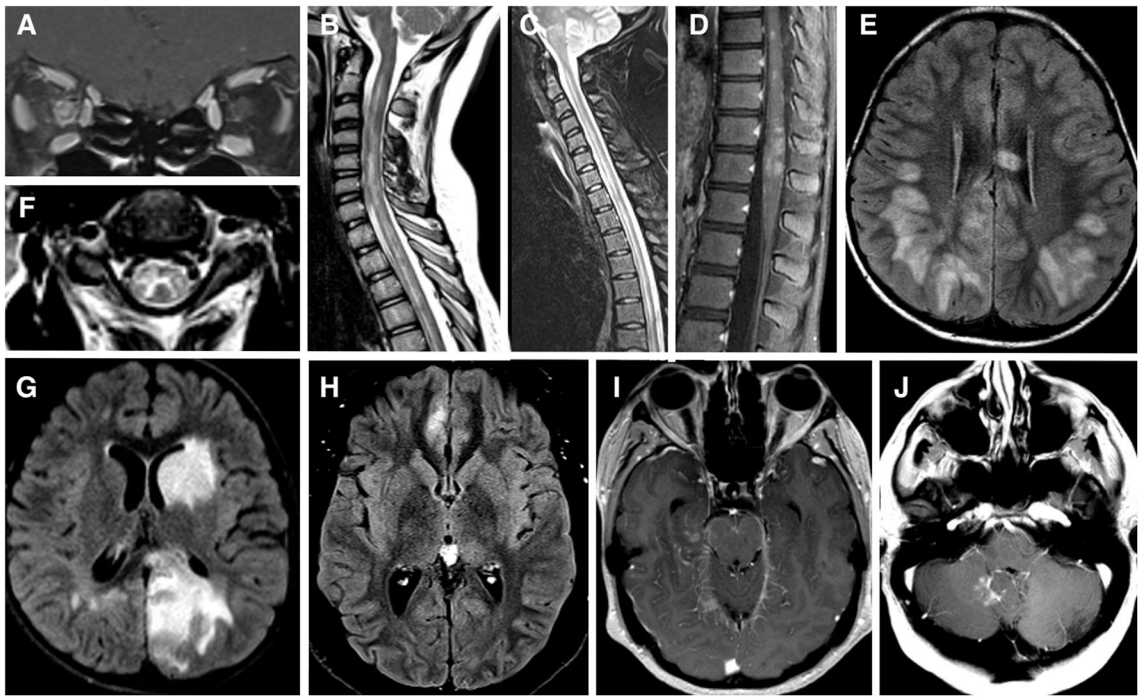

FIGURE 1 | (A) MRI brain T1 coronal post gadolinium contrast showing contrast enhancement of bilateral optic nerves and right optic nerve sheath consistent with perioptic neuritis. **(B)** MRI spine sagittal STIR showing longitudinal extensive patchy lesion spaning from cervical to thoracic cord. **(C)** MRI spine sagittal T2 showing hyperintense longitudinally extensive "pseudo-dilation" of central canal. **(D)** MRI spine sagittal T1 post gadolinium contrast showing patchy enhancement of the conus medullaris. **(E)** MRI brain axial FLAIR showing large subcortical and septal white matter lesions in a pediatric patient presenting with ADEM. **(F)** MRI brain axial T2 with hyperintense "H" sign outlining the central gray matter of the upper cervical cord in a teenager with myelitis. **(G)** MRI brain axial T2 with "fluffy" hyperintense lesion of gray and white matter of the left caudate and left occipital parietal regions in a pediatric patient who presenting with ADEM. **(H)** MRI brain axial T2 showing unilateral FLAIR hyperintensity and edema of right mesial frontal cortex in a patient with FLAMES syndrome. **(I)** MRI brain axial T1 post gadolinium contrast showing leptomeningeal enhancement of the midrain and right mesial temporal lobe. **(J)** MRI brain axial T1 post gadolinium contrast showing a lesion adjacent to the cerebellar vermis and dorsal medulla in a patient with brainstem syndrome and no other lesions.

diagnosis is possible even when MRI findings are not compatible with ADEM—for example, exclusive cortical or symmetric thalamic/basal ganglia involvement, or even normal MRI (54).

Cerebral involvement in adults is both less common and more restricted than in children, though there are exceptions (55). Syndrome of encephalitis with steroid-responsive seizures, also termed FLAMES (FLAIR-hyperintense Lesions and Anti-MOG-associated Encephalitis with Seizures), appears to be specific to MOGAD (20, 56–58). FLAMES patients present with focal-onset, tonic-clonic seizures, and have unilateral FLAIR hyperintensities with edema on MRI (**Figure 1H**). A review by Budhram et al. found 20 cases of FLAMES in the literature. The most common symptoms were seizures (85%), headache (70%), and fever (55%). CSF pleocytosis and cortical leptomeningeal enhancement (**Figure 1I**) were present in a minority of patients (57). All patients with FLAMES responded to high dose steroids with resolution of FLAIR changes. Of note, a number of patients developed ON either before or after seizures (56, 58, 59). Thus, the emergence of seizures in the context of ON or focal brain inflammatory lesions should prompt testing for MOG-Ab (52).

Isolated seizures may rarely be an index event in MOGAD. In one case, an adult patient presented with aphasic status epilepticus with initial MRI showing no abnormalities. Six months later the patient developed a tumefactive demyelinating lesion, with MOG-Ab testing positive several months later (60). A similar presentation has been described in four pediatric patients who presented with isolated seizures and normal brain MRI and developed MRI brain lesions months, and in one case years, later (61).

Several studies document an association between MOGAD and autoimmune encephalitis with NMDA-antibody (62–64). In a retrospective case review by Titulaer et al., 12 of 691 with NMDAR encephalitis patients (1.6%) tested positive for MOG-Ab. Some patients presented with MOGAD syndrome followed by encephalitis, others with encephalitis followed by MOGAD, and in some NMDA encephalitis and MOGAD were diagnosed concurrently. Three patients with NMDAR encephalitis and no clinical or MRI features to suggest MOGAD also tested positive for MOG-Ab (62).

Finally, mention should be made of rare cases when MOG-Ab was found in patients with pathologically-proven CNS vasculitis (65, 66). Two patients presented with fever, headache, confusion, and focal neurologic deficits (66), and the third had 9 months of progressive cognitive and behavioral decline

(65). MRI showed multifocal lesions in both the gray and white matter in two cases, one of whom also had open-ring contrast-enhancing lesions. The third case had findings of focal cortical encephalitis with gyriform FLAIR hyperintensities with edema, similar to findings seen in FLAMES. All three cases underwent brain biopsy, which showed small vessel perivascular inflammation, consistent with CNS vasculitis. However, fibrinoid necrosis, a pathologic requirement for small vessel CNS vasculitis, was absent in two of the cases (66, 67). Whether vasculitis should be regarded as a primary or secondary manifestation of MOGAD, or MOG-Ab is unrelated to vasculitis diagnosis, is difficult to determine given rarity of the association.

BRAINSTEM AND CEREBELLAR PRESENTATIONS

Brainstem involvement is seen in 30% of MOGAD patients, and is a risk factor for a higher disability at long-term follow-up and more active disease (68). In one large series brainstem inflammation occurred concomitantly with inflammation in optic nerves in 40% of cases, spinal cord in 89% cases and cerebrum in 66% of cases (68). However, there are reports of isolated brainstem inflammation as well (**Figure 1J**) (68). Any part of the brainstem can be affected, medulla being the most common (11, 68). Brainstem lesions are usually associated with disabling symptoms—weakness, cranial nerve deficits, ataxia, hypoventilation syndrome, impaired consciousness and, and, exceptionally, a fatal outcome (68). Area postrema syndrome (APS), one of the core syndromes of NMOSD, has also been described in MOGAD (11, 68–70).

MOGAD can mimic infective rhomboencephalitis when a patient presents with fever, CSF leukocytosis, brainstem enhancing lesions and leptomeningeal enhancement (44, 68), or Chronic Lymphocytic Inflammation with Pontine Perivascular Enhancement Responsive to Steroids (CLIPPERS), when MRI shows punctate, curvilinear enhancement in the pons (71–73). Whether CLIPPERS is a form of MOGAD or elicits an immune response to MOG-Ab is uncertain (73).

CONCLUSION

Since the first reports of MOG-Ab associated neurologic diseases appeared just a few years ago (4), the floodgates of case reporting have been opened and our understanding of MOGAD has grown exponentially. We now recognize certain clinical and radiologic features that help to differentiate MOG-ON and MOG-TM from NMOSD syndromes; that pediatric ADEM is frequently associated with MOG-Ab, especially if followed by episodes of ADEM or ON; that in adults, MOG can be associated with seizures and focal cerebral edema ("FLAMES syndrome," which appears to be unique to MOGAD); that brainstem inflammation is seen in a significant minority of MOGAD patients and may be an isolated finding; that MOG Ab is a common mimicker of infectious encephalitis (54) that MOG antibody is exceptionally rare in MS or AQ4 Ab positive NMOSD, but may co-exist with NMDA and other autoimmune encephalidites (64, 74). But many important questions remain. We need to determine sensitivity, specificity, positive and negative predictive value of MOG-Ab in the various neurologic syndromes; whether MOG-Ab shoud be tested in CSF, if it is negative in serum (75); whether various ultrarare presentions, such as isolated seizures without brain lesions, CLIPPERS, and a MOG-Ab-associated CNS vasculitis-type syndrome should be subsumed under MOGAD rubric. Most importantly, we need to better stratify risk of disease recurrence after the first or second episode and determine best treatments to prevent recurrence. With the rapid pace of progress, we can expect to answer these and other questions, and, no doubt, find new surprises along the way.

AUTHOR CONTRIBUTIONS

EP and IK wrote sections of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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OPINION
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Revisiting Transverse Myelitis: Moving Toward a New Nomenclature

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INTRODUCTION

Since its first use in case reports in the early twentieth century, the term transverse myelitis has become the preferred label for immune-mediated myelopathies. In 2002, diagnostic criteria created by an expert consensus defined transverse myelitis as a syndrome, divided into disease-associated transverse myelitis (i.e., myelitis attributed to a recognized disorder such as multiple sclerosis), and "idiopathic transverse myelitis" where no underlying cause is identified after comprehensive evaluation (1). In the years following publication of these criteria, neuroimaging research and biomarker discovery have provided important insights into the pathophysiology of many neuroimmune disorders. Accordingly, updates to clinical guidelines and diagnostic algorithms are needed to reflect a modern understanding of inflammatory myelopathies. Here, we discuss issues with the blanketed use of "transverse myelitis" and propose that the term be retired in future classification systems.

Immune-Mediated Myelopathies Are Radiographically Heterogeneous

While it has been widely propagated that the term transverse myelitis was first used by Dr. Suchett-Kaye in 1948, we find the term in case reports dating back to 1931 (2, 3). Though not explicitly stated in these reports, it is generally felt that the use of "transverse" was meant to reflect involvement of the entire axial plane of the spinal cord. While the significance of these early reports of spinal cord inflammation cannot be understated, it is now apparent that the landscape of immune-mediated myelopathies includes a wide spectrum of presentations with diverse imaging characteristics. The use of a catch-all term like transverse myelitis does not accurately reflect these complexities.

Involvement within the transverse plane is highly variable amongst myelopathies, and several causes have defining imaging characteristics. Multiple sclerosis classically causes a partial myelitis with predilection for the white matter tracts, while other causes may result in a mix of gray and white matter involvement (4). In recent years, outbreaks of a gray-matter centric myelitis associated with enterovirus D68 (EVD68) have resulted in flaccid paralysis in children (5). Such examples highlight the nuance in characterizing myelopathies in the transverse plane.

Furthermore, the extent of involvement within the rostral-caudal dimension also has important implications in myelopathy evaluations. Longitudinally-extensive myelitis (typically defined as greater than 3 vertebral segments long) carries different differential considerations than short-segment myelitis, and can be the hallmark of a recurrent disorder such as neuromyelitis optica spectrum disorder (4). Other spatial characteristics such as subpial involvement in sarcoidosis (6), also carry significant weight in the evaluation of immune-mediated myelopathies.

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"Transverse Myelitis" Does Not Inform on Etiology

The diagnostic approach to acute myelopathies can be challenging given the extensive differential diagnosis. While it is generally understood among clinicians that transverse myelitis implies an inflammatory etiology, the term does not make this distinction clear. Significant advances in the understanding of myelopathies allow for a more refined understanding of etiology, which should be reflected in terminology. Important discoveries, such as antibodies to aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG) are not accounted for in current clinical criteria of transverse myelitis (7). Furthermore, efforts to improve diagnosis of vascular myelopathies provide an opportunity to increase recognition and avoid risks of immunotherapies in certain patients (8). By labeling myelopathies by etiology, clinicians are better able to prognosticate and provide appropriate treatments, and patients will have a better understanding of their overall condition.

The Term Can Create Barriers in Communication Between Patients and Clinicians

The term transverse myelitis is often applied in two related, yet distinct, scenarios. In one instance, it is used to describe spinal cord disease associated with a neurologic or systemic autoimmune disorder. Patients with disease-associated myelitis frequently require close surveillance and treatment with immunotherapies to prevent new inflammation within the spinal cord or elsewhere. In the second scenario, the term transverse myelitis is used by clinicians as a shortened form of "idiopathic transverse myelitis," denoting an inflammatory myelopathy of unclear etiology. While neurologists are experienced in navigating transverse myelitis as both a syndrome and a distinct diagnostic entity, patients may not understand this difference when presented with a new diagnosis. Upon researching their disorder, they may grow concerned they have two unique neurological diseases, causing significant confusion and anxiety about their prognosis. Eliminating medical terms with multiple potential meanings from our lexicon serves to improve physician-patient communications and foster a constructive partnership.

PROPOSED FRAMEWORK FOR A NEW NOMENCLATURE

Given significant advances in myelopathy research, a revision to the 2002 working group criteria is needed. We propose a new naming convention for myelopathies, in which "myelitis" is used to describe myelopathies with evidence of inflammation on neuroimaging or cerebrospinal fluid analysis (**Figure 1**). This category would include both

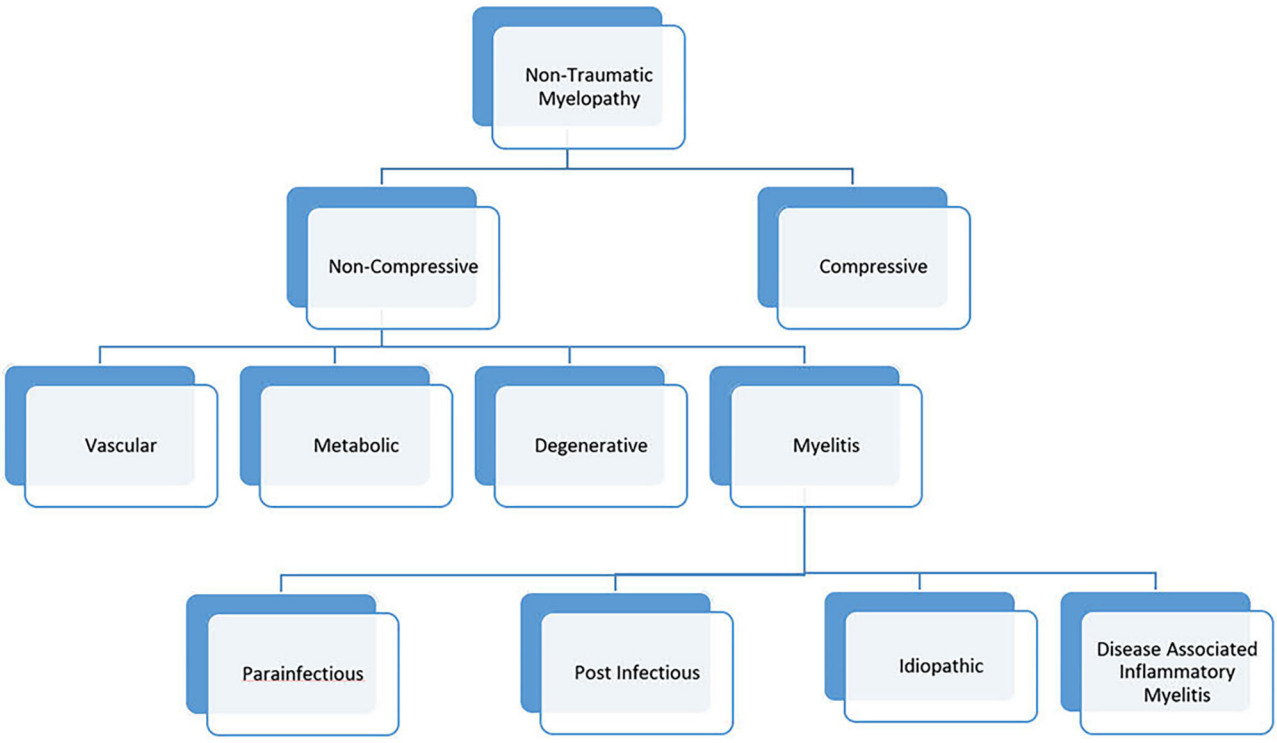

FIGURE 1 | Etiologic classification of myelopathies. In this proposed framework, the term "myelitis" is used to define any clinical presentation of myelopathy with evidence of inflammation on imaging or CSF analysis.

infectious and immune-mediated myelopathies to promote a comprehensive evaluation in myelitis. Cases of myelitis associated with an infectious pathogen could be further divided into para-infectious and post-infectious myelitis. This nomenclature would recognize that a parenchymal spinal cord infection (e.g., EVD68) can illicit an immune response causing damage (parainfectious) vs. a myelitis event caused by a deranged immune system that was triggered by a prior systemic infection (post-infectious). Similar to the 2002 criteria, myelitis associated with a known neuroimmune or systemic autoimmune disorder would be known as disease-associated inflammatory myelitis. After a comprehensive evaluation, myelitis of unknown etiology could be simply labeled "idiopathic myelitis."

In summary, it is time to retire the term transverse myelitis and overhaul current classification systems to cultivate modern, coherent definitions for myelitis.

AUTHOR CONTRIBUTIONS

KB participated in drafting and editing the manuscript. BG formulated the concept, and participated in drafting and editing the manuscript. Both authors contributed to the article and approved the submitted version.

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SYSTEMATIC REVIEW
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AQP4-IgG and MOG-IgG Related Optic Neuritis—Prevalence, Optical Coherence Tomography Findings, and Visual Outcomes: A Systematic Review and Meta-Analysis

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Background: Optic neuritis (ON) is a cardinal manifestation of multiple sclerosis (MS), aquaporin-4 (AQP4)-IgG-, and myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease. However, the prevalence of AQP4-IgG seropositivity and MOG-IgG seropositivity in isolated ON is unclear, and studies comparing visual outcomes and optical coherence tomography (OCT)-derived structural retinal measures between MS-ON, AQP4-ON, and MOG-ON eyes are limited by small sample sizes.

Objectives: (1) To assess the prevalence of AQP4-IgG and MOG-IgG seropositivity among patients presenting with isolated ON; (2) to compare visual outcomes and OCT measures between AQP4-ON, MOG-ON, and MS-ON eyes.

Methods: In this systematic review and meta-analysis, a total of 65 eligible studies were identified by PubMed search. Statistical analyses were performed with random effects models.

Results: In adults with isolated ON, AQP4-IgG seroprevalence was 4% in non-Asian and 27% in Asian populations, whereas MOG-IgG seroprevalence was 8 and 20%, respectively. In children, AQP4-IgG seroprevalence was 0.4% in non-Asian and 15% in Asian populations, whereas MOG-IgG seroprevalence was 47 and 31%, respectively. AQP4-ON eyes had lower peri-papillary retinal nerve fiber layer (pRNFL; −11.7 μm, 95% CI: −15.2 to −8.3 μm) and macular ganglion cell + inner plexiform layer (GCIPL; −9.0 μm, 95% CI: −12.5 to −5.4 μm) thicknesses compared with MS-ON eyes. Similarly, pRNFL (−11.2 μm, 95% CI: −21.5 to −0.9 μm) and GCIPL (−6.1 μm, 95% CI: −10.8 to −1.3 μm) thicknesses were lower in MOG-ON compared to MS-ON eyes, but did not differ between AQP4-ON and MOG-ON eyes (pRNFL: −1.9 μm, 95% CI: −9.1 to 5.4 μm; GCIPL: −2.6 μm, 95% CI: −8.9 to 3.8 μm). Visual outcomes were worse in AQP4-ON compared to both MOG-ON (mean logMAR difference: 0.60, 95% CI: 0.39 to 0.81) and MS-ON eyes (mean logMAR difference: 0.68, 95% CI: 0.40 to 0.96) but were similar in MOG-ON and MS-ON eyes (mean logMAR difference: 0.04, 95% CI: −0.05 to 0.14).

Conclusions: AQP4-IgG- and MOG-IgG-associated disease are important diagnostic considerations in adults presenting with isolated ON, especially in Asian populations. Furthermore, MOG-IgG seroprevalence is especially high in pediatric isolated ON, in both non-Asian and Asian populations. Despite a similar severity of GCIPL and pRNFL thinning in AQP4-ON and MOG-ON, AQP4-ON is associated with markedly worse visual outcomes.

Keywords: optic neuritis (ON), optical coherence tomography (OCT), neuromyelitis optica (NMO), neuromyelitis optica spectrum disorder (NMOsd), visual acuity, retina, aquaporin-4 (AQP4) IgG, myelin oligodendrocyte glycoprotein (MOG) IgG associated disease

INTRODUCTION

Optic neuritis (ON) is a cardinal manifestation of inflammatory conditions of the central nervous system (CNS), including multiple sclerosis (MS), aquaporin-4 (AQP4)-IgG-, and myelin oligodendrocyte glycoprotein (MOG)-IgG-associated disease (1–3). Early recognition of the underlying etiology of ON has important therapeutic implications, given that treatment approaches vary between these conditions, and therapies that are efficacious in MS may exacerbate or be ineffective in AQP4-IgG- or MOG-IgG-associated disease (4, 5). Furthermore, visual prognosis appears to differ between these conditions, with AQP4-IgG-associated ON (AQP4-ON) typically characterized by worse visual outcomes in comparison to MS-associated ON (MS-ON) and MOG-IgG-associated ON (MOG-ON) (6–8). In patients presenting with classic neuromyelitis optica (NMO) or acute disseminated encephalomyelitis (ADEM)-like phenotypes, clinical suspicion for AQP4-IgG- or MOG-IgG-associated disease is high, but diagnosis may be challenging and delayed in limited forms, such as isolated ON. Notably, the reported prevalence of AQP4-IgG and MOG-IgG seropositivity among patients presenting with isolated ON varies significantly between studies, and the available literature suggests that seropositivity for these antibodies is more common in non-white populations with ON (9, 10).

Optic nerve injury results in thinning of the retinal nerve fiber layer (RNFL), which is mainly composed of the unmyelinated axons of the retinal ganglion cells (RGCs), and the ganglion cell layer, which contains the cell bodies of the RGCs (1). Optical coherence tomography (OCT) is an imaging technique that utilizes near-infrared light to obtain high-resolution images of the retina *in vivo* and enables the quantitative evaluation of individual retinal layers, allowing assessment of the integrity of the RGC axons [peri-papillary RNFL thickness (pRNFL)] and RGC cell bodies [composite thickness of the macular ganglion cell + inner plexiform layer (GCIPL)] (11, 12). OCT studies have generally demonstrated increased severity of pRNFL and GCIPL thinning following AQP4-ON or MOG-ON, as compared to MS-ON (8). However, given the rarity of AQP4-IgG- and MOG-IgG-associated disease, OCT studies have examined relatively small numbers of participants, not permitting an in-depth characterization and comparison of the retinal neuro-axonal injury that occurs in these conditions.

The primary objectives of this systematic review and meta-analysis were as follows: (1) To determine the seroprevalence of AQP4-IgG and MOG-IgG among patients presenting with isolated ON, and to explore variation in prevalence by geographical location/ethnicity. (2) To assess pRNFL and GCIPL thicknesses in AQP4-ON and MOG-ON eyes (including comparisons to MS-ON and healthy controls), and to investigate whether distinct patterns of retinal injury are associated with AQP4-ON or MOG-ON. (3) To compare visual outcomes between AQP4-ON, MOG-ON, and MS-ON eyes.

Abbreviations: AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; ON, optic neuritis; pRNFL, peripapillary nerve fiber layer; GCIPL, ganglion cell/inner plexiform layer; VA, visual acuity; OCT, optical coherence tomography; logMAR, logarithm of the minimum angle of resolution; N, number of eyes; SD, standard deviation; CI, confidence interval.

METHODS

The present systematic review and meta-analysis is reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) statement and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (13, 14).

Search Strategy and Study Selection

The PubMed electronic database was queried using search algorithms (available in detail in **Supplementary Table 1**) including the following keywords: "mog," "myelin oligodendrocyte glycoprotein," "nmo," "neuromyelitis optica," "aquaporin 4," "aqp4," "aquaporin-4," "optic neuritis," "optical coherence tomography," "retina," "nerve fiber layer," "ganglion cell," "vision," "visual outcome," and "disability." Databases were last accessed on October 29, 2019.

All retrieved studies were imported into the Covidence platform for study eligibility screening and inclusion. The studies were screened independently by two reviewers (AGF and LM), and in cases of disagreement, another reviewer (ESS) was consulted.

For our first study objective (assessing the prevalence of AQP4-IgG and MOG-IgG seropositivity in isolated ON), we identified all studies that reported the frequency of AQP4-IgG and/or MOG-IgG seropositivity in a cohort of patients presenting with an initial episode of isolated (monosymptomatic) unilateral or bilateral ON. Study exclusion criteria included the following: (1) studies that did not report the number of

patients with pre-existing diagnoses of MS or neuromyelitis optica spectrum disorder (NMOSD) or with prior episodes of neurological dysfunction, (2) $n < 10$ participants, and (3) unclear criteria for participant inclusion or inclusion only of selected high-risk patient subgroups (e.g., bilateral or recurrent ON, normal brain MRI). As secondary analyses, we also identified studies reporting the prevalence of AQP4-IgG and MOG-IgG seropositivity in patients presenting with recurrent isolated (unilateral or bilateral) ON or bilateral simultaneous/rapidly sequential ON.

For our second study objective (comparison of OCT measures between AQP4-ON, MOG-ON, and MS-ON eyes), we identified studies that reported OCT measures from patients with AQP4-ON and/or MOG-ON and included data permitting at least one of the following comparisons: (1) AQP4-ON vs. healthy control (HC) eyes, (2) MOG-ON vs. HC eyes, (3) AQP4-ON vs. MOG-ON eyes, (4) AQP4-ON vs. MS-ON eyes, and (5) MOG-ON vs. MS-ON eyes. Comparison of MS-ON vs HC eyes was not performed as this was not the focus of our study and this has been reported in a recent large meta-analysis (15).

Similarly, for our third study objective (comparison of visual outcomes in AQP4-ON, MOG-ON, and MS-ON eyes), studies were included that reported visual outcomes in AQP4-ON and/or MOG-ON and included data permitting at least one of the following comparisons: (1) AQP4-ON vs. MOG-ON, (2) AQP4-ON vs. MS-ON, and (3) MOG-ON vs. MS-ON.

For our analyses of OCT and visual outcomes, we only included articles with assessments of ON eyes performed at least 3 months after an episode of acute ON. For studies that collected the data necessary for our analyses but did not report the results in a manner appropriate for our purposes (e.g., not separating eyes by ON history, reporting combined estimates for AQP4-IgG seropositive and seronegative NMOSD patients), corresponding authors were contacted and were asked to provide additional information. If this information was not made available, these studies were excluded. Additional unpublished data from the cohorts included in the manuscripts was occasionally provided, at the discretion of the corresponding authors. For the OCT component, studies were also excluded if they did not utilize spectral-domain OCT.

When two or more similar studies (fulfilling inclusion criteria) were reported from the same institution or author with unclear participant overlap between studies, authors were contacted to provide clarification. When unable to obtain this information, the publication with the highest number of participants was included in the analysis. Case reports, reviews, or studies published in a non-English language were excluded. Reference lists of relevant review articles were also examined to identify studies that may have been missed during the initial database search.

Data Extraction and Outcomes

Two investigators (AGF and LM) independently conducted the data extraction, and any discrepancies were resolved by consensus.

For assessment of the prevalence of AQP4-IgG and MOG-IgG in isolated ON, we recorded the total number of patients presenting with an isolated ON in each study (excluding patients with a prior neurological history), and the number of patients that tested positive for AQP4-IgG or MOG-IgG.

The main outcome measures for OCT analyses were the thicknesses (μm) of the pRNFL and the macular GCIPL [or macular ganglion cell layer complex (GCC), which additionally includes the macular RNFL] of eyes with a history of ON, and this information was recorded for each group as the mean ± SD. Additional data on quadrantal pRNFL thicknesses were collected, if available. For studies that reported OCT measures as median/interquartile range and the corresponding authors had not provided the mean ± SD, a normal distribution was assumed to calculate the SD. If macular OCT measures were reported as volumes, they were converted to thicknesses according to the formula: Thickness = Volume/Surface Area. For macular measures, the region of interest varied between studies (e.g., perifoveal area of 3 or 6 mm in diameter, including or excluding the foveal subfield); thus, the surface area was calculated separately for each study, depending on the utilized protocol. While not a primary focus of this study, we also recorded (when available) the prevalence of microcystoid macular pathology (MMP; also referred to as microcystic macular edema in the literature) in AQP4-ON and MOG-ON eyes (16–18).

For visual outcomes, the main outcome measures were the logarithm of the minimum angle of resolution (logMAR) in eyes with a history of ON and the percentage of affected eyes with high-contrast visual acuity (VA) worse than 20/200.

For MOG-IgG serostatus, only studies that reported using cell-based assays (CBAs) for testing were included, whereas for AQP4-IgG serostatus, studies utilized a variety of assays, including CBAs, indirect tissue immunofluorescence, enzyme-linked immunosorbent assay (ELISA) or fluorescence-based immunoprecipitation assay (FIPA).

Data were extracted from cross-sectional cohorts and from a single time point from longitudinal studies (typically the baseline assessment).

Data Synthesis and Statistical Analysis

For all study objectives, studies of pediatric participants were examined separately.

We estimated the pooled AQP4-IgG and MOG-IgG prevalence in isolated ON separately for Asian and non-Asian populations, given the divergence of prevalence between studies in these populations, and evidence supporting higher prevalence of NMOSD in Asian populations (10). Given the relatively low prevalence of these disorders in some of the included studies (estimates close to 0%), we utilized the variance-stabilizing double arcsine transformation method (19).

OCT measures were handled as continuous variables. Results are presented as mean differences between the groups of interest. OCT measures from different spectral-domain OCT devices were analyzed together, similar to a prior large meta-analysis in MS, given that, at a group level, it appears that data are comparable across devices and segmentation algorithms (15, 20). In terms of macular OCT measures, the GCIPL and GCC were analyzed together, given that the GCIPL accounts for the majority of the thickness of the GCC. Additionally, we estimated the pooled prevalence of MMP in AQP4-ON and MOG-ON eyes.

TABLE 1 | Characteristics of studies included in the meta-analysis for our first study objective (assessing the prevalence of AQP4-IgG and MOG-IgG seropositivity in isolated ON).

Patients with monosymptomatic ON

Study	Time period	Study setting	Adult/pediatric	Age	Female sex	Race	AQP4-IgG assay	MOG-IgG assay	Bilateral ON	Important considerations
Carnero Contentti et al. (39)	2009–2015	Argentina	Adult	Mean (±SD): 31.6 (±11.1) in AQP4-IgG positive 38.4 (±12.9) in AQP4-IgG negative	47% in AQP4-IgG positive 80% in AQP4-IgG negative	–	Tissue-based indirect IF	–	32%	–
Chen et al. (40)	1988–1991	Multicenter–USA	Adult (18–45)	Mean (±SD): 32.8 (±6.9)	76%	85% Caucasian	CBA	CBA	0%	Recruited only patients with unilateral ON
Chen et al. (41)	2015–2016	China	Pediatric	Range: 5–18. Mean (±SD): 11.8 (±3.3) in MOG-ON; 16.9 (±0.8) in AQP4-ON	70%	–	CBA	CBA	63%	–
Cobo-Calvo et al. (22)	2014–2016	France	Mixed adult pediatric	Median (range): 16.8 (1.7–64.9) for MOG-ON	52% in MOG-IgG positive	93% Caucasian in MOG-IgG positive	CBA	CBA	22% in MOG-IgG positive	–
Dale et al. (23)	–	Australia	Pediatric	Median (range): 8 (1.3–15.3)	51%	–	ELISA	CBA	67%	–
Deschamps et al. (42)	2014–2016	France	Mixed adult pediatric	Range: 16–57	75%	–	CBA	CBA	10%	MOG AQP4 only tested if patient did not meet diagnostic criteria for MS
Ducloyer et al. (24)	2017–2018	France	Adult	Mean (±SD): 35.6 (±13.8)	68%	–	–	CBA	15%	–
Hacohen et al. (25)	2009–2011	UK France	Pediatric	Range: 1.3–15.8	57%		–	CBA	–	–
Jarius et al. (26)	–	Multicenter–Europe	Mixed adult pediatric	Median (range): 34 (14–72)	75%	96% Caucasian	FIPA	–	22%	–
Kim et al. (28)	2013–2014	South Korea	Adult	Mean (±SD): 38.7 (±11.5) in AQP4-IgG positive 42.3 (±14.7) in AQP4-IgG negative	67%	Asian	CBA	–	7%	–
Kim et al. (27)	2007–2016	South Korea	Adult	Mean (±SD): 43 (±13)	63%	–	CBA	–	21%	–
Liu et al. (29)	2014–2016	China	Adult	Range: 18–72	80%	·	CBA	CBA	20%	–
Petzold et al. (30)	1995–2007	UK	Mixed adult pediatric	Range: 15–71	67%	–	CBA	CBA	–	–
Rostasy et al. (31)	2004–2010	Germany Austria	Pediatric	Median (range): 13 (2–18)	73%	–	CBA	CBA	8%	–

(Continued)

TABLE 1 | Continued

Study	Time period	Study setting	Adult/pediatric	Age	Female sex	Race	AQP4-IgG assay	MOG-IgG assay	Bilateral ON	Important considerations
Patients with monosymptomatic ON										
Soelberg et al. (32)	2014–2016	Denmark	Mixed adult pediatric	Median (range): 38 (16–66)	69%	100% Caucasian	CBA	CBA	8%	–
Song et al. (33)	2016–2017	China	Pediatric	Mean (±SD): 10.6 (±4.4)	56%	–	CBA	CBA	52%	–
Storoni et al. (34)	2009–2010	UK	Adult	–	–	61% Caucasian 14% African 15% Asian 10% Other	FIPA	–	–	–
Waters et al. (35)	2004–2017	Canada	Pediatric	Median (IQR): 10.8 (6.2–13.9)	51%	–	CBA	CBA	–	–
Zhao et al. (36)	2015–2016	China	Adult	Mean (±SD): 31.3 (±5.3) for MOG-ON 40.7 (±15.3) for AQP4-ON 31.3 (±13.2) for other	71%	–	CBA	CBA	25%	–
Zhou et al. (38)	2013–2014	China	Mixed adult pediatric	Range: 13–73	66%	–	CBA	–	26%	–
Zhou et al. (37)	2009–2010	China	Adult	Median (range): 36.8 (18–73)	66%	–	CBA	–	24%	–
Patients with recurrent isolated ON										
Benoilid et al. (43)	2010–2011	France	Adult	Mean (±SD): 33.1 (±14.8)	73%	97% Caucasian	CBA	–	33%	–
de Seze et al. (44)	2005–2007	France	Adult	Mean (±SD): 35.4 (±11.9)	92%	–	Tissue-based indirect IF	–	–	–
Jarius et al. (26)	–	Multicenter - Europe	Mixed adult pediatric	Median (range): 34 (14–72)	75%	96% Caucasian	FIPA	–	22%	
Jitprapaikulsan et al. (45)	2010–2017	USA	Mixed adult pediatric	Range: 12–72	72%	83% Caucasian	CBA	CBA	22%	–
Li et al. (46)	2008–2013	China	Adult	Mean (±SD): 39.0 (±15.4)	75%	–	CBA	–	23%	–
Martinez-Hernandez et al. (47)	2005–2014	Spain	Mixed adult pediatric	Median (range): 28 (5–65)	71%	–	CBA	–	45%	Only recruited patients with normal or nonspecific MRI findings

AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; ON, optic neuritis; CBA, cell-based assay; FIPA, Fluorescence based immunoprecipitation assay; IF, immunofluorescence; ELISA, enzyme-linked immunosorbent assay; MRI, magnetic resonance imaging; IQR, interquartile range; SD, standard deviation.

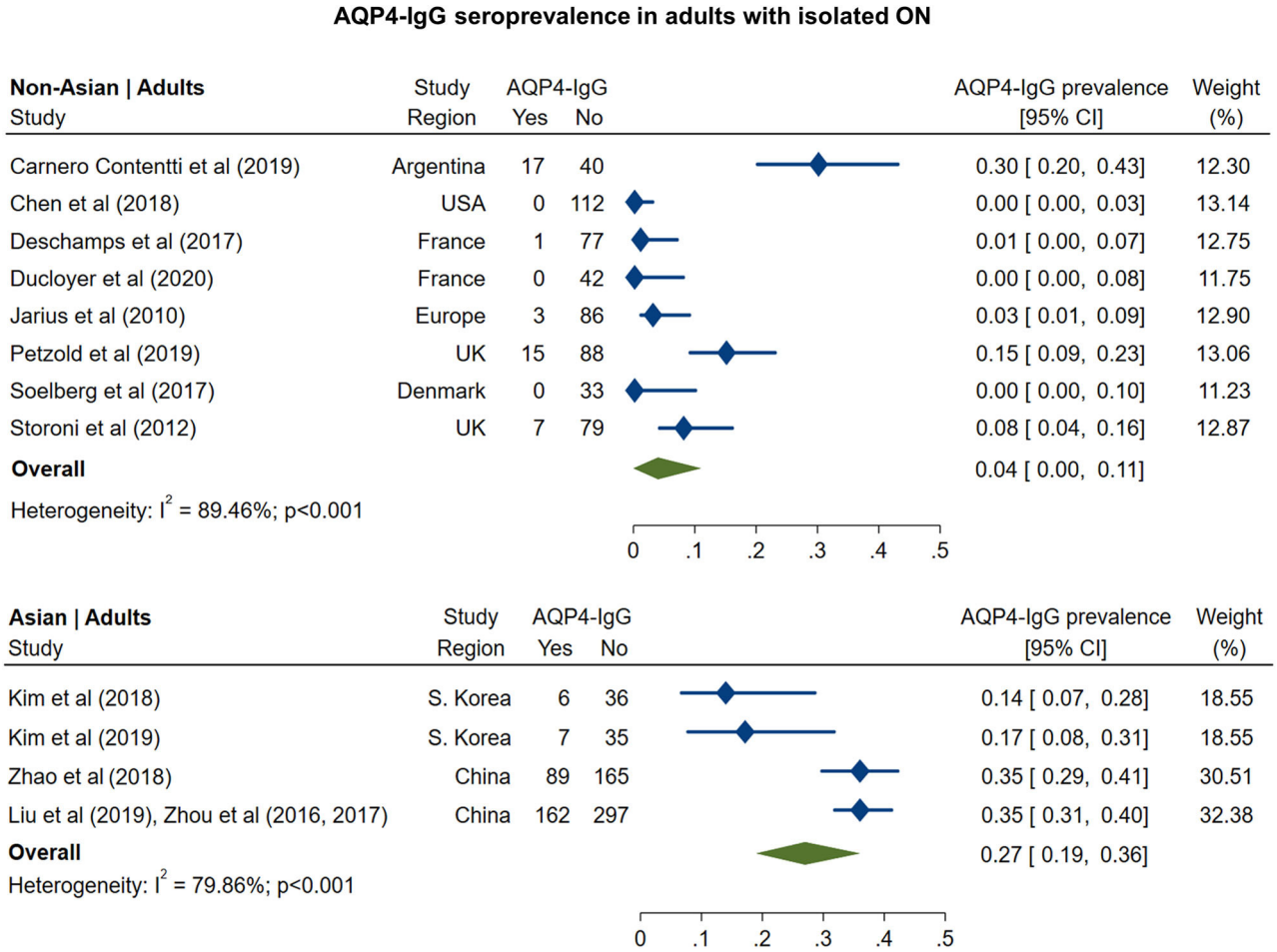

FIGURE 1 | Forest plot of the prevalence of AQP4-IgG seropositivity in adults with monosymptomatic isolated ON.

For studies reporting VA measurements in logMAR format, logMAR was handled as a continuous variable and results are presented as mean differences between groups of interest. For studies reporting visual outcomes as percentage of eyes with VA worse than 20/200, we calculated the relative risk of this unfavorable visual outcome (i.e., VA $<$ 20/200). Studies reporting visual outcomes in any other formats were included in the qualitative, but not the quantitative, synthesis.

All analyses were performed with random effects models, since the heterogeneity was expected to be high due to varying OCT devices, differing scan protocols and macular regions of interest, and differences in the demographic and clinical characteristics of the participants across studies. To minimize the impact of the study heterogeneity, we did not compare OCT measures or visual outcomes across studies; rather, we estimated between-group differences in each study and then performed a pooled analysis of these estimated differences. We assessed for heterogeneity between the included studies using the I^2 estimate. $I^2 > 75\%$ was considered to indicate significant heterogeneity.

Statistical analyses were performed with Stata version 16 (StataCorp, College Station, TX). For the meta-analysis of prevalence, the Stata package "metaprop" was used (21).

RESULTS

Prevalence of AQP4-IgG and MOG-IgG Seropositivity in Monosymptomatic ON

Study Selection and Study Characteristics

A PubMed search identified 1,187 records. Of these, 197 articles were selected and assessed for eligibility at the full-text level. After careful evaluation, 21 studies, comprising 1,876 patients, were included that met the inclusion criteria (22–42). The detailed flow chart is presented in **Supplementary Figure 1**. For our secondary analysis in patients with recurrent ON, six studies, comprising 510 patients, were included that met our inclusion criteria (26, 43–47). There was an insufficient number of studies/participants to analyze the prevalence of AQP4-IgG or MOG-IgG seropositivity among patients presenting with isolated bilateral simultaneous or sequential ON. The included studies are summarized in **Table 1**.

AQP4-IgG Prevalence in Monosymptomatic ON

The pooled prevalence of AQP4-IgG seropositivity in adults with isolated ON (**Figure 1**) was 4% in non-Asian cohorts (95% CI: 0 to 11%) and 27% in Asian cohorts (95% CI: 19 to 36%). In pediatric cohorts (**Figure 2**), similar to adults, AQP4-IgG seroprevalence was again higher in Asian cohorts (15%; 95% CI: 9 to 23%), whereas in the three available studies of non-Asian populations, the prevalence of AQP4-IgG seropositivity was 0.4% (95% CI: 0 to 3.2%).

MOG-IgG Prevalence in Monosymptomatic ON

The prevalence of MOG-IgG seropositivity in adults with isolated ON (**Figure 3**) was 8% in non-Asian cohorts (95% CI: 4 to 13%) and 20% in Asian cohorts (95% CI: 16 to 24%). In pediatric cohorts (**Figure 4**), in contrast to adults, MOG-IgG seroprevalence was higher in non-Asian populations (47%; 95% CI: 36 to 58%) relative to Asian populations (31%; 95% CI: 22 to 40%), but both had higher prevalence compared to adults.

AQP4-IgG and MOG-IgG Prevalence in Recurrent Isolated ON

In non-Asian cohorts, the prevalence of AQP4-IgG seropositivity in patients with recurrent isolated ON (**Figure 5**) was 16% (95% CI: 12 to 21%). Only one study reported the frequency of AQP4-IgG seropositivity in Asian patients with recurrent ON (41%; 95% CI: 31 to 51%). For MOG-IgG, we were able to identify only two studies fulfilling the inclusion criteria; based on these studies (**Figure 6**), the prevalence of MOG-IgG seropositivity in non-Asian cohorts with recurrent ON was 15% (95% CI: 11 to 19%). No eligible pediatric studies were identified.

OCT Findings in AQP4-ON and MOG-ON

Study Selection and Study Characteristics

A PubMed search identified 351 records. Of these, 98 articles were selected and assessed for eligibility at the full-text level. After careful evaluation, 31 studies were included that met the inclusion criteria (8, 29, 33, 36, 41, 48–73). The detailed flow chart is presented in **Supplementary Figure 2**. The included studies, comprising a total of 814 HC eyes, 611 AQP4-ON eyes, 237 MOG-ON eyes, and 361 MS-ON eyes, are summarized in **Table 2**.

OCT Measures in Adult ON

As expected, pRNFL and GCIPL thicknesses were lower in AQP4-ON and MOG-ON eyes, as compared with HC eyes (**Supplementary Figures 3, 4**). The pooled mean pRNFL difference for AQP4-ON eyes was −38.0 μm (95% CI: −46.5 to −29.6 μm) and −35.7 μm (95% CI: −43.1 to −28.4 μm) for MOG-ON eyes. The pooled mean GCIPL difference was −25.8 μm (95% CI: −29.1 to −22.5 μm) for AQP4-ON eyes and −26.7 μm (95% CI: −32.6 to −20.8 μm) for MOG-ON eyes.

AQP4-ON eyes had lower pRNFL (−11.7 μm; 95% CI: −15.2 to −8.3 μm) and GCIPL (−9.0 μm; 95% CI: −12.5 to −5.4 μm) thicknesses compared with MS-ON (**Figure 7**), but there were no differences in these OCT measures between AQP4-ON and

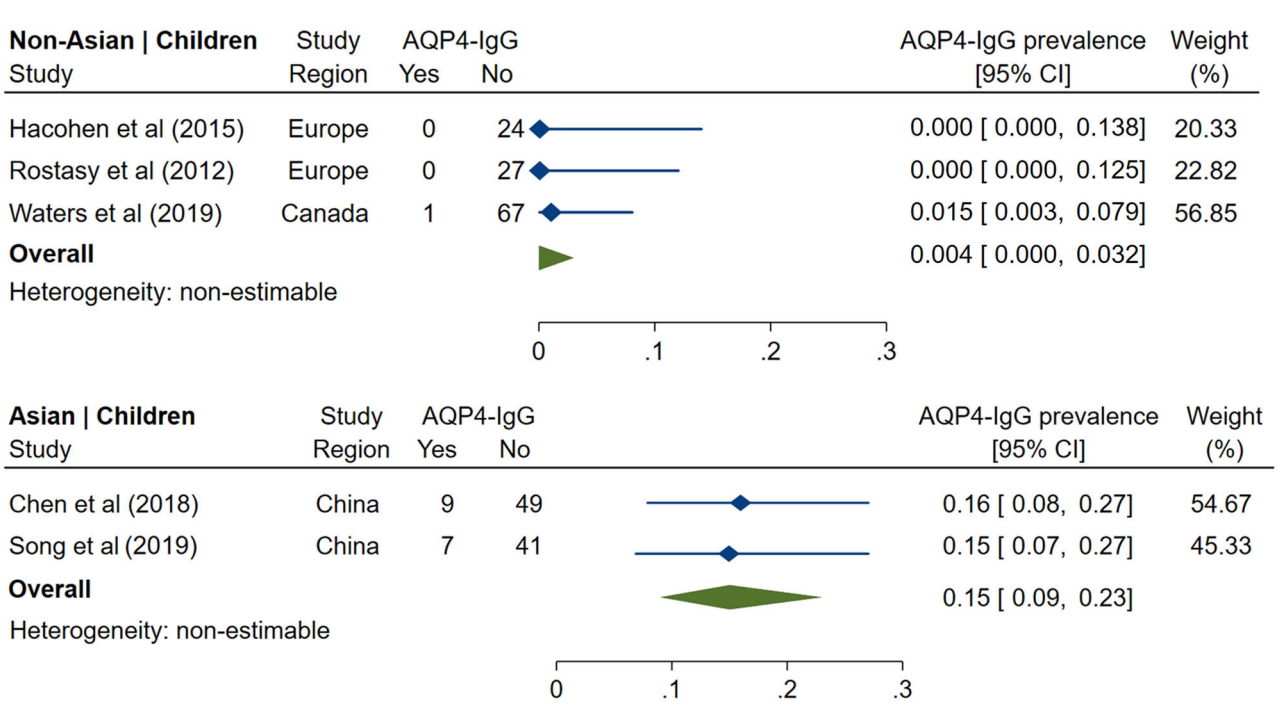

FIGURE 2 | Forest plot of the prevalence of AQP4-IgG seropositivity in children with monosymptomatic isolated ON.

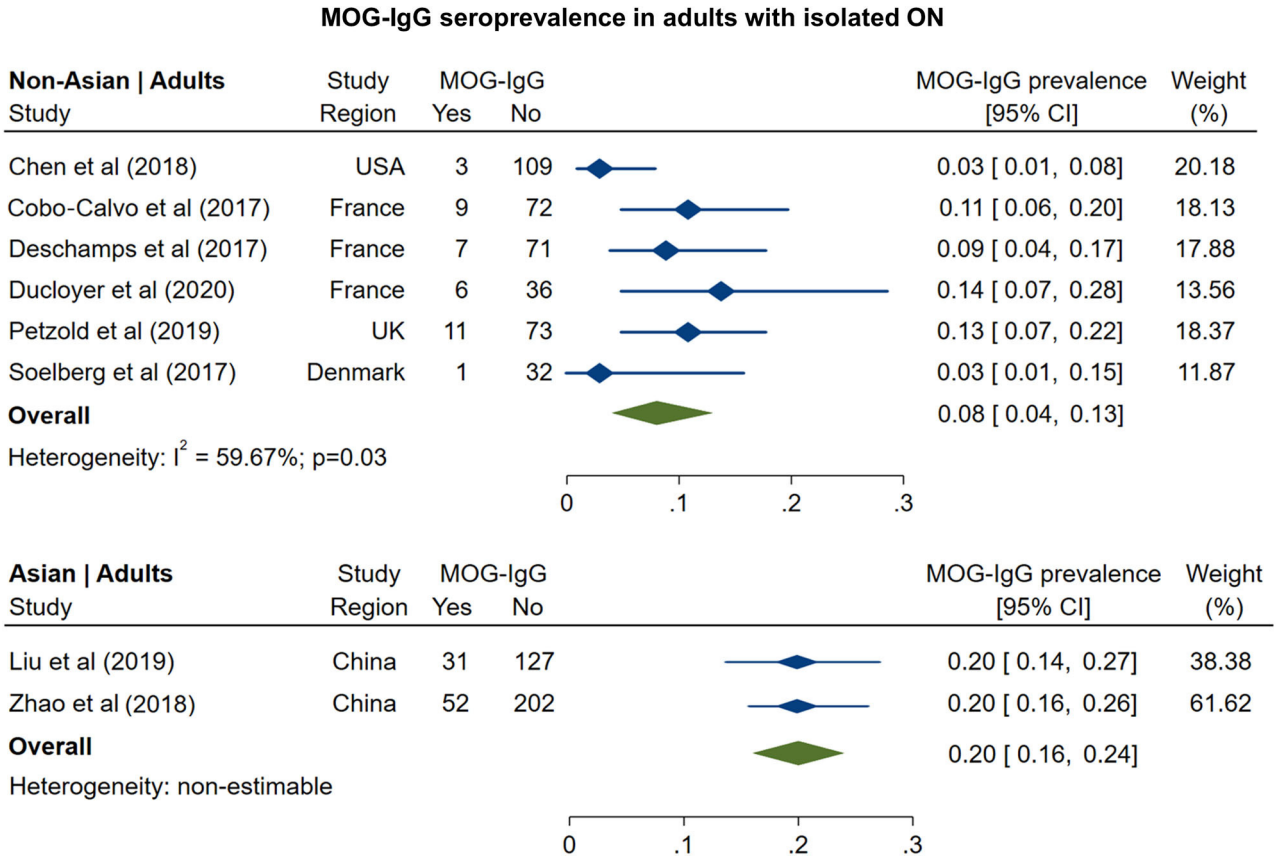

FIGURE 3 | Forest plot of the prevalence of MOG-IgG seropositivity in adults with monosymptomatic isolated ON.

MOG-ON eyes (pRNFL: −1.9 μm; 95% CI: −9.1 to 5.4 μm; GCIPL: −2.6 μm; 95% CI: −8.9 to 3.8 μm; **Figure 8**). Similar to AQP4-ON, when comparing MOG-ON to MS-ON eyes (**Figure 9**), we found that MOG-ON eyes had lower pRNFL (−11.2 μm; 95% CI: −21.5 to −0.9 μm) and GCIPL thicknesses (−6.1 μm; 95% CI −10.8 to −1.3 μm).

When examining quadrantal pRNFL thicknesses, we did not observe any differences between AQP4-ON and MOG-ON (**Supplementary Figure 5**). However, AQP4-ON was associated with lower nasal, inferior, and superior quadrant pRNFL thicknesses compared with MS-ON (**Supplementary Figure 6**), but no difference was observed in temporal pRNFL thickness between AQP4-ON and MS-ON eyes (−1.4 μm, 95% CI: −5.9 to 3.1 μm). All quadrantal pRNFL thicknesses were lower in MOG-ON compared to MS-ON eyes (**Supplementary Figure 7**), but these findings did not achieve statistical significance, likely due to the small sample size.

The prevalence of MMP in ON eyes was reported in a small number of studies. The pooled prevalence of MMP was 15% in AQP4-ON eyes (95% CI: 7 to 24%; $n = 7$ studies) and 21% in MOG-ON eyes (95% CI: 11 to 32%; $n = 6$ studies), which is higher compared to the reported prevalence of MMP in MS-ON eyes (∼6%) (16, 17).

OCT Measures in Pediatric ON

We were able to identify four studies reporting OCT findings in pediatric ON, and OCT measures could be pooled for three studies (33, 41, 67). Similar to adults, pRNFL thickness did not differ between pediatric AQP4-ON and MOG-ON eyes (7.4 μm, 95% CI: −17.1 to 32.0 μm; **Supplementary Figure 8**). Further comparisons between groups of interest were not possible based on the available data.

Visual Outcomes in AQP4-ON and MOG-ON

Study Selection and Study Characteristics

A PubMed search identified 624 records. Of these, 202 articles were selected and assessed for eligibility at the full-text level. After careful evaluation, 35 studies were included that met the inclusion criteria (8, 29, 30, 33, 36, 39, 41, 45, 47, 48, 51–54, 57, 59, 63, 65, 66, 68, 69, 71, 72, 74–85). The detailed flow chart is presented in **Supplementary Figure 9**.

The included studies with their baseline characteristics are summarized in **Table 3**. In our quantitative synthesis, we included 26 studies comprising 747 AQP4-ON eyes, 426 MOG-ON eyes, and 524 MS-ON eyes.

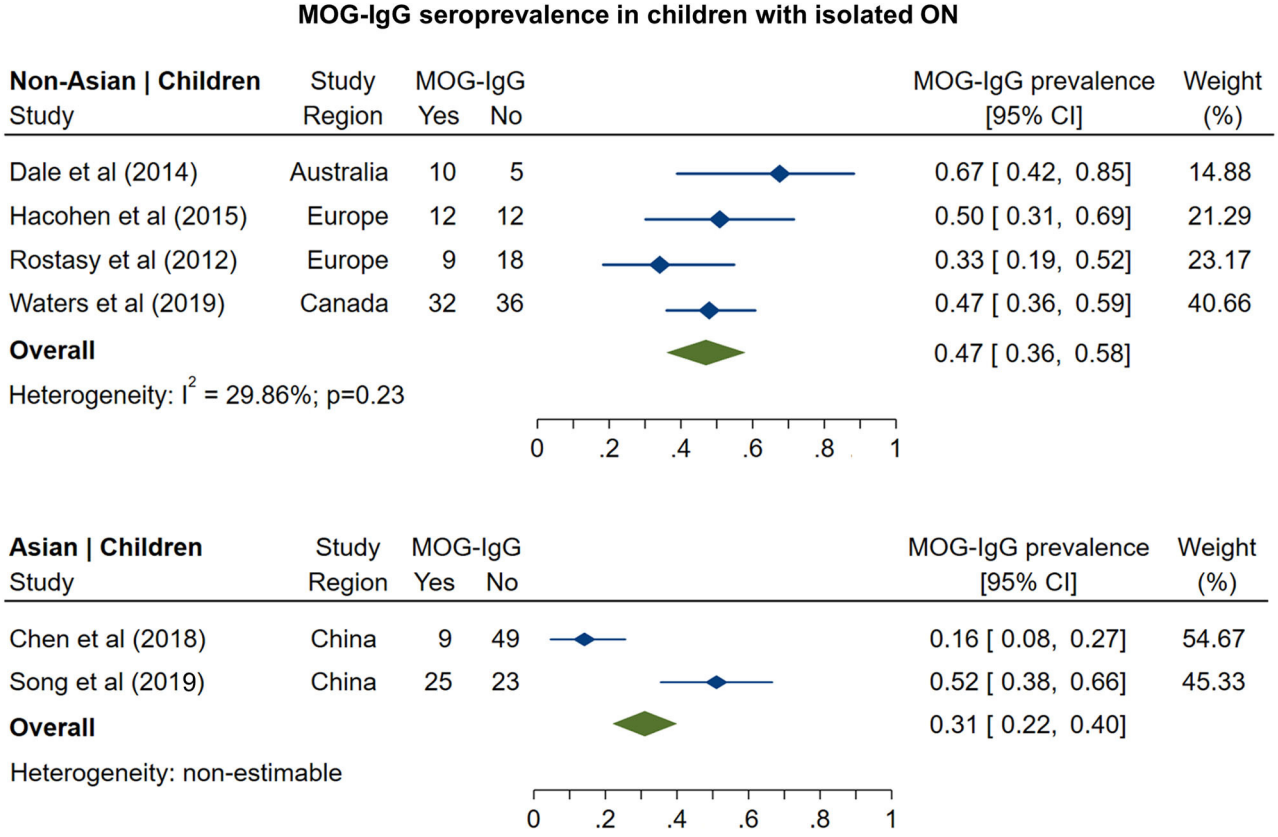

FIGURE 4 | Forest plot of the prevalence of MOG-IgG seropositivity in children with monosymptomatic isolated ON.

Visual Outcomes in Adult ON

AQP4-ON eyes had worse high contrast VA when compared to both MOG-ON (mean logMAR difference: 0.60, 95% CI: 0.39 to 0.81) and MS-ON (mean logMAR difference: 0.68, 95% CI: 0.40 to 0.96; **Figures 10**, **11**). Visual outcomes did not differ between MOG-ON and MS-ON (mean logMAR difference: 0.04, 95% CI: −0.05 to 0.14; **Figure 12**). Moreover, the risk of a poor visual outcome (VA ≤ 20/200) was higher for AQP4-ON compared to MOG-ON [relative risk (RR): 5.39, 95% CI: 2.95 to 9.86; **Figure 10**] and compared to MS-ON (RR: 3.76, 95% CI: 1.71 to 8.25; **Figure 11**).

Nine studies were excluded from our quantitative synthesis, since the visual outcomes were not presented in a format that was consistent with the other studies. The findings of the studies are presented in **Supplementary Table 2**. Importantly, all these studies reported that visual outcomes were markedly better in MOG-ON eyes, as compared with AQP4-ON eyes, in line with the results from the quantitative synthesis.

Visual Outcomes in Pediatric ON

We were able to identify three studies reporting visual outcomes in pediatric ON associated with seropositivity for AQP4-IgG and MOG-IgG (33, 41, 63). Similar to adults, the risk of a poor visual outcome (VA ≤ 20/200) was higher for AQP4-ON compared to MOG-ON (RR: 20.11, 95% CI: 4.79 to 84.34), but the sample sizes of the studies were rather small (**Supplementary Figure 10**).

DISCUSSION

The present systematic review and meta-analysis revealed variable patterns of seroprevalence of AQP4-IgG and MOG-IgG among patients presenting with isolated ON, with overall higher seroprevalence of both antibodies among Asian populations. Moreover, MOG-IgG-associated ON accounted for a large proportion of pediatric isolated ON (over a third of cases), and high MOG-IgG seroprevalence was noted across the pediatric populations included in our study. Furthermore, despite a similar severity of GCIPL and pRNFL thinning in AQP4-ON and MOG-ON, AQP4-ON was associated with markedly worse visual outcomes, compared to both MOG-ON and MS-ON.

Overall, our results support the idea that AQP4-IgG- and MOG-IgG-associated disorders are not rare entities in Asian populations and are important diagnostic considerations during the initial evaluation of ON in these populations. Notably, cohorts from China comprised the vast majority of the Asian cohorts in our study. However, relatively high seroprevalence of AQP4-IgG and/or MOG-IgG in ON has been reported in several studies (that did not however fully fulfill our inclusion criteria) from Japan, Thailand, Malaysia, and additional Chinese centers (74, 77, 86–89). Importantly, while population-based studies support the notion that Eastern Asian populations have a higher prevalence of NMOSD compared to Caucasian populations, MOG-IgG-associated disease does not appear to exhibit a

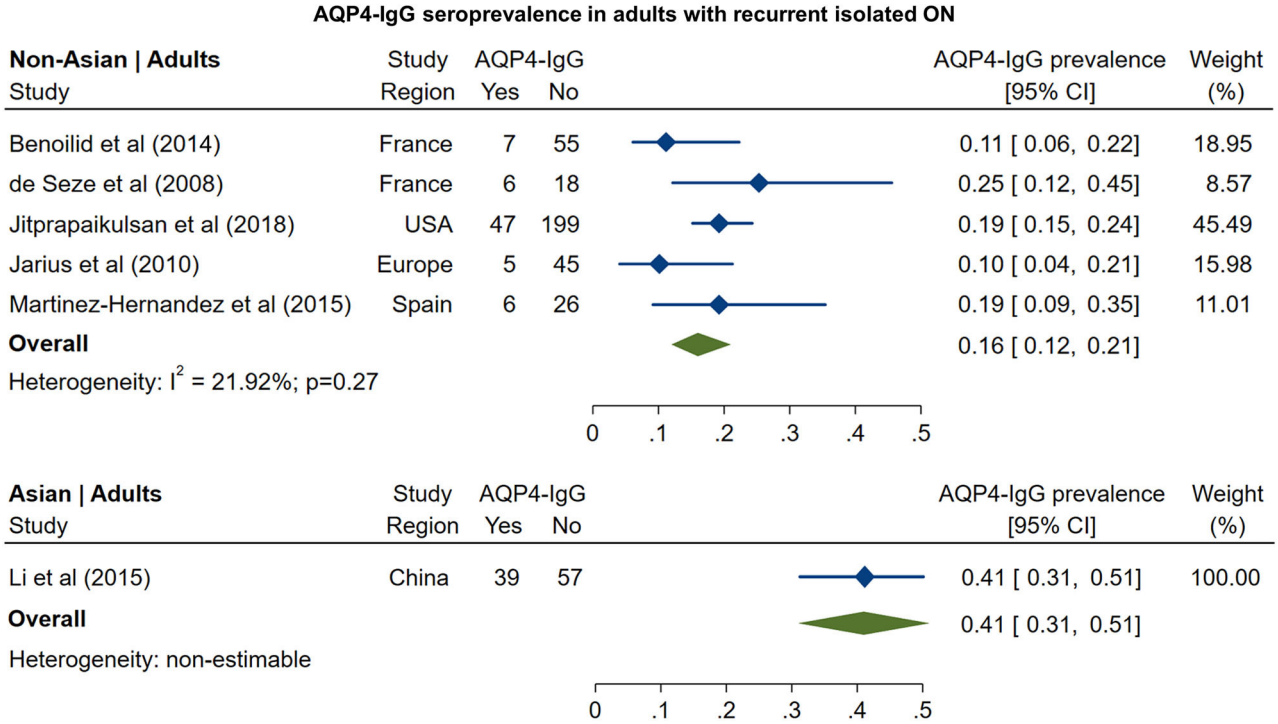

FIGURE 5 | Forest plot of the prevalence of AQP4-IgG seropositivity in adults with recurrent isolated ON.

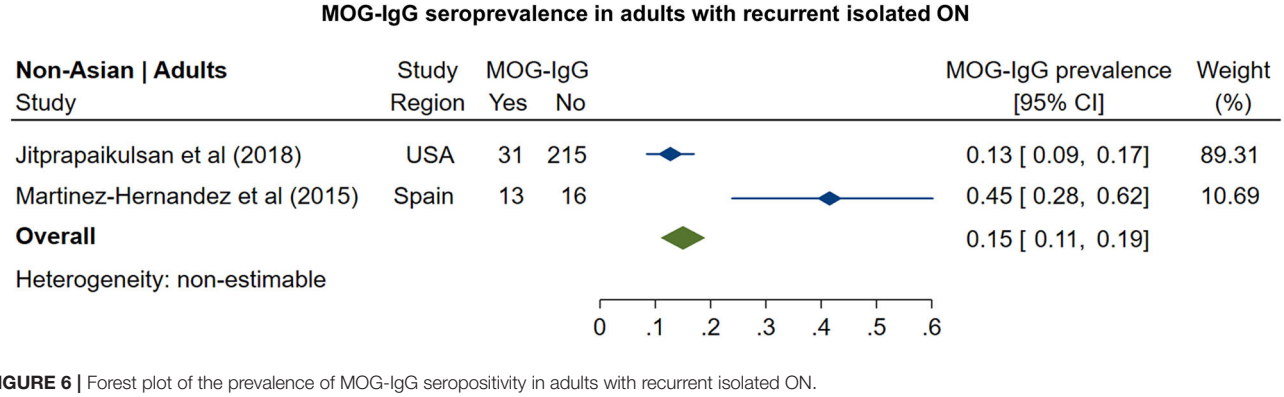

FIGURE 6 | Forest plot of the prevalence of MOG-IgG seropositivity in adults with recurrent isolated ON.

significant racial preponderance based on data from existing hospital-based studies (90). This suggests that our findings of high AQP4-IgG seroprevalence in ON in Asian populations are likely accounted for by both a higher prevalence of NMOSD and a lower prevalence of MS, whereas for MOG-IgG seroprevalence, the latter may be a more important factor. A noteworthy exception to our finding of overall lower seroprevalence of AQP4-IgG seropositivity in non-Asian populations was the study by Carnero-Contentti et al. (39), which enrolled patients from Buenos Aires, Argentina, and reported an AQP4-IgG seroprevalence of 30% among patients with ON (39). This finding is unexpected, given evidence supporting that the relative frequency of NMO vs. MS in Buenos Aires is low, and similar to that observed in Caucasian populations (91). Notably, this study did not report the ethnic/racial composition of the cohort, and it is possible that referral bias or other factors, which we were unable to detect on our review of the manuscript, contributed to this observation. While the frequency of AQP4-IgG and MOG-IgG seropositivity in ON appears to be lower in non-Asian populations, it remains crucial to consider these entities, especially in patients with atypical characteristics including recurrent or bilateral ON, longitudinally extensive optic nerve lesions, peri-neuritis (MOG-IgG), chiasmal/optic tract involvement (AQP4-IgG >> MOG-IgG), and/or poor visual recovery (AQP4-IgG) (6, 92). As expected, we found markedly higher seroprevalence of AQP4-IgG and MOG-IgG in recurrent isolated ON; however, the number of available studies was small, and mainly limited to non-Asian adult populations.

TABLE 2 | Characteristics of studies included in the meta-analysis for our second study objective (comparison of OCT measures between AQP4-ON, MOG-ON, and MS-ON eyes).

Study	Time period	Study setting	Adult/ pediatric	Age	Female sex	Race	Device	Protocol/ROI	MMP	Macular measure
Akaishi et al. (48–50)	2005–2013	Japan	Mixed adult pediatric	Mean (±SD): 37.5 (±18.2) in MOG-ON 30 (±9.9) in MS-ON 44.2 (±14.5) in AQP4-ON	75%	–	Topcon (OCT-2000)	–	–	GCC
Chen et al. (41)	2015–2016	China	Pediatric	Range: 5–18	58%	–	Zeiss (Cirrus)	Optic disc cube 200x200 Macular cube 512x128	–	n/a
Deschamps et al. (51)	2011–2016	France	Mixed adult pediatric	Range: 16–63	94% in AQP4-ON 56% in MOG-ON	–	Heidelberg Engineering (Spectralis)	–	–	n/a
Eyre et al. (63)	–	UK Ireland	Pediatric	Median: 8.5 in AQP4-ON MOG-ON 13 in MS-ON	62%	–	Heidelberg Engineering (Spectralis)	–	–	n/a
Havla et al. (52)	2013–2015	Germany France	Adult	Mean (±SD): 41.4 (±14.0) in MOG-ON 39.9± 12.5 in MS-ON 48.3± 8.9 in AQP4-ON 41.5± 13.8 in HC	46% in MOG-ON/MS-ON/HC 79% in AQP4-ON	–	Heidelberg Engineering (Spectralis)	Optic disc: 12° 3.4 mm 50ART Macula: 25 vertical scans ROI: 3 mm ETDRS perifoveal rim	13% of AQP4-ON eyes 46% of MOG-ON eyes 0% of MS-ON eyes	GCIPL
Hokari et al. (53)	2000–2013	Japan	Adult	Median (IQR): 47 (39–62) in AQP4-ON 38 (30–47) in MS-ON	97%	–	Optovue (RTVue-100)	–	–	GCC
Hu et al. (64)	2013–2015	China	Mixed adult pediatric	Mean (±SD): 26.0 (±10.2) in AQP4-ON 28.3 (±3.2) in HC		–	Zeiss (Cirrus)	Optic disc cube 200 x 200 Macular cube 512 x 128	–	GCIPL
Lim et al. (65)	1993–2012	Korea	Adult	Mean (±SD): 30.9 (±11.2) in AQP4-ON 33.7 (±14.8) in MS-ON	73%	–	–	–	–	n/a
Liu et al. (29)	2014–2016	China	Adult	Range: 18–72	80%	–	Zeiss (Cirrus)	–	–	n/a
Martinez-Lapiscina et al. (66)	–	Spain	Adult	Median (IQR): 34.9 [19.4–43.8] in AQP4-ON 54.4 [53.4–58.1] in MOG-ON	66% in AQP4-ON 50% in MOG-ON	-	Heidelberg Engineering (Spectralis)	Optic disc: 12° 100 ART 1536 A scans per B scan). Macula: 20 × 20 degree raster scan 25 horizontal scans (ART?9; 512 A scans per B scan)	0% of AQP4-ON 0% of MOG-ON	GCC
Mekhasingharak et al. (54)	2015–2016	Thailand	Adult	Range: 19–76	92%	–	Zeiss (Cirrus)	Optic disc cube 200x200 Macular cube 512x128	–	GCIPL
Narayan et al. (67)	2009–2018	USA	Pediatric	Mean (±SD): 14.1 (±4.6) in AQP4-ON 18 (±4.9) in MOG-ON	86%	–	Zeiss (Cirrus)	Optic disc cube 200x200 Macular cube 512x128	–	n/a

(Continued)

TABLE 2 | Continued

Study	Time period	Study setting	Adult/ pediatric	Age	Female sex	Race	Device	Protocol/ROI	MMP	Macular measure
Oertel et al. (55)	–	Germany UK	Adult	Mean (±SD): 47.3 (±14.4) in AQP4-ON 43.1 (±9.8) in HC	84% in AQP4-ON 79% in HC	76% Caucasian 10% African-Caribbean 8% Asian 2% Middle Eastern 2% mixed 2% unknown	Heidelberg Engineering (Spectralis)	Multiple protocols ROI: 3mm cylinder	–	GCIPL
Oertel et al. (56)	–	Germany France	Mixed adult pediatric	Mean (±SD): 43.1 (±9.8) in HC 40.7 (±13.) in MOG-ON	79% in HC 62.5% in MOG-ON	–	Heidelberg Engineering (Spectralis)	Multiple protocols ROI: 3mm cylinder	30% of MOG-ON eyes	GCIPL
Outteryck et al. (68)	–	France	Adult	Mean (±SD): 44.1 (±9.7) in AQP4-ON 39.7 (±11.3) in MS-ON 38.1 (±12.2) in HC	78% in AQP4-ON 69% in MS-ON 68% in HC	–	Heidelberg Engineering (Spectralis)	ROI: 3mm ETDRS perifoveal rim	15% of AQP4-ON eyes 3% of MS-ON eyes	GCIPL
Pache et al. (57)	–	Germany Denmark	Adult	Mean (±SD): 44.0 (±15.2) in MOG-ON 43.2 (±13.9) in AQP4-ON	97%	100% Caucasian	Heidelberg Engineering (Spectralis)	Optic disc: 12° 768 or 1536 A-scans 16≤ART≤100. Macula: 25° × 30° 61 vertical or horizontal B-scans 768 A-scans per B-scan 9 ≤ ART ≤ 15	19% of AQP4-ON eyes 22% of MOG-ON eyes	GCIPL
Pandit et al. (73)	–	India	Mixed adult pediatric	Median (range): 21 (6–53)	43%	South Asian	Heidelberg Engineering (Spectralis)	Optic disc: 12° 1 536 A-scans ART 100). Macula: 15° x 15° 25 vertical: B-scans ART 100 1024 A-scans per B-scan	21% of MOG-ON eyes	GCC
Peng et al. (58)	–	China	Mixed adult pediatric Excluded patients with AQP4-IgG seropositive NMO (only isolated AQP4-ON)	Range: 17–66	74%	–	Heidelberg Engineering (Spectralis)	ROI: 6 mm ETDRS rim excluding central 1mm	6% of AQP4-ON eyes	GCIPL

(Continued)

TABLE 2 | Continued

Study	Time period	Study setting	Adult/ pediatric	Age	Female sex	Race	Device	Protocol/ROI	MMP	Macular measure
Shen et al. (69, 71)	2015–2017	Australia	Adult	Mean (±SD): 48.2 (±16.1) in AQP4-ON/MOG-ON, 43.6 (±10.1) in MS-ON, 39.6 (±14) in HC	68%	–	Heidelberg Engineering (Spectralis)	Optic disc: 3.50 mm Macula: radial star-like scan ROI: Central macular region (2 mm diameter), 6 slices of the star-like scan.	–	GCIPL
Song et al. (33)	2016–2017	China	Pediatric	Mean (±SD): 10.6 (±4.4)	56%	–	Zeiss (Cirrus)	–	–	GCIPL
Sotirchos et al. (8)	2008–2018	USA	Adult	Mean (±SD): 43.7 (±12.7) in AQP4-ON, 43.8 (±13.3) in MOG-ON, 41.5 (±12.6) in MS, 41.5 (±14.1) in HC	78%	61% Caucasian, 34% African American, 5% Other	Zeiss (Cirrus)	Optic disc cube 200 x 200, Macular cube 512 x 128	19% of AQP4-ON eyes, 11% of MOG-ON eyes, 6% of MS-ON eyes	GCIPL
Srikajon et al. (72)	2009–2015	Thailand	Adult	Mean (±SD): 36.7 (±14.0) in AQP4, 34.4 (±13.5) in MS	94%	–	Zeiss (Cirrus)	–	–	n/a
Stiebel-Kalish et al. (59)	2003–2015	Israel	Mixed adult and pediatric	Mean (±SD): 46.3 (±17.6) in AQP4-ON, 41.7 (±9.4) in MOG-ON	69%	–	Zeiss (Cirrus)	Optic disc cube 200x200	–	n/a
Tian et al. (60)	2013–2014	China	Adult *Included only 1 eye per patient	Mean (±SD): 30.5 (±16.7) in MS-ON, 40.5 (±13.6) in AQP4-ON, 32.0 (±13.8) in HC	66%	–	Optovue (RTVue-100)	Optic disc: 4 circular scans (1,024 A-scans/scan), 3.45 mm	–	n/a
vonGlehn et al. (70)	2011–2012	Brazil	Mixed adult and pediatric	Range: 14–76	85%	–	Heidelberg Engineering (Spectralis)	-	–	n/a
Zhang et al. (61)	2012–2017	China	Mixed adult and pediatric	Range: 15–74	74%	-	Zeiss (Cirrus)	Optic disc: 3.45mm	-	n/a
Zhao et al. (36)	2015–2016	China	Mixed adult and pediatric	Mean (±SD): 31.3 (±15.3) in MOG-ON, 40.7 (±15.3) in AQP4-ON	78%	-	Optovue (RTVue-100)	Optic disc: 3.45mm, 4 circular scans (1024 A-scans/scan)	-	GCIPL

(Continued)

TABLE 2 | Continued

Study	Time period	Study setting	Adult/ pediatric	Age	Female sex	Race	Device	Protocol/ROI	MMP	Macular measure
Zhao et al. (62)	2013–2015	China	Adult *Included only eyes with a single ON episode	Median (IQR) 36.5 (21–47) in AQP4–ON	88%	–	Heidelberg Engineering (Spectralis)	Optic disc: 3.5 mm, ≥50 ART. Macula: 25 horizontal scans	32% of AQP4-ON eyes	n/a

*Ganglion Cell Complex (GCC) = macular nerve fiber layer + ganglion cell/inner plexiform layer (GCIPL).

OCT, Optical Coherence Tomography; AQP4, aquaporin 4; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; ON, optic neuritis; MMP, microcystoid macular pathology; HC, healthy control; IQR, interquartile range; SD, standard deviation; GCIPL, ganglion cell/inner plexiform layer; GCC, ganglion cell complex; ROI, region of interest; ART, automatic real time; ETDRS, early treatment diabetic retinopathy study.

A similar finding was expected in bilateral ON; however, there was an insufficient number of studies/participants eligible to systematically study this. Finally, in children with isolated ON, our results show that MOG-IgG is very commonly detected, across both Asian and non-Asian populations. However, AQP4-IgG seropositivity was exceedingly rare among non-Asian pediatric populations, but relatively common (15%) in Asian pediatric cohorts. The causes of these ethnic and age disparities are poorly understood, but it is likely that there is a genetic component, although environmental factors may also play a role (93, 94).

An important consideration is the fact that the included studies recruited very few patients of African ancestry. This is a critical point since NMOSD occurs frequently in individuals of African ancestry, and African-Americans/Europeans with NMOSD are more likely to experience severe attacks with poor recovery and appear to have higher mortality (95–97). Nevertheless, the frequency of AQP4-IgG and MOG-IgG seropositivity in isolated ON in these populations could not be investigated in the present meta-analysis.

Furthermore, we have found that AQP4-ON and MOG-ON eyes exhibited similarly severely decreased pRNFL and macular GCIPL thicknesses after ON, which was greater than that observed in MS-ON eyes. When examining quadrantal pRNFL thicknesses, we were unable to identify any quadrantal patterns of retinal injury that were specific to MOG-ON. However, when comparing AQP4-ON and MS-ON, AQP4-ON was associated with decreased inferior, superior, and nasal pRNFL thickness, but the temporal pRNFL did not appear to differ between the two groups. This finding suggests that the temporal pRNFL is relatively preserved in AQP4-ON or disproportionally affected in MS-ON. Temporal preponderance of pRNFL damage in MS-ON compared to AQP4-ON was also reported in a study by Schneider et al. (98), which, however, did not fulfill inclusion criteria for our meta-analysis. The pathophysiology underlying the observed differences is not clear; however, the arcuate fibers (located in the superior and inferior quadrants) are commonly injured in vascular optic neuropathies (99). This pattern of quadrantal thinning may suggest that vascular compromise is a mechanism of tissue injury in AQP4-ON. Notably, retinal vascular alterations have been reported *in vivo* in NMO and pathologic studies have identified prominent vascular fibrosis and hyalinization in NMO lesions (99, 100).

Interestingly, and in line with our prior observations (8), we found that, despite a similar severity of pRNFL and GCIPL thinning in AQP4-ON and MOG-ON, visual outcomes clearly diverged between these two entities, with MOG-ON eyes having relatively preserved visual acuity, whereas AQP4-ON eyes experienced markedly worse visual outcomes compared to both MOG-ON and MS-ON. The biological underpinnings of this observation remain unclear. AQP4-IgG-associated disease is recognized as an autoimmune astrocytopathy with secondary demyelination (101). In pathologic studies, a spectrum of changes in astrocytes has been described, including astrocyte necrosis and dystrophic astrocytic profiles (101). AQP4 is highly expressed in the retina, predominantly in retinal astrocytes and Müller glial cells; it is therefore conceivable that AQP4-IgG may cause

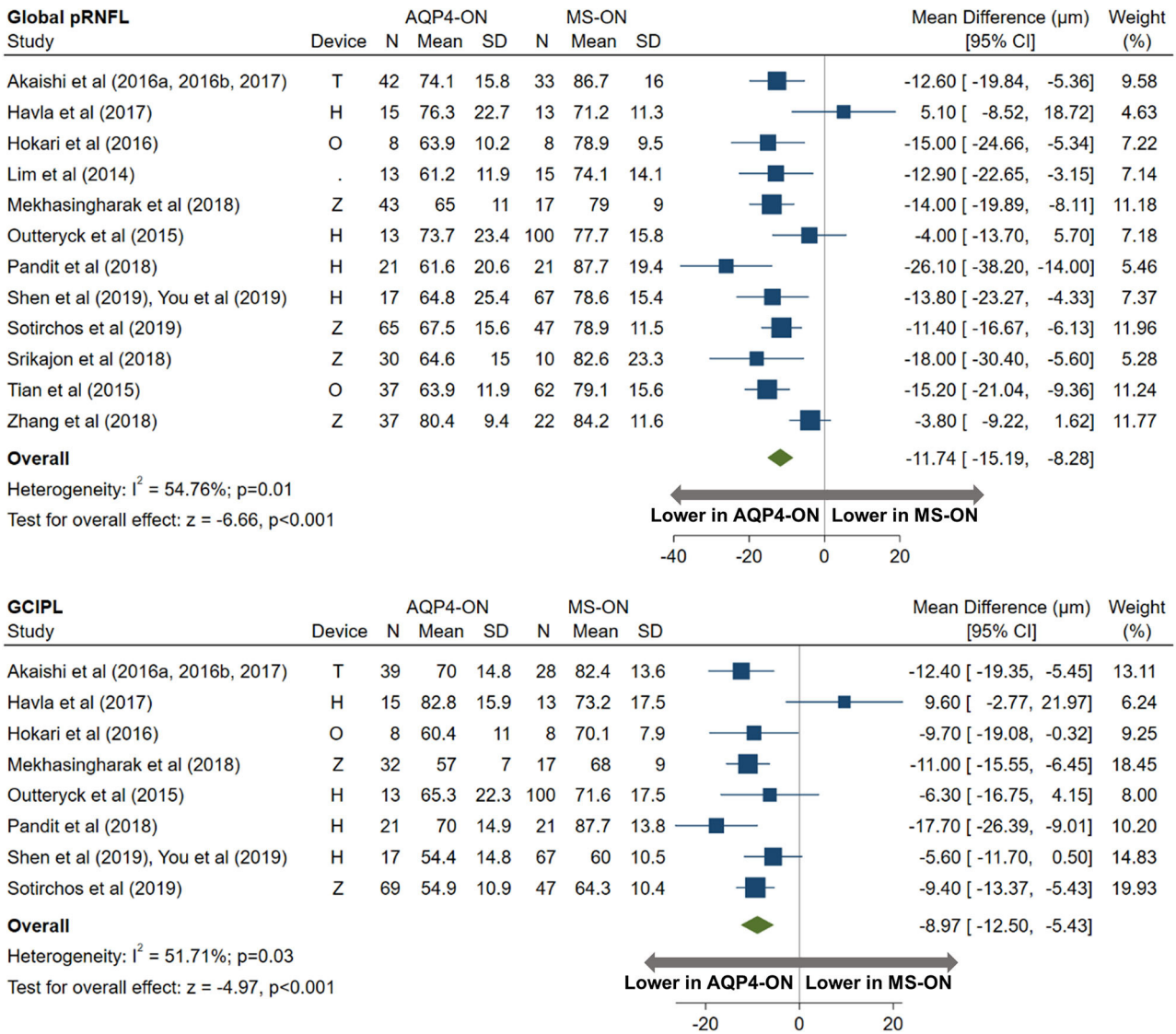

FIGURE 7 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between AQP4-ON and MS-ON. The SD-OCT devices used are indicated as H (Spectralis, Heidelberg Engineering; Heidelberg, Germany), O (RTVue, Optovue Inc; Fremont, CA, USA), and T (3D OCT-2000, Topcon Corporation; Tokyo, Japan), Z (Cirrus, Carl Zeiss Meditec; Dublin, CA, USA).

direct retinal injury. Interestingly, foveal thinning and altered foveal morphology have been reported in AQP4-IgG seropositive eyes without a history of ON, suggesting that subclinical direct retinal involvement may occur in AQP4-IgG-associated disease (102–104). In a pathological study of human retinas, AQP4-IgG seropositivity was associated with loss of AQP4 immunoreactivity on Müller cells, while intravitreal AQP4-IgG injection in mice resulted in reduced AQP4 expression by Müller cells, reactive retinal gliosis and loss of RGCs (53, 105). Notably, AQP4 deletion renders Müller cells incapable of handling osmotic stress and may induce an inflammatory response in the retina (106). These findings suggest that the poor visual prognosis in AQP4-ON may be partially mediated by alterations in the dynamics of astrocyte and Müller cell function.

MMP has also been proposed as a factor that is associated with poor outcomes following ON, since MMP eyes have worse visual outcomes and more severe GCIPL and pRNFL thinning (16–18). However, when accounting for GCIPL thickness and ON etiology, MMP does not appear to be independently associated with visual acuity, suggesting that MMP may represent a marker of optic neuropathy severity, rather than a direct contributor to visual dysfunction following ON (8). The prevalence of MMP was reported by a small number of studies included in our meta-analysis but appeared to be overall similar in AQP4-ON (15%) and MOG-ON (21%) and higher in both compared to the reported prevalence in MS-ON (∼6%). Further work is needed to clarify the pathoetiology of MMP and whether MMP is causally associated with poor visual outcomes after ON.

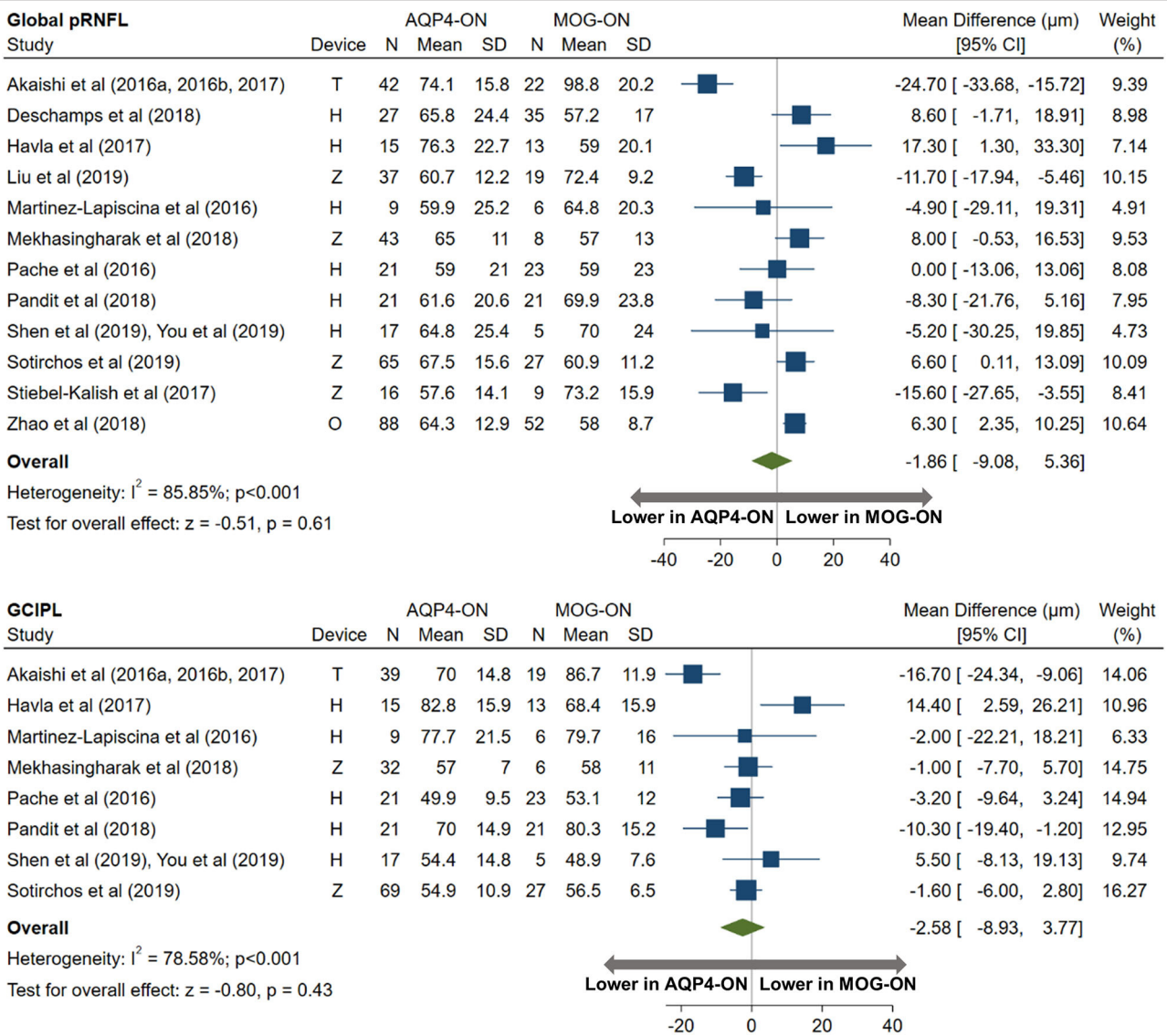

FIGURE 8 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between AQP4-ON and MOG-ON. The SD-OCT devices used are indicated as H (Spectralis, Heidelberg Engineering; Heidelberg, Germany), O (RTVue, Optovue Inc; Fremont, CA, USA), and T (3D OCT-2000, Topcon Corporation; Tokyo, Japan), Z (Cirrus, Carl Zeiss Meditec; Dublin, CA, USA).

Furthermore, we observed an impressive discordance between structural and functional outcomes in MOG-ON; even though MOG-ON was associated with severe pRNFL and GCIPL thinning, high-contrast visual acuity was remarkably preserved and did not differ from MS-ON. Contrary to AQP4, MOG is not expressed in the human retina; therefore, the observed inner retinal thinning is expected to be due to secondary change due to retrograde degeneration and not primary retinal pathology. The pathophysiology underlying the observed structure-function mismatch in MOG-ON is unclear; however, an important consideration is that, with OCT, we are not able to visualize the histological composition of each retinal layer. Therefore, it is conceivable that the relative contributions of the RGCs and their axons to GCIPL and RNFL thicknesses differ between AQP4-ON and MOG-ON, despite a similar severity of retinal layer thinning. In fact, the glial content of the RNFL is considerable and microglia constitute a significant component of the inner plexiform layer, whose thickness is measured as a composite with the ganglion cell layer as GCIPL (107, 108). Given the markedly different pathogenic mechanisms in these disorders, it is conceivable that the observed discrepancies may be related to differences in glial activation and migration, resulting in differing compositions of the pRNFL and the GCIPL and, consequently, different functional capacity of the retina. Another important consideration is that there is a floor effect present for OCT measures, and a single AQP4-ON or MOG-ON attack can lead to marked pRNFL and GCIPL atrophy, while subsequent attacks may not lead to appreciable changes in inner retinal layer

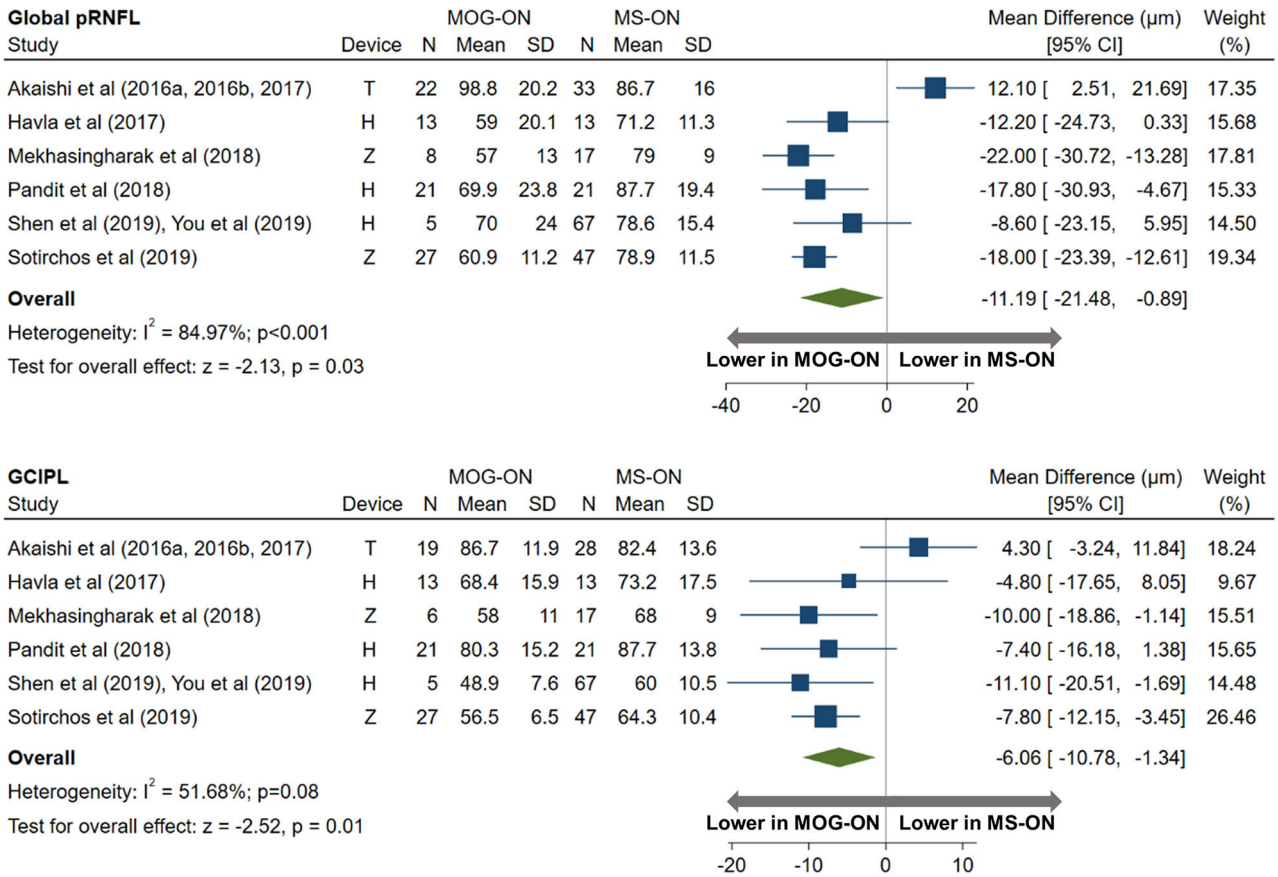

FIGURE 9 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between MOG-ON and MS-ON. The SD-OCT devices used are indicated as H (Spectralis, Heidelberg Engineering; Heidelberg, Germany), O (RTVue, Optovue Inc; Fremont, CA, USA), and T (3D OCT-2000, Topcon Corporation; Tokyo, Japan), Z (Cirrus, Carl Zeiss Meditec; Dublin, CA, USA).

thicknesses, despite worsening visual function (109). Analyses comparing visual and structural measures between groups after a single attack of ON would be useful to address this issue; however, the vast majority of studies included in our meta-analysis did not report OCT or visual acuity separately for patients with single and recurrent ON. However, since both AQP4-ON and MOG-ON frequently relapse, we do not expect that this may have significantly affected our findings when comparing outcomes in AQP4-ON vs. MOG-ON, although this may have influenced comparisons with MS-ON (6).

In this meta-analysis, we also attempted to examine OCT findings and visual outcomes in pediatric ON associated with AQP4-IgG and MOG-IgG seropositivity. However, this population has not been studied extensively and a systematic review of the literature revealed only four studies, with small numbers of participants (33, 41, 63, 67). OCT measures could be pooled for three of these, two of which included Asian children (33, 41). Therefore, our meta-analysis is clearly underpowered to study characteristics of pediatric AQP4-ON and MOG-ON. Nevertheless, the OCT findings and visual outcomes appear to be similar to those observed in adults. The inclusion of pediatric cases should be an important consideration for future studies, especially since MOG-IgG antibodies are commonly detected in children with ON.

Despite the strengths of the present report, several limitations must be acknowledged. Firstly, the majority of the included prevalence studies were performed at tertiary academic referral centers, with clinical expertise in neuro-ophthalmology. Therefore, it is conceivable that the patients who were recruited in these studies are not a representative sample of patients presenting with isolated ON and are likely enriched for cases with increased severity or atypical characteristics. Thus, it is possible that our results may overestimate the true prevalence rate of these disorders in the general population due to referral bias. This issue should also be considered when interpreting the OCT and visual outcomes, since patients with more severe attacks of ON and poor recovery are potentially more likely to be referred to a tertiary center for further management, and mild cases with favorable outcomes may be underrepresented in the existing literature. Furthermore, between-study heterogeneity was considerable in almost all pooled analyses of OCT measures or visual outcomes. A potential source of heterogeneity in analyses of OCT measures is the fact that the included studies

TABLE 3 | Characteristics of studies included in the meta-analysis for our third study objective (comparison of visual outcomes in AQP4-ON, MOG-ON and MS-ON eyes).

References	Time period	Study setting	Adult/pediatric	Age	Female sex	Race	Visual outcome–considerations
Akaishi et al. (48, 74, 75)	2005–2013	Japan	Mixed adult and pediatric	Mean (±SD): 37.5 (±18.2) in MOG-ON, 30 (±9.9) in MS-ON, 44.2 (±14.5) in AQP4-ON	75%	-	Outcome at eye level
Chen et al. (41)	2015–2016	China	Pediatric	Range: 5–18	58%	-	Outcome at eye level
Cobo-Calvo et al. (76)	2014–2017	France	Adult	Median (range): 36.5 (19–76.8) in MOG-ON, 39.3 (18.2–85) in AQP4-ON	69%	86% Caucasian	Outcome at patient level
Contentti et al. (39)	2009–2015	Argentina	Adult	Mean (±SD): 31.6 (±11.1) in AQP4-ON, 38.4 (±12.9) in other	70%	-	Outcome at patient level
Deschamps et al. (51)	2011–2016	France	Mixed adult and pediatric	Range: 16–63	94% in AQP4-ON, 56% in MOG-ON	-	Outcome at eye level
Eyre et al. (63)	-	UK, Ireland	Pediatric	Median: 8.5 in AQP4-ON and MOG-ON, 13 in MS-ON	62%	-	Outcome at eye level
Falcão-Gonçalves et al. (83)	2004–2016	Brazil	Adult	Median (IQR): 31.6 (22.6–37.4) in AQP4-ON, 27.2 (23.3–37.45) in MS-ON	80%	-	Outcome at eye level
Havla et al. (52)	2013–2015	Germany, France	Adult	Mean (±SD): 41.4 (±14.0) in MOG-ON, 39.9 (±12.5) in MS-ON, 48.3 (±8.9) in AQP4-ON, 41.5 (±13.8) in HC	46% in MOG-ON/ MS-ON/ HC, 79% in AQP4-ON	-	Outcome at eye level
Hokari et al. (53)	2000–2013	Japan	Adult	Median (IQR): 47 (39–62) in AQP4-ON, 38 (30–47) in MS-ON	97%	-	Outcome for number of attacks, not eyes
Ishikawa et al. (77)	2015–2018	Japan	Mixed adult and pediatric	Range: 3–87	84% in AQP4-ON, 51% in MOG-ON	-	Outcome at patient level
Jitprapaikulsan et al. (45)	2000–2017	USA	Mixed adult and pediatric	Range: 5–72	72%	83% Caucasian	Outcome at patient level
Kim et al. (78)	-	South Korea	Adult	Mean (±SD): 39.4 (±12.0) in AQP4-ON, 35.2 (±10.0) in MS-ON	78%	-	Outcome at eye level
Kitley et al. (79)	2010–2013	UK	Adult	Mean (±SD): 32.3 (±17.1) in MOG-ON, 44.9 (±14.8) in AQP4	44% in MOG-ON, 90% in AQP4-ON	66% Caucasian	Outcome at patient level
Lim et al. (65)	1993–2012	Korea	Adult	Mean (±SD): 30.9 (±11.2) in AQP4-ON, 33.7 (±14.8) in MS-ON	73%	-	Outcome at eye level
Liu et al. (29)	2014–2016	China	Adult	Range: 18–72	80%	-	Outcome at eye level
Martinez-Lapiscina et al. (66)	-	Spain	Adult	Median (IQR): 34.9 [19.4–43.8] in AQP4-ON, 54.4 [53.4–58.1] in MOG-ON	66% in AQP4-ON, 50% in MOG-ON	-	Outcome at eye level

(Continued)

TABLE 3 | Continued

References	Time period	Study setting	Adult/pediatric	Age	Female sex	Race	Visual outcome–considerations
Martinez-Hernandez et al. (47)	2005–2014	Spain	Mixed adult and pediatric	Range: 5–65	71%	-	Outcome at patient level
Mekhasingharak et al. (54)	2015–2016	Thailand	Adult	Range: 19–76	92%	-	Outcome at eye level
Merle et al. (84)	-	Martinique	Adult	Mean (±SD): 47.5 (±10.5) in AQP4-ON, 44.5 (±10.1) in MS-ON	87%	-	Outcome at eye level
Outteryck et al. (68)	-	France	Adult	Mean (±SD): 44.1 (±9.7) in AQP4-ON, 39.7 (±11.3) in MS-ON, 38.1 (±12.2) in HC	78% in AQP4-ON, 69% in MS-ON, 68% in HC	-	Outcome at eye level
Pache et al. (57)	-	Germany, Denmark	Adult	Mean (±SD): 44.0 (±15.2) in MOG-ON, 43.2 (±13.9) in AQP4-ON	97%	100% Caucasian	Outcome at eye level
Peng et al. (85)	2014–2015	China	Adult	Mean (±SD): 33 (±12), Range: 30–51	74%	-	Outcome at eye level
Petzold et al. (30)	1995–2007	UK	Mixed adult and pediatric	Range: 15–71	67%	-	Outcome at eye level
Piccolo et al. (80)	2008–2014	UK	Mixed adult and pediatric	Range: 3–59	78%	67% Caucasian	Outcome at patient level
Ramanathan et al. (81)	2001–2014	USA, Australia	Mixed adult and pediatric	Median (range): 15 (3–58)	82%	-	Outcome at patient level
Sepulveda et al. (82)	2013–2015	Spain	Mixed adult and pediatric	Median (range): 39 (10–77)	87%	86% Caucasian	Outcome at patient level
Shen et al. (69) and You et al. (71)	2015–2017	Australia	Adult	Mean (±SD): 48.2 (±16.1) in AQP4-ON/MOG-ON, 43.6 (±10.1) in MS-ON	68%	-	Outcome at eye level
Song et al. (33)	2016–2017	China	Pediatric	Mean (±SD): 10.6 (±4.4)	56%	-	Outcome at eye level
Sotirchos et al. (8)	2008–2018	USA	Adult	Mean (±SD): 43.7 (±12.7) in AQP4-ON, 43.8 (±13.3) in MOG-ON, 41.5 (±12.6) in MS-ON, 41.5 ±14.1 in HC	78%	61% Caucasian, 34% African American, 5% Other	Outcome at eye level
Srikajon et al. (72)	2009–2015	Thailand	Adult	Mean (±SD): 36.7 (±14.0) in AQP4-ON, 34.4 (±13.5) in MS-ON	94%	-	Outcome at eye level
Stiebel-Kalish et al. (59)	2003–2015	Israel	Mixed adult and pediatric	Mean (±SD): 46.3 (±17.6) in AQP4-ON, 41.7 (±9.4) in MOG-ON	69%	-	Outcome at eye level
Zhao et al. (36)	2015–2016	China	Mixed adult and pediatric	Mean (±SD): 31.3 (±15.3) in MOG-ON, 40.7 (±15.3) in AQP4-ON	78%	-	Outcome at eye level

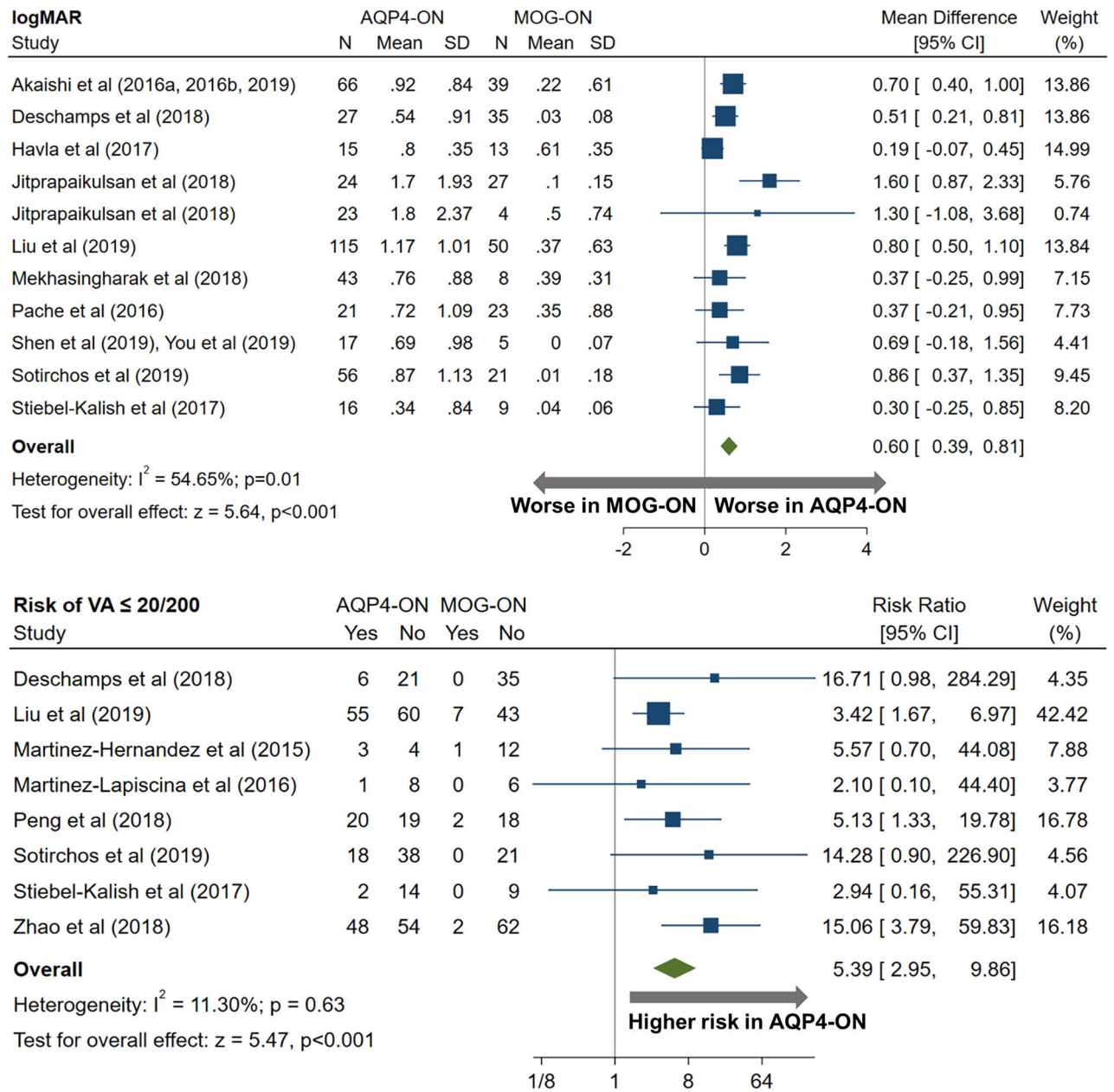

FIGURE 10 | Forest plot of the mean difference in logMAR (high-contrast visual acuity) between AQP4-ON and MOG-ON; forest plot of the relative risk of a poor visual outcome (VA worse than 20/200) in AQP4-ON vs MOG-ON.

utilized a variety of spectral-domain OCT devices, as well as scanning and segmentation protocols. Moreover, participants' demographics and clinical characteristics varied considerably between studies and it is likely that there is variability in the phenotype, disease course, and outcomes among different racial or age groups. To minimize the impact of these differences on our results, we did not compare OCT measures or visual outcomes across studies; rather, we estimated the differences in retinal layer thicknesses or logMAR between groups that were included in the same study and performed a pooled analysis of these estimated differences. In analyses of OCT measures and visual outcomes, we were also notably unable to account for the number of ON attacks, since some studies included patients with a single event, while others recruited patients with multiple ON episodes. It is expected that the number of ON episodes has an impact on OCT findings and final visual acuity, especially since recurrent ON in common in cases of AQP4-ON and MOG-ON; this should be a consideration in future studies. Additionally, even though we attempted to analyze findings in adult ON separately from pediatric ON, some studies (noted in **Tables 1–3**) recruited mixed adult and pediatric or adolescent populations; this is an important

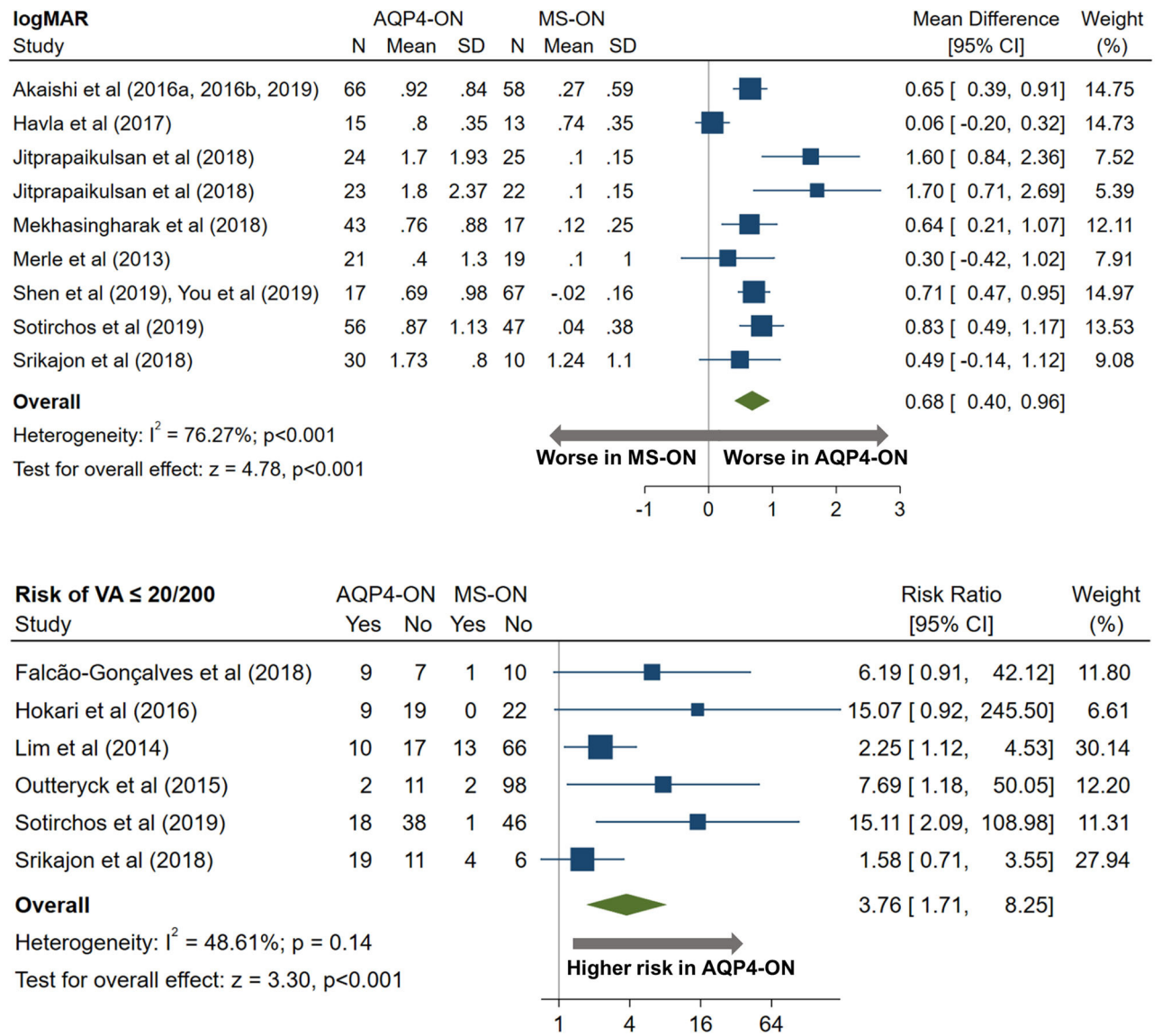

FIGURE 11 | Forest plot of the mean difference in logMAR (high-contrast visual acuity) between AQP4-ON and MS-ON; forest plot of the relative risk of a poor visual outcome (VA worse than 20/200) in AQP4-ON vs MS-ON.

consideration when attempting to draw conclusions regarding potential differences in the characteristics of these disease entities between these age groups. Finally, AQP4-IgG serostatus was determined using a variety of assays, including ELISA in some studies, which is known to have an inferior performance in terms of sensitivity and specificity compared to CBAs (110, 111). This is a relevant point, since the use of an assay with sub-optimal diagnostic accuracy may have led to misclassification of patients. Nevertheless, the majority of studies included in our meta-analysis (including 79% of studies assessing the prevalence of AQP4-IgG in ON) utilized CBA to determine the AQP4-IgG serostatus of their participants. MOG-IgG serostatus was determined exclusively using CBAs with full-length human MOG, given that MOG-IgG detected by ELISA or Western blot lacks disease specificity. Notably, commonly used MOG-IgG CBAs demonstrate overall good agreement for high-positive and negative samples, although agreement is lower for borderline results, and this is another factor that could potentially influence diagnostic accuracy in the included studies (112).

CONCLUSIONS

Our systematic review and meta-analysis provides a comprehensive overview of the epidemiology and structural and functional outcomes in ON associated with AQP4-IgG and MOG-IgG seropositivity. Our findings support the idea that AQP4-IgG- and MOG-IgG-related disease are more common causes of ON in Asian vs. non-Asian populations and that

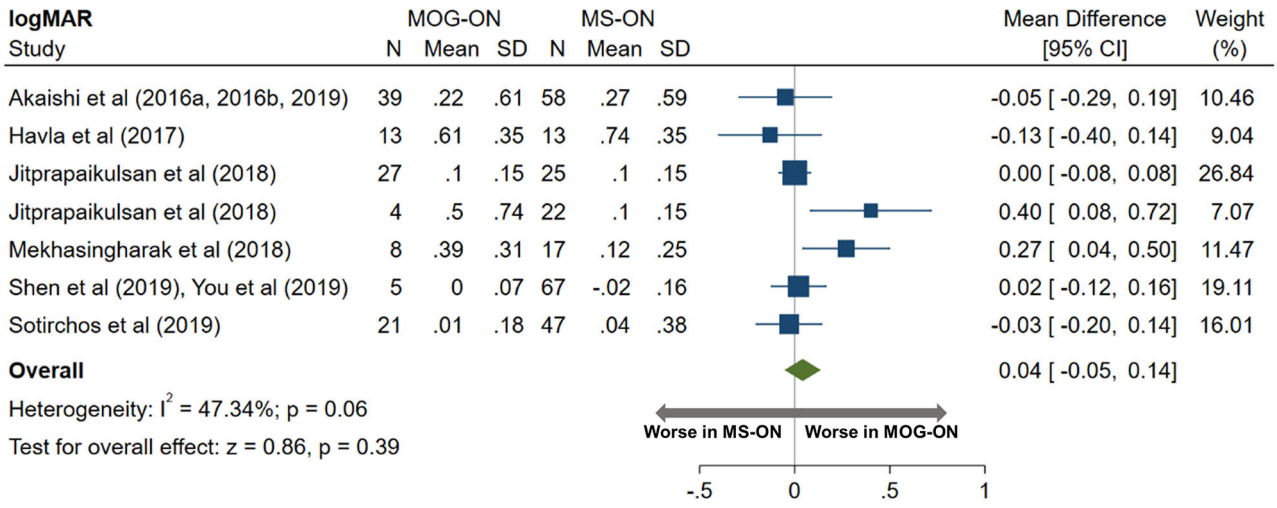

FIGURE 12 | Forest plot of the mean difference in logMAR (high-contrast visual acuity) between MOG-ON and MS-ON.

MOG-IgG seroprevalence is especially high in pediatric ON, and we provide estimates of seroprevalence in these groups. We have also shown that MOG-ON and AQP4-ON are associated with similar severity of retinal thinning; however, visual outcomes appear to be markedly worse in AQP4-ON. Future studies should seek to investigate the pathoetiology of these findings, as well as to provide insights regarding optimal acute and chronic treatment strategies for these disorders.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

AF and ES: study conception and design, data acquisition, analysis and interpretation, drafting, and revision of the manuscript for important intellectual content. LM: data acquisition and interpretation and revision of the manuscript for important intellectual content. SS and PC: data interpretation and revision of the manuscript for important intellectual content. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.540156/full#supplementary-material

Supplementary Figure 1 | Study selection for our first study objective (assessing the prevalence of AQP4-IgG and MOG-IgG seropositivity in isolated ON).

Supplementary Figure 2 | Study selection for our second study objective (comparison of OCT measures between AQP4-ON, MOG-ON and MS-ON eyes).

Supplementary Figure 3 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between AQP4-ON and HC.

Supplementary Figure 4 | Forest plot of the mean difference in global pRNFL and GCIPL thickness between MOG-ON and HC.

Supplementary Figure 5 | Forest plot of the mean difference in quadrantal pRNFL thicknesses between AQP4-ON and MOG-ON.

Supplementary Figure 6 | Forest plot of the mean difference in quadrantal pRNFL thicknesses between AQP4-ON and MS-ON.

Supplementary Figure 7 | Forest plot of the mean difference in quadrantal pRNFL thicknesses between MOG-ON and MS-ON.

Supplementary Figure 8 | Forest plot of the mean difference in global pRNFL thickness between AQP4-ON and MOG-ON in pediatric ON.

Supplementary Figure 9 | Study selection for our third study objective (assessment of the visual outcome in AQP4-ON, MOG-ON and MS-ON eyes).

Supplementary Figure 10 | Forest plot of the relative risk of a poor visual outcome (VA worse than 20/200) in AQP4-ON vs MOG-ON in pediatric ON.

Supplementary Table 1 | Search terms.

Supplementary Table 2 | Visual outcome in AQP4-ON, MOG-ON and MS-ON; qualitative synthesis.

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SYSTEMATIC REVIEW
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Pregnancy and Neuromyelitis Optica Spectrum Disorder – Reciprocal Effects and Practical Recommendations: A Systematic Review

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Introduction: Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory disorder of the central nervous system characterized by severe, antibody-mediated astrocyte loss with secondary demyelination and axonal damage, predominantly targeting optic nerves and the spinal cord. Recent publications have alluded to increased disease activity during pregnancy, and adverse maternal and fetal outcomes in patients with NMOSD. Our objective was to systematically review published literature to help counsel and manage women with NMOSD contemplating pregnancy.

Methods: We searched five databases including MEDLINE and EMBASE, for English-language publications describing pregnancies in women with NMOSD. Article selection, data extraction, and risk-of-bias assessment using Joanna Briggs' critical appraisal tool for case reports and case series, were performed in duplicate. Pooled incidences were calculated where possible, and a narrative summary was provided.

Results: Of 2,118 identified titles, 22 case reports and seven case series, representing 595 pregnancies in 389 women, were included. The mean maternal age was 28.12 ± 5.19 years. At least 20% of cases were first diagnosed during pregnancy. There were no maternal deaths. Pooled estimates for clinical outcomes could not be obtained due to inadequate reporting. NMOSD-related disability and relapses increased considerably during pregnancy and especially in the immediate postpartum period. Although a high proportion of early pregnancy losses were reported, an association with disease activity or therapeutic interventions could not be established. Apart from one publication which reported an increased risk of preeclampsia, there was no increase in adverse obstetric outcomes including preterm birth, fetal growth restriction or congenital malformations. Initial attacks and relapses were successfully managed with oral or intravenous

corticosteroids and immunosuppressants, and refractory cases with immunoglobulin, plasma exchange and immunoadsorption.

Conclusion: Increased NMOSD-related disability and relapses during pregnancy the postpartum period may respond to aggressive management with corticosteroids and immunosuppressants such as azathioprine, which are safely administered during pregnancy and lactation. Emerging safety data on monoclonal antibodies during pregnancy, make these attractive options, while intravenous immunoglobulin, plasma exchange and immunoadsorption can be safely used to treat severe relapses. The complex interplay between NMOSD and pregnancy outcomes would be best understood through prospective analysis of data collected through an international registry.

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Keywords: neuromyelitis optica spectrum disorder, pregnancy, devic syndrome, systematic review, maternal and fetal risks

INTRODUCTION

Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory disorders of the central nervous system characterized by severe, immune-mediated demyelination, astrocyte loss, and axonal damage, predominantly targeting optic nerves and the spinal cord (1, 2). Unlike multiple sclerosis, which many believe to be primarily a cell-mediated disorder, NMOSD is thought to be primarily mediated by the humoral immune system, and is associated with a specific target antigen, the astrocytic water channel aquaporin-(3) (AQP4) (4). Circulating immunoglobulin-G antibodies (AQP4-IgG), which are now known to play a direct role in the development of NMOSD, have revolutionized the understanding of the condition (3), and have influenced the development of a new set of diagnostic criteria to define and further stratify NMOSD (1).

Women are more likely to be affected by seropositive (AQP4+) NMOSD than men, and in some series the ratio of women-to-men affected was as high as 9:1 (5). This gender disparity, the humoral basis of the condition, and the fact that NMOSD can affect those in the reproductive age group (median age of onset 32–41 years) (2), has generated much interest in NMOSD and pregnancy over the past decade, with a number of publications suggesting increased risk of relapse and greater disability during and immediately after pregnancy (6–13). Some others have also suggested an increased association between NMOSD and adverse pregnancy outcomes such as miscarriage and preeclampsia, especially in the presence of other autoimmune conditions (14). However, most publications, including multi-center studies, are limited by the small number of cases, making it difficult to interpret results and make firm conclusions.

The primary aim of this publication is to systematically review all published literature on pregnancy and NMOSD, with a view to determining the effect of the condition on pregnancy outcomes, and that of pregnancy on disease progression. The secondary aim is to explore management considerations, with a view to guiding clinical practice and future research.

MATERIALS AND METHODS

The study protocol was registered with PROSPERO (CRD42017055230) (15), and conducted and reported according to PRISMA (16) and MOOSE (17) guidelines, respectively.

Data Sources and Searches

A medical information specialist conducted a literature search with the help of the study investigators, using the OvidSP search platform in MEDLINE, EMBASE, Web of Science, the Cochrane databases and PubMed in-process (for non-Medline articles, and those not yet indexed). A combination of subject headings and keywords was used to capture pregnancy (including pregnancy, pregnancy complications, obstetrics, and breastfeeding), various names for what now is known as NMOSD (including Devic syndrome/disease, neuromyelitis optica, NMO and NMOSD) and various terms used for anti-NMO antibody (including aquaporin-4 and AQP4), with articles included if indexed as of 23 October 2017. A more focussed search was repeated in March 2020 to include new publications. The search was limited to human data and restricted to the English language. No other restrictions were applied. The search strategy is presented as **Supplementary Data 1**. Additional articles were identified by scanning reference lists of included articles as well as excluded commentaries, editorials and review articles.

Study Selection

Type of Studies

All prospective and retrospective studies reporting cases of NMO or NMOSD previously diagnosed, or diagnosed for the first time in pregnancy, were included. Given the rarity of the condition,

we opted to include case reports and small case series, so as not to miss vital information with regard to disease progression and treatment modalities.

Types of Participants

We included all publications involving pregnant women with NMOSD, ideally diagnosed using the Updated Diagnostic Criteria (1). Given that these criteria were only revised in 2015, the diagnosis of NMO or NMOSD based on previous criteria (1, 18) were also included. Further, we have included cases based on the clinical phenotype. Therefore, patients were heterogenous with regard to AQP4 serotype, i.e. we included both seropositive and seronegative cases. Cases of multiple sclerosis and neurologic disorders mimicking NMO or NMOSD, or with uncertain diagnosis, were excluded.

Outcomes

Maternal Outcomes

Maternal outcomes were maternal death, area postrema syndrome, details of neurologic presentation and progression including motor and sensory symptoms, spasticity, visual and hearing impairment, bladder or bowel dysfunction and seizures). We also made note of respiratory and cardiovascular symptoms, as well as obstetric outcomes including hyperemesis gravidarum, hypertensive disorders of pregnancy, gestational diabetes mellitus, antepartum and postpartum hospitalization including the need for admission to intensive care unit, mode of delivery, and labor and delivery complications such as postpartum hemorrhage or major perineal lacerations.

Fetal and Neonatal Outcomes

Fetal and neonatal outcomes included a miscarriage (fetal loss $<$ 20 weeks), stillbirth (fetal loss $>$20 weeks), neonatal death (death within the first 28 days of life), growth restriction (weight $<$10th centile for gestational age), premature birth (birth before 37 weeks of gestation), admission to the neonatal intensive care unit (NICU), length of NICU stay, Apgar scores at birth and long-term neonatal outcomes if reported.

Treatment Outcomes

Treatment outcomes included details on treatment strategies and the maternal response to these strategies, including the involvement of multidisciplinary teams, peripartum obstetric and anesthetic management, management of obstetrical complications and emergencies, neonatal management, postpartum management of maternal symptoms and modifications to maintenance therapies.

Data Extraction

A data extraction form was designed to include all available information on disease progression and the above pregnancy outcomes and pre-piloted. Two reviewers independently screened titles, abstracts and full texts, and disagreements were resolved through discussion, or through adjudication by a senior investigator, when disagreements persisted. Data from all included papers was extracted in duplicate and where clarification on interpretation of data was required, senior investigators with expertise in high-risk obstetrics and neurology, adjudicated. Data was extracted on year of publication, country and study setting; study design; number of pregnant persons and pregnancies; patient demographics and baseline characteristics; age at diagnosis of NMOSD; whether the patient had received another diagnosis prior to receiving the diagnosis of NMOSD; medical co-morbidities predating pregnancy and clinical status at onset of pregnancy; details of primary and secondary outcomes as outlined above; methods of identifying and controlling for confounders, if reported; methods of handling missing data if reported; and details on analysis, as presented. Although originally intended, based on the retrospective nature of most studies, and since information provided was sufficient to make decisions with regard to inclusion, we did not contact authors for additional information, as this was not likely to yield any more information than presented in the original manuscript.

Quality Assessment

Since all included studies were either case reports and case series, to enable comparative scoring between studies, quality assessment was performed using Joanna Briggs' critical appraisal tool for case reports and series.

Data Synthesis

Primary Analysis

Pooled incidences and 95% confidence intervals (CI) were planned for all maternal, fetal and neonatal outcomes, should the data have permitted this form of analysis. As considerable clinical and methodological heterogeneity between studies was anticipated, analysis was planned using DerSimonian-Laird binary random-effects meta-analyses on OpenMetaAnalyst® software (19). We planned on assessing statistical heterogeneity using I^2 statistic, treating I^2-values $>$75% as having a high degree of heterogeneity (20). Given the rarity of this condition, included studies were mostly case reports and case series with small numbers of patients and considerable heterogeneity between studies. For this reason, we primarily used tabulation and narrative synthesis in summarizing the data.

Subgroup and Sensitivity Analyses

Given the small-anticipated numbers of case series, we did not propose any a priori subgroup or sensitivity analysis. We aimed to assess publication bias using visual inspection of funnel plots with 95 and 99.7% control limits, in analyses where more than 10 studies were included.

RESULTS

Included Publications and Pregnancies

Our search identified a total of 2,118 titles and abstracts, of which 1,582 remained after removing duplicates. Following the first round of screening, 1,520 were found not to be relevant to pregnancy and NMOSD. We sourced the remaining 62 full-texts and excluded a further 33 were excluded for reasons identified in **Figure 1** and described in **Supplementary Table 2**. Of the 29 included papers, 22 reported on individual cases [one pregnancy, a number of pregnancies in a single patient, or an account of all pregnancies in a number of patients] (21–42). The remaining

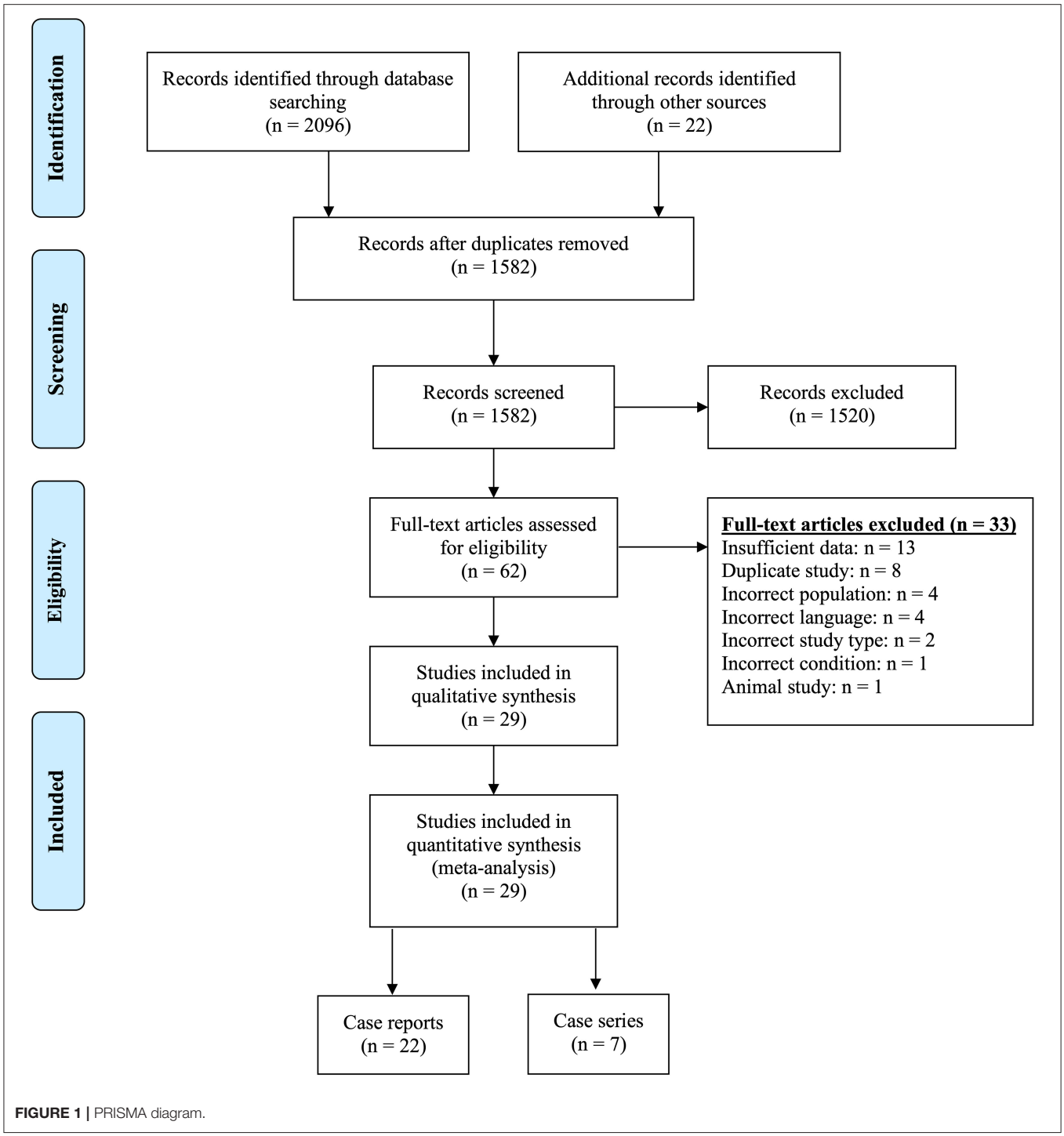

FIGURE 1 | PRISMA diagram.

seven publications summarized data on all pregnancies managed at one or more centres (6–11, 14).

Characteristics of Included Pregnancies

The 22 case reports described 71 pregnancies in 54 women, and the seven case-series described 524 pregnancies in 335 women. Thus, this systematic review included a total of 595 pregnancies in 389 women with a diagnosis of NMOSD. The publications were mostly from Europe, the Americas and Asia, and the characteristics of included pregnancies are presented in **Table 1**.

Demographic Details

The mean maternal age (during pregnancy) for all included patients was 28.12 ± 5.19 years. Reporting of patient demographics was limited, especially in the case series. For

TABLE 1 | Characteristics of included publications and pregnancies.

	Case reports	Case series
Number of publications	22	7
Patients (pregnancies)	54 (71)	335 (524)
Geographical region		
• Europe	• 7/22	• 1/7
• North America	• 6/22	• 0/7
• South America	• 2/22	• 1/7
• Asia	• 6/22	• 3/7
• Multiple centers	• 1/22	• 2/7
Maternal age in years (mean ± SD)	28.12 ± 3.91	29.9 ± 5.19
Maternal ethnicity		
• Not reported	• 18/54 (33.3%)	• 153/197 (77.7%)
• Asian	• 23	• 38
• Black	• 7	• 4
• White	• 5	• 2
• Mixed	• 1	• 0
Gravidity	1.93 ± 1.41	1.63 ± 1.23*
Parity		
• Not reported	• 31	• 503
• Nulliparous	• 20	• 4
• Multiparous	• 21	• 17
NMOSD diagnosis	(denominator 71 pregnancies)	
• Diagnosed in index pregnancy	• 31	• 107/524
• Correct diagnosis prior to pregnancy	• 28	• Unclear
• Incorrect diagnosis prior to pregnancy	• 12	• Unclear
Diagnostic criteria for NMOSD met	43/71	524/524
• Aquaporin antibodies	• 65/71	
• Acute myelitis	• 38/71	
• Optic neuritis	• 23/71	
• MRI findings	• 31/71	
Medical comorbidities	(denominator 71 pregnancies)	Reported in 3/7 series and ranged from 12 to 63%
• Type 2 diabetes mellitus	• 1	
• Hashimotos thyroiditis	• 1	
• Sjogren syndrome	• 1	
• Systemic lupus erythematosus	• 2	
• Myasthenia gravis	• 1	
• Other autoimmune disease	• 1	

**Only reported in two case-series; MRI, magnetic resonance imaging; NMOSD, Neuromyelitis optica spectrum disorder; SD, standard deviation.*

example, maternal ethnicity was not reported in one third of the case reports and for over three quarters of patients included in the case series, and we opted not to make assumptions with regard to ethnicity based on country of publication. Similarly, information on gravidity and parity was missing in most case series. Medical comorbidities were poorly reported in both case reports and case series. Where reported, the most common conditions included autoimmune disorders such as systemic lupus erythmatosus and Sjogren's syndrome, thyroid dysfunction, myasthenia gravis and antiphospholipid antibody syndrome. The reported demographic data are summarized in **Table 1**.

Diagnosis of NMOSD

In the case reports 31/71 (42%) described the diagnosis of NMOSD being made during the index pregnancy, while 28/71 were diagnosed as NMOSD prior to pregnancy, and in 12/71 (17%) cases, an alternate diagnosis (multiple sclerosis, transverse myelitis or neurosarcoidosis) made prior to pregnancy, was changed to NMOSD during pregnancy, but did not affect treatment decisions during pregnancy. Case series described 107/524 (20%) *de novo* diagnosis of NMOSD in pregnancy, but were unclear in their reporting of diagnoses made prior to pregnancy. Where reported, the average age at diagnosis of NMOSD for the entire cohort, was 31.49 ± 7.41 years (for case reports alone, 29.9 ± 5.91 years). While the case series confirmed that criteria for NMOSD diagnosis were met in 100% of cases, details on the specific criteria based on which the diagnosis was made, were lacking. Case reports on the other hand, provided greater detail on the specific criteria being met, in terms of AQP4 antibodies (65/71), clinical symptoms (61/71) and MRI findings (31/71).

Outcomes

Maternal Outcomes

Maternal Medical Outcomes

The most commonly reported maternal neurologic signs and symptoms reported during pregnancy included sensory abnormalities including dysesthesias, paraesthesias, hypoesthesia, allodynia, and neuropathic pain (29 episodes in 16 pregnancies, between 9 weeks' gestation and 2-weeks postpartum), motor weakness (22 episodes in 10 pregnancies, occurring between 9 weeks and 2-months postpartum), visual symptoms (17 episodes in 10 pregnancies, occurring between 9 and 34-weeks of gestation), bladder and/or bowel incontinence (10 episodes in 6 pregnancies, occurring between 9 and 34 weeks' gestation) and spasticity (five episodes in five pregnancies, between six and 34 weeks of gestation). In addition, there were three reports of "features of transverse myelitis" without specifying signs or symptoms, between the first trimester and 10-days postpartum, two reports of severe respiratory symptoms (dyspnea requiring oxygen therapy as part of a relapse that also involved severe spastic tetraparesis and widespread sensory disturbances, and acute respiratory failure requiring intubation and mechanical ventilation), and one of seizures, although no

further details on the seizures were provided. There were no maternal deaths or gait abnormalities.

Disability

The dramatic progression of NMOSD-related symptoms often results in considerable disability during pregnancy, which has been quantified as Expanded Disability Status Scale (EDSS) scores, that range from 0 (normal) to 10 (death by the disease) and increase in degrees of 0.5 points. Bourre et al. noted a considerable increase in the EDSS score from 1.5 ± 1.7 to 2.6 ± 1.9, $p = 0.027$), suggesting that pregnancy might have a greater effect on disability in NMOSD than in multiple sclerosis (10). Huang et al. reported a statistically significant increase in EDSS scores from 1.55 ± 0.38 before conception to 1.93 ± 1.41 during pregnancy, and 2.88 ± 2.14, in the postpartum period. Fragoso reported an increase in EDSS scores from 1.33 ± 1.60 before pregnancy to 3.01 ± 1.83 a year after childbirth ($p = 0.06$) (7). In summary, 42% of cases had increased EDSS scores during or soon after pregnancy (6).

Maternal Obstetric Outcomes

The only antenatal obstetric outcome reported was that of hypertensive disorders of pregnancy including preeclampsia, which affected 17/146 (11.6%) pregnancies (7, 14, 21, 23, 39). It must be noted that only two case series and eight case reports commented on this outcome. Two of these developed eclamptic seizures during pregnancy. There were limited data on the mode of initiation of labor (spontaneous vs. induced) or the use of labor analgesia. In the 100 instances, where the mode of delivery was reported, most (60%) had vaginal births. Where cesarean deliveries were undertaken, limited data were presented on their indication. The gestational age at delivery was only mentioned in 37 pregnancies, of which 7 (19%) occurred preterm (before 37 weeks of gestation). Two of these were vaginal births at 35 weeks' gestation, with no mention on whether they occurred spontaneously or were medically induced. Of the other five, one was induced at 31 + 3 weeks following the diagnosis of intrauterine fetal death; two preterm cesarean deliveries were performed for obstetric indications (severe preeclampsia at 25 weeks and fetal well-being concerns at 33 weeks); and two cesareans were performed at 32 and 35 weeks in view of refractory neurological symptoms (respiratory symptoms in one, and progressive weakness and blindness in the other), despite treatment. A mention was made of one patient presenting in very advanced labor, on account of not feeling uterine activity.

Relapses

Annualized relapse rate (AAR), which refers to the number of relapses per patient and per year has often been used to describe relapses in patients with NMOSD, including during pregnancy and in the postpartum periods. Studies have suggested increased risk of relapse and greater disability during and immediately after pregnancy (6–8, 10), especially in those not on immunosuppressive treatment at the time of conception (9). With regard to the antepartum period, it is unclear whether relapses occur with greater frequency during any particular trimester. Tong et al. reported no increase in relapses during pregnancy in 234 pregnancies (11). Fragoso et al. reported that relapses were most common in the first trimester (7), while Bourre reported it to be highest in the third trimester (10). Huang et al. reported a 0.44-times decrease in relapse in the third trimester when compared with the year before conception (6). It is possible that these variations depend not just on the natural course of the disease, but also upon the use of suppressive medications, and/or the ARR prior to conception. With regard to the postpartum period, most studies reported an increased relapse rate in the first few months following childbirth, but there is no consensus on whether the relapse rate stabilized within 6 months (6, 10–13). Of the postpartum relapses described in the literature, most occurred within the first 3 months postpartum. Relapses were described as early as within 7–10 days, and as late as 17–30 months following childbirth, which are unrelated to the course of pregnancy. Eight studies reported no relapse during the study follow up period, which when described, ranged between 3 months and 2 years. In addition to the stage of pregnancy, there seems to be a positive correlation between relapse rates and seronegative AQP4-IgG status [OR 3.84, $p = 0.025$)], the presence of other autoimmune conditions or antibodies [OR 2.48, $p = 0.025$)] and those receiving no treatment during remission [OR 1.19, $p = 0.025$)] (6). The lack of immunosuppressive treatment was identified as a risk factor for relapses in several studies (9, 11, 39) while factors that were not found to be correlated with relapses included age at onset of NMOSD (6), maternal age at pregnancy (7), presence of initial symptoms (6), pre-pregnancy relapses (7), regional analgesia/anaesthesia (7, 10) or breast feeding (10). Information on the effect of race or mode of delivery on relapse rates was insufficient to draw conclusions.

Fetal and Neonatal Outcomes

Mortality Outcomes

Data on pregnancy loss were explicitly presented for 531 pregnancies, of which 139 pregnancy losses occurred prior to viability (spontaneous miscarriages or pregnancy terminations on account of the condition or medications), and two were stillbirths. The trimester/ gestational age at pregnancy loss was only presented in 12 instances, eight of which were in the first trimester, three in the second and one in the third trimester. The temporal association between exacerbation in the maternal medical condition and fetal loss, was mentioned in three instances—two miscarriages following episodes of transverse myelitis requiring treatment with high-dose steroids and plasma exchange, and one stillbirth at 31 + 3 weeks concurrent with seizure activity in the mother. For the remainder of the pregnancy losses, temporality could not be ascertained. Data were also lacking in most instances, on the proportions of pregnancies that were lost spontaneously vs. those that were terminated, and the reasons for terminations.

Fetal Growth Restriction and Preterm Birth

There were three reported cases of fetal growth restriction in two publications (38, 39). However, birth-weight centiles based on gestational age could only be calculated for eight publications that provided details on birth weight, and fetal

growth restriction could be confirmed only in one case (1,635 g at 33 weeks' gestation, which is under the 3rd centile) (38). Of the 98 pregnancies for which data on gestational age at birth was available, there were 12 reported preterm births (under 37 weeks' gestation). Of these, one followed preterm premature rupture of membranes at 36 weeks, three others occurred at 35 weeks, and the gestational age for four presumably spontaneous births was not known. The other four occurred between 25 and 33 weeks of gestation. In two of these cases, labor was induced (severe preeclampsia at 25 weeks and intrauterine fetal death at 31 + 3 weeks) and two cesarean deliveries were performed at 32- and 33-weeks' gestation, for uncontrolled maternal symptoms and suspected fetal growth restriction, respectively (7, 23, 27, 39).

Neonatal Outcomes

There were no reports of neonatal deaths. Six case reports presented Apgar scores at birth, to indicate the condition in which the baby was born. Besides the preterm infants that were admitted to the NICU, neonatal admissions were also described for five other infants, for transient myasthenia gravis in the absence of AQP4-Ig antibodies, which responded to intravenous immunoglobulin (IVIg) treatment but required prolonged hospitalization (25 days) (31), third-degree congenital heart block treated with intravenous dexamethasone (in a mother who had anti SS-A and anti SS-B antibodies) (33), hydrocephalus (14), congenital anomaly (aplastic left lung and fusion of digits) and seizures (40), and an unknown indication (7 days) (7). Congenital malformations, or their absence, were explicitly reported in 10/28 publications, while an additional 10 reported on a healthy newborn, presumably without any anomaly and with an intact neurological examination. A normal neurological examination was explicitly mentioned in five publications, four of which also described the AQP4-IgG titres/ levels at birth. Two of these publications, also described levels at follow-up, which in one case dropped to one-quarter of the original levels in 8-weeks (26), and the other wherein titres of 1:100 normalized over 6 months (28). Two studies described infant follow up ranging from 14 months to 18 years (7) and 6 months to 12 years (9), respectively.

Management Strategies

All publications provided details on management strategies during pregnancy, and to some extent, the response to these strategies.

Multidisciplinary Team

Eleven publications explicitly described the involvement of a multidisciplinary team, mostly involving a neurologist or internal medicine physician and an obstetrician, but in three instances each, also involved anaesthesiologists and neonatologists. Where multidisciplinary team involvement was not explicitly mentioned, three publications were authored by a team involving neurologists and obstetricians, with one each additionally co-authored by an anaesthesiologist and ophthalmologist. Seven publications were authored by neurologists alone, one by obstetricians and in nine instances, the team of physicians was unreported.

Medical Management of Symptoms

Medical management was not always described in detail, especially in case series, which tended to focus more on disability and relapse rates during pregnancy. Where described, 29/74 (39%) pregnancies did not receive any medical management. When treatment was administered, oral corticosteroids and immunosuppressive agents formed the mainstay, both for prophylaxis against relapses, as well as for the initial management of relapses. The immunosuppressive agents of choice were azathioprine (35 pregnancies), tacrolimus (7 pregnancies), cyclophosphamide (2 pregnancies) and methotrexate (2 pregnancies). Neuropathic pain was most commonly managed with agents such as gabapentin, amytriptiline and clonazepam, and painful spasticity with baclofen.

Management of Relapses

The initial management of relapses involved high-dose corticosteroids and/or the introduction of immunosuppressive agents, as described above. In addition, the use of intravenous corticosteroids was described in 15 pregnancies, 14 of which used methylprednisone, while one described the use of intravenous dexamethasone (5 mg/day for 5 days) to treat sphincter disturbance. The use of plasma exchange, with no adverse pregnancy events, was described in 12 cases, with as many as 24 sessions, until resolution of symptoms. The use of IVIg was described in six pregnancies, with one publication (6), suggesting lower birth weight of neonates of those treated with intravenous methylprednisone and/or IVIg during pregnancy (2,444 ± 440 vs. 3,060 ± 466 g, $p = 0.002$). However, this paper did not adjust for confounding variables such as maternal comorbidities, placental insufficiency, fetal growth restriction and prematurity. The use of biologics (rituximab) was described in 15 pregnancies, but treatment in all cases was deferred until after childbirth, or initiated in the postpartum period. In those on biologics prior to pregnancy, biologics were often withheld until childbirth, and re-introduced in the postpartum period. The use of postpartum mitroxantrone was described in one case, along with corticosteroids. It must be noted that in many instances, patients had concurrent autoimmune conditions which may have warranted the above treatments.

Labor Analgesia and Anesthesia

This was not described in most included publications. Where mentioned, regional analgesia and anesthesia (epidural and spinal) were successfully used. In general, while most anesthetists would avoid regional techniques in the setting of acute exacerbation of myelitis, there is no evidence to suggest a causal relationship between regional analgesia/anesthesia and onset of symptoms or relapses described by some (43), and therefore decisions should be individualized (44). This is particularly important since neuromuscular blockade administered as part of general anesthesia for cesarean deliveries is associated with a risk of aspiration and respiratory muscle weakness (44).

Risk of Bias (ROB) Assessment

ROB assessments for case reports and case series are presented in **Figure 2**. Case reports generally scored well on ROB assessment,

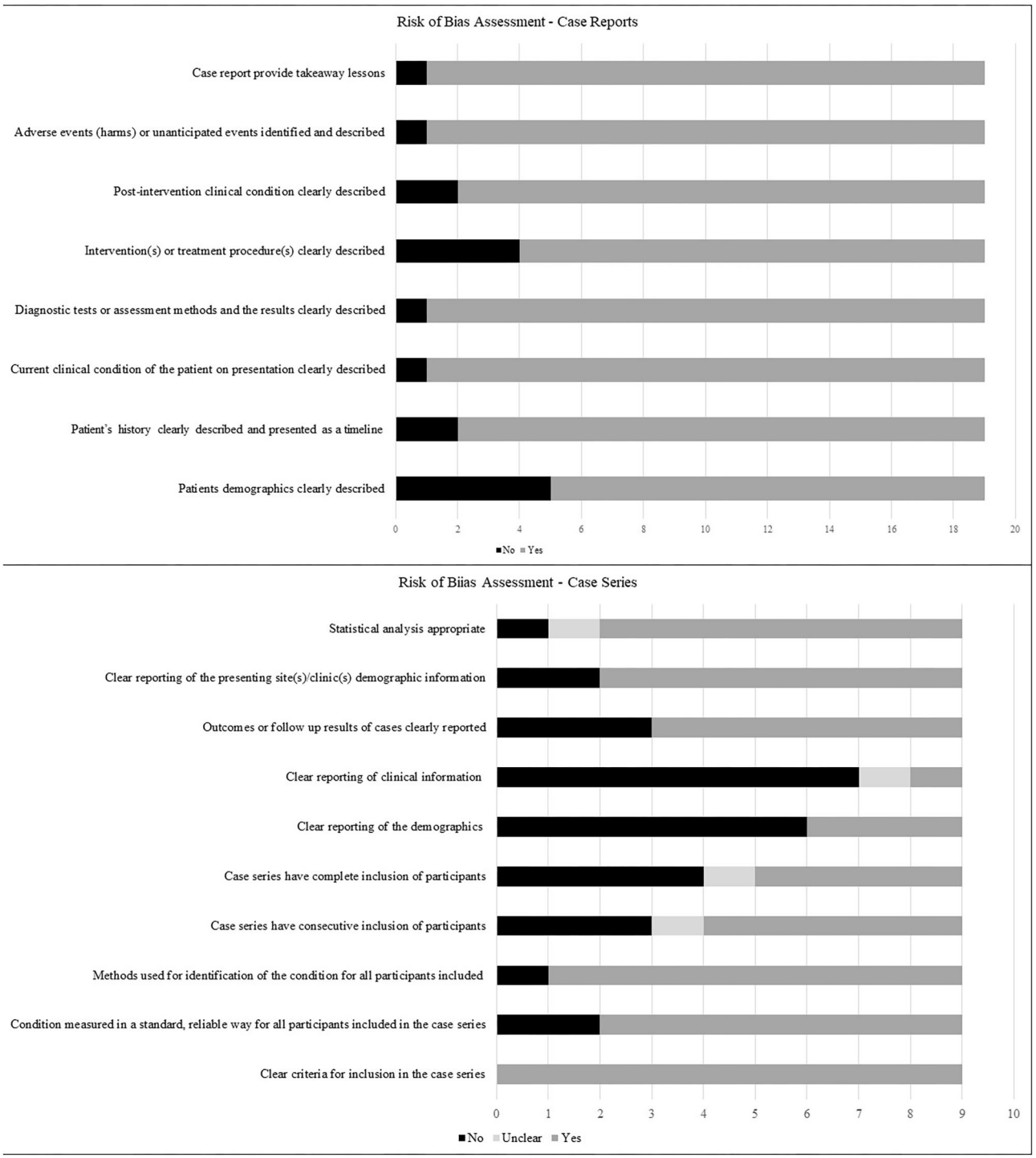

FIGURE 2 | Risk of bias of included studies describing the proportions of studies fulfilling the criteria for case reports and case series as outlined in Joanna Briggs' critical appraisal tools.

with ∼90% of them or greater, describing the patient's history, assessment methods, the clinical condition pre- and post-intervention, adverse events and take-away lessons. Patient demographics and interventions were described by 74 and 79% of the studies, respectively. ROB assessments for case series were less robust, with only the criteria for inclusion and the methods used for identification of the condition, clearly described in 100 and 89% of the series, respectively. In addition, 78% of series clearly

reported patient demographics, performed adequate statistical analysis, and reported whether the condition was measured in a standard manner. In contrast, outcomes and follow up was adequately described in 67% of series, confirmation that cases were consecutive in 56%, complete inclusion of participants in 44% and patient demographics described in 33%, while clinical information regarding pregnancies was adequately reported only in 11% of the series.

DISCUSSION

This systematic review that included 22 case reports and seven case series described 595 pregnancies in 389 women with NMOSD. Despite inadequacies in reporting of pregnancy outcomes, the inability to determine the association between relapses and outcomes, or the effect suppressive treatment on preventing relapses and improving pregnancy outcomes, this review was able to confirm the following with regard to NMOSD and pregnancy.

First, pregnancy and the postpartum period are associated with increased NMOSD disease activity. There are a number of explanations for why pregnancy might accelerate the course of the condition, or the nature/frequency of symptoms. During pregnancy, the fetoplacental unit synthesizes Th2 cytokines, which induce downregulation of maternal Th1 cytokines that mediate cellular immunity, thereby increasing humoral immunity. This would imply that the disease activity of NMOSD (a Th2- mediated disease) should be considerably higher than that of multiple sclerosis, which many believe is primarily a Th1-mediated disease. However, a recent study has shown this not to be the case, suggesting that Th1/Th2 cytokine imbalance is not the primary pathophysiological pathway of NMOSD activity during pregnancy (11). It has also been suggested that the higher estrogen levels in pregnancy can lead to development of self-reactive peripheral B cells, which can increase antibody production in NMOSD (vs. multiple sclerosis which is not an antibody-mediated disease) (45). Although AQP4-IgG has been shown to cause placental inflammation and lead to negative pregnancy outcomes in animal studies, a recent study of the placentae of patients with NMOSD showed no clear decrease in placental AQP4 expression, no obvious placental inflammation or signs of damage in placental AQP4-IgG seropositive NMOSD patients, and no negative effects in term-born infants (46). It is possible that the increased disease activity and adverse pregnancy outcomes in patients with NMOSD is due to a multitude of factors, including the effect of pregnancy hormones such as estrogen, progesterone and glucocorticoids (11, 45). In fact, this review indicates that pregnancy and the postpartum period appears to be a high-risk time for disease activity and relapses. This is particularly true in the immediate postpartum period, where initiation or augmentation of immunosuppressive therapy might offer an opportunity for reducing relapses. In addition, disease activity might also be increased during the course of pregnancy, and increased disease activity may be associated with worse pregnancy outcomes. This suggests a role for immunosuppressive therapy to reduce disease activity and prevent relapses.

Second, although no maternal deaths have been reported, relapses are associated with considerable disability, both during and after pregnancy, which again may be amenable to the prompt initiation or increasing the dose of pre-pregnancy immunosuppressant medication. The commonest neurologic abnormalities occurring during pregnancy were sensory, although motor weakness, spasticity, visual symptoms, sphincter disturbances and serious respiratory morbidity were all reported.

Third, maternal obstetric outcomes may be no different from the general population. Although difficult to deduce the exact incidence of conditions from case reports and case series, especially when most did not report on obstetric conditions, it seems like the incidence of spontaneous preterm births are no greater in patients with NMOSD than with the general population. The one study which provided detailed information on preeclampsia, reported a higher rate [11.5% (6.27–18.9%)] than in population studies, and higher odds in women with other autoimmune disorders or prior miscarriages (14). However, NMOSD was not identified as an independent risk factor for preeclampsia. Based on this limited data, and given that the definition of preeclampsia has changed considerably over time, it would not be possible to conclude that the incidence of preeclampsia is truly increased in those with (or as a consequence of) NMOSD.

Area postrema syndrome, which refers to attacks of intractable nausea, vomiting, or hiccups, in the context of a lesion in the dorsal medulla, occurs in ∼30% of patients with NMOSD and must be differentiated from hyperemesis gravidarum or severe nausea and vomiting in pregnancy, which occurs in ∼1% of pregnant women (47). Although there is considerable overlap between the two, hyperemesis gravidarum often does occurs exclusively in the first half of pregnancy and may be associated with liver enzyme derangements and abnormalities in thyroid function testing, both of which would not be typical of area postrema syndrome. If in doubt, a brain MRI should be performed with any new acute presentation of severe vomiting in a woman with NMOSD. Identification of a lesion in the dorsal medulla would support the diagnosis of area postrema syndrome of NMOSD. Of course, it is more challenging if this is the first presenting sign of NMOSD in a pregnant woman. Area postrema syndrome usually responds well to high-dose corticosteroid therapy.

The vast majority of pregnancies resulted in vaginal birth, although some cesarean deliveries were undertaken on account of disease activity. Unless clinically indicated for fetal or maternal reasons, cesarean delivery is not required in those with NMOSD. No conclusions could be drawn with regard to the effect of the mode of delivery on the postpartum course. Although there are theoretical concerns that pre-existing demyelinated neurons may be more susceptible to neurotoxicity from local anesthetic agents, general anesthesia, in addition to its pregnancy-related risks also carries the risk of increased neuromuscular junction responses to muscle relaxants in those with NMOSD. Decisions on the

TABLE 2 | Therapeutic recommendations for Neuromyelitis Optica Spectrum Disorder patients during pregnancy and breastfeeding.

Medication	Pregnancy Risk (50)		Breastfeeding (50, 52, 53)	
	Teratogenicity (congenital malformation)	Other toxicity (Fetal/neonatal loss, prematurity, growth-and-developmental concerns)	Relative infant dose (RID)	Comment
Corticosteroids	Human data suggests no increased risk of congenital malformations including orofacial clefts	Human data suggest no increased risk of fetal loss, but a possible association with preterm birth and low birth weight	Prednisone—0.35–0.53%; Prednisolone—0.09–0.18%	Compatible with lactation, especially with short term use. Suggest delaying breastfeeding for 4 h if on high doses
Azathioprine	Observational studies did not find a higher rate of birth defects in the offspring of women who received azathioprine therapy during pregnancy than in the general population	Exposure in the 3rd trimester has been linked to immunosuppression, and bone marrow suppression of the newborn has been reported, but modification of the dose in the 3rd trimester appears to reduce the risk of this toxicity	0.05–0.6%	Compatible with lactation. Suggest delaying breastfeeding for 4 h
Cyclophosphamide	Congenital defects when exposure occurs during organogenesis	Fetal bone marrow suppression is a potential toxicity when exposure occurs later in pregnancy	0.8% on day 1 to 0.9% on day 4	Reported cases of neutropenia and thrombocytopenia, and the potential for adverse effects relating to immunosuppression and carcinogenesis
Methotrexate	Methotrexate embryopathy	Exposure in second and third trimesters may be associated with fetal toxicity and mortality	0.5%	Contraindicated
Mitoxantrone	Animal studies do not suggest teratogenicity. However, due to its cytocidal effect on proliferating and non-proliferating human cells, its use is not recommended in the first trimester.	Toxic to some case reports suggest increase risk of spontaneous miscarriages and growth restriction	NA	Contraindicated
Mycophenolate mofetil	Human and animal data suggest risk. The use of mycophenolate mofetil (MMF) during early pregnancy is associated with major birth defects that may represent a characteristic phenotype	Associated with spontaneous miscarriages	NA	Limited information from few infants that have reportedly been breastfed with no adverse effects reported. Alternate drugs are recommended until more evidence is available.
Tacrolimus [Calcineurin inhibitor]	Human studies suggest low risk for congenital malformations, although animal studies indicate dose-related teratogenicity.	Animal studies indicated abortifacient properties in three species, but this has not been seen in human studies. Human studies suggest association with neonatal hypertension, hyperkalemia, and possibly prematurity (54–56)	0.06–0.5%	Compatible based on limited data
Eculizumab [Humanized monoclonal anti-C5 (terminal complement) antibody]	Case series suggest low risk of congenital malformations	Case series suggest no increased risk of fetal or neonatal loss	NA	Compatible based on limited data (57)
Inebilizumab	Evidence under review		NA	Evidence under review
Ocrelizumab	Evidence under review		NA	Limited data does not show harm-Evidence under review
Rituximab	Case series suggest no increased risk of congenital malformations	All human live births were healthy and none had structural anomalies that were thought to be related to rituximab	NA	Limited data does not show harm. Until more data available should be used with caution.

(Continued)

TABLE 2 | Continued

Medication	Pregnancy Risk (50)		Breastfeeding (50, 52, 53)	
	Teratogenicity (congenital malformation)	Other toxicity (Fetal/neonatal loss, prematurity, growth-and-developmental concerns)	Relative infant dose (RID)	Comment
Tocilizumab [Humanized monoclonal anti-IL-6 antibody]	Case series and registry data suggest no increased rate of congenital abnormalities	Case series and registry data suggests no increased rate of spontaneous miscarriages	NA	Compatible based on limited data
Immune Globulin	No embryo-fetal risk attributable to immunoglobulin has been identified		NA	No human data-probably compatible
Plasmapheresis	Potentially safe in pregnancy		NA	Probably compatible
Gabapentin	Animal studies suggest congenital anomalies. Based on available human data, its use is recommended if benefits are deemed to outweigh risks.	Low birth weight, associated with increased risk of preterm birth and neonatal intensive care	2.34%	Limited human data-probably compatible
Amitriptyline	Occasional reports of congenital malformations but generally regarded as safe during pregnancy	Animal and human studies suggest no increased risk of fetal loss or other fetal toxicity	0.9%	Not expected to cause any adverse effects in breastfed infants, especially if the infant is older than 2 months. However, rare cases of sedation have been reported in neonates.

DNA, deoxyribonucleic acid; NA, not available.

Legend	*Compatible/Benefits > Risk*	*Limited data; probably safe*	*Weigh risks vs. benefits*	*Limited data; probably risky*	*Contraindicated*	*No human data*

choice of anesthesia should be individualized and involve shared decision-making with a multi-disciplinary team (48).

Fourth, the high fetal loss rate reported cannot be definitively attributed to NMOSD disease activity. Many series did not distinguish between pregnancy loss due to spontaneous miscarriage vs. pregnancy termination, and even when they did, it was difficult to determine whether spontaneous miscarriages, which are not uncommon even in healthy pregnancies, were the consequence of increased disease activity, co-existing autoimmune conditions or medications. Based on information provided, there was no increase in rates of congenital malformations, fetal growth restriction, stillbirths, or neonatal deaths. Neonates were delivered in good condition, although detailed neurological examinations were not provided. AQP4-Ig levels in cord blood were reported only in a small number of pregnancies. When reported, levels tended to return to normal within 6 months.

Fifth, a condition as rare as NMOSD is unlikely to be encountered by many healthcare professionals, and multidisciplinary input that includes neurologists, internal medicine physicians, high-risk obstetricians, ophthalmologists, anaesthesiologists and neonatologists is vital to optimize outcomes for mother and baby.

Sixth, pharmacologic management of NMOSD in pregnancy is highly variable and targets disease modification or symptom relief. It can range from supportive management with close observation to oral and intravenous corticosteroids (pulse and maintenance), various immunosuppressive treatments, IVIg, plasma exchange, and supportive treatment for symptoms. Although, after careful discussion of risks and benefits, and the knowledge that symptoms of NMOSD often worsen in pregnancy, an approach involving conservative (unmedicated) management may be an option for those with stable disease activity (22, 28), emphasis should be placed on the safety of many immunosuppressive treatments during pregnancy and while breastfeeding. This review shows that although relapses were managed aggressively, 39% of pregnancies were not on any medications during pregnancy. It is unclear whether this is the result of a general reluctance to administer medications during pregnancy, and whether the lack of suppressive treatment with steroids/ immunosuppressants could explain the high relapse rates. Initiation of prophylactic immunosuppressive treatment or increasing the dose of existing medication during pregnancy and in the early postpartum period could prevent relapses. A detailed account of therapeutic considerations with NMOSD and pregnancy has been recently published (49). A summary of various medications and their safety during pregnancy and lactation, based on most up-to-date evidence (49–53) is presented in **Table 2**, and discussed below

- Corticosteroids: Glucocorticoids are administered to patients with NMOSD both at high doses (1,000 mg/day for 5 days, administered intravenously) as a treatment for acute attacks and at lower doses (30 mg) as oral immunosuppressive therapy (49). Non-fluorinated glucocorticoids such as prednisone, prednisolone and methylprednisolone have a plasma half-life of 1–3 h and a duration of action of 12–36 h (49) Systemic

corticosteroids are generally well-tolerated in pregnancy. Also, only 10% crosses into the fetal circulation due to placental metabolism and initial concerns with regard to their association with fetal orofacial clefts (58) has now been disproven (59–61). There may be a small association between the administration of corticosteroids and maternal obstetric outcomes such as gestational diabetes and hypertension, but in general the benefits in pregnancy outweigh risks. Lactation is compatible with glucocorticoid use, as glucocorticoid levels in breast milk are typically very low and no modifications to breastfeeding are recommended with short-term use. However, in those receiving high doses, delaying breastfeeding for 4 h theoretically would decrease the dose received by the infant (49, 52).

- Immunosuppressive Agents: Along with corticosteroids, other immunosuppressive agents form the mainstay of treatment of initial attacks and relapses. Azathioprine is a relatively safe option for use during pregnancy and lactation (49, 61), despite indications of a slightly increased risk of adverse outcomes, and should be initiated or continued, regardless of gestational age, should the clinical condition require pharmacologic management (62, 63). Tacrolimus has been used effectively, but is not among the first line treatments approved for NMOSD. Although associated with a low risk for congenital malformations (50) human studies suggest association with neonatal hypertension, hyperkalemia, and possibly prematurity (54–56). Cyclophosphamide is contraindicated for use in the first trimester and during lactation. Other drugs contraindicated during pregnancy and/or lactation included mycophenolate mofetil (MMF) and methotrexate due to a high risk of spontaneous miscarriage and congenital malformations, and mitoxantrone on account of ovarian toxicity resulting in permanent infertility, and substantial transfer in breast milk (61).
- Monoclonal antibodies: are being increasingly used in pregnancy. A recent systematic review of systemic autoimmune conditions showed that there is no association between their use during pregnancy and the risk of congenital anomalies or preterm deliveries compared with disease matched unexposed pregnant women (64). Owing to their high molecular weight, only small amounts are likely to be transferred into breast milk. These clinically insignificant amounts are also expected to be destroyed by proteolytic enzymes in the infant's gastrointestinal tract and, therefore, not absorbed into the bloodstream. Although women are generally advised not to breastfeed during treatment with monoclonal antibodies, this advice is likely to change in the near future. Rituximab crosses the placenta and induces a decrease in fetal B cell counts. However, this is reversible within 6 months of birth. Given during or after the second trimester, rituximab might lead to B cell depletion in the newborn baby, so B cell counts should be monitored in the baby and vaccinations planned accordingly. The concentration of rituximab in breast milk is found to be 240 times lower than in maternal serum (65). Eculizumab does not seem to have an adverse impact on pregnancy outcomes and umbilical cord blood concentrations are not sufficient to have a pharmacological effect on the fetus (66, 67). The drug has also not been detected in breast milk of mothers taking eculizumab, making it a potential treatment option in pregnant or lactating women with aggressive NMOSD disease. However, larger case series and long-term infant follow-up are required to further investigate the effects of eculizumab treatment during pregnancy and lactation. Studies on Tocilizumab suggest that there may be no increased risk of congenital malformations but a slightly increased risk of spontaneous miscarriage (25% vs. baseline risk of 12–15%) (68–72). Tocilizumab concentration in breast milk peaks on the third day after treatment administration, with a breast milk to maternal serum concentration ratio ranging from 1:500 to 1:1,000, and infants showing no signs of health problems, developmental delays or adverse events following routine vaccinations (73). Current phase-III clinical trials are ongoing on satralizumab (74) and inebilizumab (75), neither of which are expected to have teratogenic effects in humans, although pregnancy and lactation risks need to be further investigated.
- IVIg: is considered safe during pregnancy and lactation (76). The lower birthweight in those on IVIg reported in one publication (6), cannot be directly attributed to its use in pregnancy, and could be the result of other confounding variables, such as prematurity. Plasma exchange is not associated with increased risk of adverse effects during pregnancy and can be used after risk–benefit evaluation. General risks that include infection, coagulopathy, disturbances of electrolyte homeostasis, fluid shifts and hypovolemia need to be borne in mind. Immunoadsorption, wherein plasma is separated from blood cells, cleared of antibodies with an IgG-adsorbing column and reinfused, reduces the antibody burden more efficiently than plasma exchange. It is not known to be associated with clinically relevant adverse effects during pregnancy or lactation.

The safety of pharmacotherapy for NMOSD during pregnancy and lactation is summarized in **Table 2**.

This is the first systematic review on NMOSD and pregnancy, whose strengths include an exhaustive search strategy drawing on clinical data not only from case series but also case reports, to enable synthesis of as much information as possible. Despite the methodologic rigor of its conduct, it still has a number of limitations. First, the number of publications on NMOSD is limited, and data presented was insufficient to stratify relapses based on their nature, or draw firm conclusions with regard to ethnic variation, the effect of parity or comorbidities on disease activity, and whether disability and relapse rates are modified by pregnancy events, medications, trimester of pregnancy, use of regional analgesia, mode of delivery, or other pregnancy parameters. Second, although the inclusion of case reports added valuable information on disease progression, these publications are inherently biased, making it hard to determine incidences of various outcomes. Third, poorly and inconsistently reported outcomes as well as considerable heterogeneity between studies precluded any formal meta-analysis. Fourth, it is possible that some of the earlier case reports and series, all of which were

TABLE 3 | Key findings and recommendations for NMOSD and pregnancy (modified from Mao-Draayer et al.) (49).

1. Pregnancy and the postpartum period, in particular, are associated with increased NMOSD disease activity and relapses. Initiation, continuation and/or augmentation of immunosuppressive therapy during pregnancy and in the immediate postpartum period should be considered to reduce attacks.
2. Although Aquaporin-4 (AQP4) is expressed at high levels in the placenta, and high pregnancy loss rates have been reported in NMOSD patients, especially in the first trimester, this review was not able to determine causality between NMOSD activity and spontaneous miscarriages, or comment on the influence of treatment on its risk. Similarly, apart from one publication which reported an increased risk of preeclampsia, there was no increase in adverse obstetric outcomes including preterm birth, fetal growth restriction or congenital malformations in patients with NMOSD.
3. Oral corticosteroids and azathioprine have proven safety for the treatment of initial attacks and relapses during pregnancy. In addition, high-dose intravenous corticosteroids, intravenous immunoglobulin, plasma exchange and immunoadsorption are safe and effective for the management of severe relapses in pregnancy.
4. There is emerging evidence on the safety of monoclonal antibodies such as rituximab. eculizumab and toclizumab during pregnancy and the postpartum period. Management should include monitoring of fetal growth by ultrasound, checking of neonatal B cell counts, and careful planning of newborn vaccination.
5. Mycophenolate mofetil, methotrexate and mitoxantrone are contraindicated, and should be discontinued prior to conception. Accidental administration during pregnancy warrants a discussion on teratogenic risks, and close follow up with ultrasound scans for structural anomalies and monitoring of fetal growth.

retrospective, did not fully fulfill the revised diagnostic criteria for NMOSD. In particular, there were limited data on MRI findings, AQP4 antibodies and clinical symptoms, to determine whether the diagnostic criteria were met. Fifth, the lack of experimental studies in the area, made it difficult to make strong recommendations based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria. Finally, we recognize that the disease course and biology is driven by the serotype, AQP4 vs. myelin oligodendrocyte glycoprotein (MOG) vs. dual negative, rather than the clinical phenotype of NMOSD. However, serologic testing has changed considerably over time; MOG antibody testing was not widely available prior to around 2015, and was not widely reported in the included studies. Hence, some of the seronegative cases may have been MOG+ve, but there was no way of accurately guessing what number. The change in serologic testing as well as the poorer sensitivity of AQP4 testing in the past, makes it challenging to report findings based on the serotype, whether MOG or AQP4. Future research is needed to see if disease activity in pregnancy and postpartum differs by serologic status, and is beyond the scope of this review.

Despite these limitations, our systematic review adds to the growing body of literature on the pregnancy-specific risks to patients with NMOSD, key findings and recommendations of which have been presented in **Table 3**. Understanding the effect of pregnancy on NMOSD and vice versa, as well as the relationship between disease activity, relapses and treatment and adverse pregnancy outcomes, is critical to the management of NMOSD in pregnancy. Given the limitations of retrospective studies in determining temporality and guiding clinical practice, the initiation of an international prospective registry for pregnancy and NMOSD is strongly recommended, until which time, the findings of this systematic review may be used to counsel patients and encourage shared decision-making.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

AUTHOR CONTRIBUTIONS

RD'S conceived the study, provided methodologic and content expertise, oversaw the analysis, and wrote all drafts of the manuscript. DW, KA, VN and NZ performed title and full-text screening and data extraction. DR provided input with regard to the interpretation of neurological symptoms and reviewed the manuscript. NZ and RD'S performed the analysis. RA reviewed the literature with regard to treatment options, helped with formatting and editing of the manuscript and helped with revising the manuscript. AW provided assisted with data extraction and writing up, and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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REVIEW
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Central Nervous System Demyelination Associated With Immune Checkpoint Inhibitors: Review of the Literature

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Immune checkpoint inhibitors (ICI) are a novel class of antineoplastic treatment that enhances immunity against tumors. They are associated with immune adverse events, and several neurological syndromes have been described, including multiple sclerosis and atypical demyelination. We performed a systematic literature review of case reports with neurological immune adverse events that presented with central nervous system demyelination, up to December 2019. We found 23 cases: seven with myelitis, four isolated optic neuritis, one neuromyelitis optica spectrum disorder, five multiple sclerosis, and six with atypical demyelination. Ipilimumab was the most frequently used ICI (11/23). The median time to develop symptoms from the onset of ICI was 6.5 weeks [range 1.0–43.0], and from last ICI dose was 14 days [range 0–161]. Anatomopathological examination was performed in four cases, with the finding of a T-cell mediated immune response. Outcomes were generally favorable after immunosuppression: 18 patients had improvement or a full recovery, three patients did not respond to treatment, three patients died, and in one, treatment was not reported. We describe the patients' clinical presentation, treatment administered, and outcomes. We further speculate on possible pathophysiological mechanisms and discuss potential treatments that may be worth investigating.

Keywords: demyelination, cancer immunotherapy, anti-PD-L1, anti-CTLA-4, anti-PD-1, immune-related neurological adverse events, immune checkpoint inhibitors (ICI)

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INTRODUCTION

Immune checkpoint inhibitor (ICI) is a novel class of antineoplastic drugs that enhance antitumor immune responses through the upregulation of T cell activity. Their mechanism consists of blocking receptors that normally inhibit the T cell response, the so-called inhibitory immune checkpoints. The main targets of these medications are cytotoxic T lymphocyte antigen 4 (CTLA-4) receptor, programmed cell death 1 (PD-1) receptor, and programmed cell death 1 ligand (PD-L1) (1), which are molecules that ultimately break the T cell immune-mediated response. CTLA-4 is expressed on activated $CD4^+$ T helper cells, regulatory T cells, and $CD8^+$ cytotoxic T lymphocytes; they bind to its ligands, CD80 and CD86, expressed on professional antigen-presenting cells (APCs) (2). PD-1 is predominantly expressed on T cells—but also in B cells, natural killer cells,

and macrophages—and bind to PD-L1, expressed by professional and non-professional APCs (including some tumor cells) (3). Specific monoclonal antibodies that block the inhibitory action of these checkpoint molecules lead to persistent and generalized activation of the humoral and cellular adaptative immune system, enhancing antitumor immunity (4).

ICIs have shown clinically effective antitumor response and improved survival for melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma, as for an increasing number of other indications. Six of them are currently available in clinical practice: pembrolizumab and nivolumab (anti-PD-1); atezolizumab, avelumab, durvalumab (anti-PD-L1); and ipilimumab (anti-CTLA-4) (1). However, because of their effect in activating the immune system, they are associated with immune-related adverse events (irAE). The most common irAEs are reactions involving the gastrointestinal tract, endocrine glands, skin, and liver (5). Most of them are mild and can be treated with symptomatic medications, but some require interruption or discontinuation of the ICI and the use of IV steroids or other immunosuppressive drugs (i.e., infliximab for colitis) (6).

Although less common, neurologic irAEs (nirAE) may be severe and require prompt recognition and treatment (7). The incidence of high-grade nirAE in clinical trials was <1% in a review study and was slightly more common for anti-CTLA-4 (0.7%) and combined anti-CTLA-4 plus anti-PD-1 (0.7%) than for anti-PD-1 treatment (0.4%) (7). Headache, encephalopathy, meningitis, Guillain Barré-like syndrome, peripheral neuropathy, and myasthenic syndrome were the most common events reported. Several cases of paraneoplastic neurologic syndromes, with or without demonstration of autoantibodies (4), have also been reported, including anti-NMDA (8, 9), anti-Ma2 (10, 11), anti-SOX1 (8), anti-Ri (9), anti-CASPR2 (12), anti-GAD65 (13) encephalitis, anti-Hu sensory neuronopathy, encephalomyelitis and/or limbic encephalitis (9, 14, 15), and myasthenia gravis (11, 16–20).

Worsening or development of multiple sclerosis (MS) associated with ICIs has previously been reviewed in a study using the United States Food and Drug Administration Adverse Event Reporting System (FAERS) data (21). They found 13 MS cases amongst 42,529 reported adverse events plus one from their institution, with five of them having more detailed clinical data published in case reports (21–25). History of MS was confirmed in 8 (57%) cases, the median time to the beginning of symptoms was 29 days, two patients died because of their relapse, and there was no difference in outcomes between CTLA-4 and PD-1/PD-L1 inhibitors. We systematically assessed published cases of demyelinating syndromes in the central nervous system (CNS) associated with ICIs, including cases not classified as MS. This article includes 14 additional new case reports published since 2018, not discussed in previous reviews (7, 21, 26), and focuses on the clinical manifestations, outcomes, and possible mechanisms involved in ICI-associated demyelination.

MATERIALS AND METHODS

We performed a systematic literature search on PubMed up to December 2019 mentioning treatment with immune checkpoint inhibitors and demyelinating conditions, using the terms: "demyelination or multiple sclerosis or white matter or optic neuritis or encephalomyelitis or myelitis" combined with "anti-CTLA4 or anti-CTLA-4 or anti-PD1 or anti-PD-1 or ipilimumab or tremelimumab or nivolumab or pembrolizumab or lambrolizumab or pidilizumab or durvalumab or avelumab or atezolizumab." Additional articles were identified from other sources (i.e., articles cited in reviews). Two investigators (MCBO and MHB) performed the search and collected the data independently for internal validity. We selected published case reports of CNS demyelinating conditions (including optic neuritis) that were temporally related to ICI use, regardless of the time. We relied mainly on the opinion of the reports' authors that the demyelination was ICI-associated. We defined the presence of demyelination based on the description of imaging studies, the authors' interpretation of these studies in the reports, and/or findings on anatomopathological studies. Cases of CNS encephalitis without evidence of demyelination, with imaging suggestive of vasculitis, and without detailed clinical data were excluded.

Primary cancer, treatment regimen, patients characteristics, clinical manifestations of neurological disorder, MRI, CSF, and other tests, other immune-related adverse events (irAE), time to development of neurological symptoms from ICI start and last ICI dose, oncologic response after ICI treatment, antibodies tested, treatment of nirAE, response to treatment and cessation of ICI were noted. Patients were classified into a "clinical syndrome" based on reported previous diagnosis, clinical and imaging features, and current diagnostic criteria. Cases that did not fulfill criteria for multiple sclerosis (27), optic neuritis (28), neuromyelitis optica spectrum disorder (NMOSD) (29), and demyelinating myelitis (30) were classified as "atypical demyelination." We included in this last group cases that would fit into an encephalomyelitis clinical picture (31, 32). A descriptive statistical analysis was performed for demographic and clinical data. This review is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (33).

RESULTS

We found 96 articles through the PubMed search and an additional 54 articles through other sources. We excluded 92 articles after screening the title and abstract. From the 58 articles assessed for eligibility, 25 articles were excluded because they did not comprise a case report with CNS demyelination (**Supplementary Figure 1**). Articles included in this review contained 23 case reports of patients who developed CNS demyelination after ICI administration. Of these cases, patients were classified as having the following syndromes: 7 with myelitis (19, 34–39), four isolated optic neuritis (40–43), one NMOSD (44), three had a relapse from a previously diagnosed MS (21,

23, 24), and two evolved from a radiologically isolated syndrome (RIS) to MS (22, 45). Six patients had atypical demyelination (14, 25, 46–49). Class of ICI used was anti-PD-L1 in four patients, anti-CTLA-4 in eight, anti-PD-1 in eight, and a combination of anti-PD-1 and anti-CTLA-4 in three patients (in one of them used concomitantly); ipilimumab was the most frequently used ICI (11/23). Patients had a median age of 59 years old [range: 9–75]; 8 of 23 patients were female; median time to development of symptoms from the onset of ICI was 6.5 weeks [range 1.0–43.0], and from last ICI dose was 14 days [range 0–161]; seven of them had other non-neurological irAE reported. Seventeen cases had oncologic outcomes after ICI treatment reported: six partially remitted, five completely remitted, and six had a progression of the oncologic disease (**Table 1**).

All patients but one were investigated with MRI, and anatomopathological examination was performed in four patients (two biopsies and two autopsies). CSF exam was reported in 18 patients, with elevated protein being the most common finding (14/18 cases; median protein of 93.5 mg/dL; range: 50–380), followed by pleocytosis (10/18 cases; median white blood count = 22 cells/mm^3; range: 14–1,195); oligoclonal bands (OCB) were reported positive in seven patients. Anti-aquaporin4 (anti-AQP4) antibodies were tested in four patients and were positive in one; a paraneoplastic panel was assessed in nine patients, with a positive result in two of them (anti-Hu and anti-CRMP5); one patient was negative for anti-myelin oligodendrocyte glycoprotein (anti-MOG) antibodies. ICI treatment was at least temporarily discontinued in 20 of 23 patients because of the nirAE; in two patients, ICI treatment was maintained because of good oncologic response and benefits overweighting the risks (23, 45); in two cases, ICI treatment was reinstituted after the resolution of nirAE without the development of new irAE (22, 36). Treatment of demyelination included systemic steroids (21/23), plasma exchange (PLEX) (5/23), intravenous immunoglobulin (IVIg) (4/23), infliximab (2/23), interferon (2/23), cyclophosphamide (2/23), glatiramer (1/23), and mycophenolate mofetil (1/23); two patients received no systemic treatment other than discontinuation of ICI, and in one patient treatment was not reported. Outcomes of demyelination were reported in all cases but one: 14 patients had improvement, four patients had a full recovery, three did not respond to treatment, and three died (**Table 2**).

Multiple Sclerosis

We found two distinct patterns of MS patients on reports of ICI-associated demyelination: (1) three patients already diagnosed with the disease who had a relapse during ICI use, and (2) two patients with RIS [i.e., with demyelinating lesions highly suggestive of MS but without clinical symptoms of the disease (50)] who developed symptoms after the use of ICI and then fulfilled criteria for the diagnosis of MS [according to the 2017 revised McDonald criteria (27)]. Except for patient 1 (21), who had encephalopathic symptoms in her relapse, clinical, and imaging characteristics were typical of multiple sclerosis events in both groups, with no pattern suggesting a different mechanism due to ICI use.

Patient 1 (21) was known to have MS when she was started on atezolizumab; glatiramer was maintained during treatment. She developed atypical symptoms for MS, such as fever and confusion, and MRI showed nonspecific T2 hyperintense lesions within the subcortical, deep, and periventricular white matter. She received the presumptive diagnosis of MS relapse based on her history, but she had no improvement despite high dose steroids treatment. Patient 2 (23) had a previous diagnosis of MS, and MS treatment was withheld before ipilimumab started; she subsequently relapsed after treatment and had a good response with steroids and reintroduction of glatiramer. Patient 3 (24) had a lung adenocarcinoma metastatic to the brain and received whole-brain radiotherapy. She had untreated white matter hyperintensities on MRI suggestive of MS and also relapsed after nivolumab; she had a full recovery with high dose steroids.

Patients 4 (22) and 5 (45) had MRI demyelinating white matter lesions without symptoms, fulfilling RIS criteria. Patient 5 developed an enhancing spinal cord demyelinating lesion several months after treatment with pembrolizumab; she was improved after high dose steroids and had no new relapses after interferon-beta treatment, even though ICI was not discontinued. Patient 4 developed new symptomatic periventricular enhancing demyelinating lesions after the second cycle of ipilimumab, followed by optic neuritis. He improved after high dose steroids, and his lesions remained stable with interferon beta-1a treatment. A biopsy was performed in one of the white matter lesions and was compatible with pattern 1 (T cell type) MS. A next-generation analysis of the T cell receptor repertoire was compared between the primary melanoma histology and CSF collected 5 months and 1 year after ipilimumab infusions. They found distinct clonal expansions of $CD4^+$ and $CD8^+$ T cells in the melanoma and CSF, with considerable overlap between the T cell receptor repertoire in the tumor and the first, but not second CSF sample. They concluded that antitumor response and the inadvertent anti-CNS autoimmune response were directed against different antigens, and therefore, composed of distinct T cell receptor clonotypes. They further hypothesized that activated, tumor-specific T cells transiently entered the CNS compartment, possibly acting as autoaggressive effectors (22).

Myelitis

We found seven case reports of myelitis associated with ICI. In four of them (34–37), patients were exposed to radiotherapy on the cervical spine for bone metastases before (cases 7, 8, and 11) or during (case 10) ICI treatment. In all cases, delayed radiation myelopathy (DRM) was considered, but some features implicated an immune etiology, at least superimposed. In all four cases, the total dose of radiation was <30 Gy, which is not usually associated with myelopathy. Time was also more compatible with a complication of ICI treatment than with DRM, which is usually a late (more than 6 months) complication of radiotherapy. In two cases (8 and 10), the myelitis extension was much wider than the area exposed to radiation.

Moreover, in three cases (8, 10, and 11), CSF had findings suggesting an inflammatory process: pleocytosis in case 8, positive oligoclonal bands (OCB) in case 10, and high protein

TABLE 1 | Clinical syndromes of demyelination and demographic and oncologic data.

	Clinical syndrome	Drug (number of cycles)	Age	Gender	Primary cancer	TTO	ILD	Other irAE	Cancer outcome after ICI	Reference
MULTIPLE SCLEROSIS										
1	MS relapse	Atezolizumab (1)	49	F	Colon adenocarcinoma	2w	2w	–	PD	(21)
2	MS Relapse[e]	Ipilimumab (NR)	56	M	Melanoma	4w	NR	–	CR	(23)
3	MS Relapse	Nivolumab (1)	42	F	Lung adenocarcinoma	1w	1w	–	NR	(24)
4	Evolution from RIS to MS	Ipilimumab (4)	29	M	Melanoma	16w	7w	Hypophysitis	PR	(22)
5	Evolution from RIS to MS	Pembrolizumab (14)	67	F	Lung adenocarcinoma	43w	NR	–	PR	(45)
MYELITIS										
6	Myelitis	Atezolizumab (3)	63	F	Small cell lung cancer	NR	NR	–	NR	(38)
7	Myelitis[c]	Durvalumab (3)	69	M	Lung adenocarcinoma	4w	days	–	NR	(34)
8	Myelitis[c]	Ipilimumab (2)	58	M	Melanoma	26w	23w	–	CR PD	(37)
9	Myelitis	Ipilimumab (3)	62	M	Melanoma	7w	4d	Uveitis, dermatitis, colitis, genitourinary symptoms, acute renal failure	PD	(19)
10	Myelitis[c]	Ipilimumab + Nivolumab –> Pembrolizumab (NR)	68	M	Melanoma	2w[b]	2w	–	PD	(35)
11	Myelitis[c]	Pembrolizumab (8)	68	M	Lung adenocarcinoma	24w	NR	–	PR	(36)
12	Myelitis	Ipilimumab (3)	39	F	Melanoma	7w	days	Hypophysitis	CR	(39)
NMOSD										
13	NMOSD	Nivolumab (1)	75	M	Lung squamous cell carcinoma	8w	8w	–	PD	(44)
OPTIC NEURITIS										
14	Optic neuritis	Atezolizumab (1)	53	M	Lung adenocarcinoma	3w	3w	–	PR	(41)
15	Optic neuritis	Ipilimumab (3)	53	M	Melanoma	21w	15w	Skin rashes, colitis, Hypophysitis	PR	(43)
16	Optic neuritis	Ipilimumab (4)	70	M	Melanoma	12w	NR	Anterior uveitis	NR	(40)
17	Optic neuritis	Nivolumab (2)	9	M	Glioblastoma multiforme	2w	2d	–	NR	(42)
ATYPICAL DEMYELINATION										
18	Brain demyelination[d]	Ipilimumab (4)	76	F	Melanoma	17w	6w	–	PR	(25)

(Continued)

TABLE 1 | Continued

	Clinical syndrome	Drug (number of cycles)	Age	Gender	Primary cancer	TTO	ILD	Other irAE	Cancer outcome after ICI	Reference
19	Brain demyelination[d]	Ipilimumab (1) –> Nivolumab (11)	44	M	Melanoma	38w[a]	NR	Colitis (after 1 infusion of ipilimumab, treated with infliximab), skin rash (with nivolumab)	CR	(48)
20	Demyelinating encephalitis	Ipilimumab (4) –> Nivolumab (4)	60	M	Melanoma	6w[a]	2d	–	PD	(47)
21	Brain and spine demyelination	Pembrolizumab (3)	58	F	Melanoma	6w	NR	Thyroiditis	CR	(46)
22	Brain demyelination	Nivolumab (1)	59	F	Laryngeal squamous cell carcinoma	2w	2w	–	NR	(49)
23	Anti-Hu encephalomyelitis	Nivolumab (3)	61	M	Lung pleomorphic carcinoma	5w	5d	–	PD	(14)

TTO, Time to onset of neurologic immune-related adverse event (nirAE) during immune checkpoint inhibitor (ICI) treatment; ILD, Interval from last ICI dose to nirAE; irAE, immune-related adverse event; NR, not reported; w, weeks; d, days; MS, multiple sclerosis; RIS, radiological isolated syndrome; NMOSD, neuromyelitis optica spectrum disorder; +, combination of ICIs; –>, followed by other ICI; PD, progression of oncologic disease; CR, complete remission; PR, partial remission. [a]*From the onset of nivolumab;* [b]*From the onset of pembrolizumab;* [c]*Exposure of spinal cord to radiotherapy before ICI;* [d]*Treatment for brain metastases with stereotactic radiosurgery before and/or during ICI;* [e]*Previously with stable relapsing-remitting multiple sclerosis, glatiramer, and methotrexate were stopped when ipilimumab started.*

in all. Patient 8 progressed despite steroid and IVIg treatment. Patient 10 had a progression in the extension of the myelitis despite treatment with steroids, PLEX, cyclophosphamide, and improved after infliximab administration. Interestingly, in case 11, there was an improvement of myelitis with oral steroids, after which pembrolizumab was rechallenged without new relapses.

Patient 12 (39) presented with lymphocytic meningitis without malignant cells and nodular leptomeningeal enhancement days after the third infusion of ipilimumab and was treated with steroids. A few months later, she developed paraparesis, and MRI showed a tumefactive longitudinally extensive cervical myelitis. High dose steroids were administered and, subsequently, infliximab was initiated, after which she had clinical and radiological improvement. Patient 9 (19) developed T9–T10 transverse myelitis in the setting of a diffuse systemic inflammatory process, which included uveitis and colitis, after ipilimumab infusions; he had improvement after discontinuation of ICI and high dose steroids. Patient 6 (38) developed a longitudinally extensive transverse myelitis associated with CRMP-5 IgG antibodies and improved with steroids. Even though 5 of 7 patients presented with longitudinally extensive myelitis, none of them fulfilled the criteria for NMOSD. Nevertheless, only two patients were tested for anti-AQP4 (cases 8 and 10); both resulted negative. There was no report of anti-MOG testing for any of the cases.

Optic Neuritis

We found four case reports (40–43) of isolated optic neuritis associated with ICI. Patients 14 and 17 had been exposed to radiotherapy to treat brain metastases. Patient 15 (43) presented with left eye anterior optic neuropathy associated with aseptic meningitis after ipilimumab treatment and progressed with recurrent bilateral optic neuritis. All four patients had bilateral and anterior optic neuritis, with optic disk swelling. Except for patient 16 (40), who was treated only for associated uveitis with topical steroids, all patients received high dose steroids, and the four had a good outcome. MRI showed optic nerve enhancement in two patients (cases 15 and 17) and was not reported in one (case 16). CSF was only reported in two patients; it was normal in case 16 and revealed pleocytosis in case 15. There was no mention of anti-MOG or anti-AQP4 testing for any of the cases.

Neuromyelitis Optica Spectrum Disorder

Patient 13 (44) developed a longitudinally extensive tumefactive myelitis after one cycle of nivolumab. CSF showed marked pleocytosis (1,195 cells/mm^3, 53% neutrophils); although levels this high are uncommon, pleocytosis in NMOSD is usually higher than 50 cells/mm^3. Based on a positive anti-AQP4, a diagnosis of NMOSD was made. He had no brain or optic nerve involvement and a negative anti-MOG and paraneoplastic panel. Although he had an improvement of MRI lesions after treatment with high dose steroids and PLEX, he had a minimal symptomatic response. Anti-AQP4 testing, performed on the serum collected on the day of nivolumab infusion, was negative. This report suggests seroconversion after ICI treatment and strengthens a causal relationship between nivolumab use and NMOSD.

TABLE 2 | Paraclinical information and treatment outcomes of demyelination cases.

	MRI	CSF	Other tests	Antibodies	Treatment	Interruption of ICI	Outcome	Reference
MULTIPLE SCLEROSIS								
1	Hyperintensities within the subcortical, deep, and periventricular white matter	Elevated protein	NR	NR	Steroids, glatiramer	Yes	No response, died	(21)
2	New enhancing lesion consistent with active demyelination	NR	NR	NA	Steroids, glatiramer restarted	No	Improvement	(23)
3	New hyperintense pons lesion with incomplete ring enhancement	NR	NR	NA	Steroids	NR	Full recovery	(24)
4	Multiple white matter hyperintensities with enhancement	WBC = 15, Prot 50, Positive OCB	Biopsy: active MS, T-cell type (pattern 1)	NA	Steroids, interferon	Yes[a]	Improvement	(22)
5	Multiple white matter hyperintensities, nodular spinal cord enhancing lesion	Positive OCB	VEP: increase of latency in both eyes; SSEP: increased cortical latency for stimulation of limbs	NA	Steroids, interferon	No	Improvement	(45)
MYELITIS								
6	Extensive thoracic spinal cord lateral tracts hyperintensity with contrast enhancement	WBC = 46, Prot = 105	NR	Anti-CRMP5 positive: 1:3840 (serum) and 1:1024 (CSF)	Steroids, cyclophosphamide	Yes	Improvement	(38)
7	T5–T8 Spinal cord hyperintensity	Normal	NR	NA	Steroids	Yes	Improvement	(34)
8	T7–L1 Spinal cord hyperintensities	WBC = 16, prot = 57	NR	Negative anti-AQP4 and paraneoplastic panel	Steroids, IVIg	Yes	No response	(37)
9	T9–T10 Spinal cord hyperintensity	WBC = 28, Prot = 50	NR	NA	Steroids	Yes	Improvement	(19)
10	T5–T10 Spinal cord hyperintensity with patchy enhancement	Prot = 99, positive (matched) OCB, MBP = 31.6	NR	Negative anti-AQP4 and paraneoplastic panel	Steroids, plasma exchange, cyclophosphamide, infliximab	Yes	Improvement	(35)
11	T12–L1 Spinal cord edema, patchy gadolinium enhancement	Prot = 84	NR	Negative antineural antibodies	Steroids	Yes[c]	Full recovery	(36)
12	Leptomeningeal and cranial nerve enhancement; extensive cervical spinal cord hyperintensities with enhancement	Lymphocytic pleocytosis, Prot = 120	NR	Negative paraneoplastic panel	Steroids, IVIg, Infliximab	Yes	Almost full recovery	(39)
NMOSD								
13	Spinal cord hyperintensities	WBC=1195 (53% neutrophils), Prot = 380, Gluc = 40	NR	Anti-AQP4 positive, anti-MOG negative, negative paraneoplastic antibodies panel	Steroids, plasma exchange	Yes	Improvement	(44)
OPTIC NEURITIS								
14	Unremarkable	NR	NR	NA	Steroids	Yes	Improvement	(41)
15	Optic nerve enhancement	WBC = 62, Prot = 105	NR	NA	Steroids, mycophenolate mofetil, plasma exchange	Yes	Improvement	(43)

(Continued)

TABLE 2 | Continued

	MRI	CSF	Other tests	Antibodies	Treatment	Interruption of ICI	Outcome	Reference
16	NR	Normal	NR	NA	Topical corticosteroids	Yes	Spontaneous improvement	(40)
17	Bilateral thickening of the optic nerves	NR	NR	NA	Steroids	Yes	Full recovery	(42)
ATYPICAL DEMYELINATION								
18	Optic nerve and white matter hyperintensities	NR	Biopsy: acute/subacute inflammatory demyelination, myelin reactive T cells	NA	Steroids, Cyclophosphamide	Yes	No response, died	(25)
19	Multiple hyperintense lesions with incomplete ring enhancement, Dawson's fingers	WBC=14, Prot=59, Negative OCB	NR	Negative paraneoplastic panel	None other than discontinuation of nivolumab	Yes	Full recovery	(48)
20	White matter lesions consistent with tumefactive demyelination	WBC = 0, Prot = 88, positive OCB, MBP = 11.0	Autopsy: widespread white matter demyelination	NA	Steroids, IVIg	Yes	Transitory response, died	(47)
21	Multiple periventricular white matter hyperintensities, multiple spinal cord hyperintensities, one of them with gadolinium enhancement	Elevated protein, positive CSF OCB	NCS: normal; SSEP: absence of responses in the limbs	Negative anti-AQP4 and paraneoplastic antibodies panel	Steroids, Plasma exchange	Yes	Almost full recovery	(46)
22	Multiple white matter hyperintensities	WBC = 74, elevated protein, positive OCB	EEG: diffuse generalized slowing	NA	Steroids, IVIg	Yes	Improvement	(49)
23	Temporal, thalamus, cerebral aqueduct, spinal cord hyperintensities	WBC = 16, prot = 162, positive OCB	Autopsy: CD8-positive T cells and macrophages infiltrate, microglia activation	Serum: Anti-Hu antibodies[b]	Steroids, plasma exchange	Yes	No response	(14)

MRI, magnetic resonance imaging; CSF, cerebrospinal fluid; ICI, immune checkpoint inhibitors; WBC, white blood count (in cells/mm^3); prot, protein (in mg/dL); gluc, glucose (in mg/dL); MBP, myelin basic protein (in ng/mL); OCB, oligoclonal bands; EEG, electroencephalogram; NCS, nerve conduction study; SSEP, somatosensory evoked potentials; VEP, visual evoked potentials; Anti-AQP4, aquaporin4 antibodies; Anti-MOG, myelin oligodendrocyte glycoprotein antibodies; NR, not reported; NA, not assessed. [a]A new cycle of ipilimumab was administered 1 year after the first cycle; [b]present before treatment, [c]Interrupted initially, but after clinical improvement of neurological symptoms and pulmonary progression, within 14 weeks, pembrolizumab was reintroduced.

Atypical Demyelination

Six patients developed atypical demyelination and did not fit into previous diagnostic groups (14, 25, 46–49). Imaging patterns were typical for MS in two cases, with periventricular white matter lesions with incomplete gadolinium enhancement (patient 19) and small non-enhancing periventricular and spinal cord white matter lesions (patient 21). Even though these two patients had radiologic findings suggestive of a clinically isolated syndrome (CIS) and MS, respectively, we chose to classify them in the atypical demyelination group because of their monophasic presentation and because the authors do not mention those diagnoses being made. The remaining 4 cases had atypical demyelination imaging: cases 18 and 20 presented with tumefactive white matter lesions, case 22 had multiple hyperintense T2 flair signal white matter lesions, and case 23 developed longitudinally extensive myelitis associated with pons and mesial temporal lobe hyperintensities typical for limbic encephalitis. All four patients had focal deficits and altered mental status.

Two cases had reported brain metastasis treated with radiosurgery either after (patient 18) or between (patient 19) ICI infusions. In case 18, one of the several demyelinating lesions bordered the previously irradiated neoplastic lesion. Patients who had a higher volume of T2 hyperintense lesions, including tumefactive (patients 20 and 23) or large lesions (patient 18), had a worse outcome, with no response and death despite steroids and other immunosuppressive treatments, as opposed to patients 19, 21, and 22 who had smaller demyelinating lesions and satisfactory response to steroids and/or discontinuation of ICI.

An autopsy was performed for case 20, which showed white matter widespread demyelination, with infiltration of macrophages containing myelin debris, reactive astrocytes,

focal perivascular lymphoid inflammation, and areas of early cavitation. $CD8^+$ T cells were seen perivascularly and at the edge of acutely demyelinating plaques, whereas $CD4^+$ T cells were confined to perivascular spaces and in smaller numbers (47). In case 18, a biopsy of the lesion that showed acute/subacute demyelination was processed to assess the functional profiles of the patient's T cells. The functional profiles of the patient's myelin-reactive T cells were compared to a T-cell library of MS and healthy controls. Similarly to MS, proliferation rates and pro-inflammatory cytokine production of myelin-reactive $CD4^+$ T cells were higher, and anti-inflammatory cytokine IL-10 production was lower than healthy controls, consistent with a T_H1/T_H17 immune phenotype (25).

Patient 23 (14) had a strongly positive Anti-Hu antibody in the serum. Although anti-Hu was present before ICI treatment, he developed symptoms only after receiving nivolumab, which suggests the role of checkpoint blocking on the development of the paraneoplastic syndrome. He presented with an anti-Hu associated encephalomyelitis, with temporal lobe involvement suggestive of limbic encephalitis and longitudinally extensive cervical myelitis with imaging consistent with demyelination. The postmortem autopsy findings showed that microglia were highly expressed in the hippocampus, pons, and spinal cord, and CD8-positive T cells and macrophages invaded the medial aspect of the temporal lobe, thalamus, cerebellum, and spinal cord.

DISCUSSION

Immune checkpoint molecules appear to play a critical role in tolerance to self-antigens and have been implicated in several immune-mediated disorders (51). Some of the proposed mechanisms by which general immunological adverse events occur with the use of ICI include (1) a shift toward the pro-inflammatory profile of T lymphocytes dominated by Th1/Th17 differentiation that increases the production of pro-inflammatory cytokines, (2) autoreactive antibody production, (3) activation of potentially pre-existing self-reactive T cells, and (4) a cross-reactivity between normal tissue antigens and tumor neo-antigens (52–54).

Before ICI advent, there were few reports of focal or multifocal white matter demyelination associated with cancer, and the paraneoplastic nature of these findings was not clear (55). The most convincing cases are those associated with seminoma (56–59). Other reports, many of which are associated with lymphoma, are less convincing because of the possibility that brain lymphoma treated with corticosteroids may have interfered with diagnosis (55). There does not appear to be an increased risk of cancer in patients with multiple sclerosis, possibly except for breast cancer (60). Nevertheless, we believe that the cases compiled here are not paraneoplastic *per se*, but rather a complication of the immune response triggered by the ICI treatment, with or without the participation of tumoral antigens.

CNS demyelination can be induced in animal models through the modification of the checkpoint pathways. For example, blocking CTLA-4 in a relapsing–remitting experimental autoimmune encephalomyelitis mice model has been shown to exacerbate clinical disease and inhibit clinical remission through enhanced T cell reactivity to epitopes associated with induction and relapse (61). ICI also upregulates costimulatory T cell activation pathways such as the CD28-B7, which appears to play an important role in the pathogenesis of demyelination (62). The suppression of mechanisms that inhibit those pathways could potentially increase the incidence of demyelinating conditions. The activation of the checkpoint pathways, conversely, can be used to treat immune-mediated disorders. Abatacept, a CTLA4-Ig fusion protein, is approved to treat rheumatoid arthritis and juvenile idiopathic arthritis and has been evaluated in a phase II clinical trial for MS, although failed to show efficacy (63).

In our review, the four cases that underwent anatomopathological studies (14, 22, 25, 47) all had a $CD8^+$ T cell predominant infiltrate on the CNS, consistent with a T_H1 immune response. In case 18, $CD4^+$ T cells profiles suggested a pathogenic T cell response against myelin (25). Moreover, further CSF examination in case 4 concluded that T cell antitumor response and the CNS autoimmune response were aimed at different antigens, suggesting a more direct effect of ICI in the development of demyelination than the activation of a paraneoplastic reaction (22). In contrast, in case 23, demyelination and limbic encephalitis were thought to result from the induction of a paraneoplastic response associated with anti-Hu antibodies (14).

We found a median of 6.5 weeks from ICI's start to the onset of the demyelinating event. This delay is in keeping with the timing of irAE due to ICI in general. Usually, irAE are subacute and temporally associated with ICI introduction, with serious adverse events tending to occur days to weeks after treatment initiation, whereas paraneoplastic disorders tend to have a slower evolution (64). Despite this, neurologic irAE have been reported throughout treatment and even after treatment discontinuation (65). In this review, the case with the later appearance of symptoms after immunotherapy was case 5, 43 weeks after introducing pembrolizumab.

Neurologic immune-related adverse events are described to be most commonly seen after a combined checkpoint blockade, with agents targeting both PD1/PD-L1 and CTLA4 pathways (66). Nevertheless, only three patients in this review were exposed to a combination of ICIs (cases 10, 19, and 20), probably because of the less frequent use of combined block in current clinical practice. We could not ascertain if single or double checkpoint blockade had differences in nirAE outcomes because of the small number of cases in our review. Additionally, nine out of the 23 cases had been exposed to radiotherapy directed to CNS or spinal metastases. It is conceivable that exposure of myelin antigens by radiotherapy could have triggered an immune response in combination with ICI. The risk of demyelination with the association of CNS radiotherapy and ICI is unclear and should be further studied.

We believe it is essential to question patients undergoing evaluation for ICI about immune antecedents, including a previous diagnosis of immune-mediated disorders and current or previous symptoms that may be caused by an undiagnosed inflammatory condition, such as paraneoplastic disorders (67). In patients who underwent brain MRI for another reason, even without symptoms of MS, it is also interesting to evaluate whether lesions suggestive of demyelination already existed before ICI treatment, as these patients may be more at risk of developing

more severe nirAEs (21). Nevertheless, MS relapses seem to be a rare complication of ICI treatment (21, 68), and case reports presumably could overestimate its incidence because of publication bias. For example, we found only one report of a patient who had MS and remained stable when treated with ipilimumab while receiving interferon-beta (69).

Treatment and Prognosis

According to the European Society for Medical Oncology (ESMO) clinical practice guideline for the management of immunotherapy-related toxicity (6), the recommended treatment for nirAE is the suspension of ICI, associated with corticosteroids in low-dose for mild to moderate cases, or high doses for severe cases, either intravenously or orally. The guideline suggests using intravenous plasmapheresis or immunoglobulin in specific cases, such as myasthenia gravis and Guillain Barré syndrome, and they consider extrapolating this treatment to severe cases of isolated optic neuritis, myelitis, and cases that meet criteria for NMOSD. This recommendation is based on the indication of these treatments for demyelinating syndromes not related to ICI.

Almost all patients presented in this review (18/23) were treated with immunosuppressors, and most of them had a partial or total improvement of nirAE. Overall, nirAE is treatable, has a good prognosis, and is known to be relatively rare, although some groups may have a higher risk (7). Given this, the risk-benefit of introducing ICI is usually favorable, as they are indicated mostly for advanced cancers or those with poor independent prognosis (1).

The demyelination should be treated according to the current guidelines for each specific syndrome (i.e., MS). Three of four MS cases, for example, improved with interferon and glatiramer. In one case (23), MS treatment was withheld when starting ICI because of the preoccupation that it would interfere with the cancer treatment, and the patient relapsed but had a good outcome after treatment. On the other side, glatiramer was maintained in another case (21), and the patient developed demyelination that was unresponsive to steroids. It is not clear if it is safe to start ICI on MS patients. If decided for ICI, MS patients should be monitored closely, and MS treatment should be carefully discussed.

In this context, although not used by any of the reported cases, Natalizumab would be an attractive drug to treat ICI-related demyelination. It is a monoclonal antibody approved for the treatment of multiple sclerosis. Its mechanism of action consists of blockage of lymphocyte migration through the blood-brain barrier due to its anti-α4 integrin effects. As this mechanism is specific, it is not expected to interact with the therapeutic effects of ICIs. Natalizumab has been used in a patient with limbic encephalitis induced by ICI immunotherapy against small cell lung cancer (70), and possibly could have its indication expanded to cases of atypical demyelination related to ICI, using this same rationale.

Despite the potential biological role of TNF-α blockers in triggering or aggravating demyelination (71), infliximab may be another treatment option in refractory ICI-related demyelination. This drug is already used more widely in ICI-related refractory colitis with good outcomes (6, 72), suggesting that decreasing the pro-inflammatory state associated with TNF-α is useful in treating irAE. Based on that, there is a possibility to generalize these findings to treat other refractory immune adverse events related to ICI. Patients 5 (41) and 17 (33) used infliximab after failure of other medications, with an improvement of neurological symptoms, corroborating this hypothesis.

Limitations

We chose to perform a review only with case reports of demyelination, a rare complication of ICI treatment, to describe the clinical presentation and outcomes in these patients. Nevertheless, there is an inherent limitation of extracting data from reports, which can sometimes be incomplete or lacking a description of investigations that could change the data's interpretation. We feel, though, that most of the cases were well reported. A prospective study, which would be ideal, is difficult in rare complications such as these. Pharmacovigilance reporting as in Food and Drug Administration Adverse Event Reporting System (FAERS) database or European databases is an interesting method to collect prospective data on adverse events of medications. However, currently, the data found there are, in general, not as detailed as case reports.

Since we did not have contact with the patients reported, it is difficult to extrapolate a diagnosis beyond what is mentioned by the authors in the original papers. That is why we included patients 19 and 21 in the atypical demyelination group, despite somewhat typical imaging for CIS or MS. In the same line, one could argue that some of the atypical demyelination cases could be classified as ADEM. Although acute demyelinating encephalomyelitis (ADEM) is well defined in children (31), in adults it does not appear to be a homogeneous entity and remains to be better understood (32). Diagnostic criteria for ADEM in adults have been proposed (32), but they have not yet been validated in larger studies. In our review, cases 18, 20, and 22 had ADEM features such as atypical demyelinating lesions, confusion, and generalized slowing on EEG (patient 22), although two of them (cases 20 and 22) had positive OCB, which is usually absent in ADEM. Since the authors did not mention this diagnosis, we chose to classify them merely as atypical demyelination.

CONCLUSIONS

Demyelination is a rare complication of ICI treatment. Although potentially severe, it is treatable, and outcomes after immunosuppression seem favorable in most patients. At first glance, cases with a higher demyelinating disease burden (i.e., higher lesions volume) appear to have had a worse prognosis. Considering the four cases that underwent pathological examination, we hypothesize that a T_H1 immune response is possibly the mechanism by which these patients develop demyelination (14, 22, 25, 47). Furthermore, we speculate that the ICI treatment, in addition to improving the T cell immune response against the tumor, may trigger the

effector functions of T-cell clonotypes directed toward myelin epitopes (22). Further studies are needed to determine the exact pathophysiology of demyelination associated with ICI and the best treatment for these cases. Natalizumab appears to be a promising treatment candidate and remains to be tested.

AUTHOR CONTRIBUTIONS

MO and MS contributed in the conception and design of the study. MO and MB organized the database, performed the statistical analysis, and wrote the first draft of the manuscript. MO, MB, and MS wrote sections of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

SUPPLEMENTARY MATERIAL

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Myelin Oligodendrocyte Glycoprotein (MOG) Antibody Positive Patients in a Multi-Ethnic Canadian Cohort

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Introduction: Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease is a recently described central nervous system (CNS) inflammatory disorder with phenotypic overlap with Neuromyelitis Optica Spectrum Disorder (NMOSD). NMOSD seronegative patients, and those with limited forms of the disorder, become suspects for MOG antibody-associated disease. We describe a multi-ethnic population with MOG antibody seropositivity from the University of British Columbia MS/NMO clinic.

Methods: AQP4-antibody seronegative patients presenting 2005–2016 with CNS inflammatory disease suspicious for NMOSD, as well as 20 MS controls, were retrospectively tested for MOG-IgG1 antibodies by live cell-based assay at Oxford Autoimmune Neurology Diagnostic Laboratory (UK) and by a commercial fixed cell-based assay at MitogenDx (Calgary, Canada). Additional MOG seropositive cases were identified through routine clinical interaction (2016–2018) using one of these laboratories. Clinical data was reviewed retrospectively.

Results: Retrospective testing identified 21 MOG seropositives (14 by live assay only, 3 by fixed assay only and 4 by both) representing 14% of the "NMOSD suspects" cohort. One multiple sclerosis (MS) control serum was MOG seropositive. Twenty additional MOG positive cases were identified prospectively. Of 42 patients (27 female), median disease onset age was 29 years (range 3–62; 9 pediatric cases), 20 (47%) were non-Caucasian, and 3 (7%) had comorbid autoimmune disease. Most common onset phenotypes were optic neuritis (23, 55%; 8 bilateral) and myelitis (9, 21%; 6 longitudinally extensive) Three of the patients in our cohort experienced cortical encephalitis; two presented with seizures. Onset was moderate-severe in 64%, but 74% had good response to initial steroid therapy. Cumulative relapse probability for the MOG positive group at 1 year was 0.428 and at 4 years was 0.628. Most had abnormal brain imaging, including cortical encephalitis and poorly demarcated subcortical and infratentorial lesions. Few "classic MS" lesions were seen. Optic nerve lesions (frequently bilateral) were long and predominantly anterior, but 5 extended to the chiasm. Spinal cord lesions were long and short, with involvement of multiple spinal regions simultaneously, including the conus medullaris.

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Conclusions: Our MOG seropositive patients display phenotypes similar to previous descriptions, including cortical lesions with seizures and conus medullaris involvement. Many patients relapsed, predominantly in a different CNS location from onset. Serologic data from two different cell-based antibody assays highlight the discrepancies between live and fixed testing for MOG antibodies.

Keywords: myelin oligodendrocyte glycoprotein (MOG) antibodies, aquaporin 4 antibodies, multiple sclerosis (MS), demyelination, neuroinflammation, neuromyelitis optica

INTRODUCTION

Myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease is a recently described central nervous system (CNS) inflammatory disorder. There are a few large published adult case series (1–5), however the full clinical and radiological spectrum, and optimal management are not yet clear. The majority of published studies are based on Caucasian populations.

MOG antibody-associated disease has similarity to Neuromyelitis Optica Spectrum Disorders (NMOSD) in terms of clinical and imaging phenotypes (6), suggesting that patients within the aquaporin 4 (AQP4) antibody seronegative cohort become suspects for MOG antibody-associated disease. Previously published literature suggests approximately 40% of NMOSD AQP4-negative cohorts are MOG antibody positive (7). Additionally, MOG antibodies can be present in 10–20% of idiopathic atypical demyelinating diseases not meeting full NMOSD criteria (7, 8). MOG antibody-associated disease is however a distinctly different disorder from NMOSD, both immunologically and pathologically (9, 10). This distinction means recognition of these patients is important.

The University of British Columbia (UBC) MS/NMO referral clinic is the largest in British Columbia for CNS inflammatory disorders. NMOSD are known to be more prevalent in non-Caucasian populations. Given the multi-ethnicity of the British Columbian population, this clinic serves a NMOSD cohort of over 200 patients. Whilst primarily an adult clinic, some pediatric cases are also referred.

The primary aim of the study was to describe the population of MOG antibody seropositive patients at the UBC MS/NMO referral clinic, both clinically and radiologically, with comparison to other published MOG antibody-associated disease cohorts, as well as to the rest of our "NMO-suspects" AQP4 negative cohort.

A secondary aim was to systematically examine for autoantibody comorbidity [MOG, AQP4, and N-methyl-D-aspartate receptor subunit 1 (NMDAR) antibodies] within patients with CNS inflammatory disorders.

METHODS

We identified a cohort of MOG antibody patients within our clinic from two sources: retrospectively via batch testing of stored serum samples and prospectively via routine clinical testing. Two different laboratories were utilized for the testing.

We searched our database for AQP4 antibody seronegative patients who were seen at the UBC MS/NMO clinic between 2005 and 2016. We included those who were NMOSD criteria positive (11) or had acute disseminated encephalomyelitis (ADEM) (12), longitudinally extensive or severe transverse myelitis (LETM), severe or recurrent optic neuritis (ON), tumefactive brain lesions, and patients with encephalopathy with white matter lesions and/or cortical lesions, with no clear diagnosis. Patients with neurosarcoidosis, lymphoma, stroke, or vasculitis were excluded. Additionally, we included 20 randomly selected patients with clinically definite multiple sclerosis (CDMS) (13) as controls.

Stored serum samples were tested by live cell-based assay at the Oxford Autoimmune Neurology Diagnostic Laboratory, UK, and on a fixed commercial cell-based assay (Euroimmun AG, Lübeck, Germany) by MitogenDx in Calgary, Canada.

Additional MOG antibody positive cases, in most cases tested only at a single center, were identified (2016–2019) through routine clinical testing at MitogenDx or Oxford Autoimmune Neurology Diagnostic Laboratory. Testing for MOG antibodies was at the discretion of the attending clinician, in most cases being sent due to demyelinating presentations atypical for MS or suggestive of NMOSD.

The systematic testing for AQP4-antibodies and NMDAR antibodies was performed for the retrospective cohort at Oxford Autoimmune Neurology Diagnostic Laboratory via cell-based assay. All prospective cases had AQP4-antibodies tested at MitogenDx via cell-based assay.

Prospective testing of NMDAR antibodies (MitogenDx, via cell-based assay) was not uniformly performed for prospective cases. The timing of serum sampling for MOG antibody testing in relation to clinical disease activity was not standardized. The majority of samples were taken at routine clinic visits, which may or may not have been at the time of a relapse. MOG titers were unfortunately not available, nor were serial test results.

We compared the phenotypic features of our MOG antibody positive patients with the published literature, as well as with the AQP4-antibody and MOG-antibody seronegative patients (from our retrospective cohort) who remained in the idiopathic CNS inflammatory disorders category.

Clinical data pertaining to demographics, disease onset and course, clinical syndromes and response to treatment, was collected by 3 clinicians (HC, NA, and AM) via retrospective chart review of the clinic electronic medical records system (established 2015), as well as provincial health databases for earlier clinical interaction records. Detailed ophthalmic examinations were mostly not documented. Cerebrospinal fluid

studies were not performed for many patients and this data was therefore not captured.

Radiological review for the MOG positive patients only was performed by a neuroradiologist (FS), by reviewing the magnetic resonance (MR) imaging available for these patients from the time of first disease presentation, or the first MRI within 5 years of this time. T2 lesions were counted and lesion locations and characteristics were noted. Where possible brain, spinal cord, and orbital imaging was reviewed. Where serial imaging was available, only the first scan was analyzed to maintain consistency.

Ethnicity was captured as Caucasian (European ancestry), Asian (Chinese, Japanese, Korean, Vietnamese or Filipino ancestry), South Asian (Indian Subcontinent), or Other (First Nations or other non-Caucasian ancestry). Clinical severity of disease at onset was classified as mild [VA < 20/100, sensory only (excluding marked neuropathic pain), non-disabling motor], moderate (VA ≥ 20/100, ≤ 20/800, marked neuropathic pain, disabling motor, bladder and bowel involvement) or severe (VA > 200/800, inability to walk, incontinence). Where unable to find specific information, we were guided by clinical impression of severity. Response to initial steroid therapy was graded as good (full recovery or minor residual disability), or poor (minimal change in clinical picture or significant ongoing disability) based on the assessment at the subsequent clinic visit (≥1 month later, but the timing of this was not standardized). Recovery on follow-up was assessed at the patient's last recorded clinic visit, and graded as full/very good (no or minimal disability on clinical impression at last follow-up or EDSS ≤ 2.0), predominantly moderate-severe residual visual disability (VA > 20/100 in worse affected eye), predominantly moderate-severe residual motor disability (motor disability affecting function), predominantly moderate-severe residual bladder, bowel or sexual disability (disability impacting lifestyle), or combination disability when more than one moderate-severe category was present.

No new clinical or radiological data, or blood samples were collected specifically for the study.

Statistical procedures were performed using IBM SPSS Statistics, Version 25.0 (IBM Corp., Armonk, NY). An independent samples *t*-test was used to determine if there were significant differences in numerical variables such as age at onset and duration of follow-up.Chi-square tests and Fisher's exact tests were used to compare the clinical data between the MOG seropositive and the double seronegative groups of patients, with $p < 0.05$ considered to be significant.

TABLE 1 | Results of antibody testing in retrospective cohort.

	n samples analyzed	MOG antibody+	AQP4 antibody+	NMDAR antibody+	Remaining seronegative
Seronegative "NMO suspects" cohort*	146	21	8	2	115
MS controls	20	1	0	1	18

**Previously seronegative for AQP4 antibodies. MOG = myelin oligodendrocyte glycoprotein. AQP4 = aquaporin four. NMDAR = N-Methyl-D-aspartate receptor. MS = multiple sclerosis.*

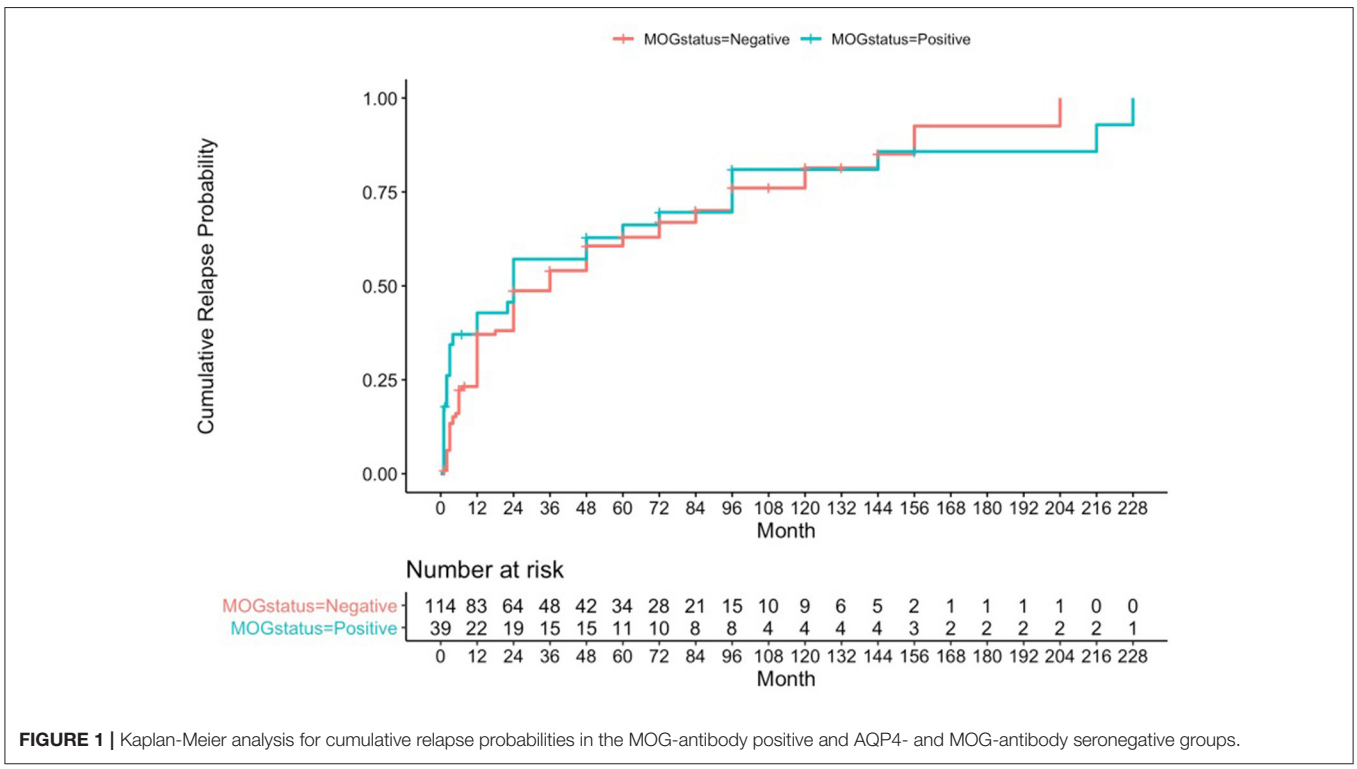

FIGURE 1 | Kaplan-Meier analysis for cumulative relapse probabilities in the MOG-antibody positive and AQP4- and MOG-antibody seronegative groups.

A Kaplan-Meier analysis was used to determine the cumulative relapse curves and cumulative relapse probabilities. Four patients had to be excluded for this analysis due to lack of specific time data for first relapse. A formal comparison of relapse probability at 1 year between the MOG positive and seronegative group was performed with a *z*-test.

All our clinic patients are offered the option of voluntary participation in research conducted at our center. If they provide written consent, their clinical and imaging information is included in our research database. Additional specific ethics approval for this sub-study was obtained (H19-01146) and it was carried out in compliance with the Helsinki Declaration of 1975 for human studies as revised in 2013.

RESULTS

Retrospective Cohort

We identified a total of 146 patients (4% pediatric, 70% female) who fulfilled our search criteria. Twenty-one of these patients (14% pediatric, 52% female) were found to have MOG antibody positivity on testing: 14 by live assay only, 3 by fixed assay only and 4 by both, representing 14% of patients who were clinically suspicious for NMO and seronegative for AQP4 antibodies. One of the CDMS patients was MOG antibody positive by the live assay test. AQP4 antibodies were detected by live cell-based assay in eight patients previously considered seronegative by a fixed test. Two otherwise seronegative patients and one CDMS patient were found to have NMDAR antibodies by the live test (see **Table 1**). No patient was found to have dual antibody seropositivity.

Prospective Cohort

An additional 20 MOG positive cases were identified through routine clinical practice (19 via fixed assay at Mitogen and 1 via live assay at Oxford). One of these patients was also found to have positive NMDAR antibodies.

Across the two cohorts, the median timing of test serum sample collection in relation to disease onset or last relapse was 1 month (range 0–132) (see **Supplementary Table 2**).

The clinical features of patients identified by the two different tests are presented in **Supplementary Table 1**, in comparison to the cohort as a whole. The text below refers to the entire MOG antibody positive cohort.

TABLE 2 | Comparison of MOG-antibody positive and AQP4, MOG-antibody seronegative cohorts.

	MOG-antibody positive	AQP4 and MOG antibody negative	*p*-value
	***n* = 42**	***n* = 115**	
% female	64	71	0.26
Median age at onset (y; and range)	29 (3–62)	39 (14–78)	**<0.001**
Comorbid autoimmune disease	3 (7%)	18 (15%)	0.17
Onset location			
ON	23 (55%) (bilateral in 8/23)	23 (20%) (bilateral in 3/23)	**0.001**
TM	9 (21%) (LETM in 6/9)	66 (57%) (LETM 36/66)	**<0.001**
Cerebral	6 (14%) (3 TL, 2 ADEM, 1 cortical)	5 (4%) (4 TL, 1 ADEM, 0 cortical)	0.069
Brainstem	2 (4.8%)	7 (6.1%)	1
Combination	2 (4.8%) (ON + TM 100%)	14 (12.2%) (ON + TM 8 57%)	0.193
Clinical syndromes (at any time)			
ON	31 (73.8%)	46 (40%)	**<0.001**
TM	22 (52%)	92 (80%)	**0.001**
Brainstem	16 (38.1%)	24 (20.9%)	**0.038**
Cerebral	9 (21%) (3 TL, 3 ADEM, 3 cortical)	9 (7.8%) (5 TL, 4 ADEM, 0 cortical)	0.077
Moderate to severe at onset	27 (64.3%)	65 (56.5%)	0.472
Relapse probability at 1 year	0.428	0.371	0.54
Good response to steroids	31 (73.8%)	37 (32.2%)	**<0.001**
Recovery			
Full/very good	24 (57.1%)	57 (49.6%)	0.472
Mod-sev bl/b	5 (11.9%)	4 (3.5%)	0.058
Mod-sev visual	3 (7.1%)	11 (9.6%)	0.184
Mod-sev motor	1 (2.4%)	11 (9.6%)	0.184
Combination disability	8 (19%)	28 (24.3%)	0.529
Unclear	1 (2.4%)	4 (3.5%)	1

y, years; ON, optic neuritis; TM, transverse myelitis; LETM, longitudinally extensive transverse myelitis; TL, tumefactive lesion; ADEM, acute disseminated encephalomyelitis; mod-sev, moderately severe, bl/b, bladder/bowel/sexual dysfunction.

MOG Cohort Clinical Data

Of the 42 patients (27 female) with a median disease onset age of 29 years (range 3–62; 9 pediatric cases), 20 (47%) were non-Caucasian (9 Asian, 7 South Asian, 4 other), and 3 (7%) had comorbid autoimmune disease (thyroid disease and psoriasis).

Most common phenotypes at onset were isolated optic neuritis in 23 patients (55%; bilateral in eight) and isolated myelitis in nine (21%; longitudinally extensive in six). Other onset phenotypes included brainstem presentations, combinations of optic neuritis, and myelitis and cerebral syndromes [which included focal deficits due to tumefactive lesions (3), seizures due to cortical lesions (1), or ADEM (2)]. As the majority of our cohort was adult, the proportion of cases with ADEM at onset was low.

Severity of disease at onset was moderate-severe in 64%, but the majority (74%) had good response to initial steroid therapy. Twenty-one percent of patients received other acute treatments in addition to high dose steroids, including plasma exchange, mitoxantrone, and intravenous immunoglobulins.

Using a formal Kaplan-Meier assessment, 3 patients who had relapsed had to be excluded due to lack of clarity on exact time to relapse. The cumulative relapse probability for the MOG positive group at 1 year was 0.428 (95% CI 0.244–0.567), at 4 years was 0.628 (95% CI 0.431–0.757), and at 10 years was 0.81 (95% CI 0.602–0.909) (see **Figure 1**).

TABLE 3 | MRI results summary: combined MOG cohort.

MRI available 35/42		**(18 administered Gd)**			
Brain	35 MRI				
	9 no lesions				
	26 abnormal	Lesion number	≤3	10 patients	
			4–9	6 patients	
			>9	10 patients	
		Lesion location	Supratentorial	24/26	(Bilateral lesions 18/24: fluffy/poorly demarcated 11/24; 7 of these >2 cm; 5 had CE)
				Subcortical	23
				Cortical	7
				Callosal	6 (nil with diffuse splenium involvement)
				BG	4
				AdjacentV3	1
				No PV lesions	14
				"MS features"	Dawsons Fingers 1, inferior temporal lesions 5, U or S shape juxtacortical 3
			Infratentorial	8 out of 26	All brainstem, 3 with additional cerebellum
				1 diffuse	
				PAG 5 (1 other MB lesion)	
				Pons 7	
				Medulla 4 (2 area postrema)	
				Adjacent V4 6	
				Cerebellar peduncles 6	
Spine	27 MRI (5 cervical only, 22 whole cord)				
	15 no lesions				
	12 abnormal	3 STM only			
		3 LTM only			
		6 STM+LTM			
		7 with CM lesions			
		0 with atrophy ≥3 VS			
	Lesions location	Cervical, thoracic, and conus 5			
		Cervical and thoracic 5			
		Thoracic and conus 1			
Orbits	14 with dedicated orbital imaging				
	1 no lesions				
	13 with orbital nerve lesions			Long 13	(5 involving chiasm)
				Short 3	
				Bilateral 8	

Gd, gadolinium; CE, contrast enhancement; BG, basal ganglia; V3, third ventricle; PV, periventricular; PAG, periaqueductal gray; MB, midbrain; V4, fourth ventricle; STM, short transverse myelitis; LTM, long transverse myelitis; VS, vertebral segments; CM, conus medullaris.

Upon examining correlations between onset phenotype and future relapses, it was shown that 68% of patients with isolated optic neuritis and 78% of isolated transverse myelitis relapsed, whilst 100% of those who had presented with cerebral or combination presentations relapsed. Relapses most frequently affected the optic nerves or spinal cord, but the majority experienced different phenotypes on relapse to that experienced at onset (26/34 patients), including brainstem and cerebral or cortical phenotypes. Patients experiencing restricted phenotypes with recurrent disease were most likely to present with optic neuritis (6/7); one patient had pure recurrent transverse myelitis.

No patients had a progressive disease course, although patients with this phenotype are not routinely tested for MOG antibodies at our center.

In total 57% had no or minimal disability at last follow-up. Significant ongoing disability affected predominantly bladder/bowel in 12%, vision in 7%, motor in 2%, and a combination poor outcome was seen in 19%. Chronic steroid-sparing therapies were used in 25/42 patients (59.5%).

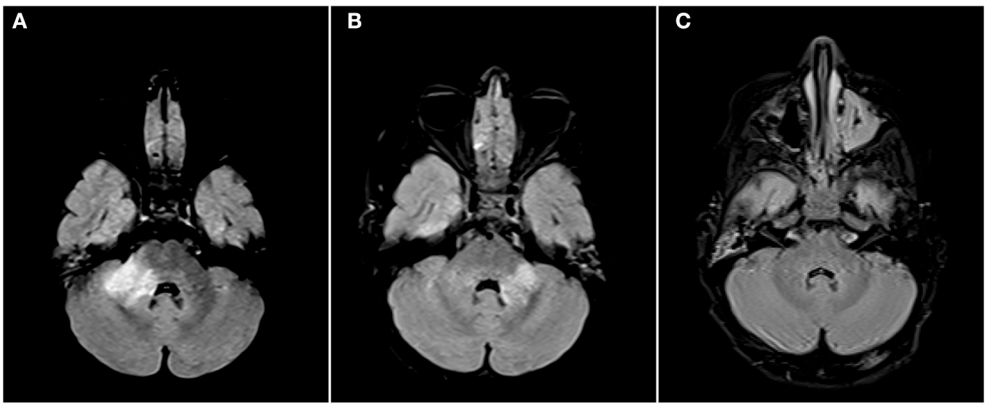

FIGURE 2 | Axial FLAIR images of the brain from the same patient across serial examinations. **(A)** At the time of disease presentation: a FLAIR hyperintense lesion involves the right middle cerebellar peduncle. **(B)** Approximately 2 months later: the lesion in the right middle cerebellar peduncle has nearly completely resolved and there has been interval development of a new lesion in left middle cerebellar peduncle. **(C)** More than 1 year later: The posterior fossa lesions as well as other supratentorial lesions (not shown) have completely resolved.

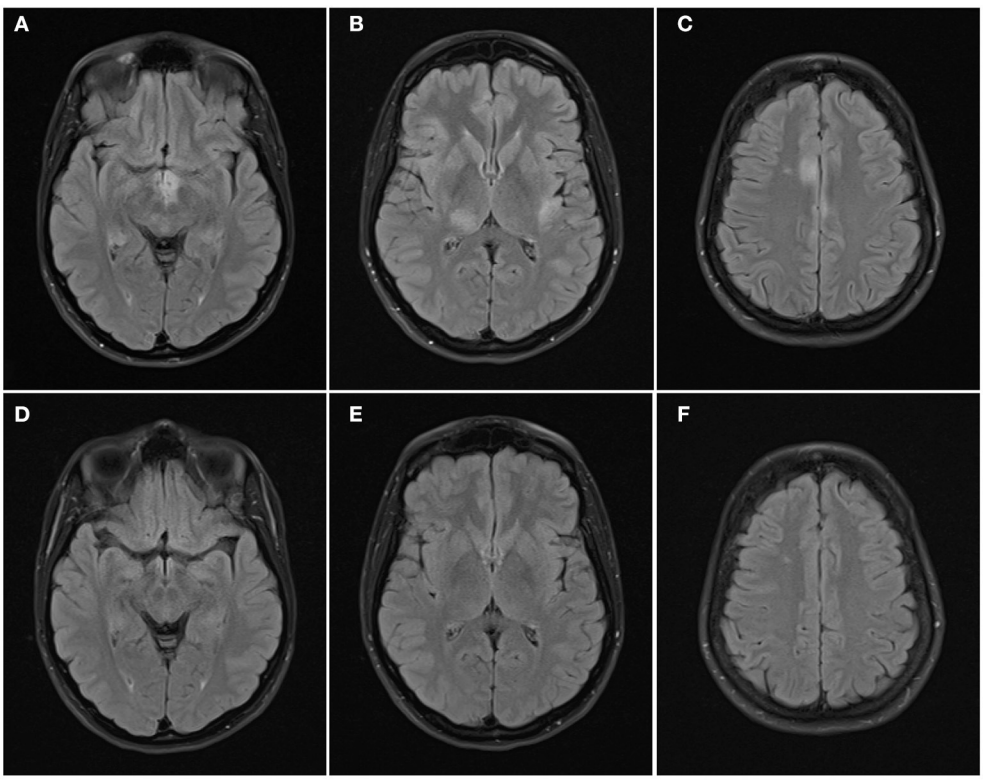

FIGURE 3 | Axial FLAIR images of the brain from the same patient across serial examinations. **(A–C)** At the time of disease presentation: FLAIR hyperintense lesions involve the hypothalamus and optic tracts **(A)**, right thalamus and left insular cortex **(B)**, and parasagittal frontal cortex bilaterally and right centrum semiovale **(C)**. **(D–F)** 5 months later: the lesions have all resolved except for the lesion in the right centrum semiovale.

Azathioprine was the most common first line agent (15/25), but mycophenolate mofetil (MMF) (4/25), and B-cell depleting monoclonal antibody therapies (6/25) were also used. Nine patients required a second line therapy, and one required a third line of treatment. (These constituted mostly MMF and B cell depleting therapies for those not previously using, as well as maintenance IVIG and an interleukin 6 receptor inhibiting monoclonal antibody). **Supplementary Tables 2, 3** provide further details on the individual patient presentations.

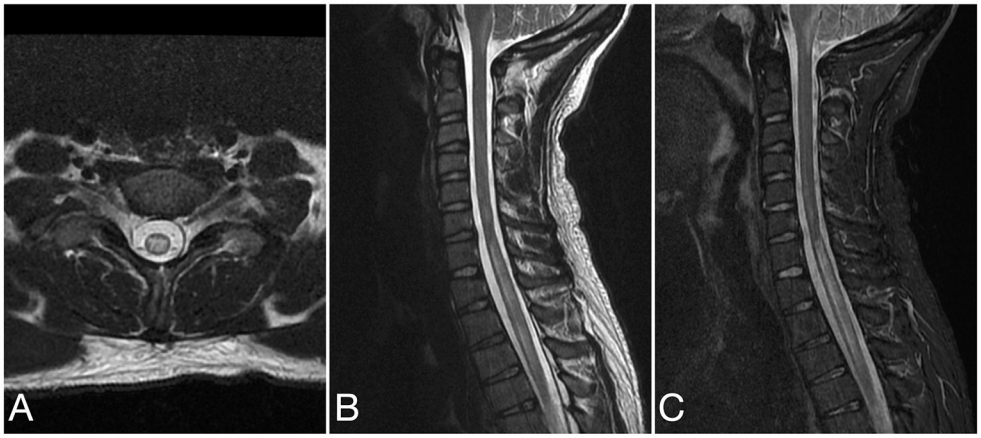

FIGURE 4 | Axial T2 **(A)**, sagittal T2 **(B)**, and sagittal STIR **(C)** images of the cervical spine from the same patient at the time of disease presentation. A longitudinally extensive T2/STIR hyperintense lesion (≥3 contiguous vertebral segments) involve the spinal cord at the cervicothoracic junction.

Comparison of MOG-antibody Positive and AQP4, MOG-antibody Seronegative Cohorts

In comparison to the MOG-antibody positive patients, the AQP4- and MOG-antibody negative patients showed a higher female predominance 2.5:1 vs. 1.8:1, and a slightly older age at onset (median 39 vs. 29 years).

The seronegative patients were more likely to present with isolated myelitis (57%) at onset than isolated optic neuritis (20%). Onset with neurological deficits in more than one location was more common in the seronegative group (12%) compared to the MOG-antibody positive group (5%). Disability at onset was similarly moderate to severe in both groups, but more patients in the MOG-antibody positive group showed a good response to initial steroid therapy (74 vs. 32%).

Cumulative relapse probabilities in the AQP4- and MOG-antibody seronegative group was 0.371 at 1 year (95% CI 0.274–0.455), 0.606 at 4 years (95% CI 0.498–0.691), and 0.814 at 10 years (95% CI 0.682–0.891) (see **Figure 1**). A formal z-test comparison was performed for estimated relapse probability at 12 months vs. the MOG positive group using their two standard error estimates of 0.04605 and 0.08148, and this was found to be non-significant ($z = -0.609$, 95% CI -0.240 to 0.126, p-value $= 0.54$).

In terms of clinical syndromes experienced at any point during the disease course, MOG-antibody positive patients were more likely to have experienced optic neuritis (74 vs. 40%) or brainstem (38 vs. 21%) presentations than the seronegative group. Myelitis was more common in the seronegative group (80 vs. 52%).

Tumefactive cerebral lesions presenting with the expected focal neurological deficits were common in both groups. Other symptomatic cerebral presentations also occurred, with some difference between the two groups. In the MOG-antibody group, two patients presented with seizures due to cortical lesions. In the seronegative group one patient presented with chorea and another with psychosis.

Both groups had a significant proportion of patients with residual disability affecting function at last follow-up −43% in the MOG-antibody positive group and 51% in the seronegative group (see **Table 2**).

Chronic maintenance therapies were also used by some patients in the persistently seronegative group (62/115, 54%). Azathioprine was again most common (43/62 patients), but MMF (5) and antiCD20 monoclonal antibodies (5) were also used for some patients, as were traditional MS therapies (10). Second line therapy (predominantly MMF) was used by 22 (19%), and third line (predominantly antiCD20 monoclonal antibodies) by 11 (9.5%).

Radiological Data

MR imaging was available for 35/42 of the MOG-antibody positive patients (**Table 3**); 32/35 were performed on 1.5 tesla MRI and three on 3 tesla MRI. Gadolinium contrast was administered in 18/35 cases. The majority of scans (22/35) were performed at the time of first disease presentation.

All 35 patients had brain imaging available for review. In nine, no lesions were detected, whilst 26 had abnormal scans. Number of lesions varied widely from ≤3 lesions in 10 patients, four to nine lesions in six patients and more than nine lesions in the remaining 10 patients. Supratentorial lesions were seen in 24/26 patients, bilateral in 18, and "fluffy" or poorly demarcated in 11. Seven of the 24 had lesions larger than two centimeters and five (of these seven) demonstrated contrast enhancement. In the majority of patients (23/26) the lesions were located in the subcortical white matter, but in 14 of these there were no lesions adjacent to the lateral ventricles. Seven patients had cortical lesions. Six patients had lesions in the corpus callosum, but none displayed diffuse splenial involvement. Four patients had lesions in the basal ganglia. One had lesions adjacent to the third ventricle. Whilst five patients had one or two of the components of previously described "classic MS" lesion

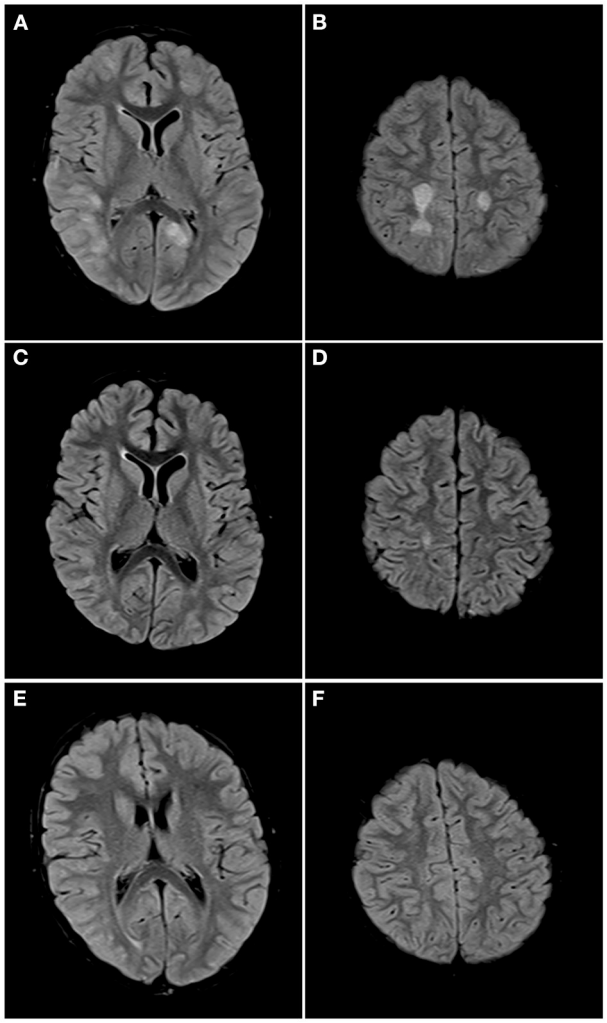

FIGURE 5 | Axial FLAIR images of the brain from the same patient across serial examinations. **(A,B)** At the time of disease presentation: FLAIR hyperintense lesions involve the cortex and subcortical white matter of the right posterior temporal, right lateral occipital and left parasagittal occipital lobes **(A)** and the centrum semiovale bilaterally **(B)**. **(C,D)** Approximately 1 month later: The lesions in both cerebral hemispheres have nearly completely resolved with a small residual lesion in the right centrum semiovale. **(E,F)** One year later: All the lesions have completely resolved.

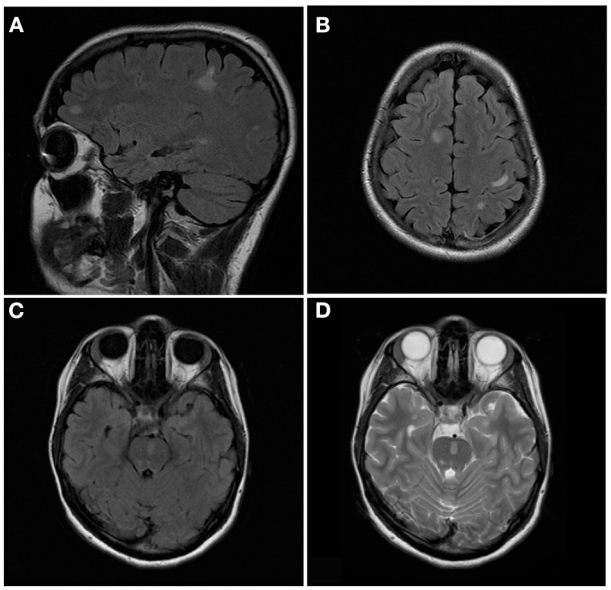

FIGURE 6 | Sagittal FLAIR **(A)**, axial FLAIR **(B,C)**, and axial T2 **(D)** images of the brain from the same patient at the time of disease presentation. **(A,B)** Multiple FLAIR hyperintense lesions involve the juxtacortical and subcortical white matter of both cerebral hemispheres. **(C,D)** Additional T2/FLAIR hyperintense lesions involves the juxtacortical white matter of the left temporal lobe and pons.

findings (14) of Dawson's fingers, inferior temporal lobe lesions and S- or U-shaped juxtacortical lesions, no patients had all three characteristics.

8/26 patients had infratentorial brain involvement. In all eight the brainstem was involved, three had additional cerebellar involvement. In terms of location in the brainstem, seven patients had pontine lesions, six cerebellar peduncular lesions and five had lesions in the periaqueductal gray matter. Four patients had medullary lesions (two in the area postrema) and six had lesions adjacent to the fourth ventricle. Only one patient had diffuse brainstem involvement.

Orbital imaging (with minimum coronal T2 views with fat suppression) was available for 14 patients. Thirteen patients showed abnormality in their optic nerves, with bilateral involvement in eight patients. All 13 patients had long lesions, eight of these were exclusively anteriorly situated in the optic nerve, but five extended posteriorly to involve the chiasm.

Spinal cord imaging was available for 27 patients (however five of these had only had cervical cord imaging). 15/27 scans were normal. The 12 abnormal scans showed mixed patterns of involvement: three had only longitudinally extensive lesions (more than or equal to three vertebral segments), three had only short lesions and five had both longitudinally extensive and short lesions. In terms of lesion location, all patients had involvement of more than one spinal region. 7/12 patients had involvement of the conus medullaris. No patients displayed significant cord atrophy.

See attached **Figures 2**–**7** for sample images from our patient cohort, and **Table 3** and **Figure 8** for a summary of MRI features.

DISCUSSION

We report a mixed pediatric (9) and adult (33) cohort of 42 MOG antibody positive patients from our multi-ethnic clinic in British Columbia, Canada. Retrospectively we identified 21/146 MOG antibody positives representing a frequency of 14% within the seronegative NMOSD "suspects"/idiopathic atypical demyelinating syndrome cohort which is similar to previous reports (8–20%) (7, 15, 16).

Demographically our patients are similar to other MOG cohorts (1–4, 8) in terms of a balanced gender distribution

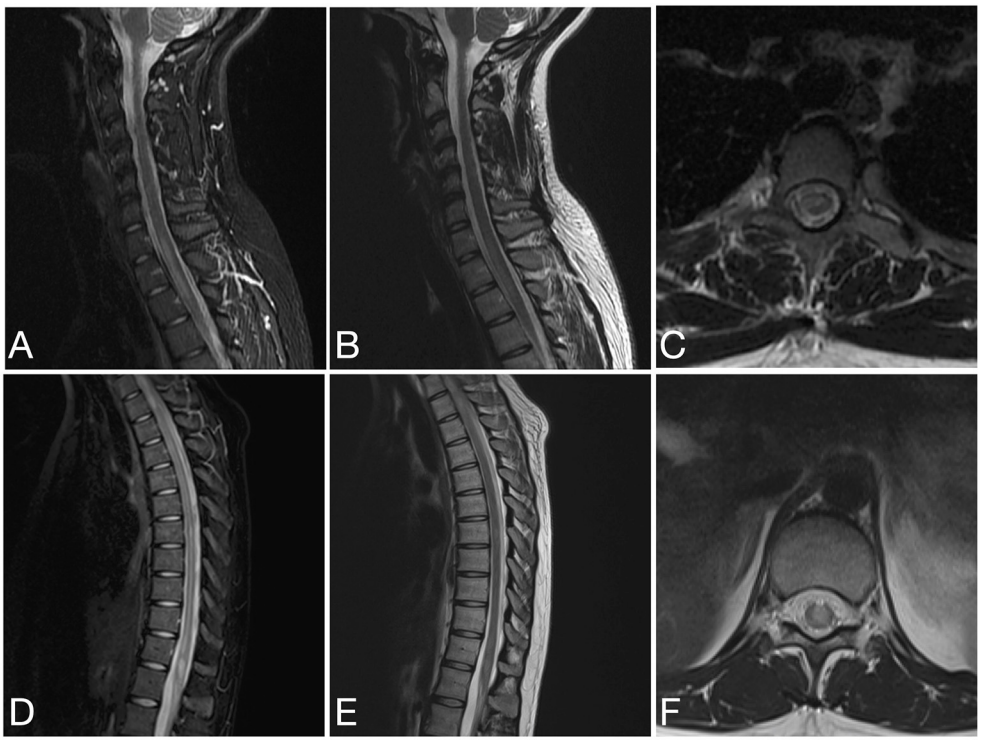

FIGURE 7 | Sagittal STIR **(A)**, sagittal T2 **(B)** and axial T2 **(C)** images of the cervical spine and sagittal STIR **(D)**, sagittal T2 **(E)**, and axial T2 **(F)** images of the thoracic spine from the same patient as in **Figure 6** at the time of disease presentation. **(A–C)** A short segment T2/STIR hyperintense lesion (2 contiguous vertebral segments) involve the spinal cord at the cervicothoracic junction. **(D–F)** Other short segment T2/STIR hyperintense lesions involve the thoracic spinal cord and conus medullaris.

(64% female vs. 44–68%), onset age (29 vs. 27–37 years) and rate of comorbid autoimmune disorders (7 vs. 7–11%), but our cohort had a higher proportion of non-Caucasian patients (47 vs. 8–27%). Additionally, the onset phenotype was characteristic: 55% with optic neuritis, 21% transverse myelitis (including 7 patients with radiologically confirmed lesions in the conus medullaris, a feature frequently identified in MOG antibody mediated myelitis). With only 9 pediatric patients (median age 7, range 3–14 years) we did not see a high number of ADEM cases, which is typically seen in children under the age of 11 years. This finding was confirmed in a Chinese study examining differences in presentation between adult and pediatric MOG antibody disease (17).

More recently seizures and neuropsychiatric change related to cerebral cortical encephalitic lesions (5, 18–20) have been added to the MOG-antibody clinical phenotype (5, 18–20). Three of the patients in our cohort experienced cortical encephalitis, two of whom presented with seizures. This is not a rare presentation, in fact in a large Chinese series (5), 20.7% of the MOG cohort presented with cortical encephalitis. One of our patients with this presentation on relapse was also found to have NMDAR receptor antibodies. This coexistence of NMDAR and MOG antibodies has been previously described (21, 22). MOG-associated demyelinating episodes can occur simultaneously to NMDAR encephalitis, or can precede or follow (21).

One of our "clinically definite multiple sclerosis" cases was found to be MOG-antibody positive. This patient had presented with recurrent optic neuritis and a mild brainstem relapse, and had minimal MRI lesions. The clinical course of this patient has been atypical for MS, and the attending physician had recently been questioning the diagnosis. MOG antibody disease is felt to be distinct from MS, however as there is not yet a biomarker for MS, we are bound by clinical diagnostic criteria (McDonald criteria) which are limited in their sensitivity and specificity. One caveat of the McDonald criteria is that other potential disorders need to be excluded. A study from Germany (23) examined different groups of MS patients for MOG antibodies and found a rate of 5% MOG-antibody positivity in a group selected for "NMOSD-type presentations" with severe optic neuritis, myelitis and brainstem presentations. The authors suspect that the rate of MOG-antibody positivity in an unselected MS cohort is likely closer to 1%. Overall MOG antibodies are considered a marker of a non-MS disease (23, 24).

Radiologically, MOG antibody disease has some phenotypic overlap with NMOSD but can usually be distinguished from MS (13, 25). Brain imaging can be normal in MOG antibody disease (26, 27), but when lesions are seen they tend to be few, poorly demarcated or tumefactive and most often infratentorial (2, 25, 26). On follow-up imaging, lesions frequently show marked improvement or even resolution (2, 28). Seventy-four percent of our analyzed MRI brain scans were abnormal. The

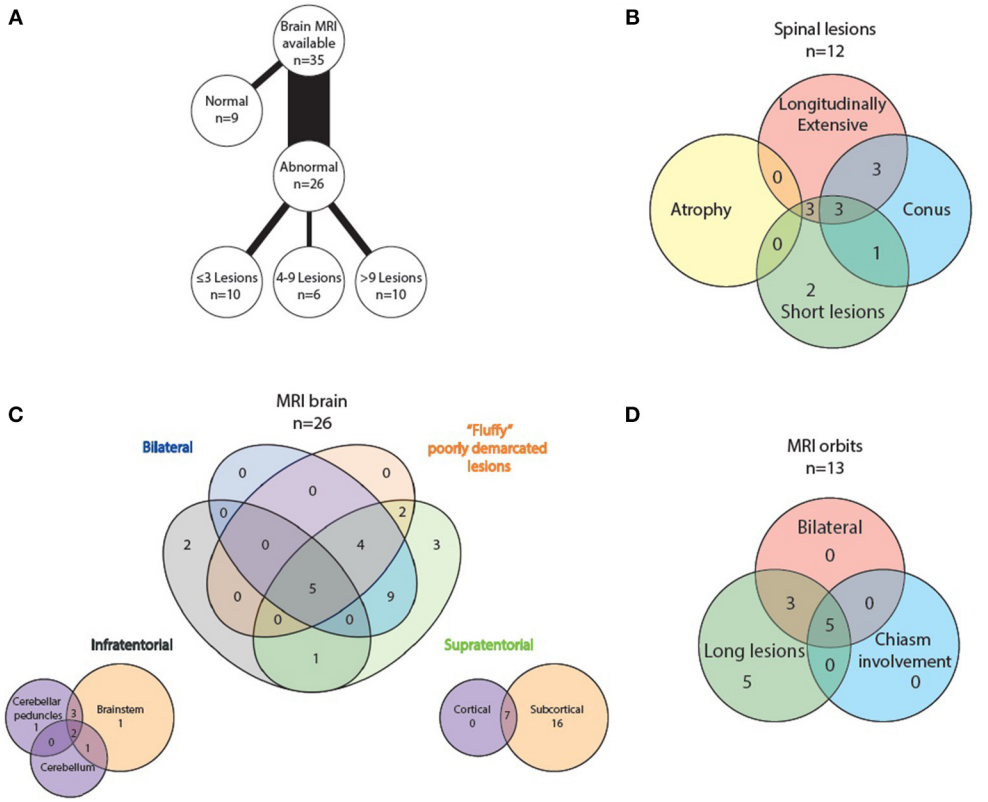

FIGURE 8 | Radiological features of MOG positive MRI scans: **(A)** lesion load on abnormal brain scans, **(B)** spinal lesion characteristics, **(C)** MRI brain topography, and **(D)** optic nerve lesion characteristics.

lesion frequency appeared bimodal with 42% (10/24) having <4 lesions and an equal number (10/24) with more than 9 lesions. Infratentorial involvement was relatively less common in our population, however as we only formally examined the first set of MR imaging performed for each patient, this may reflect what we found in our clinical onset phenotypes—that only five percent had brainstem involvement at first clinical presentation. We did not systematically analyse follow-up scans, but lesion resolution was noted in some patients anecdotally which is highlighted with the representative images displayed (see **Figures 2**–7).

In MOG antibody-associated disease, optic nerve lesions tend to be longer, but more anteriorly situated, sparing the optic chiasm with frequent optic disc edema at presentation (29). Our cohort demonstrated predominantly long lesions, but optic chiasm involvement was seen (5/13), previously reported as rare in this disorder (30, 31).

Spinal cord lesions are most frequently longitudinally extensive, but can also be short (32, 33). This was seen in our cohort with 3/12 abnormal spinal MRIs showing LETM only, 3/12 short lesions only, and both short and long lesions were present in 6/12 scans. Involvement of the conus medullaris is particularly characteristic (32), and was seen in 7/12 of our abnormal spinal MRIs.

Due to the retrospective nature of the study, follow-up times were not standardized so a simple relapse proportion could not be calculated, however a cumulative relapse probability at 10 years was 0.81 (although for this duration $n = 4$). This is a higher proportion of relapsing patients than some other series (1–3), however groups from Germany (33) and Spain (34) report similar high relapse rates of 80 and 78%, particularly optic neuritis relapses. Our cohort is from a referral center for CNS autoimmune disorders and could therefore have a referral bias for more severe or relapsing patients. In addition, due to the selection criteria of the AQP4 seronegative cohort for retrospective testing, it is likely that more severe cases are included in our cohort. Length of initial steroid treatment was not standardized and this data were not available for all patients. It is therefore possible, that early relapses occurred in those with short steroid exposure.

Whilst 57% of patients in our cohort had a good functional outcome at last assessment, 43% were left with significant residual disability after repeated relapses. This is in contrast to earlier reports of MOG-antibody associated disease being relatively benign in comparison to NMOSD, however as our experience with the disease grows, more reports are emerging that indicate that significant (especially visual) disability accrual is in fact occurring in many patients with repeated relapses (4, 33, 35). These data are important for ongoing treatment decisions where

lesion resolution is often dramatic and short-term treatment over months is routine.

Our study was not able to incorporate MOG antibody titers or serial test results. We were therefore unable to determine if these factors had influence on disease severity or likelihood of relapse. It has been reported that higher antibody titers at onset may be associated with a more severe disease presentation, but may not be predictive of future relapses (17, 36). Longitudinal persistence of MOG seropositivity may be associated with increased relapse risk (2, 37). The serologic data in this study are from two different cell-based antibody assays, one presenting native human MOG as the substrate (live test) and the other one presenting MOG overexpressed in cells that have been chemically stabilized (fixed test). These tests were discordant. Of the 22 sera retrospectively tested as positive for MOG antibodies, only 4 were positive on both assays, 15 patients were only identified by live testing while 3 were uniquely positive on the fixed test. This highlights the significant discrepancies between live and fixed testing for MOG antibodies which, although not the focus of this study, requires formal investigation (38). In a similar fashion 8/146 serum samples, identified as seronegative AQP4 by stabilized commercial testing (Euroimmun AG), were identified as AQP4 antibody seropositive by live testing on sera that had been stored for many years (range 1–12). These data are not trivial and have important implications for clinical decisions in managing patient care in this severely disabling disease. These data recapitulate multiple other studies (38–40).

CONCLUSION

Our multi-ethnic clinic population from British Columbia, Canada display similar demographic and phenotypic features to those previously described. We confirm rarer presenting features or "red flags" suggesting MOG-antibody positivity in patients, such as seizures with cortical lesions and conus medullaris involvement in patients with myelitis. Positive anti-MOG antibodies can rule out MS in patients with an atypical clinical MS disease course. Importantly, many of our MOG-antibody positive patients relapsed and were left with significant disability. International collaborative research efforts could address the clear need for a biomarker to identify patients likely to relapse as well as to establish formal treatment guidelines.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of British Columbia Clinical Research Ethics Board. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HC drafted and coordinated the manuscript, she was also involved in study design, data collection, and analysis. FS collected the neuroradiology data. NA was involved in study design and initial data collection. AM assisted with data collection. SA performed some of the statistical analysis. MW performed laboratory analyses at Oxford. BS created the venn diagrams. VD, RC, ALS, VB, ASc, and JC contributed patients and assisted with manuscript review. MF coordinated laboratory assessments at MitogenDx and assisted with manuscript review. PW coordinated laboratory assessments at Oxford and assisted with manuscript review. AT was involved in study design, manuscript review, and coordination of the team. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.525933/full#supplementary-material

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Conflict of Interest: MF is the director of MitogenDx. He is a paid consultant, has received honoraria or gifts in kind from Inova Diagnostics (San Diego, CA). PW is the director of Oxford Autoimmune Neurology Diagnostic Laboratory. He holds patents for antibody testing and has received consulting honoraria from Biogen Idec, Euroimmun AG, Mereo Biopharma, UBC, and retrogenix.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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