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Clinical and diagnostic spectrum of optic neuritis: A single-center retrospective study of disorders associated with multiple sclerosis, anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies

Dana R. Siegel

Meredith Van Harn
Henry Ford Health, mvanhar1@hfhs.org

Meari Taguchi
Henry Ford Health

Poonam Bansal
Henry Ford Health, pbansal2@hfhs.org

Mirela Cerghet
Henry Ford Health, mcerghe1@hfhs.org

See next page for additional authors

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Authors
Dana R. Siegel, Meredith Van Harn, Meari Taguchi, Poonam Bansal, Mirela Cerghet, and Anza B. Memon

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Clinical and diagnostic spectrum of optic neuritis: A single-center retrospective study of disorders associated with multiple sclerosis, anti-aquaporin-4 and anti-myelin oligodendrocyte glycoprotein antibodies

Dana R. Siegel [a], Meredith Van Harn [b], Meari Taguchi [d], Poonam Bansal [c,d], Mirela Cerghet [a,d], Anza B. Memon [a,d,*]

[a] Wayne State University School of Medicine, 540 East Canfield, Detroit, MI 48201, USA
[b] Department of Public Health Sciences, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202, USA
[c] Department of Ophthalmology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202, USA
[d] Department of Neurology, Henry Ford Hospital, 2799 West Grand Blvd, Detroit, MI 48202, USA

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ABSTRACT

Objective: Optic neuritis (ON) is an immune-mediated optic neuropathy associated with multiple immune-mediated neurological conditions. Our aim was to characterize the clinical and diagnostic features of first or initial episodes of ON associated with multiple sclerosis (MS)-associated (typical) and antibody-related (atypical) ON.

Methods: Retrospective, single institution, medical record review. We analyzed demographic, clinical, laboratory, and radiographic findings of 139 patients who presented with first episodes of MS-associated ON (MS-ON), aquaporin 4 antibody–associated ON (AQP4-ON), and myelin oligodendrocyte glycoprotein antibody–associated ON (MOG-ON) between January 2015 and October 2019 without preceding diagnosis. Simple hypothesis testing assessed differences between groups were performed.

Results: Of 139 patients (109 [79 %] women; 29 [21 %] men; mean age 47 [SD, 14] years), 106 had MS-ON, 25 had AQP4-ON, and 8 had MOG-ON. Patients with MOG-ON had the highest recurrence rate (88 %) relative to MS-ON (28 %) and AQP4-ON (56 %) patients ($P < .001$). Patients with AQP4-ON had the highest mean visual functional system scores (4.3 [SD, 1.8]) relative to MS-ON (2.0 [SD, 1.9]) and MOG-ON patients (2.8 [SD, 2.0]) ($P < .001$).

Conclusion: Patients presenting with initial episodes of ON exhibit a range radiographic and laboratory feature depending on the underlying associated disease. Understanding the variable characteristics of typical (MS-associated) and atypical (antibody-associated) ON may help physicians accurately diagnose and effectively treat ON.

1. Introduction

Optic neuritis (ON) is an immune-mediated optic neuropathy with a range of presentations and is associated with numerous conditions, including infections, autoimmune disorders, and other diseases. Typical ON presents as eye pain, impaired color vision, and monocular visual loss that occurs over one week or less. The eye pain often worsens with movement, and the onset typically coincides with visual acuity (VA) changes.[1,2] ON can be the initial presenting symptom of various immune-mediated neurological diseases.[3–6] In most cases, typical ON has a well-known association with multiple sclerosis (MS). Atypical ON is a severe form of the disease characterized by poor VA and outcomes. Atypical ON may manifest as an autoimmune antibody disorder and is mostly associated with neuromyelitis optica spectrum disorder (NMOSD).[2] The novel discovery that auto-antibodies against aquaporin-4 (AQP4) and myelin oligodendrocyte glycoprotein (MOG) can lead to ON has changed the clinical paradigm of this disorder. Whereas acute episodes of ON associated with MS often self-resolve, antibody-associated ON involving AQP4-IgG or MOG-IgG is more severe and may have a longer disease course [7,8].

* Correspondence to: K11, Henry Ford Hospital, 2799 W. Grand Blvd, Detroit, MI 48202, USA.
E-mail address: AMEMON2@hfhs.org (A.B. Memon).

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ON is often diagnosed based on clinical parameters, and magnetic resonance imaging (MRI) of the brain and orbits with gadolinium contrast can help to confirm the diagnosis. MRI of the brain can also be used to assess the risk of subsequent development of MS, where the affected optic nerve reveals abnormal enhancement on MRI orbit in the majority of patients.[9,10] However, ON associated with MS, anti-AQP4 antibodies, and anti-MOG antibodies can have similar clinical presentations. They can be challenging to differentiate at the onset of disease, where serologic testing is required to distinguish these forms. The long-term prognosis in MOG-ON is still controversial. There is no registered prospective comparative study. Maybe, there are some differences between races.

This retrospective study aimed to characterize and compare the clinical, radiographic, and laboratory features of ON associated with MS, anti-AQP4 antibodies, and anti-MOG antibodies at the onset of disease without preceding diagnosis. A thorough clinical definition outlining the characteristics of different ON manifestations will help physicians effectively diagnose and treat this variable disorder.

2. Materials and methods

2.1. Method and data collection

This was a retrospective study of electronic health records that included patients diagnosed with ON and who were treated in the neurology and ophthalmology clinics at the Henry Ford Health System (Detroit, MI) between January 2015 and mid-October 2019. This study was approved by the Henry Ford Health System's Institutional Review Board. A natural language search of the electronic medical record system (Epic, Verona, WI) used the keywords "optic neuritis" (ICD-10-CM Diagnosis Code G36.0) to identify patients. We identified 220 patients with the diagnosis of ON. Clinical, demographic, radiographic, and laboratory data, as well as treatment and symptoms recurrence were recorded.

We included patients (N = 139) with a presentation consistent with a first episode of clinical ON associated with MS (MS-ON), anti-AQP4 antibodies (AQP4-ON), and anti-MOG antibodies (MOG-ON).[11] We excluded 35 patients who had optic neuropathy secondary to other etiologies such as traumatic (N = 12), compressive (N = 6), ischemic (N = 11), and toxic (N = 6). Patients with chronic relapsing inflammatory optic neuritis (N = 6) who tested negative for both anti-AQP and anti-MOG IgG were also excluded. Additionally, patients with sarcoidosis associated ON (n = 5), and idiopathic ON (N = 35) who did not full fill the diagnostic criteria for MS, AQP-4 and MOG were also excluded from the study.

MS cases were confirmed based on McDonald's 2010 revised criteria.[12,13] A cell-based assay analyzed by cytometry was used for anti-AQP4 and anti-MOG IgG surface antibody detection in serum.[13,14] Samples were sent to the Mayo Clinic (Rochester, MN) for interpretation.

Records indicating MRI of the brain and orbit with and without gadolinium contrast performed at the time of symptom onset were analyzed. All patients obtained a standardized imaging protocol with a 1.5 Tesla MRI scanner that had axial T2 weighted and/or fluid-attenuated inversion recovery (FLAIR) sequences, coronal T2, or FLAIR sequences of the whole brain and coronal sequences with or without axial T2 fat suppressed (FS) sequences. Coronal and/or axial T1 weighted FS sequences were performed following gadolinium administration. Additionally, cerebrospinal fluid (CSF) studies such as white blood cell count (WBC), CSF protein, CSF oligoclonal bands (O bands), and CSF IgG index were documented and were analyzed. We also analyzed patient treatment with pulse steroids, weaning oral prednisone, and maintenance immunosuppressive therapy and symptom recurrence, when present.

All patient records included calculated visual functional system scores (VFSS) from the expanded disability status scale based on visual acuity (VA) at the time of presentation (rated from 0 to 6). Lower VFSS scores indicate better VA, and higher VFSS scores indicate poor VA.

Patients with a history of ON who had alternative diagnoses such as lupus, granulomatous optic neuropathies (e.g., sarcoidosis), or traumatic, toxic, ischemic, infectious, and compressive optic neuropathies were excluded. We also excluded patients who did not have a dedicated orbital imaging, clinical follow-up, or who were not tested for anti-AQP4 and anti-MOG IgG antibodies. 87 patients were tested for AQP4-IgG and only 25 tested positive. For the race comparison for VFSS, the overall difference was significant ($p = 0.0015$) with pairwise comparisons showing that Blacks have a significantly higher mean VFSS when compared to Whites (supplementary table).

2.2. Statistical analysis

All continuous variables used means and standard deviations (SD), while categorical variables used counts and column percentages. Univariate two-group comparisons used chi-square or Fisher exact tests (if expected cell counts were < 5) for categorical variables and Wilcoxon rank-sum tests for continuous variables. Nonparametric tests were chosen when group sizes were small and when normality assumptions were violated. Continuous data were compared between > 2 groups using Kruskal-Wallis tests. Given the number of demographic, clinical, radiological and spinal fluid characteristics being considered, the statistical significance was set at a more conservative value of $P < 0.01$. P-values between 0.01 and 0.05 were considered as showing a trend. Post hoc analyses used Benjamini-Hochberg adjustments to assess pairwise comparisons of the three ON groups. All analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

3. Results

3.1. Patient characteristics

Patient demographic information and clinical characteristics by diagnosis are in Table 1. Diagnostic study results such as MRI orbit data and CSF laboratory results are in Table 2. Of the 139 patients included in this analysis, 106 (76 %) had MS-ON, 25 (18 %) had AQP4-ON, and 8 (5.7 %) had MOG-ON. The mean (SD) age at diagnosis was 47 (14) years, with no statistical difference in age of onset between the 3 groups. The majority of patients were White (49 %) and were women (79 %).

Whereas 91/134 (68 %) of patients presented with unilateral ON, 43 (32 %) presented with bilateral ON. Although proportionately more patients with AQP4-ON (46 %) had bilateral ON than patients with MS-ON (30 %) or MOG-ON (13 %), there was no significant difference across groups ($P = .163$).

A total of 51/139 patients (37 %) had recurrent ON, with the highest rate of recurrence within the MOG-ON group (88 %) relative to patients in the AQP4-ON (56 %) and MOG-ON (28 %) groups ($P < .001$). VFSS scores (rated from 0 to 6) measured at the onset of symptoms were recorded for 98 patients, where the overall mean (SD) VFSS score was 2.7 (2.1). VFSS scores differed significantly between groups ($P < .001$), with the highest mean (SD) score of 4.3 (1.8) for patients with AQP4-ON, followed by 2.8 (2) for MOG-ON and 2.0 (1.9) for MS-ON patients.

All 8 patients in the MOG-ON group received high-dose pulsed intravenous methylprednisolone (IVMP) treatment followed by an oral steroid taper. A total of 20 patients (80 %) with AQP4-ON and 54 with MS-ON (51 %) received IVMP treatment ($P < .001$), while 3 patients with AQP4-ON received plasmapheresis for steroid-refractory ON. Only 101 health records included notation for steroid taper therapy, and the proportions of patients receiving this therapy differed between groups ($P < .001$).

3.2. Radiological and spinal fluid characteristics

All 139 patient records included MRI results (Table 2). Optic nerve

Table 1
Demographic and descriptive clinical characteristics of patients with optic neuritis.

[a]Variable (N = 139)	Overall	MS-ON (n = 106)	AQP4-ON (n = 25)	MOG-ON (n = 8)	[b]*P*-value
Age in years, mean (SD) (N = 139)	47 (14)	45 (13.9)	52 (14.9)	51 (8.6)	.084
Sex, No. (%) (N = 138)					.303
female	109 (79)	83 (78)	21 (88)	5 (63)	
male	29 (21)	23 (22)	3 (13)	3 (38)	
Race/ethnicity, No. (%) (N = 137)					.020
Black	45 (33)	33 (31)	12 (52)	0	
White	67 (49)	49 (4)	10 (44)	8 (100)	
Other/Unknown	25 (18)	24 (22)	1 (4)	0	
Side of ON, No. (%) (N = 134)					0.163
Unilateral	91 (68)	71 (70)	13 (54)	7 (88)	
Bilateral	43 (32)	31 (30)	11 (46)	1 (13)	
Recurrence, No. (%) (N = 139)					<.001
No	88 (63)	76 (72)	11 (44)	1 (13)	
Yes	51 (37)	30 (28)	14 (56)	7 (88)	
VFSS, mean (SD) score (N = 98)	2.7 (2.1)	2.0 (1.9)	4.3 (1.8)	2.8 (2.0)	< .001
IVMP, No. (%) (N = 139)					<.001
No	56 (40)	52 (49)	4 (16)	0	
Yes	82 (59)	54 (51)	20 (80)	8 (100)	
Unknown	1 (1)	0	1 (4)	0	
Steroid taper, No. (%) (N = 101)					<.001
No	35 (35)	34 (49)	1 (4)	0	
Yes	65 (64)	36 (51)	21 (91)	8 (100)	
Unknown	1 (1)	0	1 (4)	0	

Abbreviations: AQP4-ON, aquaporin 4–associated ON; IVMP, intravenous methylprednisolone; MS-ON, multiple sclerosis–associated ON; MOG-ON, myelin oligodendrocyte glycoprotein–associated ON; ON, optic neuritis; VFSS, visual function system score

[a] Some patient records did not contain information for certain variables

[b] Kruskal-Wallis test for continuous data and chi-square or Fisher exact test for categorical, data

intra-orbital segment T2 signal abnormalities on MRI orbit scan were reported in 48 (35 %) patients. Of these patients, signal changes were seen in 6 MOG-ON (75 %), 18 AQP4-ON (72 %), and 24 MS-ON (23 %) patients ($P < 0.001$). A total of 49 (35 %) patients demonstrated optic nerve intra-orbital segment enhancement on MRI orbit. While 7 of 8 patients (88 %) with MOG-ON had orbit enhancement, 18 (72 %) AQP4-ON and 24 (23 %) MS-ON patients ($P < .001$) showed this result. Optic nerve intracanalicular segment involvement was seen in 22 patients (16 %), including 10 (40 %) patients in the AQP4-ON group and 12 (11 %) in the MS-ON group; however, it was not observed in patients with MOG-ON ($P = .001$). Optic chiasm enhancement was seen only in 5 AQP4-ON patients (4 % of all patients; 20 % of AQP4-ON group; $P < .001$).

A total of 74 patients had CSF O band analysis performed, where 33 (45 %) had positive and 41 (55 %) had negative results. While none of the 7 patients with MOG-ON who were tested had positive CSF O bands, 31/50 (62 %) of the tested MS-ON patients and only 2/17 of the tested AQP4-ON patients had positive O bands ($P < 0.001$). The highest mean (SD) CSF IgG index was seen in the MS-ON group at 1.1 (0.5) compared to 0.8 (1.1) for the MOG-ON and 0.5 (0.4) for the AQP4-ON groups ($P < 0.001$). The mean CSF WBC and protein levels showed difference trends ($P < 0.05$) between the 3 groups (Table 2).

Table 2
Radiological and spinal fluid characteristics of patients with optic neuritis.

[a]Variable (N = 139)	Total	MS-ON (n = 106)	AQP4-ON (n = 25)	MOG-ON (n = 8)	[b]*P*-value
Positive MRI intra-orbital T2 signal changes, No. (%)	48 (35)	24 (23)	18 (72)	6 (75)	< .001
Positive MRI orbit enhancement, No. (%)	49 (35)	24 (23)	18 (72)	7 (88)	< .001
Presence of MRI intracanalicular segment involvement, No. (%)	22 (16)	12 (11)	10 (40)	0	.001
Presence of MRI orbit optic chiasm involvement, No. (%)	5 (4)	0	5 (20)	0	< .001
CSF O bands, No. (%) (N = 74)		MS-ON n = 50	AQP4-ON n = 17	MOG-ON n = 7	< .001
positive	33 (45)	31 (62)	2 (12)	0	
negative	41 (55)	19 (38)	15 (88)	7 (100 %)	
	Overall	MS-ON n = 48	AQP4-ON n = 17	MOG-ON n = 8	
CSF IgG index, mean (SD) (N = 73)	0.9 (0.6)	1.1 (0.5)	0.5 (0.4)	0.8 (1.1)	< .001
	Overall	MS-ON n = 47	AQP4-ON n = 20	MOG-ON n = 8	
CSF WBC, leukocytes/mm^3, mean (SD) (N = 75)	9.7 (14.4)	12 (16.4)	8.0 (11.1)	2.1 (2.5)	.023
	Overall	MS-ON n = 47	AQP4-ON n = 19	MOG-ON n = 8	
CSF protein, mg/dL, mean (SD) (N = 74)	40.8 (32.9)	39 (29.6)	41 (44.2)	48 (20.0)	.048

Abbreviations: AQP4-ON, aquaporin 4–associated ON; CSF, cerebrospinal fluid; MOG-ON, myelin oligodendrocyte glycoprotein-associated ON; MRI, magnetic resonance imaging; MS-ON, multiple sclerosis-associated ON; O band, oligoclonal band; ON, optic neuritis; WBC, white blood cells

[a] Some patient records did not contain information for certain variables

[b] Kruskal-Wallis test for continuous data and chi-square or Fisher's exact for categorical data

3.3. Post hoc analysis

Table 3 gives the adjusted *P* values from post hoc analysis comparing each pair of the significant variables from Tables 1 and 2. A Benjamini-Hochberg adjustment was applied to all raw *P* values to account for the inflation of the type I error rate inherent to pairwise comparisons. There were significantly more recurrences in the MOG-ON group compared to the MS-ON group (7/8 [87 %] vs 30/106 [28.3 %]; adjusted $P = 0.004$). Average VFSS was significantly higher in the AQP4-ON group than in the MS-ON group.

4. Discussion

This single-institution retrospective study assessed the diversity of clinical presentations and treatments of patients who presented with the first or initial episode of 3 different types of ON: MS-ON, AQP4-ON, and MOG-ON. In our study group, most of the patients were women, which is in accordance with other studies that have shown a female preponderance of 90 % in AQP4-ON patients, greater than the MS-ON group.[16, 17] In a study of 531 ON cases in Japan, the male to female ratio was 1:1.22. But our patient population showed a higher proportion of women compared to the Japanese cohort,[18] with the highest proportion of female patients in the AQP4-ON group (84 %) followed by the MOG-ON group (51 %). The median age of onset for AQP4-ON has been

Table 3
Adjusted *P* values from post hoc pairwise comparisons.

Variable	Comparison	MS-ON vs AQP4-ON	MS-ON vs MOG-OM	AQP4-ON vs MOG-ON
Recurrence	Yes vs No	0.073	0.004	0.101
VFSS	Yes vs No	< 0.001	0.352	0.097
IVMP	Yes vs No	0.011	0.015	0.550
Steroid taper	Yes vs No	< 0.001	0.015	0.733
MRI intraorbit T2 signal	Positive vs Negative	0.003	0.008	0.626
MRI orbit enhancement	Positive vs Negative	< 0.001	0.001	0.643
MRI intracanalicular segment involvement	Yes vs No	0.005	0.597	0.143
MRI orbit optic chiasm involvement	Yes vs No	< 0.001	N/A[2]	0.302
MRI brain lesions consistent with MS	Yes/ Nonspecific vs No	< 0.001	0.017	0.999
CSF O bands	Positive vs Negative	< 0.001	0.005	0.999
CSF IgG index	Positive vs Negative	< 0.001	0.022	0.834

Abbreviations: AQP4-ON, aquaporin 4–associated ON; CSF, cerebrospinal fluid; MOG-ON, myelin oligodendrocyte glycoprotein-associated ON; MRI, magnetic resonance imaging; MS-ON, multiple sclerosis-associated ON; O band, oligoclonal band; ON, optic neuritis; WBC, white blood cells
1There are no Other/Unknown or Black patients in the MOG-ON group
2There are no patients with MRI orbit optic chiasm involvement in the MS-ON or MOG-ON groups

reported to be 35–45 years,[14,15] whereas for MOG-ON, onset occurs at 31–37 years, with a female-to-male ratio of 2:1–3:1.[17,19] However, the median age for our study population was older than in those reports.

Recent studies estimate that the annual incidence of ON is about 2.57 per 100,000 person-years, which is consistent with several previous population-based studies.[20–22] In our study population, White patients were more frequently affected than other ethnicities overall: while we observed a higher number of African American patients within the AQP4-ON group, all of the 8 patients with MOG-ON were White. However, these differences in our study were not significant, and our findings support our patient cohort's geographic location.

In our study, patients with AQP4-ON presented with severe visual deficits with high VFSS scores (mean 4.3), indicating lower VA: these observations align with what was seen in a Japanese cohort, where the VA was poor in the AQP4 IgG-positive patients, with 53 % of patients showing VA restricted to finger counting or worse. In an 8-year retrospective descriptive study of patients with ON, 50/150 (33 %) were diagnosed with the anti-AQP4 disorder, and a high number of these patients (74 %) presented with worse than 20/200 VA.[23] Although optic nerve susceptibility in patients with AQP4-ON is multifaceted, the leading hypothesis for severe visual loss is that a highly vulnerable isoform of the autoantibody targeting AQP4 is expressed preferentially in astrocytes located in the optic nerve, which initiates the intense inflammatory demyelinating cascade. [24] Another interesting finding of our study is the significantly higher VFSS ($p = 0.00015$) in African American patients compared to Caucasians. In a cross sectional study comparing the visual outcome in patients with ON associated with MOG-IgG, AQP4-IgG and MS included 39 % African American patients. This study showed a lower thickness of macular ganglion call+ inner plexiform layer in AQP4-ON group compared to MS-ON and MOG-ON groups with poor visual outcome. Age, sex and race did not alter these findings. [25] A study by Ramanathan et al.[26] assessed a cohort of 50 patients with ON associated with AQP4 antibodies, MOG antibodies, and MS and reported that bilateral ON was more common in MOG-ON and AQP4-ON patients (84 % and 82 %) than in MS-ON (23 %) patients. We observed that bilaterality was more common in the AQP4-ON group (46 %) than in patients with MS-ON or MOG-ON (30.4 % and 12.5 %). Our results differ from the Ramanathan study[26] and may reflect a higher overall number of MS-ON and AQP4-ON patients in our cohort and the relatively lower number of MOG-ON patients in our group. However, despite the small number of MOG-ON patients in our group, a higher percentage of recurrence was seen in this group than in the AQP4-ON and MS-ON groups.

In our study group, only 61 % of patients received high-dose pulsed IVMP for ON treatment, mostly in the AQP4-ON and MOG-ON groups. Almost half of the MS-ON patients were not treated with IVMP given normal (20/20) or low normal VA (20/20–20/30) scores and subtle or no changes seen on orbital MRI. A higher proportion of patients in the AQP4-ON and MOG-ON groups received oral prednisone taper after IVMP. These results indicate that steroid taper might be needed in these two groups, given severe and atypical ON features with low VA and poor visual recovery after IVMP treatment.

ON can be diagnosed based on the clinical and ophthalmologic evaluation. However, an MRI of the brain and orbits with gadolinium contrast is recommended for most patients with suspected ON to determine its clinical association with immune-mediated neurological conditions, which is needed for a better long-term treatment plan that will affect the clinical outcome.[27–29] Features on the MRI orbit can be conducive for distinguishing typical ON from atypical ON.

Optic nerve lesions seen in patients with MS are typically short segments and are anteriorly located (intra-orbital).[30] Posterior optic pathway involvement (intracranial segment, optic tract, and optic chiasm), bilateral involvement, and enhancement are rare and should raise suspicion for atypical ON.[26,30] The orbital MRI features of our patients were similar to other published reports. Our study showed that only 23 % of MS-ON cases had a radiological correlation with the orbital MRI, somewhat different from what was reported in Ramanathan et al., which showed 62 % of MS patients (8/13) having optic nerve T2 hyperintensity. The authors also reported that these changes were either mild (5/13) or moderate (2/13), and that only 1/13 patients demonstrated significant T2 signal changes, with a moderate degree of T2 hyperintense changes seen in both AQP4-ON and MOG-ON groups. However, these results should be interpreted with caution because of the small sample size of their MS cohort [26].

One of our study's showed the intracanalicular segment involvement of the optic nerve in 40 % of AQP4-ON and 11 % of the MS-ON groups. The optic nerve has 4 portions moving from anterior to posterior: intraocular, intra-orbital, intracanalicular, and intracranial. While the anterior visual pathway is usually affected in typical ON (MS-associated), the posterior visual pathway is more often involved in atypical ON (eg, AQP4-ON)[16]; however, the intracanalicular segment lies in between the anterior and the posterior pathways, making involvement in this region somewhat difficult to interpret. Although it is commonly seen in AQP4-ON, a small proportion of MS-ON patients can show the intracanalicular segment's involvement: thus, abnormalities in this region should be interpreted with caution. One should be skeptical in automatically attributing this finding to atypical ON, AQP4-IgG and MOG-IgG antibody testing should be performed for this subgroup. Intracanalicular lesion is not so rare in MOG-ON. Furthermore, correctly evaluating intracanalicuar lesions on orbital MRI images is not easy, and the interpretation may differ between physicians.

Although CSF studies are not considered a necessity in the diagnostic workup for ON, they can help assess some atypical cases.[31] About 90 % of MS patients may have CSF O bands, which rarely present in anti-AQP4 and anti-MOG disorders,[18] where they are seen in about 20 % of patients with AQP4-ON.[18] The presence of CSF O bands also supports the dissemination in time criteria for MS that is incorporated in the revised 2017 McDonald's criteria.[12,13] Our finding that 62 % of patients with MS-ON had positive CSF O bands aligns with previous findings.[18] Interestingly, the mean CSF IgG index was elevated in both the MS-ON and MOG-ON groups. We also looked at the mean CSF protein level and WBC count, and the results showed difference trends. This finding is different from other published reports, where higher CSF WBC

cell counts (> 50 cells) in AQP4-ON patients than in MS-ON patients have been observed [32,33].

In our study, almost all patients received maintenance immunomodulatory / immunosuppressive medications, including glatiramer acetate (40.7 %), rituximab (11 %), azathioprine (6 %), methotrexate (1.7 %), teriflunomide (3.4 %), natalizumab (7.6 %), interferon-beta (25.4 %), fingolimod (7.6 %), dimethyl fumarate (16.9 %), mycophenolate mofetil (7.6 %), and cyclophosphamide (0.7 %). Treatment details are listed in the Supplementary Table. Multiple patients were switched from one immunotherapy to another either due to side effects or disease recurrence. MS patients on low or intermediate efficacy drugs were switched to high efficacy treatment due to the disease's recurrence.

4.1. Limitations

The retrospective study design and the relatively small number of patients in the MOG-ON group are our study's main limitations. However, this study provides important demographic, clinical, and radiographic distinctions of patients with 3 distinct forms of ON: AQP4-ON, MOG-ON, and MS-ON. Early recognition of these conditions may affect patient clinical outcomes, as patients with anti-AQP4 and anti-MOG associated ON may present with high VFSS score at the onset of disease, indicating possible severe and sustained visual impairment with an increased risk of recurrence, usually requiring long-term steroid use.

5. Conclusion

The characterization of 3 unique ON manifestations at the onset of MS, NMOSD, and MOG described here should help clinicians diagnose these various disease forms with due diligence. In addition, understanding specific ON etiologies and presentations will help physicians initiate appropriate maintenance immunotherapy to prevent patients from having future attacks, which could lead to poor clinical recovery and outcomes.

Declarations

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Ethics approval

Study was approved by the Henry Ford Health System IRB.

Code availability

Not applicable.

CRediT authorship contribution statement

Anza Memon, MD: Drafting/revising of the manuscript for content including medical writing for content, major role in acquisition of data, study concept for design, analysis or interpretation of data and approval of the final draft. Dana R. Siegel, MD: Major role in the acquisition of data, design and conceptualized study, analyzed the data; and helped drafting the manuscript. Meredith Van Harn, MPH: Interpreted the data; helped with the statistical analysis revised the manuscript for intellectual content. Meari Taguchi, MD: Interpreted the data; revised the manuscript for intellectual content. Poonam Bansal, MD: Interpreted the data; revised the manuscript for intellectual content. Mirela Cerghet, MD, PhD: Interpreted the data; revised the manuscript for intellectual content.

Conflicts of interest

The authors report no known conflicts of interest.

Data Availability

Will be available upon request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2022.107381.

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