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Myelin Oligodendrocyte Glycoprotein Antibody–Positive Optic Neuritis: Clinical Characteristics, Radiologic Clues, and Outcome

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Abstract

- **PURPOSE:** To characterize the clinical phenotype of myelin oligodendrocyte glycoprotein antibody (MOG-IgG) optic neuritis.
- **DESIGN:** Observational case series.
- **METHODS:** SETTING: Multicenter. PATIENT/STUDY POPULATION: Subjects meeting inclusion criteria: (1) history of optic neuritis; (2) seropositivity (MOG-IgG binding index > 2.5); 87 MOG-IgG-seropositive patients with optic neuritis were included (Mayo Clinic, 76; other medical centers, 11). MOG-IgG was detected using full-length MOG-transfected live HEK293 cells in a clinically validated flow cytometry assay. MAIN OUTCOME MEASURES: Clinical and radiologic characteristics and visual outcomes.

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- **RESULTS:** Fifty-seven percent were female and median age at onset was 31 (range 2–79) years. Median number of optic neuritis attacks was 3 (range 1–8), median follow-up 2.9 years (range 0.5–24 years), and annualized relapse rate 0.8. Average visual acuity (VA) at nadir of worst attack was count fingers. Average final VA was 20/30; for 5 patients (6%) it was ≤20/200 in either eye. Optic disc edema and pain each occurred in 86% of patients. Magnetic resonance imaging showed perineural enhancement in 50% and longitudinally extensive involvement in 80%. Twenty-six patients (30%) had recurrent optic neuritis without other neurologic symptoms, 10 (12%) had single optic neuritis, 14 (16%) had chronic relapsing inflammatory optic neuropathy, and 36 (41%) had optic neuritis with other neurologic symptoms (most neuromyelitis optica spectrum disorder–like phenotype or acute disseminated encephalomyelitis). Only 1 patient was diagnosed with MS (MOG-IgG-binding index 2.8; normal range ≤ 2.5). Persistent MOG-IgG seropositivity occurred in 61 of 62 (98%). A total of 61% received long-term immunosuppressant therapy.
- **CONCLUSIONS:** Manifestations of MOG-IgG-positive optic neuritis are diverse. Despite recurrent attacks with severe vision loss, the majority of patients have significant recovery and retain functional vision long-term.

Two novel glial autoantibodies discovered in the past 15 years enable recognition of patient subsets with antigen-specific central nervous system (CNS) inflammatory demyelinating autoimmunity manifesting as optic neuritis. The first autoantibody targets the astrocytic aquaporin-4 (AQP4) water channel and improved understanding and detection of the clinical entity neuromyelitis optica spectrum disorders (NMOSD).[1,2] The second autoantibody, specific for myelin oligodendrocyte glycoprotein (MOG-IgG), was initially erroneously associated with multiple sclerosis in early literature with use of solid-phase assays.[3] Since introduction of live transfected cell–based assays, MOG-IgG has emerged as a reproducible marker for a subset of patients with optic neuritis,[4] AQP4-IgG-seronegative inflammatory CNS demyelinating disorders with NMOSD-like phenotype, and acute disseminated encephalomyelitis (ADEM) predominantly in children.[5,6] Neither glial autoantibody is typically detected in multiple sclerosis.[5,6] Recent studies have suggested association of MOG-IgG seropositivity with recurrent optic neuritis attacks that can lead to significant visual morbidity.[7] Because there are few large studies of MOG-IgG-seropositive optic neuritis, the clinical phenotype is poorly defined. In order to better define the clinical entity and anticipate visual outcomes, the goal of this study is to report the presenting signs and symptoms, radiologic abnormalities, accompanying neurologic deficits, and visual outcomes of a large cohort of patients with MOG-IgG-seropositive optic neuritis.

METHODS

This was an observational case series on patients with MOG-IgG-positive optic neuritis. The Mayo Clinic Institutional Review Board approved this retrospective study and participants provided informed consent. We included patients seen at Mayo Clinic between January 1, 2001 and March 31, 2017 or elsewhere (2016–2017) who (1) had a clinically documented history of optic neuritis at any time point; and (2) had serum available (mostly archived for Mayo Clinic historical cases) that tested positive for MOG-IgG by a Clinical Laboratory Improvement Amendments–validated, fluorescence-activated cell sorter (FACS) testing in the Mayo Clinic Neuroimmunology Laboratory.

The patients' medical records were reviewed for presence of pain, fundus appearance at onset, visual acuity (VA) at the worst optic neuritis attack nadir and at last follow-up, number of attacks, other neurologic symptoms, magnetic resonance imaging (MRI) findings, and immunotherapy and outcome. Relapse of optic neuritis was defined as any repeat attack at least 30 days after the initial attack. VA was evaluated in each eye by Snellen VA charts and converted to logarithm of minimum angle of resolution (logMAR) values for statistical analysis. The following logMAR values were used for nonnumeric visual acuities: no light perception (NLP) = 3.0, light perception (LP) = 2.3, hand motion (HM) = 2.0, and count fingers (CF) = 1.7.[8] The definition of severe permanent visual loss was 20/200 (logMAR 1.0) or worse in either eye at most recent follow-up. Final visual acuities were not included if final follow-up visit was within 3 months of the last optic neuritis attack. Annualized relapse rate was calculated as the ratio of the number of optic neuritis attacks and years since onset of the disease among patients with at least 18 months of follow-up.

Patients were classified as having single optic neuritis, recurrent optic neuritis, chronic relapsing inflammatory optic neuropathy (CRION),[9] NMOSD-like phenotype as defined by Wingerchuk and associates in 2015,[2] ADEM (multifocal CNS disorder plus widespread inflammation on head MRI as defined by Krupp and associates in 2013[10]), multiple sclerosis, or "optic neuritis plus" for patients with additional neurologic symptoms that did not fulfill criteria for NMOSD-like phenotype or ADEM. CRION was defined as a steroid-responsive and steroid-dependent recurrent optic neuritis with other etiologies excluded (eg, sarcoidosis).[9]

Thirty-one of the included patients were reported in an earlier series of 246 recurrent optic neuritis subjects.[11]

- **MYELIN OLIGODENDROCYTE GLYCOPROTEIN ANTIBODY ASSAY:**

  All MOG-IgG testing was performed by Mayo Clinic Neuroimmunology Laboratory technicians masked to diagnosis, using a flow cytometric assay (MOG-IgG-FACS) based on that reported by Waters and associates.[12] The antigenic protein (MOG) was expressed on the surface of the human HEK293 cell line that was transiently transfected with a recombinant expression vector that also expressed an independent fluorescent marker protein (AcGFP) via an internal ribosomal entry site (pIRES2). We used an IgG1-Fc region–specific secondary antibody directly conjugated to AlexaFluor 647 to detect human IgG bound to cells exposed to diluted serum samples. The IgG binding index, calculated as the ratio of median AF647 fluorescence of GFP-positive cells to that of GFP-negative cells, was considered positive when ≥ 2.5. Patients were defined as having persistently positive or transiently positive MOG-IgG. Persistent seropositivity was defined as both initial and follow-up sample positive or, if no sample at onset was available, samples obtained > 1 year after optic neuritis episode were positive. All AQP4-IgG and MOG-IgG1 testing was performed masked to clinical data.

RESULTS

There were a total of 87 patients (57% [N = 50] female) with optic neuritis and MOG-IgG positivity included (76 seen at Mayo Clinic; 11 seen by non-Mayo US

neuroophthalmologists). Seventy-three (84%) were white, and the median age at neurologic symptom onset was 31 years (range 2–79 years; Table), with 66% older than 18 years. Among the patients with follow-up serial samples or samples obtained > 1 year after the initial optic neuritis attack, MOG-IgG remained persistently positive in 61 of 62 (98%). The remaining 25 were tested at a single time point <1 year after onset and, therefore, persistency of MOGIgG could not be determined.

Optic neuritis was the presenting symptom in 71 of 87 patients (82%) and was without other accompanying neurologic symptoms in 60 of 87 (69%). Sixty-nine (80%) had 2 or more attacks of optic neuritis, the median number being 3 (range 1–8), with median follow-up time 2.9 years. The annualized relapse rate of optic neuritis was 0.8 attacks per year. The median interval between the first and second optic neuritis attack was 4 months (range 1–408 months) (Figure 1). The right optic nerve was involved at least once in 62 patients (72%), the left optic nerve in 60 patients (70%), and both optic nerves in 33 (38%).

Twenty-six patients (30%) had recurrent optic neuritis without other neurologic symptoms; median follow-up was 4 years (range 0.5–22 years). Ten patients (12%) had a single optic neuritis without relapse or other neurologic symptoms without long-term immunosuppressant therapy; median follow-up was 2 years (range 0.5–9.6 years). Fourteen patients (16%) had CRION. Nineteen patients (22%) had an NMOSD-like phenotype, and 16 (18%) had ADEM (12 of the 16 ADEM patients were ≤18 years old). One patient had optic neuritis and subsequently developed brainstem lesions that did not fulfill NMOSD or ADEM, and was thus designated as “optic neuritis plus.” Multiple sclerosis was the assigned diagnosis in a single patient whose MOG-IgG titer was low (IgG binding index 2.8; normal range 0–2.5) (Table).

Fifty-three patients (61%) received long-term immunosuppressant therapy, and this treatment was recommended for an additional 7 patients for whom follow-up information was lacking. The most commonly used medications for long-term immunosuppression were mycophenolate, azathioprine, and rituximab.

Ten of the 60 (17%) patients presenting with optic neuritis in isolation subsequently developed extra–optic nerve neurologic symptoms (eg, transverse myelitis, n = 8), which led to a diagnosis of NMOSD-like phenotype (n = 6) or ADEM (n = 3). In this group, the median in terval from optic neuritis onset to involvement of other CNS regions was 1.5 months (<2 months for all but 3 patients).

- **CHARACTERISTICS OF THE OPTIC NEURITIS:**

  Pain with extraocular movements was present in 71 of 83 patients (86%) (Table). Edema was noted in 36 of 42 patients (86%) for whom optic disc appearance was documented and was rated moderate or severe in 52% (Figure 2). There were 32 of 86 (37%) patients who had bilateral simultaneous optic neuritis during at least 1 of the attacks. The median and mean VA at the nadir of the worst optic neuritis attack was HM and CF (range 20/25 to NLP), respectively. The median and mean VA at follow-up was 20/20 and 20/30, respectively (range 20/20 to NLP). Treatment at the time of acute optic neuritis consisted of intravenous (IV) methylprednisolone in 72 patients (83%), IV methylprednisolone and plasmapheresis in

8 (9%), IV methylprednisolone and IV immunoglobulin (IVIG) in 3 (3%), and IVIG alone in 1 (1%); 3 (3%) received no treatment. There was no difference in final visual outcomes between the treatment groups ($P = .86$).

Final VA was 20/200 or worse in only 5 (6%) patients (either eye), with 1 patient having 20/200 in both eyes. Among those 5 patients, the median interval to poor visual outcome was 3 months (range 0–10 months), during which an additional 0–4 optic neuritis attacks occurred. Four of those 5 patients were treated with IV methylprednisolone alone, and 1 received both IV methylprednisolone and plasmapheresis. One patient had a poor outcome after the initial optic neuritis attack, 1 had a single recurrent optic neuritis attack with poor recovery, and 3 of the 5 met the criteria for CRION and had a poor outcome from recurrent optic neuritis attacks before being stabilized on a chronic immunosuppressive therapy.

- **OTHER NEUROLOGIC SYMPTOMS:**

  Thirty-seven patients (43%) had either transverse myelitis or other neurologic symptom in addition to optic neuritis during the disease course (Table). Thirty-one (36%) had symptoms of trans-verse myelitis; and of 14 for whom MRI spine was available to review, 9 (64%) had longitudinally extensive lesions. Other neurologic findings (documented in 22 patients [25%]) included encephalopathy, diplopia, seizure, and dysarthria.

- **CEREBROSPINAL FLUID FINDINGS:**

  Among the patients with cerebrospinal fluid (CSF) available to review, 24 of 55 (44%) had pleocytosis of >5 white blood cells/μL, 21 of 50 (42%) had an elevated protein of >50 mg/dL, and 0 of 45 (0%) had elevated oligoclonal bands (≥4 unique IgG bands in CSF) (Table). A pleocytosis of ≥50 white blood cells was present in 14 of 55 (25%) and was not seen in patients with isolated monophasic or recurrent optic neuritis without other neurologic symptoms (Table).

- **RADIOLOGIC FINDINGS:**

  Among the 50 patients with optic nerve MRIs available for review, all patients had enhancement of the optic nerve, and 25 (50%) had perineural enhancement with extension of enhancement to the surrounding orbital tissues during at least 1 optic neuritis attack (Figure 2; Table). More than half of the prechiasmic optic nerve length was affected in 80% of patients: the orbital portion in 46 (92%), intracranial portion in 36 (72%), chiasm in 6 (12%), and optic tract in 1 (2%).

DISCUSSION

Five major findings in our review of visual outcomes and characteristics of the largest cohort of MOG-IgG-positive optic neuritis cases reported to date were as follows: (1) the inflammatory course is diverse; in most cases optic neuritis is recurrent, with or without additional neurologic features; (2) despite recurrence of attacks, most patients retain functional vision; (3) optic disc edema and bilateral disease are common; (4) MRI evidence of optic nerve sheath and periorbital tissue involvement is common in the acute attack; (5) MOG-IgG-positive neuroinflammation is a distinct entity from multiple sclerosis.

Optic neuritis associated with MOG-IgG seropositivity occurs with or without other neurologic symptoms and is recurrent in most cases.[6,7,13] In only 10 patients (12%) was optic neuritis monophasic and without other neurologic attacks. These cases would formerly have been classified as clinically isolated syndrome. The number of patients with recurrent disease in our cohort was similar compared to the cohort reported by Jarius and associates[14] but higher than the 50% monophasic disease found in the UK study by Jurynczyk and associates.[6] Our median follow-up time was longer than the UK study (35 months vs 26 months), which may partially explain the higher relapse rate in our cohort. In addition, the vast majority of our patients were also persistently positive for MOG-IgG, which likely contributes to the high relapse rate of optic neuritis in this cohort. Persistent MOG-IgG has been associated with higher relapse in other studies as well.[15,16] Although there is a bias toward recurrent disease in our cohort, MOG-IgG is clearly associated with recurrent attacks, with at least 50% having a relapse according to the literature.[6,14] Future studies on single monophasic patients with serial MOG-IgG testing will be necessary to determine the importance of titer and persistent MOG-IgG for predicting future relapse and the need for immunosuppression.

As reported in earlier but smaller case series,[13,17] CRION phenotype with steroid response and dependence was diagnosed in 16% of our MOG-IgG patients. In our unpublished observations, about 1 in 4 CRION patients are MOG-IgG-positive. As-yet-undiscovered autoanti-bodies may account for remaining seronegative cases.

Neurologic symptoms other than optic neuritis occurred at some point during the follow-up period in 43% of MOG-IgG-positive patients, leading many to be assigned a diagnosis of NMOSD-like phenotype or ADEM. The majority of MOG-IgG patients with optic neuritis developed recurrent optic neuritis without other neurologic symptoms. In the 17% of cases with subsequent extra–optic nerve manifestations, the majority of these occurred within 2 months of initial optic neuritis. Therefore, when other neurologic symptoms do not develop early after an initial optic neuritis attack, subsequent attacks will likely be restricted to the optic nerves.

Although MOG-IgG-positive optic neuritis attacks tended to be severe at nadir and recurrent, for the majority of patients the ultimate visual outcome was good. In only 6% of patients was the final visual acuity in either eye 20/200 or worse, and only 1 patient was legally blind in both eyes. Good visual outcome was also reported for 3 MOG-IgG-positive patients in the Optic Neuritis Treatment Trial, of whom 2 had a recurrent attack.[18] This is a significantly better visual outcome than previously reported for aquaporin-4-IgG-seropositive NMOSD-related optic neuritis, in which over a third of patients had a poor visual outcome.[19–21] For patients with recurrent optic neuritis, visual outcomes are even more disparate, with 59% of AQP4-IgG-positive patients developing poor vision.[11] Therefore, MOG-IgG-positive disease can cause a phenotype that mimics AQP4-IgG NMOSD, but outcomes are different and, therefore, would be better called an NMOSD-like phenotype in cases that fufill the current NMOSD disease criteria to distinguish this from AQP4-IgG-mediated disease. It is noteworthy that poor visual outcome among our 5 MOG-IgG-positive patients occurred within 10 months of presentation and was not the result of a remote attack. In previous reports of MOG-IgG-positive optic neuritis, vision loss was rated

significant in 13%–26% of patients.[4,6,7] Thus, although MOG-IgG-positive optic neuritis has the potential to cause severe long-term vision loss, our large cohort study suggests that the risk is lower than previously reported. Variability in use of acute treatments (steroids or plasma exchange) or maintenance chronic immunosuppression across studies could impact this comparison.

The majority of patients received IV methylprednisolone at the onset of the attack, while some received plasma exchange or IVIG. There was no difference in visual outcomes for the various treatment arms, but this likely reflects the physician's choice to use plasma exchange or IVIG in more severe cases of visual loss or cases that do not recover, which can bias these treatments toward worse visual outcomes. Future prospective randomized clinical trials will be required to determine if plasma exchange or IVIG in conjunction with IV methylprednisolone provides better outcomes. Prior studies indicate that plasma exchange likely provides better outcomes for AQP4-IgG-mediated cases of severe optic neuritis,[22,23] so we tend to use plasma exchange for MOG-IgG-related optic neuritis with poor recovery. Furthermore, this retrospective study cannot determine the impact of long-term prophylactic immunosuppression on ultimate visual outcomes or risk of relapse. However, because of its tendency to relapse, we would recommend chronic immunosuppression for patients who are MOG-IgG-positive and have had prior recurrent optic neuritis with incomplete recovery, especially if they demonstrate persistent MOG-IgG seropositivity.

Optic disc edema was present in 86% of patients, which confirmed that this is a common feature of MOG-IgG-positive optic neuritis.[5,24,25] Optic disc edema was moderate to severe in half of the cases, which is not usually seen in multiple sclerosis–related optic neuritis. Only 1 in 3 patients had optic disc edema in the Optic Neuritis Treatment Trial; and at the 15-year follow-up point, no patient presenting with severe optic disc edema had been assigned the diagnosis of multiple sclerosis.[26] In addition, bilateral simultaneous optic neuritis was seen in 37% of patients, which is similar to what has been reported in other studies.[5,6,14,27] Bilateral optic neuritis is also more common in AQP4-IgG-associated optic neuritis but less common in MS-associated optic neuritis.[21,24,28]

While all MRIs reviewed had enhancement of the optic nerve, 50% of patients also had perineural involvement with contrast enhancement of the optic nerve sheath and surrounding orbital tissue, a finding previously reported in 33%–47% of patients with MOG-IgG-positive optic neuritis in smaller case series.[4,25,29] Perineural optic nerve enhancement is unusual in optic neuritis associated with AQP4-IgG seropositivity or multiple sclerosis.[29] Its presence, therefore, is suggestive of MOG-IgG-positive optic neuritis or other inflammatory optic neuritis. In addition, the optic nerve enhancement tended to be long and involve the nerve's orbital portion, consistent with the high frequency of optic disc edema in cases of MOG-IgG-positive optic neuritis.

Another noteworthy point is that only a single patient with MOG-IgG-positive optic neuritis was assigned the diagnosis of multiple sclerosis and that the MOG-IgG titer in that patient only slightly exceeded the upper limit of normal. In addition, none of the patients had elevated oligoclonal bands in their CSF. In optimizing the anti-MOG assay, we found that patients with classic multiple sclerosis almost never had an elevated MOG-IgG titer.[11] Thus,

MOG-IgG seropositivity usually predicts a different disease course than multiple sclerosis. Others have similarly found that MOG-IgG-seropositive patients do not meet the clinical or radiographic criteria for multiple sclerosis.[24,29]

Limitations to this study include its retrospective nature, with variable investigations, descriptions, and follow-up. For example, MRI was only available to review in 50 of the 87 patients (57%). Secondly, because the majority of patients were seen in Rochester, Minnesota, which is a predominantly white population, this biased the ethnicity toward being predominantly white. Thirdly, because the cohort was drawn mostly from a single tertiary center, referral bias to more severe and recurrent disease is anticipated. This was reflected in the high percentage of patients that had persistent MOG-IgG positivity. In addition, our inclusion of a cohort of MOG-IgG-positive patients with recurrent optic neuritis biased the study toward more recurrent disease. However, even with exclusion of those patients, 70% had at least 1 recurrent attack of optic neuritis. Thus, MOG-IgG positivity associates with relapsing optic neuritis.

In conclusion, MOG-IgG seropositivity predicts a relapsing inflammatory disease process with recurrent optic neuritis as a common feature. MOG-IgG positivity should be suspected if disc edema is moderate to severe at onset or if MRI shows optic nerve sheath involvement. Despite optic neuritis attacks being severe and recurrent, the majority of patients retain good functional vision. It remains to be determined whether or not MOG-IgG serostatus in the remission phase of optic neuritis will predict future attacks.

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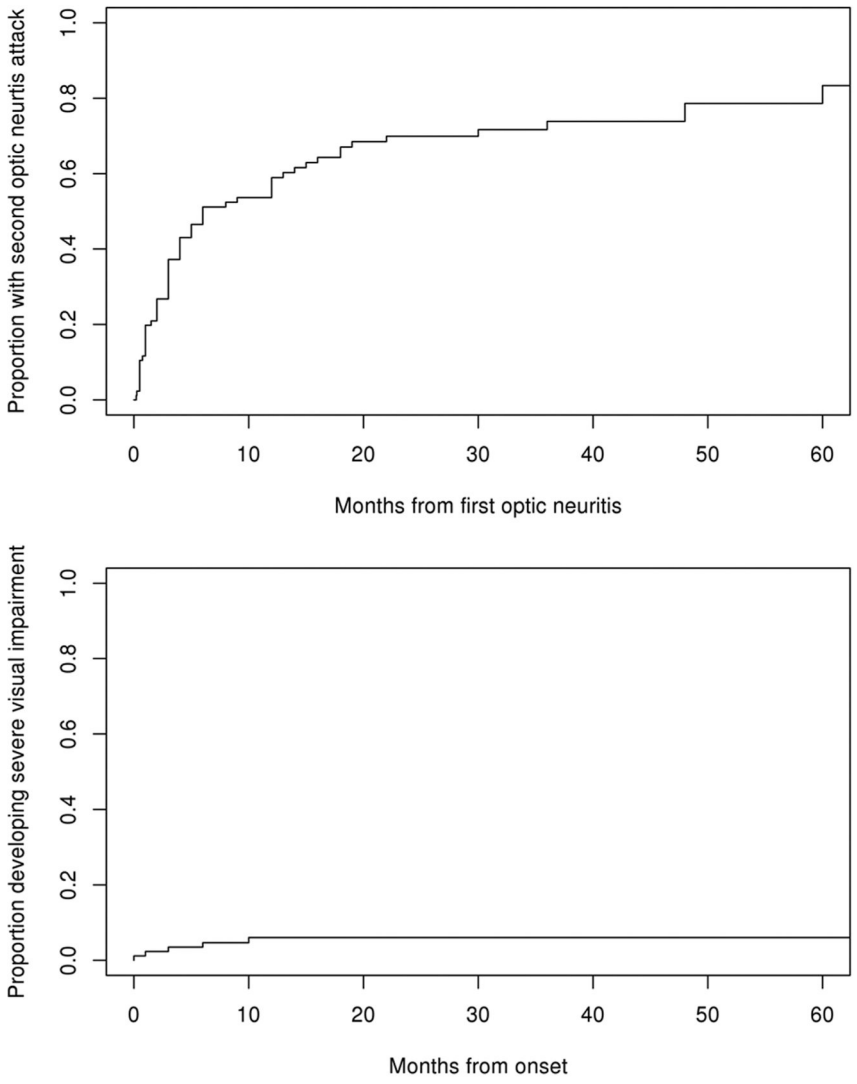

FIGURE 1.

Kaplan-Meier estimates of time to (Top) Second optic neuritis attack and (Bottom) permanent severe visual loss.

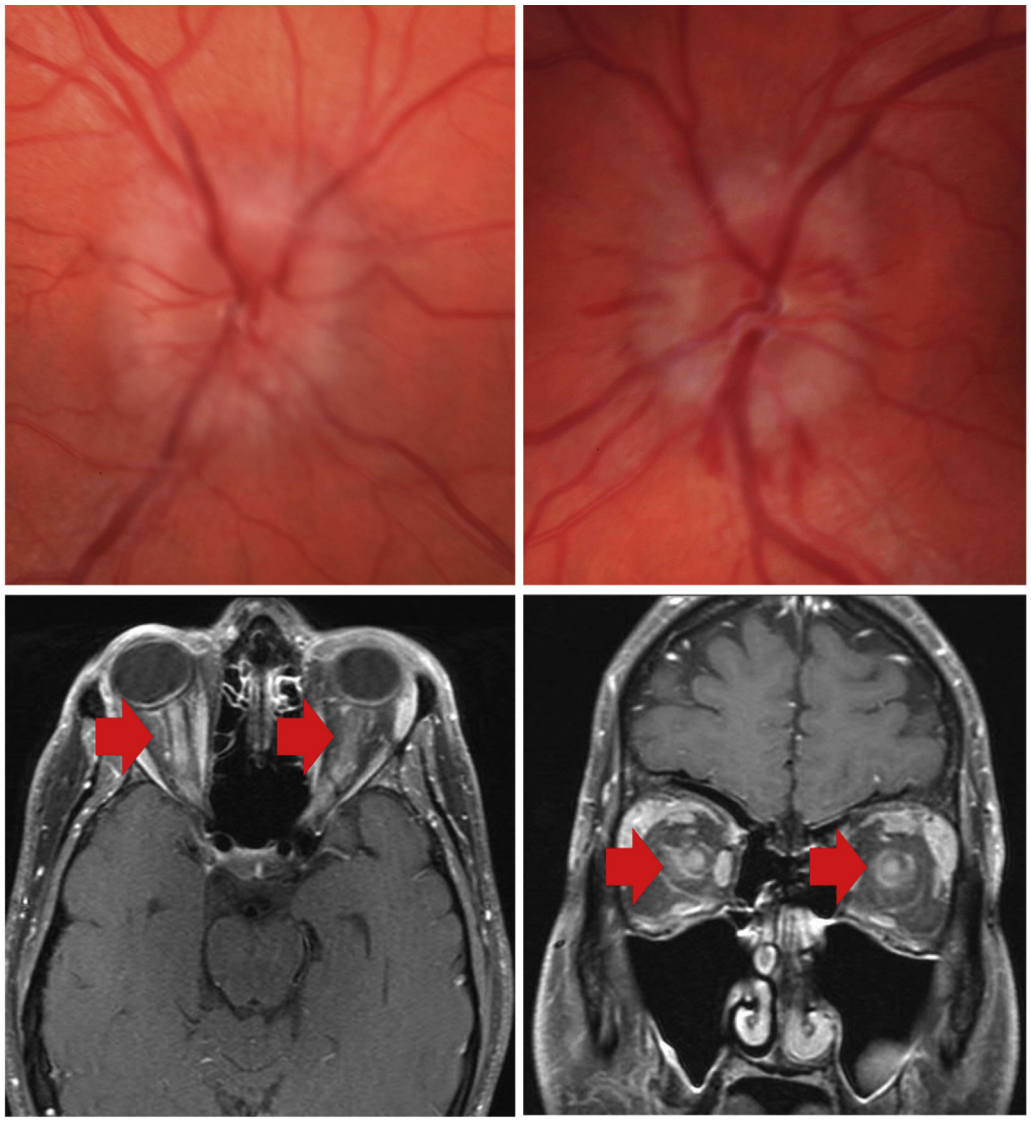

FIGURE 2.

Fundus photograph and magnetic resonance imaging (MRI) findings of a patient with myelin oligodendrocyte glycoprotein antibody–positive optic neuritis. (Top) Funduscopy: Moderate bilateral optic disc edema with some peripapillary hemorrhages in the left eye. (Bottom) MRI with contrast: Bilateral prominent enhancement of optic nerve and sheath (perineural enhancement), extending along almost the entire nerve (red arrows).

TABLE.

Demographic and Clinical Features in Myelin Oligodendrocyte Glycoprotein Antibody–Positive Patients (N = 87) With a History of Optic Neuritis

Characteristics	Results
Age at onset, y, median (range)	31 (2–79)
Sex, female, n (%)	50 (57%)
Ethnicity, white, n (%)	73 (84%)
Median (range) follow-up period after onset, y	2.9 (0.6–24)
Number of optic neuritis attacks, median (range)	3 (1–8)
Average visual acuity at nadir of the worst optic neuritis, Snellen (logMAR)	CF (1.6)
Average final visual acuity, Snellen (logMAR)	20/30 (0.2)
Optic disc edema at presentation	36/42 (86%)
Pain frequency	71/83 (86%)
Transverse myelitis, associated or subsequent	31/87 (36%)
Transverse myelitis at presentation	14/87 (16%)
Longitudinally extensive transverse myelitis	9/14 (64%)
Other neurologic symptoms	22/87 (25%)
Other neurologic symptom at presentation	14/87 (16%)
Cerebral spinal fluid findings	
Pleocytosis	24/55 (44%)
White blood cells, median (range)	4 (0–568)
Elevated protein	21/50 (42%)
Protein, median (range)	46 (19–181)
Elevated oligoclonal bands	0/45 (0%)
Optic nerve MRI findings	
Perineural enhancement	25/50 (50%)
Length involved more than half	40/50 (80%)
Orbital portion involved	46/50 (92%)
Intracranial portion involved	36/50 (72%)
Chiasm involved	6/50 (12%)
Optic tract involved	1/50 (2%)
Disease phenotype	
Recurrent optic neuritis	27 (31 %)
Monophasic optic neuritis	9 (10%)
CRION	14 (16%)
Optic neuritis “plus”	1 (1 %)
NMOSD-like phenotype	19 (22%)
ADEM	16 (18%)
Multiple sclerosis	1 (1 %)[a]
Maintenance immunosuppressant medication	53 (61 %)

ADEM = acute demyelinating encephalomyelitis; CF = count fingers; CRION = chronic relapsing inflammatory optic neuropathy; MRI = magnetic resonance imaging; NMOSD = neuromyelitis optica spectrum disorder.

Denominator was provided for variables that had missing data for some of the patients.

[a]Patient had myelin oligodendrocyte glycoprotein–IgG binding index 2.8 (normal range ≤2.5).