Population-Based Incidence of Optic Neuritis in the Era of Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein Antibodies

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• PURPOSE: To re-evaluate the population-based incidence of optic neuritis in the era of aquaporin-4-immunoglobulin G (AQP4-IgG) and myelin oligodendrocyte glycoprotein (MOG)-IgG, which are biomarkers of optic neuritis that is distinct from multiple sclerosis (MS). Over the past 15 years, 2 new biomarkers have been discovered that allow for further characterization of the cause of atypical optic neuritis: AQP4-IgG and MOG-IgG.

• DESIGN: Retrospective, population-based cohort. Setting: population-based. Participants: all residents of Olmsted County, Minnesota, with optic neuritis diagnosed between January 1, 2000, and December 31, 2018.

• METHODS: The Rochester Epidemiology Project database was used to identify patients. Sera were tested for AQP4-IgG and MOG-IgG by using a live-cell-based flow cytometry assay. Main outcome measurements were the incidence and cause of optic neuritis.

• RESULTS: Optic neuritis was diagnosed in 110 patients, providing an annual incidence of 3.9 per 100,000. The final diagnosis was MS in 57%, idiopathic in 29%, MOG-IgG-associated disorder in 5%, AQP4-IgG-seropositive neuromyelitis optic spectrum disorder (NMOSD) in 3%, infectious type in 2%, sarcoidosis in 2%, seronegative NMOSD in 1%, and medication-related in 1%. All 3 patients positive for AQP4-IgG had more than 1 optic neuritis attack, 2 with residual no light perception vision in at least 1 eye. Among MOG-IgG-positive patients, 4 of 6 patients had recurrent optic neuritis, and all 6 had a final visual acuity of 20/30 or better.

• CONCLUSIONS: At a population level, AQP4-IgG and MOG-IgG account for 9% of optic neuritis and are associated with recurrent attacks, but MOG-IgG optic neuritis has a better visual outcome than AQP4-IgG optic neuritis. (Am J Ophthalmol 2020;220:110–114. © 2020 Elsevier Inc. All rights reserved.)

OPTIC NEURITIS HAS BEEN CONVENTIONALLY associated with multiple sclerosis (MS). The Optic Neuritis Treatment Trial (ONTT) demonstrated that the 15-year overall risk of developing MS was 50% and increased with the presence of more than 1 demyelinating lesion on magnetic resonance imaging (MRI).[1] The population-based incidence of optic neuritis in Olmsted County, Minnesota, in 1991 was found to be 5.1 per 100,000.[2] Approximately half of those patients (52%) were found to have MS. Over the past 15 years, 2 new biomarkers have been discovered that allow for further characterization of the cause of atypical optic neuritis.[3,4] Antibodies targeting aquaporin-4 (AQP4), discovered in 2004, are pathogenic and highly specific for neuromyelitis optica spectrum disorder (NMOSD).[3] AQP4-immunoglobulin G (IgG)-positive NMOSD, in contrast to MS, is associated with more severe episodes of optic neuritis and poor visual recovery.[5] Antibodies targeting the conformational epitopes of myelin oligodendrocyte glycoprotein (MOG), as reported by O'Connor and associates in 2007, are now recognized as a biomarker of MOG-immunoglobulin G (IgG)-associated disorder (MOGAD).[4,6] MOGAD is associated with recurrent optic neuritis.[7] Given the discovery of these new biomarkers and their unique clinical presentations, the purpose of this study was to re-evaluate the incidence and causes of optic neuritis in the population-based cohort within Olmsted County, Minnesota, and to evaluate their visual outcomes.

METHODS

THE MEDICAL RECORDS OF ALL PATIENTS RESIDING IN Olmsted County, Minnesota, with diagnoses of optic neuropathies, excluding glaucoma, from January 1, 2000, through December 31, 2018, were retrospectively reviewed to identify incident cases of optic neuritis. Patients were identified using the Rochester Epidemiology Project, a linked system of medical records for all patient-physician encounters among Olmsted County, Minnesota,

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residents.[8,9] Optic neuritis was diagnosed based on a combination of at least 3 of the following clinical findings: decreased visual acuity, pain with eye movement, visual field defect, a relative afferent pupillary defect, changes in color vision, fundus examination findings, and/or MRI findings. Other forms of acute optic neuropathy, such as ischemic optic neuropathy, were excluded. Patients were included only if their first episode of optic neuritis occurred during the study period. At last follow-up, MS, NMOSD, and MOGAD were diagnosed based on the 2017 McDonald criteria, the 2015 international consensus criteria for NMOSD, and the 2018 proposed diagnostic criteria for MOGAD, respectively.[5,10,11] This cohort study was approved by the Institutional Review Boards of the Mayo Clinic and Olmsted Medical Center. This study conforms to the requirements of the U.S. Health Insurance Portability and Accountability Act and the Declaration of Helsinki.

Each patient's demographic information, clinical presentation, radiologic features, and clinical course were collected. Visual acuity was converted to logMAR visual acuity for analysis. The final visual acuity was obtained from a visit at least 6 months after the optic neuritis attack to allow time for recovery. AQP4-IgG and MOG-IgG were detected using transfected live HEK293 cells in a clinically validated live flow cytometry cell-based assay.[12,13] Sera were available for testing for AQP4-IgG and MOG-IgG in 72% of patients.

The overall incidence of optic neuritis was estimated using the total number of cases divided by the population in Olmsted County in that time period. Overall populations of Olmsted County were estimated using the census results and an interpolation of the populations in the years between the census years. The Olmsted population in 2010 was 86% white, and therefore, the incidence rates were adjusted for age and sex to the 2010 U.S. population of whites, as has been done for prior Rochester Epidemiology Project incidence studies.[14] Comparisons between groups for any categorical factors were completed using the Fisher exact test. Two-sided P values of $<.05$ were considered statistically significant. Analysis was completed using SAS version 9.4 software (Cary, North Carolina).

RESULTS

A TOTAL OF 110 PATIENTS HAD A DIAGNOSIS OF OPTIC neuritis during the study period. The overall age- and sex-adjusted incidence was 4.0 per 100,000 individuals (95% confidence interval [CI], 3.2-4.7). The median age at diagnosis of the initial optic neuritis was 37.5 years (interquartile range [IQR], 28, 47); 67% were female, and 92% were white. A total of 32% had more than 1 optic neuritis attack during a median follow-up of 6.5 years. The clinical diagnosis was MS in 63 patients (57%), idiopathic in 32 (29%), MOGAD in 6 (5%), AQP4-IgG-seropositive NMOSD in 3 (3%), seronegative NMOSD in 1 (1%), infectious in 2 (2%; Lyme and group B *Streptococcus*), sarcoidosis in 2 (2%), and medication-related in 1 (1%; etanercept [Enbrel]) (Table).

MS was diagnosed in 63 patients. The overall age- and sex-adjusted incidence was 2.3 per 100,000 individuals (95% CI, 1.7-2.8) for MS-optic neuritis. The median age at diagnosis of the initial MS optic neuritis was 37 years (IQR, 28, 45). Seventy-three percent were female, and 92% were white. Thirty-six percent had more than 1 optic neuritis attack during a median follow-up of 6.6 years (IQR, 2.6, 12.8). Eighteen patients (29%) had bilateral involvement (1 bilateral simultaneously, 17 bilateral sequentially). Optic disc edema was absent in 64%, mild in 25%, moderate in 9%, and severe in 2%. Peripapillary hemorrhage was present in 2%. Eye pain was present in 75%. On initial diagnosis, the median visual acuity at nadir was 20/60, with a final median visual acuity improving to 20/20. Two of 63 patients (3.2%) had visual acuity of 20/200 or worse at final follow-up.

Six patients were MOG-IgG positive, providing an overall age- and sex-adjusted incidence of 0.2 per 100,000 individuals (95% CI, 0-0.4). The median age at diagnosis of the initial MOG-IgG optic neuritis was 26 years (IQR, 6, 33). A total of 83% were male, and 67% were white. Sixty-seven percent had more than 1 optic neuritis attack during a median follow-up of 5.5 years (IQR, 1.6, 8.4). All six patients (100%) had bilateral involvement (5 bilateral simultaneously, 1 bilateral sequentially). Optic disc edema was moderate or severe in 67%, and peripapillary hemorrhage was present in 20%. Optic disc edema was absent in 1 patient (16%). Eye pain was present in all patients. On initial diagnosis, the median visual acuity at nadir was 20/200, with the final median visual acuity improving to 20/25 (range, 20/20-20/30). Two patients had an acute demyelinating encephalomyelitis (ADEM)-like presentation. One patient, who had had transverse myelitis for 5 years after the initial optic neuritis, was the only MOG-IgG-positive patient who met the 2015 diagnostic criteria for seronegative NMOSD. No MOG-IgG-positive patients met 2017 McDonald criteria for MS or were positive for AQP4-IgG.

Three patients were found to be positive for AQP4-IgG, providing an overall age- and sex-adjusted incidence of 0.12 per 100,000 individuals (95% CI, 0-0.3). The median age at diagnosis of the initial AQP4-IgG optic neuritis was 54 years old (IQR, 36, 64). All 3 patients were female and white. All patients had more than 1 attack of optic neuritis during a mean follow-up of 6.5 years (IQR, 1.7, 11.0). Two patients (67%) had bilateral involvement (1 bilateral simultaneously, 1 bilateral sequentially). Optic disc edema and peripapillary hemorrhage were absent in all patients. Eye pain was present in all patients. Visual acuity at nadir was light perception or worse in 2 of the 3 patients, both initially and at final follow-up. The third patient presented with a visual acuity of 20/500 but recovered to 20/20. All 3 patients positive for AQP4-IgG had longitudinally extensive transverse myelitis !!(LETM) at some point in their disease course. One patient had had LETM 7 years prior to the optic neuritis, and 2 patients had LETM 6 months after the optic

TABLE. Demographics and Clinical Characteristics of Optic Neuritis Based on Cause

	MS (n = 63)	Idiopathic (n = 32)	MOG-IgG (n = 6)	AQP4-IgG (n = 3)	Infectious (n = 2)	Sarcoidosis (n = 2)	Seronegative NMOSD (n = 1)	Medication (n = 1)
Incidence per 100,000 (95% CI)	2.3 (1.7-2.8)	1.2 (0.8-1.6)	0.2 (0-0.36)	0.12 (0-0.26)	0.07 (0-0.18)	0.07 (0-0.18)	0.03 (0-0.10)	0.05 (0-0.15)
Median IQR age, y	37 (28-45)	38 (26-49)	26 (6-33)	54 (36-64)	47 (38-55)	43 (41.44)	33	60
Sex	Female 73%	Female 66%	Male 83%	Female 100%	Male 100%	Female 100%	Female 100%	Male 100%
Ethnicity	White 92% Black 3% Unknown 3% Other 2%	White 94% Black 3% Other 3%	White 66% Black 17% Other 17%	White 100%	White 100%	White 100%	White 100%	White 100%
Optic disc edema	Absent 64% Mild 25%	Absent 42% Mild 32%	Absent 17% Mod/Sev 67%	Absent 100%	Absent 50% Severe 50%	Mild: 100%	Mild 100%	Absent 100%
Peripapillary hemorrhage	2%	10%	20%	0%	0%	50%	0%	0%
Acute Treatment	IVMP 65% None 29% IVMP+PLEX 6%	None 53% IVMP 47%	IVMP 100%	IVMP+PLEX 67% IVMP 33%	IVMP 50% None 50%	IVMP 100%	IVMP+PLEX 100%	IVMP 100%
Median IQR follow-up, y	6.6 (2.6-11.8)	6.5 (2.8-11.3)	5.5 (1.6-8.4)	6.5 (1.7-11.0)	5.2 (0.5-9.8)	10.1 (9.7-10.6)	10.8	2.5
Number of attacks	1: 65% 2: 29% 3: 5% 4: 2%	1: 84% 2: 16%	1: 33% 2: 67% 3: 0%	1: 0% 2: 67% 3: 33%	1: 100%	1: 100%	2: 100%	1: 100%
Annualized relapse rate	0.19	0.17	0.32	0.36	0.19	0.10	0.18	0.40
Median worst VA	20/60	20/40	20/200	67% ≤ LP	20/800	20/25	NLP	CF
Median final VA	20/20	20/20	20/25	67% ≤ LP	20/40	20/20	LP	20/125

AQP4 = aquaporin-4; CF = counting fingers; CI = confidence interval; IgG = immunoglobulin G; IQR = interquartile range; IVMP = IV methylprednisolone; LP = light perception; Mod/Sev = moderate/severe; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NA = not applicable (too few cases); NLP = no light perception; NMOSD = neuromyelitis optica spectrum disorder; PLEX = plasma exchange; VA = visual acuity.

neuritis. No AQP4-IgG-positive patients met 2017 McDonald criteria for MS or were positive for MOG-IgG.

MRI of the orbits using fat suppression was available at disease onset in 38 MS patients and 5 MOG-IgG patients. In the MS patients, enhancement of the optic nerve sheath was present in 3 of 38 (7.9%) with 1 of 38 (2.6%) having enhancement that extended beyond the sheath involving the peribulbar fat (perineural enhancement). The extent of enhancement was longer than half the length of the entire optic nerve in 4 of 38 patients (10.5%). In comparison, among the MOG-IgG patients, 5 of 5 (100%) had optic nerve sheath enhancement ($P < .001$) with 3 of 5 (60%) with perineural enhancement ($P = .003$). All 5 patients (100%) had enhancement that was longer than half the length of the entire optic nerve ($P < .001$).

DISCUSSION

THERE WERE 110 INCIDENT CASES OF OPTIC NEURITIS IN Olmsted County, Minnesota, during the 19-year study period, yielding an age- and sex-adjusted incidence of 4.0 per 100,000 individuals. The population-based incidence study in Olmsted Country that went through 1991 found that 51% of optic neuritis cases were due to MS, which was similar to the 57% found in this study that covered 2000-2018.[2] A higher percentage of MS was expected in the current study because it was easier to fulfill the criteria of MS under the recent 2017 McDonald criteria.[10] The similar percentages between the 2 studies likely reflects the opposing effects of the less stringent MS criteria and the addition of AQP4-IgG and MOG-IgG, which accounted for 9% of optic neuritis cases, several of which may have been incorrectly diagnosed as "atypical" MS in the prior study.

Currently, there are few other epidemiologic studies that incorporate both AQP4-IgG and MOG-IgG serological status. A population-based study in Denmark showed that 2 of 51 patients (4%) with a diagnosis of optic neuritis were positive for MOG-IgG, and no patients were positive for AQP4-IgG.[15] However, that study excluded patients with a history of NMOSD, which likely accounted for the lower incidence of AQP4-IgG. Additionally, another larger study from the Netherlands showed that 7% of patients with demyelinating disease were positive for MOG-IgG, with ADEM being the most common phenotype in children and optic neuritis being the most common presenting symptom in adults.[16] Within the present study, 1 of 2 pediatric patients with MOGAD presented with simultaneous ADEM and optic neuritis whereas 1 of 3 adult patients presented with ADEM and optic neuritis.

Compared to MS optic neuritis, MOG-IgG optic neuritis tended to affect younger patients without a predilection for sex; had more optic disc edema, peripapillary hemorrhage, perineural and longer enhancement on MRI; and was more likely to be recurrent. On the other hand, AQP4-IgG optic neuritis affected older patients, with a female predominance, and had more devastating visual outcomes. These findings in this population-based cohort supported the current understanding of MOG-IgG optic neuritis and AQP4-IgG optic neuritis from nonpopulation-based studies.[5,7,17–23] Notably, no patients with MS were positive for AQP4-IgG or MOG-IgG, which is similar to most of the studies showing that these are 3 distinct demyelinating clinical entities.[5,7,17,22,24] Only 1 MOG-IgG-positive patient met 2015 diagnostic criteria for seronegative NMOSD and had the transverse myelitis attack 5 years after the presenting optic neuritis attack. Two of 3 AQP4-IgG NMOSD patients presented with optic neuritis prior to the transverse myelitis attack. Therefore, serologic testing at the time of any atypical optic neuritis is warranted because it can confirm a diagnosis of MOGAD or NMOSD before subsequent attacks occur.

Limitations of this study include its retrospective nature, which may have limited follow-up data for some patients. With longer follow-up, it is possible some of the idiopathic patients could have converted to MS. Moreover, Olmsted County has a predominantly white population, which may limit the ability to generalize this study's findings to other populations with different ethnic proportions. Finally, serum for biomarker testing was not available in 31 patients (28%) patients, meaning that some patients with AQP4-IgG or MOG-IgG might have been missed. However, of these 31 patients, only 13 were idiopathic, whereas 15 had a diagnosis of MS, 2 had an infectious cause, and 1 had a diagnosis of sarcoidosis. In addition, none of the remaining 13 had a phenotype that was suspicions for MOGAD or AQP4-IgG NMOSD.

This population-based study confirms that AQP4-IgG and MOG-IgG confer unique presentations of optic neuritis. These 2 entities make up 9% of optic neuritis, with MOG-IgG twice as common as AQP4-IgG. Although both biomarkers are associated with recurrent optic neuritis attacks, MOG-IgG optic neuritis has better visual outcomes.

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