AMERICAN ACADEMY OF OPHTHALMOLOGY®

Aquaporin-4 and Myelin Oligodendrocyte Glycoprotein Autoantibody Status Predict Outcome of Recurrent Optic Neuritis

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Purpose: To determine the aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG) immunoglobulin G (IgG) serostatus and visual outcomes in patients with recurrent optic neuritis (rON) initially seeking treatment.

Design: Cross-sectional cohort study.

Participants: The study identified patients by searching the Mayo Clinic computerized central diagnostic index (January 2000–March 2017). The 246 eligible patients fulfilled the following criteria: (1) initially seeking treatment for at least 2 consecutive episodes of optic neuritis (ON) and (2) serum available for testing.

Methods: Serum was tested for aquaporin-4 IgG and MOG IgG1 using an in-house validated flow cytometric assay using live HEK293 cells transfected with M1 aquaporin-4 or full-length MOG.

Main Outcomes Measures: Aquaporin-4 IgG and MOG IgG1 serostatus, clinical characteristics, and visual outcomes.

Results: Among 246 patients with rON at presentation, glial autoantibodies were detected in 32% (aquaporin-4 IgG, 19%; MOG IgG1, 13%); 186 patients had rON only and 60 patients had rON with subsequent additional inflammatory demyelinating attacks (rON-plus group). The rON-only cohort comprised the following: double seronegative (idiopathic), 110 patients (59%); MOG IgG1 positive, 27 patients (15%; 4 with chronic relapsing inflammatory optic neuropathy); multiple sclerosis (MS), 25 patients (13%); and aquaporin-4 IgG positive, 24 patients (13%). The rON-plus cohort comprised the following: aquaporin-4 IgG positive, 23 patients (38%); MS, 22 patients (37%); double seronegative, 11 patients (18%); and MOG IgG1 positive, 4 patients (7%). The annualized relapse rate for the rON-only group was 1.2 for MOG IgG1–positive patients, 0.7 for double-seronegative patients, 0.6 for aquaporin-4 IgG–positive patients, and 0.4 for MS patients ($P = 0.005$). The median visual acuity (VA) of patients with the worst rON-only attack at nadir were hand movements in aquaporin-4 IgG–positive patients, between counting fingers and hand movements in MOG IgG1–positive patients, 20/800 in idiopathic patients, and 20/100 in MS patients ($P = 0.02$). The median VA at last follow-up for affected eyes of the rON-only cohort were counting fingers for aquaporin-4 IgG–positive patients, 20/40 for idiopathic patients, 20/25 for MS patients and MOG IgG1–positive patients ($P = 0.006$). At 5 years after ON onset, 59% of aquaporin-4 IgG–positive patients, 22% of idiopathic patients, 12% of MOG IgG1–positive patients, and 8% of MS patients were estimated to have severe visual loss.

Conclusions: Glial autoantibodies (MOG IgG1 or aquaporin-4 IgG) are found in one third of all patients with rON. Aquaporin-4 IgG seropositivity predicts a worse visual outcome than MOG IgG1 seropositivity, double seronegativity, or MS diagnosis. Myelin oligodendrocyte glycoprotein IgG1 is associated with a greater relapse rate but better visual outcomes. *Ophthalmology 2018;■:1–10 © 2018 by the American Academy of Ophthalmology*

Recurrent optic neuritis (rON) is an inflammatory demyelinating central nervous system syndrome, and multiple sclerosis (MS) is a well-recognized cause. Autoantibodies to astrocytic aquaporin-4 and myelin oligodendrocyte glycoprotein (MOG) are recently established serum biomarkers of autoimmune monophasic and polyphasic optic neuritis (ON). Importantly, neither autoantibody is found in MS patients by contemporary transfected cell-based assays. The outcomes of rON patients stratified by cause remain poorly defined.[1]

Previous studies show that aquaporin-4 immunoglobulin G (IgG) detection in the context of a neuromyelitis optica spectrum disorder is associated with poor visual outcomes.[2,3] Aquaporin-4 IgG has been reported in 8.3% to 25% of patients with rON,[3–5] but the prevalence of and outcomes for MOG IgG–positive rON patients have not yet

https://doi.org/10.1016/j.ophtha.2018.03.041
ISSN 0161-6420/18

been reported. Although MOG autoimmunity tends to relapse more frequently than aquaporin-4 autoimmunity, the visual outcomes are uncertain because of the small numbers of patients in prior studies.[6–10]

Because autoimmune serologic analysis has the potential to predict both visual outcome and relapse propensity for ON and other demyelinating attacks, it may provide guidance for acute and chronic (preventive) immunotherapies.[11] In this study, we evaluated the visual outcomes of rON based on aquaporin-4 IgG and MOG IgG serostatus and compared the outcomes for double-negative (i.e., idiopathic) patients and MS patients (all seronegative). The overall goals of the study were (1) to inform clinicians (both ophthalmologists and neurologists) of the usefulness of testing for aquaporin-4 IgG and MOG IgG and (2) to provide a roadmap for diagnosis, management, and prognostication in patients with 2 consecutive episodes of ON.

Methods

Patients and Samples

The Mayo Clinic Institutional Review Board approved this study. All research adhered to the tenets of the Declaration of Helsinki. All information presented in this study complies with the Health Insurance Portability and Accountability Act. All participants provided informed consent. Recruited patients (1) initially sought treatment for at least 2 consecutive ON episodes (first 2 attacks were ON), with or without a subsequent other demyelinating attack; (2) had excluded infectious, granulomatous (e.g., sarcoidosis), and neoplastic causes according to serologic, microbiologic, and radiologic tests as deemed clinically appropriate; and (3) had known serostatus for aquaporin-4 IgG and MOG IgG1, tested by transfected cell-based assay, fixed (cell-based assay) or live (fluorescence-activated cell sorting), or had serum available to test. Patients with 2 consecutive ON attacks (presumed demyelination) documented between January 2000 and March 2017 (n = 326) were identified by searching the Mayo Clinic Electronic Health Record. Eighty were excluded because serum was lacking or testing was not performed for both aquaporin-4 IgG and MOG IgG1. Thus, 246 patients were included (Fig 1).

In clinical practice, the third and subsequent inflammatory central nervous system event may be restricted to the optic nerve (rON-only group), and for others, the attacks may involve the brain or spinal cord (rON-plus group). We considered these groups clinically different and classified them separately. In practice, those patients with rON only are more likely to seek treatment from ophthalmologists, whereas those with rON-plus disease commonly seek treatment from neurologists.

Recorded clinical information included visual acuity (VA), both final and at nadir of the worst ON attack, number of attacks, magnetic resonance imaging (MRI) results, occurrence of eye pain, and treatment methods and responses. Visual acuity was evaluated for each eye by Snellen VA charts and, for statistical analysis, was converted to logarithm of the minimum angle of resolution (logMAR) values. The following logMAR values were used for nonnumeric acuities: no light perception, 3.0 logMAR; light perception, 2.3 logMAR; hand movements, 2.0 logMAR; and counting fingers (CF), 1.7 logMAR.[12] Severe permanent visual loss was defined as 20/200 (0.1 logMAR) or worse in either eye at the most recent follow-up. Final VAs were excluded if final follow-up was within 3 months of the last attack (10 patients). The annualized relapse rate was calculated as the ratio of total number of attacks divided by years since first attack.

We defined chronic relapsing inflammatory optic neuropathy (CRION) as rON, steroid responsive, and steroid dependent, with other causes excluded (e.g., sarcoidosis).[13] Multiple sclerosis–like brain MRI lesions were defined as perpendicular, ovoid shaped or resembling Dawson fingers, periventricular, juxtacortical or cortical, or infratentorial (cerebellar or in the brainstem).[14,15] Spinal MRI abnormalities showing a hyperintense signal in T2-weighted images spanning at least 3 vertebral segments were designated longitudinally extensive transverse myelitis, and lesions spanning fewer than 3 segments were designated short transverse myelitis.

Autoimmune Serologic Testing

All sera were tested for aquaporin-4 IgG by clinically validated transfected cell-based assay, either fixed (Euroimmun kit; Euroimmun, Lübeck, Germany) or live (in-house fluorescence-activated cell sorting assay).[16] A similar, clinically validated fluorescence-activated cell sorting assay was used for quantitative detection of MOG IgG1. Heat-inactivated patient serum (56° C, 35 minutes) was added to live HEK293 substrate cells transiently transfected with full-length recombinant human aquaporin-4 (M1 isoform) or MOG (cloned into pIRES2-AcGFP vector, which coexpresses nonlinked green fluorescent protein). The median fluorescence intensity of bound AlexaFluor 647–conjugated antihuman IgG (for MOG, IgG1 Fc region-specific; Southern Biotech catalog no. 9054-01; Birmingham, AL) was determined for both nontransfected and transfected cells. The ratio of median fluorescence intensity values for green fluorescent protein–positive and green fluorescent protein–negative cells defines the IgG binding index; a value of 2.5 or more was considered positive. Control sera were from 42 glaucoma patients, 50 MS patients, and 50 healthy participants. All aquaporin-4 IgG and MOG IgG1 testing was performed blinded to clinical data. Persistent MOG IgG seropositivity was defined as both the initial and follow-up sample showing positive results or, if no sample at onset was available, samples obtained more than 1 year after onset of ON showing positive results.

Statistical Analysis

SAS software version 9.4 and JMP software version 10 (SAS Institute, Inc., Cary, NC) were used.[17] Continuous data for 4 patient groups classified by serostatus were analyzed by Kruskal-Wallis tests. Chi-square or Fisher exact tests were applied to compare categorical variables. The time from onset of initial attack to permanent severe visual loss was compared across patient groups using likelihood ratio tests from Cox proportional hazard regression models, and 5-year and 10-year estimates were calculated using the Kaplan-Meier method. The times from second ON attack to next ON attack or to next non-ON demyelinating attack were analyzed using the same methods. P values less than 0.05 were deemed statistically significant.

Results

The 246 eligible patients were divided into 2 clinical phenotypes: 186 with isolated rON (rON-only group; Table 1) and 60 with a subsequent central nervous system demyelinating attack beyond the optic nerve (rON-plus group; Table 2; Fig 1). The median age at first ON attack was 32 years (range, 12–72 years) for aquaporin-4 IgG–positive patients, 32 years (range, 7–66 years) for MOG IgG1–positive patients, 31 years (range, 11–50 years) for MS patients, and 31 years (range, 5–67 years) for double-seronegative patients. Among rON-only patients, the phenotype for 14 patients was steroid responsive and dependent