Differences in Clinical Features of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Optic Neuritis in White and Asian Race

TANYATUTH PADUNGKIATSAGUL, JOHN J. CHEN, PANITHA JINDAHRA, TETSUYA AKAISHI, TOSHIYUKI TAKAHASHI, ICHIRO NAKASHIMA, TAKAYUKI TAKESHITA, AND HEATHER E. MOSS

• PURPOSE: To determine whether clinical features and visual outcomes of myelin oligodendrocyte glycoprotein antibody−associated optic neuritis (MOG-ON) differ between White and Asian subjects.
• DESIGN: Multicenter retrospective cohort.
• METHODS: This was a multicenter study of 153 subjects who were White or Asian with a history of adult-onset (age 18 years or older) optic neuritis (ON) and positive MOG-IgG serology by cell-based assay. Subjects were enrolled from 2 unpublished cohorts (January 2017-November 2019) and 9 published cohorts with case-level data available (2012-2018). Subjects with alternative etiologies of demyelinating disease and positive or lack of aquaporin-4−IgG serology result were excluded. The main outcome measurements were clinical features and final visual outcomes.
• RESULTS: Of the 153 subjects who were White (n = 80) or Asian (n = 73) included in the study, 93 (61%) were women, mean age of onset was 40.8 ± 14.9 years, and median follow-up was 35.2 months (range: 1-432 months); all of these characteristics were similar between White and Asian subjects. White subjects were more likely to have recurrent ON (57 [71%] vs 20 [27%]; $P = .001$) and extra-optic nerve manifestations (35 [44%] vs 8 [11%]; $P = .001$). Optic disc swelling, neuroimaging findings, presenting visual acuity (VA), treatment, and final VA did not differ according to subjects' race. Despite the high prevalence of severe visual loss (< 20/200) during nadir, most subjects had good recovery of VA (> 20/40) at final examination (51/77 [66%] White subjects vs 52/70 [74%] Asian subjects).
• CONCLUSION: White subjects with MOG-ON were more likely to have recurrent disease and extra-optic nerve manifestations. Visual outcomes were similar between White and Asian subjects. (Am J Ophthalmol 2020;219:332–340. © 2020 Elsevier Inc. All rights reserved.)

OPTIC NEURITIS (ON) IS COMMONLY ASSOCIATED with central nervous system inflammatory demyelinating diseases. The discovery of novel serologic markers has allowed us to stratify some of the underlying disorders, which accounts for some of the observed heterogeneity in clinical characteristics and visual outcomes, ranging from favorable in multiple sclerosis−associated ON[1] to poor in neuromyelitis optica spectrum disorders (NMOSDs).[2] Recently, myelin oligodendrocyte glycoprotein antibody (MOG-IgG), an autoantibody that targets the outer surface of oligodendrocytic myelin sheaths,[3] has been identified as a marker for a subset of ON cases.[4] Elevations in serum MOG-IgG have been found in association with a range of clinical presentations, including aquaporin-4-autoantibody (AQP4-IgG)−seronegative NMOSD phenotype, acute demyelinated encephalomyelitis (ADEM), particularly in children, and ON, which has been established as a separate disorder, MOG-IgG−associated disorder (MOGAD).[5–8] Because MOG-IgG testing has become more widely available, common characteristics, including bilateral optic nerve involvement,[5–7,9] optic disc swelling at onset,[7,10,11] and a relapsing course of disease have been identified.[4,5,7,9]

Race is known to be an epidemiologic factor associated with differing clinical features and prognosis in demyelinating disease, in general, and with visual prognosis in demyelinating ON.[12–15] This study's objective was to characterize differences in clinical features and visual outcomes of myelin oligodendrocyte glycoprotein antibody-associated optic neuritis (MOG-ON) between White and Asian subjects.

Accepted for publication Jul 6, 2020.

From the Department of Ophthalmology (T.P.) and Department of Neurology (P.J.), Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; Department of Ophthalmology (T.P., H.E.M.) and Department of Neurology and Neurological Sciences (H.E.M.), Stanford University, Palo Alto, California, USA; Department of Ophthalmology and Department of Neurology, Mayo Clinic, Rochester, Minnesota, USA (J.J.C.); Department of Neurology (T.A., T.T.) and Department of Ophthalmology (T. Takeshita), Tohoku University Graduate School of Medicine, Sendai, Japan; Department of Neurology, National Hospital Organization Yonezawa National Hospital, Yonezawa, Japan (T.T.); and Department of Neurology, Tohoku Medical and Pharmaceutical University, Sendai, Japan (I.N.).

Supplementary material available at AJO.com

Inquiries to: Heather E. Moss, 2370 Watson court, Suite 200, Palo Alto, California, 94303; e-mail: hemoss@stanford.edu

© 2020 ELSEVIER INC. ALL RIGHTS RESERVED.
0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.07.008

METHODS

• **STUDY DESIGN:** This was a multicenter retrospective cohort of adult-onset MOG-ON. Case inclusion criteria were: 1) adult subjects (age 18 years or older) with a history of ≥1 episodes of adult-onset acute ON; 2) positive MOG-IgG serology by cell-based assay (CBA), interpreted according to the reference standard of the reporting institution; and 3) available race/ethnicity data. Exclusion criteria were: 1) subjects with alternative etiologies of demyelinating disease; and 2) positive or lack of AQP-4−IgG serology result. Following review of available case-level data, inclusion criteria were narrowed to White or Asian race due to limited numbers of case-level data for other races. Subjects were identified via 3 avenues: unpublished cases from the investigators' institutions; published cohorts with case-level data provided by the investigators; and from published cohorts with publicly available case-level data. Details of how each of these was identified are provided in the following.

• **UNPUBLISHED COHORTS:** *Stanford University (USA).* The Stanford Research Repository, Stanford Medicine's resource for working with clinical data for research purposes, was used to identify adult patients (age 18 years or older) seen at Stanford Healthcare with a diagnosis of ONs (International Classification of Diseases [ICD]-9th Revision code 377.30; ICD-10 code H46) and testing for MOG-IgG (search terms of MOG-IgG1 and MOG fluorescence-activated cell sorting). These potential subjects were included in the study if chart review confirmed the clinical diagnosis of ON and positive serum MOG-IgG testing. Subjects with alternative etiologies of demyelinating disease (eg, multiple sclerosis) were excluded. Because MOG-IgG by CBA became commercially available to this center in 2017, all enrolled subjects were seen between January 1, 2017 and November 30, 2019. The study was approved with a waiver of informed consent by the Stanford University Institutional Review Board.

Ramathibodi Hospital (Thailand). The Ramathibodi Hospital neuro-ophthalmology clinic ON registry was used to identify adult patients seen in the clinic with a diagnosis of ON (ICD-10 code H46) and a MOG-IgG test result. Patients were included as subjects if chart review confirmed clinical diagnosis of ON, positive serum MOG-IgG testing, and if the phenotype was consistent with MOGAD. Commercial MOG-IgG by CBA became available in early 2018, and all enrolled subjects were seen between January 1, 2018 and November 30, 2019. The ON registry was approved by Faculty of Medicine Ramathibodi Hospital Institutional Review Board, and participants provided informed consent.

• **PUBLISHED COHORTS:** To identify published cohorts, we used a systematic review approach to identify articles published between January 1, 2011 and September 1, 2019 (Figure 1). Queries of Medline and PubMed using the terms "MOG or myelin oligodendrocyte glycoprotein" and "antibody" or "IgG" and "optic neuritis" identified 330 publications. Based on abstract review, this was narrowed to 59 English language publications that included clinical characteristics of ON associated with MOG-IgG seropositivity in adult human subjects. The other 271 abstracts were excluded due to nonoriginal study, no clinical data, pediatric age group, or publication language other than English. Through full-text review of the 59 publications corresponding to the identified abstracts, 18 publications met our publication selection criteria, which included report of: 1) clinical characteristics and visual acuity (VA) outcomes of adult-onset MOG-ON; 2) MOG-IgG serology tested by CBA; and 3) homogeneous Asian or White study population or mixed-race study population with clinical data reported by race. Of these 18 selected publications, 7 publications had publicly available case-level data, and these subjects were included in our study.

For the remaining 11 publications, the corresponding authors were contacted by e-mail. Two authors of 3 publications shared de-identified case-level data for the purposes of this study. We were unable to acquire case-level data from the remaining 8 publications due to restriction of international data sharing,[16] or no response to inquiry e-mail. Thus, 9 cohorts from 10 publications (2 publications shared the same subjects) were included in our study.[6–8,10,17–22] Study population, inclusion and/or exclusion criteria, and geographic distribution of each cohort are summarized in the Supplementary Table.

• **VARIABLE DEFINITION:** Clinical characteristics and visual outcomes for each subject were abstracted from the medical records of the unpublished cohorts and from de-identified research records for the published cohorts. The primary outcomes of interest were final VA and clinical phenotype.

Demographic variables included age at the time of first ON event, sex, and race. Race information was based on self-reported race as abstracted from the medical record in unpublished cohorts and published cohorts with data provided by co-authors. The remaining published cohorts did not indicate means used to identify the race of subjects in the publication (Supplementary Table). Historical variables included presence of previous non-ON neurological attacks. Features concurrent with ON events, including presence of pain, presence of optic disc swelling, and VA at nadir of the worst ON attack, magnetic resonance imaging (MRI) findings, and other associated neurological symptoms were recorded. To create a cohesive dataset, VA was converted to logarithm of minimum angle of resolution (logMAR) values. The following logMAR values were used for non-numeric visual acuities: no light perception = 3.0; light perception = 2.3; hand motion = 2.0; and count fingers = 1.7.[23] MRI was categorized according to involvement of each of 4 optic nerve segments

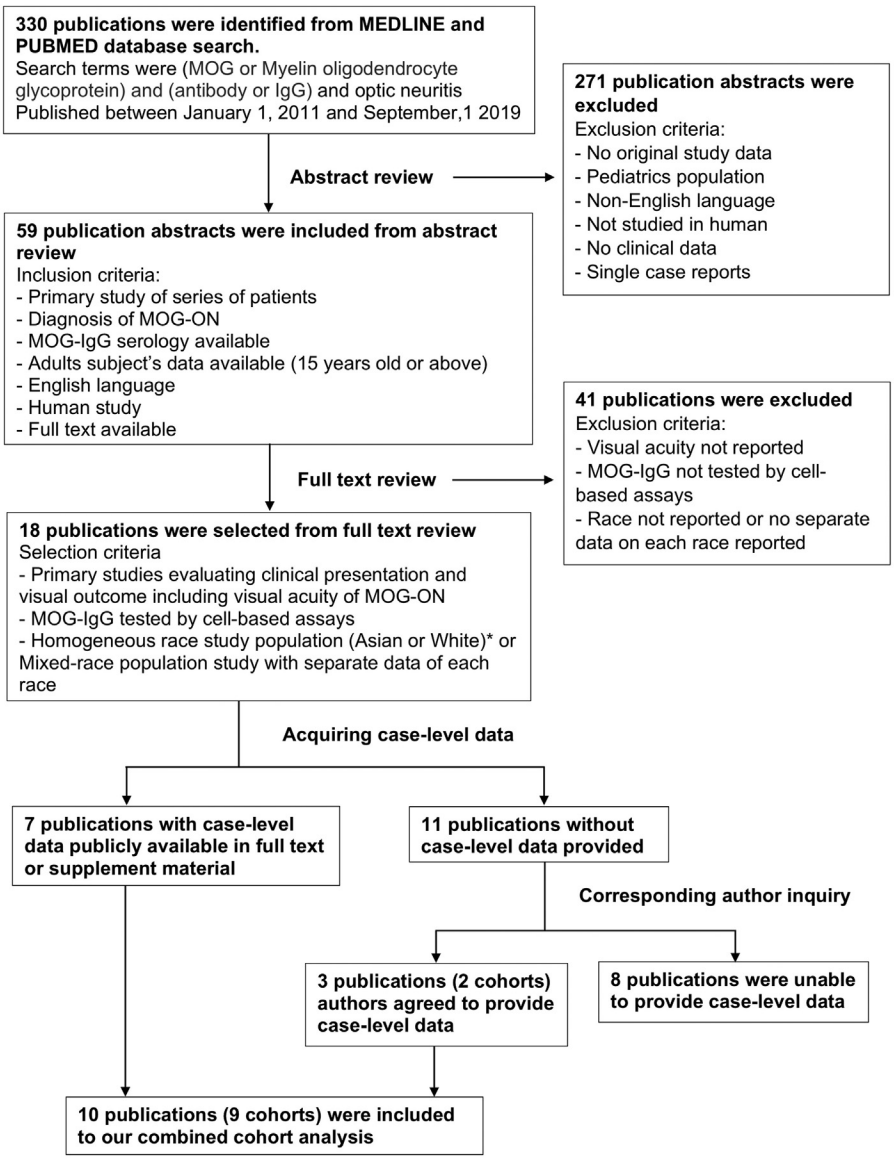

FIGURE 1. Flowchart showing process to select previously published cohorts. Nine eligible published cohorts with case-level data were included in our combined retrospective cohort study. *Review of available case-level data was narrowed to White or Asian due to limited numbers of case-level data for other races in the literature. MOG-IgG = myelin oligodendrocyte glycoprotein IgG; MOG-ON = myelin oligodendrocyte glycoprotein antibody associated optic neuritis.

(intraorbital, intracanalicular, pre-chiasmatic, and optic chiasm), presence of perioptic nerve sheath enhancement, and involvement of more than one-half of the optic nerve length. For the unpublished cohorts, this was based on review of radiology reports for the first ON episode. For the published cohorts, this was based on available data as provided by the investigators or publication.

Follow-up variables included follow-up duration from onset of ON event, VA at final examination (not included if the final examination was within 3 months of the last ON attack), presence and number of subsequent episodes of ON, bilaterality of optic nerve involvement, and type(s) of acute and/or maintenance therapies. Bilateral involvement during course of disease was defined when both optic nerves were affected either simultaneously or sequentially during the course of a subject's follow-up. ON relapse was defined as an episode of acute ON that occurred >1 month after a previous attack. For subjects with at least 1 year of follow-up, ON annualized relapsed rate (ARR) was calculated as the number of relapsed episodes (excluding initial presenting episode) divided by follow-up in years.

The final clinical phenotype was categorized as single episode versus recurrent disease and isolated ON versus ON with other neurological symptoms based on a review of

available data for each subject. Isolated ON referred to disease limited to the optic nerve without other neurological features. This included both single episode and recurrent isolated ON. Chronic relapsing idiopathic optic neuropathy, steroid-dependent and steroid-responsive recurrent ON with other etiology excluded[24] were included in the recurrent isolated ON category. Nonisolated ON was further stratified as AQP-4-IgG negative NMOSD, defined according to 2015 international consensus diagnostic criteria[25] and ADEM, and was characterized by widespread central nervous system inflammatory demyelination with a compatible neuroimaging characteristic.[26] Subjects with other neurological symptoms who did not fulfill these diagnostic criteria were defined as having ON with other neurological symptoms.

• **STATISTICAL ANALYSIS:** Subjects were grouped according to race (Asian, White). Features were compared between White subjects and Asian subjects using generalized estimating equation models to account for correlation within cohorts, age at the time of first ON event, and sex. P values $< .05$ for adjusted parameter coefficients were considered statistically significant. Statistical analyses were completed using SPSS Statistics version 26 software (IBM, Armonk, New York, USA).

RESULTS

ONE HUNDRED FIFTY-THREE SUBJECTS WHO WERE WHITE OR Asian with adult-onset MOG-ON and who met the inclusion criteria were included in the multicenter retrospective cohort. Twenty-four subjects were enrolled from the unpublished cohort (18 patients from Stanford University and 6 subjects from Ramathibodi Hospital). Seventy-six subjects were enrolled from the published cohorts that provided case-level data through collaboration. In addition, data from 53 patients were acquired from 7 publications that publicly provided case-level data. There were 7 subjects from contributing cohorts who were not White or Asian, and therefore, were excluded from our study. Geographic distribution of the multicenter cohort included subjects from USA (California, Minnesota, Florida, and Arizona), UK, Germany, Denmark, Thailand, Japan, China, and South Korea (see Supplementary Table).

Of the included subjects, 80 (52%) were White and 73 (48%) were Asian. Overall, 93 (61%) patients were women, with age at first ON event of 40.8 ± 14.9 years. Follow-up duration ranged from 1 to 432 months (median: 35.2 months).

Comparisons of clinical features and visual outcomes of MOG-ON between White subjects versus Asian subjects are summarized in Table 1. Demographic parameters, including age of onset, sex, and follow-up duration, were similar between White subjects and Asian subjects. With regard to ON features, White subjects were more likely to experience ocular pain during acute ON episodes, whereas subjects of both races had a similar prevalence of optic disc swelling and simultaneous bilateral ON. Asian subjects were more likely to have ON as a presenting symptom of MOGAD, either isolated or accompanied by other concurrent neurological symptoms.

White subjects had similar visual outcomes as Asian subjects. There were no significant differences in VA at the nadir phase (median [interquartile range]; White: logMAR VA 1.70 [0.60-2.30] vs Asian: logMAR VA 1.50 [0.70-2.00]; $P = .22$) or at last follow-up (median [interquartile range]; White: logMAR VA 0.00 [0.00-0.48] vs Asian: logMAR VA 0.00 [0.00-0.30]; $P = .16$). Subjects had comparable rates of visual recovery at last follow-up examination, regardless of race. The relationship between final VA and race was not changed when accounting for follow-up duration ($P = .36$). Prevalence of poor visual outcomes (final VA <20/200) were not different between subjects with <1 year and at least 1 year follow-up duration (<1 year: 2/33 [6%] subjects vs ≥1 year: 10/114 [9%] subjects; $P = 1.000$; Fisher's exact test). There was no difference in involvement of optic nerve segments on neuroimaging between subjects of different races. The most frequently affected segment of the optic nerve was the intraorbital segment (Table 2).

Most subjects received acute treatment for MOG-ON. Overall, intravenous methylprednisolone was the most common acute treatment followed by plasma exchange plus intravenous methylprednisolone. Other acute treatment regimens, such as intravenous immunoglobulin and oral prednisone, were used in a minority of subjects. Adjusting for age of onset, sex, and correlation within cohort, there was no difference in acute treatment patterns between subjects of both races. Maintenance immunosuppressants were prescribed in approximately one-half of the subjects, regardless of race (Table 3).

During the course of disease, Asian subjects with MOG-ON tended to have disease isolated to the optic nerve, whereas White subjects with MOG-ON were more likely to have extra-optic nerve central nervous system manifestations (35/80 [44%] subjects vs 8/73 [11%] subjects; $P = .001$). White subjects had a higher proportion of recurrent ON (57/80 [71%] subjects vs 20/73 [27%] subjects; $P = .001$), despite similar follow-up duration, with correspondingly higher ON ARR in White subjects (median [interquartile range]: 0.62 [0.07-0.96] relapsed episodes per year vs 0.00 [0.00-0.17] relapsed episodes per year; $P < .001$). Although bilateral optic nerve involvement during the disease course was more common in White subjects (61/80 [76%] subjects vs 33/73 [45%] subjects; $P < .001$), the proportion of subjects who had at least 1 episode of simultaneous bilateral ON was similar in both races.

The final clinical phenotype varied between subjects of different races. Single episode isolated ON was more common in Asian subjects than that of White subjects. In contrast, recurrent isolated ON, including chronic relapsing

TABLE 1. Comparison of Demographic and Clinical Features of MOG Antibody-Associated ON Between White and Asian Subjects

Clinical features	White (n = 80)	Asian (n = 73)	Adjusted *P* Value[a]
Age of ON onset, y, mean ± SD	40.84 ± 13.94	40.85 ± 16.05	.95
Gender, female, n (%)	51 (64)	42 (58)	.47
Duration of follow-up after onset, mos, median (range)	35.12 (1-432)	36.00 (3-276)	.17
Follow up duration after onset	None missing	None missing	
≥1 y follow-up duration, n (%)	60 (75)	57 (78)	.80
<1 year follow-up duration, n (%)	20 (25)	16 (22)	
Optic neuritis features			
ON as an initial presentation of MOG	(n = 79), missing 1	none missing	
Present, n (%)	65 (82)	72 (99)	.005
Absent, n (%)	14 (18)	1 (1)	
Ocular pain during ON episode	(n = 70), missing 10	(n = 34), missing 39	
Present, n (%)	63 (90)	25 (74)	<.001
Absent, n (%)	7 (10)	9 (26)	
Optic disc swelling during ON episode	(n = 42), missing 38	(n = 22), missing 51	
Present, n (%)	35 (83)	16 (73)	.25
Absent, n (%)	7 (17)	6 (26)	
Simultaneous bilateral ON (≥1 episode)	(n = 77), missing 3	(n = 69), missing 4	.95
Present, n (%)	32 (42)	29 (43)	
Absent, n (%)	45 (58)	39 (57)	
Visual acuity at nadir	(n = 49), missing 31	(n = 57), missing 16	
Mild visual loss (>20/40)	6 (12)	3 (5)	ref
Moderate visual loss (20/40-20/200)	11 (23)	21 (37)	.01
Severe visual loss (<20/200)	32 (65)	33 (58)	.07
Disease course features			
Visual acuity at last follow-up	(n = 77), missing 3	(n = 70), missing 3	
Mild visual loss (>20/40), n (%)	51 (66)	52 (74)	ref
Moderate visual loss (20/40-20/200), n (%)	19 (25)	13 (19)	.39
Severe visual loss (<20/200), n (%)	7 (9)	5 (7)	.36
ON involvement during course of disease	None missing	None missing	
Bilateral, n (%)	61 (76)	33 (45)	<.001
Unilateral, n (%)	19 (24)	40 (55)	
ON recurrence	None missing	None missing	
≥2 episodes of ON, n (%)	57 (71)	20 (27)	.001
1 episode of ON, n (%)	23 (29)	53 (73)	
Spatial involvement	None missing	None missing	
Isolated ON, n (%)	45 (56)	65 (89)	.001
ON with extra-optic nerve manifestation, n (%)	35 (44)	8 (11)	
Final clinical phenotype	None missing	None missing	
Isolated single episode of ON, n (%)	12 (15)	48 (66)	<.001
Isolated recurrent ON (including CRION), n (%)	33 (41)	17 (23)	.04
ADEM, n (%)	6 (8)	2 (3)	.11
NMOSD, n (%)	25 (31)	4 (5)	.001
ON + other neurological symptoms, n (%)	4 (5)	2 (3)	.54

ADEM= acute demyelinating encephalomyelitis; ARR = annualized relapsed rate; CRION = chronic relapsing idiopathic optic neuropathy; MOG = myelin oligodendrocyte glycoprotein; NMOSD = neuromyelitis optica spectrum disorder; ON = optic neuritis,

[a]*P* value for variable coefficient using generalized estimating equation, adjusting for age of onset, sex, and correlation within cohort.

TABLE 2. Comparison of MRI Findings of MOG Antibody-Associated Optic Neuritis Between White and Asian Subjects

MRI Findings	White	Asian	Adjusted *P* Value[a]
Optic nerve segment involved	(n = 39), missing 41	(n = 41), missing 32	
Intraorbital optic nerve, n (%)	34 (87)	37 (90)	.20
Intracanalicular optic nerve, n (%)	25 (64)	34 (83)	.26
Pre-chiasmatic optic nerve, n (%)	25 (64)	30 (73)	.42
Optic chiasm, n (%)	7 (18)	10 (24)	.62
Perioptic nerve sheath enhancement	(n = 38), missing 42	(n = 34), missing 39	
Present, n (%)	22 (58)	21 (62)	.65
Long segment involvement	(n = 40), missing 40	(n = 41), missing 32	
Present, n (%)	28 (70)	32 (78)	.29

MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging.
[a]*P* Value for variable coefficient (present vs absent) by generalized estimating equation adjusting for age of onset, sex, and correlation within cohort.

TABLE 3. Comparison of Myelin Oligodendrocyte Glycoprotein Antibody-Associated Optic Neuritis Treatment Between White and Asian Subjects

Treatment	White (n = 80)	Asian (n = 73)	Adjusted *P* Value[a]
No acute treatment, n (%)	3 (4)	3 (4)	.91
Acute treatment present	(n = 77)	(n = 70)	
Monotherapy, n (%)	60 (78)	67 (96)	.058[b]
IVMP, n (%)	57 (74)	64 (92)	
Oral prednisone, n (%)	2 (3)	3 (4)	
IVIG, n (%)	1 (1)	0 (0)	
Combined therapy, n(%)	17 (22)	3 (4)	
IVMP + PLEX, n (%)	16 (21)	3 (4)	
IVMP + IVIG, n (%)	1 (1)	0 (0)	
Maintenance treatment			
Present, n (%)	46 (58)	30 (41)	.11
Absent, n (%)	34 (42)	43 (59)	

IVIG = intravenous immunoglobulin; IVMP = intravenous methylprednisolone; PLEX = plasma exchange.
[a]*P* value for variable coefficient by generalized estimating equation, adjusting for age of onset, sex, and correlation within cohort.
[b]*P* value for comparison of monotherapy versus combined therapy between White and Asian subjects.

idiopathic optic neuropathy, was more common in White subjects. AQP-4-IgG negative NMOSD was more prevalent in White subjects than that in Asian subjects. Few subjects with MOG-ON in both races had other neurological symptoms, including transverse myelitis (not compatible with NMOSD criteria), and other brainstem syndromes. ADEM was rare in our adult cohort in both races.

DISCUSSION

DURING THE PAST DECADE, MULTIPLE LARGE CASE SERIES characterized the clinical features and visual outcomes of MOG-ON. However, most of the cohorts were of homogeneous race. Accordingly, the relationship among race, clinical features, and outcomes received little attention, despite well-described variations in other forms of ON between subjects who were of different races. This study aimed to directly compare clinical features and visual outcomes of MOG-ON between subjects of White race versus Asian race.

Several features of MOG-ON were similar in subjects of both races, including demographic characteristics, optic nerve appearance, neuroimaging findings, and VA outcomes. The sex distribution in our cohort reinforced previous findings of MOG-ON of having less female predominance than AQP-4-IgG–associated ON.[16,27–30] The finding of a high proportion of subjects with optic disc swelling reinforced optic disc swelling as a common

feature in MOG-ON, regardless of race.[29,31,32] MRI findings were comparable between subjects of different races, with common involvement of a long segment of the intraorbital optic nerve and presence of perioptic nerve sheath enhancement in most cases, in contrast to what was reported for AQP-4-IgG or multiple sclerosis–associated ON.[8] These imaging features were consistent with what was described as typical for MOG-ON.[32] Visual outcomes were excellent, with most subjects of either race recovering a final VA >20/40 despite having severe visual loss (<20/200) during the nadir phase. Only 7/77 (9%) of White subjects and 5/70 (7%) of Asian subjects had final VA in either eye of <20/200. Consistent with previous reports, these visual outcomes were better than those reported in AQP-4-IgG–associated ON, in which approximately one-third of patients had severe visual loss after recovery (<20/200).[2,33]

A notable difference in MOG-ON attack characteristics between White and Asian subjects was a higher frequency of ocular pain during an ON episode in White subjects compared with Asian subjects. A similarly lower prevalence of pain was also reported in other Chinese MOG-ON cohorts, which met criteria for inclusion in our cohort, but for which case-level data could not be obtained.[16,34] However, it was difficult to conclude if differences in pain, a subjective perception, were a result of disease differences or other differences, including a cultural difference in pain perception and evaluation. Interestingly, pain perception studies reported lower pain threshold and tolerance levels in Asian subjects than those in White subjects, which could not account for our observation.[35]

We found 4 additional interesting differences in the disease course between White subjects and Asian subjects. First, although ON was a common presenting manifestation of MOG-ON in subjects of both races, White subjects were more likely to have a clinical syndrome other than ON as their initial presentation. However, it should be noted that our case inclusion criteria that required ON was likely biased toward ON as the initial presenting syndrome in comparison to other studies that considered non-ON presentations of MOGAD,[5,36,37] although this bias was likely similar for subjects of either race. Second, White subjects were more likely to have recurrent ON, based on both the proportion of subjects with recurrence and ARR. Nonetheless, the comparison might be overstated because the rate of recurrent ON in our Asian subjects was lower than that reported in other Asian-predominant cohorts that were not included in our study, in which more than one-half of subjects had recurrence.[29,31,38] Third, White subjects were more likely to have bilateral optic nerve involvement during the course of their disease. However, this might have been an artifact of recurrent disease because both races had similar prevalence of simultaneous bilateral ON. Fourth, most of the Asian subjects (89%) had an isolated ON clinical phenotype compared with that of approximately two-thirds of White subjects. This difference persisted when excluding cases from 2 cohorts that excluded patients with the seronegative NMOSD phenotype.[10,17]

The results should be interpreted in the context of how race information in this study was derived, namely, by self-report without subclassification. It was demonstrated in previous studies that self-reported race correlated well with predominant genetic ancestry,[39,40] but there was heterogeneity as a result. Furthermore, subjects of both races in this study might not adequately represent the diverse subgroups in each race. For instance, our Asian study population came from East Asia (Japan, China, South Korea) and Southeast Asia (Thailand), with minimal representation from Central Asia or South Asia. This limitation also applied to White subjects, with the term White for identification of race applying to a heterogeneous population in terms of ancestry, geographic origin, and birthplace.[41] Differences in clinical features of MOG-ON between races in this study might have been confounded by geographic distribution as mediated by differences in health care systems and environments. Further study with consideration of racial subgroups and geographic location would help to clarify the role of these factors.

This study had some limitations. Combining retrospective case-level data from multiple sources captured the selection and ascertainment bias from each source due to differences in inclusion criteria and data measurement. We addressed this statistically using models that accounted for correlation within cohorts. Most patients included in this study were from tertiary centers, which could bias the cohort toward more severe or relapsing disease. However, this bias should be equal between White and Asian subjects, and therefore, should not influence the comparison between the 2 races. Missing data in certain parameters, such as ocular pain, optic disc swelling, and MRI features in some cohorts, also limited analysis of these features. Performance of this study illustrated systematic barriers to work of this kind related to issues with data sharing and race reporting. For example, in some countries, collection of race and ethnicity data for research purposes was prohibited by regulation. In addition, depending on the country and institution, international data sharing might be prohibited by government regulations.

CONCLUSION

IN THIS MULTICENTER, RETROSPECTIVE COHORT STUDY, WE found differences in clinical features of MOG-ON between White and Asian subjects. White subjects were more likely to report pain, have recurrent attacks, and have bilateral optic nerve involvement during the disease course. Asian subjects were more likely to have disease phenotype limited to the optic nerve. Visual outcomes and other clinical features were similar between subjects of different races and similar to what is typically associated with MOG-ON. It

is a matter of speculation whether differences between subjects of different races reflect genetic or environmental influences related to residential location. A multicenter, prospective population-based study is warranted to gain further insight into associations between MOG-ON and different races.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

TANYATUTH PADUNGKIATSAGUL: Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **John J. Chen:** Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Panitha Jindahra:** Funding acquisition, Writing - original draft, Writing - review & editing. **Tetsuya Akaishi:** Funding acquisition, Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Toshiyuki Takahashi:** Funding acquisition, Writing - original draft, Writing - review & editing. **Ichiro Nakashima:** Funding acquisition, Writing - original draft, Writing - review & editing. **Takayuki Takeshita:** Funding acquisition, Writing - original draft, Writing - review & editing. **Heather E. Moss:** Conceptualization, Methodology, Funding acquisition, Formal analysis, Data curation, Writing - original draft, Writing - review & editing.

FUNDING: THIS WORK WAS SUPPORTED BY THE NATIONAL INSTITUTES OF HEALTH (NIH P30 026877) AND A RESEARCH TO PREVENT BLINDNESS UNRESTRICTED GRANT TO THE STANFORD DEPARTMENT OF OPHTHALMOLOGY.

Financial disclosure: T.T. has received speaker honoraria from the Cosmic Corporation. I.N. has received funding for travel and received speaker honoraria from Mitsubishi Tanabe Pharma, Biogen Japan, Novartis Pharma, Alexion Pharma, Takeda Pharmaceutical Company, and has received research funding from LSI Medience and Grants-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (KAKENHI 17K09772). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. All authors attest that they meet the current ICMJE criteria for authorship.

REFERENCES

1. Optic Neuritis Study Group. Visual function 15 years after optic neuritis: a final follow-up report from the Optic Neuritis Treatment Trial. *Ophthalmology* 2008;115(6):1079–1082.e1075.
2. Fernandes DB, Ramos Rde I, Falcochio C, Apostolos-Pereira S, Callegaro D, Monteiro ML. Comparison of visual acuity and automated perimetry findings in patients with neuromyelitis optica or multiple sclerosis after single or multiple attacks of optic neuritis. *J Neuroophthalmol* 2012;32(2):102–106.
3. Reindl M, Di Pauli F, Rostasy K, Berger T. The spectrum of MOG autoantibody-associated demyelinating diseases. *Nat Rev Neurol* 2013;9(8):455–461.
4. Jarius S, Ruprecht K, Kleiter I, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. *J Neuroinflammation* 2016;13(1):280.
5. Jurynczyk M, Messina S, Woodhall MR, et al. Clinical presentation and prognosis in MOG-antibody disease: a UK study. *Brain* 2017;140(12):3128–3138.
6. Pache F, Zimmermann H, Mikolajczak J, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 4: Afferent visual system damage after optic neuritis in MOG-IgG-seropositive versus AQP4-IgG-seropositive patients. *J Neuroinflammation* 2016;13(1):282.
7. Chen JJ, Flanagan EP, Jitprapaikulsan J, et al. Myelin oligodendrocyte glycoprotein antibody-positive optic neuritis: clinical characteristics, radiologic clues, and outcome. *Am J Ophthalmol* 2018;195:8–15.
8. Kim S-M, Woodhall MR, Kim J-S, et al. Antibodies to MOG in adults with inflammatory demyelinating disease of the CNS. *Neurol Neuroimmun Neuroinflamm* 2015;2(6):e163.
9. Ramanathan S, Reddel SW, Henderson A, et al. Antibodies to myelin oligodendrocyte glycoprotein in bilateral and recurrent optic neuritis. *Neurol Neuroimmunol Neuroinflamm* 2014;1(4):e40.
10. Akaishi T, Sato DK, Nakashima I, et al. MRI and retinal abnormalities in isolated optic neuritis with myelin oligodendrocyte glycoprotein and aquaporin-4 antibodies: a comparative study. *J Neurol Neurosurg Psychiatry* 2016;87(4):446–448.
11. Ramanathan S, Mohammad S, Tantsis E, et al. Clinical course, therapeutic responses and outcomes in relapsing MOG antibody-associated demyelination. *J Neurol Neurosurg Psychiatry* 2018;89(2):127–137.
12. Jarius S, Wildemann B, Paul F. Neuromyelitis optica: clinical features, immunopathogenesis and treatment. *Clin Exp Immunol* 2014;176(2):149–164.
13. Moss HE, Gao W, Balcer LJ, Joslin CE. Association of race/ethnicity with visual outcomes following acute optic neuritis: an analysis of the Optic Neuritis Treatment Trial. *JAMA Ophthalmol* 2014;132(4):421–427.
14. Kim SH, Mealy MA, Levy M, et al. Racial differences in neuromyelitis optica spectrum disorder. *Neurology* 2018;91(22):e2089–e2099.
15. Kitley J, Leite MI, Nakashima I, et al. Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan. *Brain* 2012;135(Pt 6):1834–1849.
16. Zhao G, Chen Q, Huang Y, et al. Clinical characteristics of myelin oligodendrocyte glycoprotein seropositive optic neuritis: a cohort study in Shanghai, China. *J Neurol* 2018;265(1):33–40.
17. Nakajima H, Motomura M, Tanaka K, et al. Antibodies to myelin oligodendrocyte glycoprotein in idiopathic optic neuritis. *BMJ Open* 2015;5(4):e007766.

18. Siritho S, Sato DK, Kaneko K, Fujihara K, Prayoonwiwat N. The clinical spectrum associated with myelin oligodendrocyte glycoprotein antibodies (anti-MOG-Ab) in Thai patients. *Mult Scler* 2016;22(7):964–968.
19. Jitprapaikulsan J, Chen JJ, Flanagan EP, et al. Aquaporin-4 and myelin oligodendrocyte glycoprotein autoantibody status predict outcome of recurrent optic neuritis. *Ophthalmology* 2018;125(10):1628–1637.
20. Chen JJ, Tobin WO, Majed M, et al. Prevalence of myelin oligodendrocyte glycoprotein and aquaporin-4-IgG in patients in the Optic Neuritis Treatment Trial. *JAMA Ophthalmol* 2018;136(4):419–422.
21. Kitley J, Woodhall M, Waters P, et al. Myelin-oligodendrocyte glycoprotein antibodies in adults with a neuromyelitis optica phenotype. *Neurology* 2012;79(12):1273–1277.
22. Zhou L, Huang Y, Li H, et al. MOG-antibody associated demyelinating disease of the CNS: a clinical and pathological study in Chinese Han patients. *J Neuroimmunol* 2017;305:19–28.
23. Danesh-Meyer H, Savino PJ, Gamble GG. Poor prognosis of visual outcome after visual loss from giant cell arteritis. *Ophthalmology* 2005;112(6):1098–1103.
24. Petzold A, Plant GT. Chronic relapsing inflammatory optic neuropathy: a systematic review of 122 cases reported. *J Neurol* 2014;261(1):17–26.
25. Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. *Neurology* 2015;85(2):177–189.
26. Krupp LB, Tardieu M, Amato MP, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler* 2013;19(10):1261–1267.
27. Mader S, Gredler V, Schanda K, et al. Complement activating antibodies to myelin oligodendrocyte glycoprotein in neuromyelitis optica and related disorders. *J Neuroinflammation* 2011;8:184.
28. Sato DK, Callegaro D, Lana-Peixoto MA, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. *Neurology* 2014;82(6):474–481.
29. Zhao Y, Tan S, Chan TCY, et al. Clinical features of demyelinating optic neuritis with seropositive myelin oligodendrocyte glycoprotein antibody in Chinese patients. *Br J Ophthalmol* 2018;102(10):1372–1377.
30. Kitley J, Waters P, Woodhall M, et al. Neuromyelitis optica spectrum disorders with aquaporin-4 and myelin-oligodendrocyte glycoprotein antibodies: a comparative study. *JAMA Neurol* 2014;71(3):276–283.
31. Liu H, Zhou H, Wang J, et al. The prevalence and prognostic value of myelin oligodendrocyte glycoprotein antibody in adult optic neuritis. *J Neurol Sci* 2019;396:225–231.
32. Ramanathan S, Prelog K, Barnes EH, et al. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. *Mult Scler* 2016;22(4):470–482.
33. Jarius S, Frederikson J, Waters P, et al. Frequency and prognostic impact of antibodies to aquaporin-4 in patients with optic neuritis. *J Neurol Sci* 2010;298(1–2):158–162.
34. Kang H, Liu Z, Li H, et al. Simultaneous bilateral optic neuritis in China: clinical, serological and prognostic characteristics. *Acta Ophthalmol* 2019;97(3):e426–e434.
35. Rowell LN, Mechlin B, Ji E, Addamo M, Girdler SS. Asians differ from non-Hispanic Whites in experimental pain sensitivity. *Eur J Pain* 2011;15(7):764–771.
36. Hyun JW, Woodhall MR, Kim SH, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. *J Neurol Neurosurg Psychiatry* 2017;88(10):811–817.
37. Mariotto S, Ferrari S, Monaco S, et al. Clinical spectrum and IgG subclass analysis of anti-myelin oligodendrocyte glycoprotein antibody-associated syndromes: a multicenter study. *J Neurol* 2017;264(12):2420–2430.
38. Zhou Y, Jia X, Yang H, et al. Myelin oligodendrocyte glycoprotein antibody-associated demyelination: comparison between onset phenotypes. *Eur J Neurol* 2019;26(1):175–183.
39. Sinha M, Larkin EK, Elston RC, Redline S. Self-reported race and genetic admixture. *N Engl J Med* 2006;354(4):421–422.
40. Tang H, Quertermous T, Rodriguez B, et al. Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. *Am J Hum Genet* 2005;76(2):268–275.
41. Bhopal R, White Donaldson L. European, Western, Caucasian, or what? Inappropriate labeling in research on race, ethnicity, and health. *Am J Public Health* 1998;88(9):1303–1307.