Neurology Asia 2017; 22(4) : 341 – 348

The natural history of optic neuritis in Asian patients: An observational cohort study

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Abstract

Optic neuritis, which may be a precursor to multiple sclerosis (MS), is an uncommon disease in Asian patients. The Asian Collaborative Longitudinal Optic Neuritis Epidemiology (ACLONE) is an observational cohort study that assessed the risk of recurrent optic neuritis and/or progression of further neurologic events, either MS or neuromyelitis optica (NMO) in Asian patients with first-ever optic neuritis. Secondary aims were to study the presenting characteristics and visual outcome, and to identify risk factors for development of either MS or NMO. A total of 112 patients (25 men and 87 women) aged from 12 to 61 years were recruited from Singapore, Taiwan, South Korea and Malaysia. Of these, 94 (84%) had unilateral optic neuritis, with the right eye involved in 45 patients and the left eye in 49 patients and the remaining 18 (16%) had bilateral optic neuritis. Follow up data was available for 104 patients, and patients were followed for a median duration of 25.9 months. Of these patients, 6 patients were adjudicated to have reached the primary endpoint (composite of MS/NMO and optic neuritis): 3 patients with recurrent optic neuritis also subsequently experienced neurologic symptoms, and 3 patients without recurrent eye involvement had neurologic symptoms. Only one patient was considered to have prototypical MS, the other 5 were diagnosed with NMO, all with subsequent antibody confirmation. Optic neuritis in Asian patients has significantly different presenting characteristics from the classic description. However, in the majority of the patients it is usually a benign disease, with good visual outcome and no further events.

Keywords: Optic neuritis, multiple sclerosis, neuromyelitis optica

INTROUDCTION

Optic neuritis is an uncommon disease in Asian patients. The classical description is that optic neuritis is one of the clinically isolated syndromes (CIS), a precursor to multiple sclerosis (MS)[1-3], and Asian patients with optic neuritis were previously assumed to have a similar disease, variously termed 'opticospinal MS' (OSMS) or 'Asian-type MS'.[4,5] With the publication of criteria for the diagnosis of neuromyelitis optica (NMO)[6], and the discovery of the anti-NMO antibody[7], it is now known that many Asian patients have a different disease.[8] The natural history, prognostic factors for visual recovery, and risk of developing subsequent neurological symptoms, as described by previous studies, may not apply to Asian populations. For example, acute bilateral optic neuritis, which is uncommon in adult Caucasian patients, may be more frequent in Asians.[9-12] Previous studies in Asian patients with optic neuritis were either retrospective or cross-sectional.[4,5,10,11,13] Hence, there is a need for a prospective study with long-term follow up to describe the natural history of optic neuritis in Asian patients. The Asian Collaborative Longitudinal Optic Neuritis Epidemiology (ACLONE), an observational cohort study, recruited Asian patients with first-ever optic neuritis for long-term follow up. The primary aim

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was to assess the risk of recurrent optic neuritis and/or progression of further neurologic events, either MS or NMO. Secondary aims were to study the presenting characteristics and visual outcome, and to try to identify risk factors for development of either MS or NMO.

METHODS

Patient Eligibility

The ACLONE study is a multinational, prospective, longitudinal observational cohort study of Asian patients with optic neuritis. Asian patients aged between 12 and 61 years who presented at specialist clinics in Singapore, Malaysia, Taiwan and South Korea with an episode of first-ever acute visual loss caused by optic neuritis were identified and recruited for further study. Most of the patients were recruited between March 2003 and September 2009.

Inclusion criteria were visual nadir within one month of onset followed by subsequent visual stabilization or recovery, and development of subsequent optic disc pallor. Investigations were performed to exclude autoimmune, granulomatous, syphilitic, compressive and other causes of optic nerve dysfunction. Patients were also excluded if they had a known history of MS or had a history of prior neurologic episodes which could be attributed to demyelinating disease.

Study design

All patients gave informed consent prior to study entry. Details of the acute episode of visual loss, including visual acuity, color vision and fundus appearance was recorded by the enrolling physician where possible and by chart review otherwise. Visual acuity was obtained with Snellen charts and color vision with the Ishihara color plates. The presence or absence of a relative afferent pupillary defect, any associated uveitis, disc appearance, as well as the presence of a macular star or any other retinal abnormalities were also recorded and used to confirm the diagnosis. A neurological examination paying attention to the cranial nerves, pinprick and joint position sense, limb power, coordination and reflexes was also performed. Four months after study enrollment, this examination was repeated in all patients.

Because optic neuritis is a clinical diagnosis and in some patients there can be initial diagnostic uncertainty, this method of patient recruitment was adopted to minimise selection bias and fully understand the pattern of disease seen in Asian patients. For the same reason, patients who had bilateral simultaneous optic neuritis (defined as both eyes involved at presentation), were included because bilateral simultaneous optic neuritis in adult patients is not uncommon in Asia, and the relation of this to MS is unknown.

At the time of this study, the NMO antibody assay was not widely available and so this was not obtained. This was an observational study, therefore acute treatment including the use of pulse steroids was left to the discretion of the treating clinician, as it is generally agreed that steroid use is not disease-modifying (i.e. it does not prevent the underlying disease from manifesting as MS or NMO). To avoid altering the natural history of the disease, none of the patients were treated with disease-modifying drugs (e.g. beta interferon, glatirimer, or immunosuppressant drugs) at time of presentation. This prohibition was lifted when the patients developed neurological symptoms (i.e exited the study).

MS was defined according to Poser's criteria (i.e. two episodes separated by time and space)[14] and NMO was characterized based on Wingerchuk's criteria.[15]

Study centers obtained separate institutional review board (IRB) approvals; approval was obtained in January 2005 for the centers in Singapore, and in 2006 for the centers in Malaysia, Taiwan and South Korea. To maximize recruitment in this rare condition, some patients were identified before the study protocol could be finalized between the different centers, and hence before IRB approval was obtained. Therefore, the first patient had onset of optic neuritis in December 1999, although IRB approval was only obtained in 2005. Patients were followed up at regular intervals, usually 4 monthly, with clinic visits when feasible and, if not, by telephone until study termination. At each encounter, patients were reminded of the need to return for medical assessment should new ophthalmologic or neurologic symptoms occur. The last patient follow up was at the end of 2010.

Statistical analysis

Continuous variables were summarised using median and range for skewed data or mean and standard deviation for data which were approximately normally distributed, whereas categorical variables were summarised using frequencies and percentages. For subjects who were lost to follow-up, they were censored at the

date of last follow-up for inclusion in the survival analysis. The survival time was calculated from the date of baseline examination to the date of MS or recurrent optic neuritis. To identify prognostic factors for neurological symptoms, the Kaplan-Meier cumulative incidence of outcome events (time to MS or recurrent optic neuritis) was compared for each risk factor via the log rank test. All statistical analyses were performed assuming a two-sided test of 5% using STATA version 11.

RESULTS

We recruited a total of 112 patients, comprising 25 men and 87 women aged from 12 to 61 years (Table 1). The ages of the patients from Singapore, Taiwan and South Korea were comparable, while patients from Malaysia were slightly younger. Ethnic Chinese patients came from Singapore and Taiwan, all the Korean patients were from South Korea, with smaller numbers of ethnic Malay and Indian patients from the more ethnically diverse countries of Malaysia and Singapore. Shortly after recruitment, 8 subjects were lost to follow-up, leaving a total of 104 patients for whom follow up data was available.

Of 112 patients, 94 (84.0%) had unilateral

Table 1: Demographic and clinical characteristics by laterality, disc appearance and visual nadir

Characteristic	Unilateral optic neuritis (n = 94)	Bilateral optic neuritis (n = 18)	Overall (n = 112)
Median age (range)	36 (12 - 61)	39.5 (17-58)	36 (12 - 61)
	Number of patients (percent)		
Gender			
Male	21 (22.3%)	4 (22.2%)	25 (22.3%)
Female	73 (77.7%)	14 (77.8%)	87 (77.68%)
Race			
Chinese	44 (46.81%)	7 (38.9%)	51 (45.5%)
Malay	8 (8.5%)	3 (16.7%)	11 (9.8%)
Indian	4 (4.3%)	2 (11.1%)	6 (5.4%)
Korean	38 (40.4%)	5 (27.8%)	43 (38.4%)
Others	0 (0.0%)	1 (5.6%)	1 (0.9%)
	Number of patients (percent)		
Papillitis vs retrobulbar[†]			
No disc swelling	44 (46.8%)	2 (11.1%)	46 (41.1%)
Disc swelling	40 (42.5%)	13 (72.2%)	53 (47.3%)
Missing data	10 (9.4%)	3 (16.6%)	13 (11.6%)
Visual acuity at nadir[*]			
6/9 or better	20 (21.2%)	0 (0.0%)	20 (17.8%)
6/12 to 6/18	7 (7.4%)	2 (11.1%)	9 (0.8%)
6/24 to 6/60	27 (28.7%)	4 (22.2%)	31 (27.7%)
CF or HM	39 (41.4%)	5 (27.8%)	44 (39.3%)
PL or NPL	0 (0.0%)	6 (33.3%)	6 (5.4%)
Missing Data	1 (1.1%)	1 (5.6%)	2 (1.8%)

[†] Patients were classified as having papillitis (anterior optic neuritis) if the presence of disc swelling was recorded anytime during the initial few visit, and as having retrobulbar optic neuritis if disc swelling was not recorded. 13 patients had incomplete data entry regarding the disc appearance.

[*] CF = Count fingers, HM = Hand motion, PL = Perception of light only, NPL = No perception of light. One patient with unilateral optic neuritis had missing data regarding visual nadir. Another patient with bilateral optic neuritis had missing data regarding visual outcome, hence data is reported for 110 eyes. In patients with bilateral optic neuritis, visual acuity is recorded from the worse eye.

optic neuritis, with the right eye involved in 45 patients and the left eye in 49 patients, and the remaining 18 (16%) had bilateral optic neuritis (Table 1). The patients with bilateral optic neuritis came from all countries and all ethnic groups (Table 1), and the clinical characteristics of these patients are summarized in Table 2. Patients with bilateral optic neuritis were similar to patients with unilateral optic neuritis with respect to age and gender distributions.

Visual outcome after initial episode

Visual acuity at presentation is reported for 110 patients, as there was missing information for two patient (one unilateral, one bilateral). The majority of the patients had severe visual loss, with visual acuity at nadir shown in Figure 1. At follow up, the majority of patients showed a significant improvement, and the final visual outcome is presented in Figure 2.

Long term outcome

Follow up data was available for 104 patients. Patients were followed for varying intervals, either until trial closure or until they developed a neurological outcome event (i.e. fulfilled Poser's criteria of two episodes separated in time and space) or were no longer contactable. Patients who developed a second episode of optic neuritis were considered to have recurrent optic neuritis and were maintained on follow up. Patients were followed for a median duration of 25.9 (1.0 to 80.9) months.

Of these patients, 92 (88.5%) did not have any further problems at study termination. Six patients experienced at least one further episode of optic neuritis. Of these, five had recurrent episodes of optic neuritis, including one patient who had nine separate episodes of blurred vision attributed to optic neuritis, but without further involvement of the rest of the nervous system. The other three patients who had recurrent optic neuritis also subsequently experienced neurologic symptoms. Together with another three patients who did not have recurrent eye involvement but had neurologic symptoms, a total of six patients were adjudicated to have reached the study endpoint. Of these, only one patient was considered to have prototypical MS, the other five were diagnosed with NMO, all with subsequent antibody confirmation. The interval between study entry and the development of neurologic symptoms varied from 6 weeks to 5.6 years.

Prognostic factors

Poor visual acuity at presentation was the most significant prognostic factor for developing further episodes. Comparing patients with a visual nadir of count fingers (CF) or worse (44 patients) versus those with better vision (67 patients), we found that there was an increased risk of developing MS/recurrent optic neuritis amongst those with poorer visual acuity (Hazard Ratio [HR]=3.05, 95% CI: 1.04 – 8.97, logrank P=0.033).

Other risk factors, when taken singly, did not reach statistical significance (Table 3). Neither bilateral optic neuritis (p = 0.430) nor visual recovery (p = 0.828) carried any prognostic significance for subsequent disease (Table 3).

Using multifactorial regression analysis, the combination of poor visual outcome in the setting of retrobulbar optic neuritis (as opposed to papillitis, i.e no disc swelling was noted on initial presentation) was found to be statistically significant. Patients with retrobulbar optic neuritis with visual nadir of CF or worse vision had statistically significant risk of developing further episodes compared to those who did not have these combined risk factors (HR = 3.75, 95% CI 1.34 – 12.38, p = 0.020)

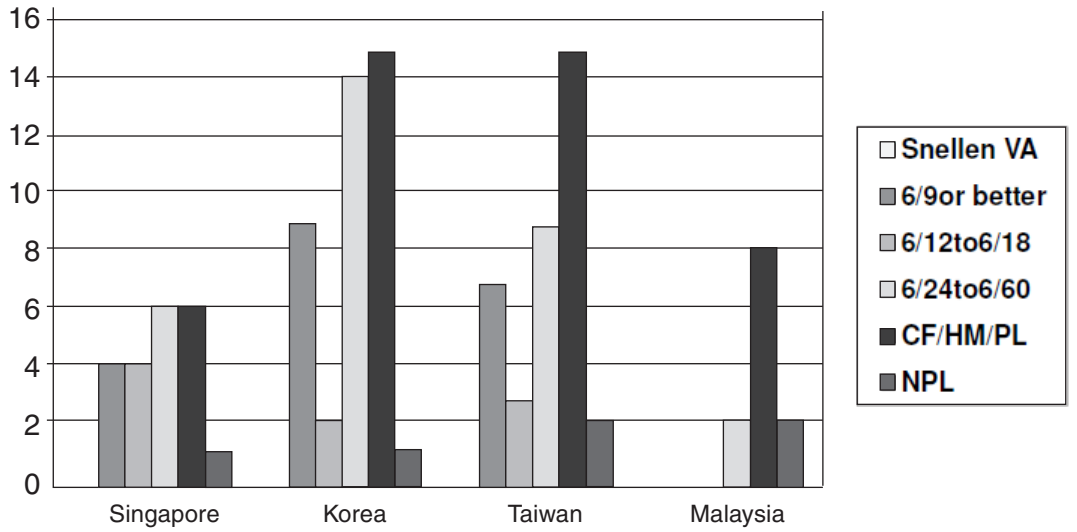
DISCUSSION

These results confirm that the clinical characteristics of optic neuritis in Asian patients differ from classic optic neuritis. Firstly, acute bilateral optic neuritis is not uncommon in Asian patients, occurring in approximately 16% of patients in the current study. This phenomenon of acute bilateral optic neuritis was first noted in Japan by Wakakura *et al*.[13] when a questionnaire-based survey of ophthalmologists, showed that as many as 28.2 % of patients with optic neuritis had overt bilateral involvement. The phenomenon of adult bilateral optic neuritis has also been mentioned in several other reports from Asia.[4,10,16-20] Unfortunately, a number of these reports have not been published in mainstream medical journals. Consequently, current opinion remains that bilateral optic neuritis, at least for Caucasian patients, occurs predominantly in children, usually after viral infection, and is not related to development of MS.[21] Therefore, bilateral optic neuritis is considered to be a different disease from unilateral, presumed demyelinating neuritis, which is considered one of the clinically isolated syndromes and a possible precursor for MD. Because of this it is possible that other reports from Asia, using retrospective search strategies,

Table 2. Clinical characteristics of patients with bilateral optic neuritis

Sex	Country	Race	Onset Age (yrs)	Worst Va		Worst Ishihara		Disc swelling		Final Va		Final Ishihara		Final disc appearance	
				OD	OS	OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
F	Singapore	Chinese	54	6/12	6/12	14	14	Yes	Yes	6/9	6/7.5	14	14	Sectoral	Sectoral
M	Singapore	Chinese	34	6/12	6/12	14	13	Yes	Yes	6/6	6/6	14	14	Diffuse	Diffuse
F	Singapore	Chinese	55	CF	6/24	NC	13	Yes	Yes	6/12	6/12	14	14	Sectoral	Sectoral
F	Singapore	Chinese	33	CF	6/6	NC	14	Yes	Yes	6/6	6/6	13	13	Sectoral	Sectoral
M	Singapore	Chinese	59	NPL	NPL	NC	NC	No	No	HM	CF	NC	NC	Diffuse	Diffuse
M	Singapore	Chinese	44	6/9	6/60	2	No control	Yes	Yes	6/7.5	6/36	0	NC	Sectoral	Diffuse
F	Korea	Korean	55	HM	HM	NC	NC	Yes	Yes	6/6	6/6	13	2	Mild	Mild
F	Korea	Korean	31	NPL	NPL	NC	NC	Yes	Yes	6/60	6/60	NC	NC	Sectoral	Sectoral
F	Korea	Korean	41	PL	CF	NC	NC	Yes	Yes	6/60	6/60	NC	NC	Sectoral	Sectoral
F	Korea	Korean	61	HM	NPL	NC	NC	Yes	Yes	ND	ND	ND	ND	ND	ND
F	Korea	Korean	32	PL	NPL	NC	NC	Yes	Yes	6/9	6/36	ND	ND	Mild	Mild
F	Taiwan	Chinese	41	6/24	6/12	14	14	Yes	Yes	6/7.5	6/6	14	14	Sectoral	Normal
F	Taiwan	Others	47	6/24	6/24	14	14	Yes	Yes	6/9	6/12	14	14	Sectoral	Normal
F	Malaysia	Indian	29	HM	6/36	ND	ND	Yes	Yes	6/12	6/12	ND	ND	ND	ND
F	Malaysia	Malay	48	6/60	6/24	ND	ND	No	No	6/9	6/9	ND	ND	Mild	Mild
F	Malaysia	Malay	20	PL	PL	ND	ND	No	No	PL	PL	ND	ND	Diffuse	Diffuse
F	Malaysia	Malay	13	HM	6/60	ND	ND	No	No	HM	6/60	ND	ND	Diffuse	Diffuse
M	Malaysia	Indian	14	ND	ND	ND	ND	Yes	Yes	ND	ND	ND	ND	Disc swelling	Disc swelling

OD = Oculus dexter (Right eye), OS = Oculus sinister (Left eye)
Va (Visual Acuity) measured in Snellen, with CF = Count fingers, HM = Hand motions, LP = Light perception only, NLP = No light perception.
Color vision measured using Ishihara color plates, with NC = No control (Unable to see the 1st plate) and the rest scored as number of correct plates out of 14.
Final disc appearance scored as diffuse, sectoral, or mild pallor, or normal. One patient had persistent disc swelling at last recorded visit.
ND = No data.



* 1 patient with missing data from Singapore

Figure 1. Visual acuity at nadir by country

have included only patients with unilateral optic neuritis.[4]

A recent US-based study, despite noticing an increase in the number of adult patients with acute bilateral optic neuritis, only managed to accumulate 15 patients (6.8%), including one patient with sarcoidosis, over a 4-year period in a large tertiary center which managed 220 patients with unilateral optic neuritis over the same time period.[22] Unfortunately, the ethnic origin of these patients was not mentioned. In marked contrast, the rate of acute bilateral optic neuritis is 16% in our prospective study, which is broadly comparable to other published reports in Asian patients.

In our study, there were no obvious demographic differences between those patients with bilateral and unilateral optic neuritis. Neither was there any difference in clinical outcome in terms of further development of either recurrent optic neuritis or other neurologic disease. Admittedly, our numbers are small, however, bilateral optic

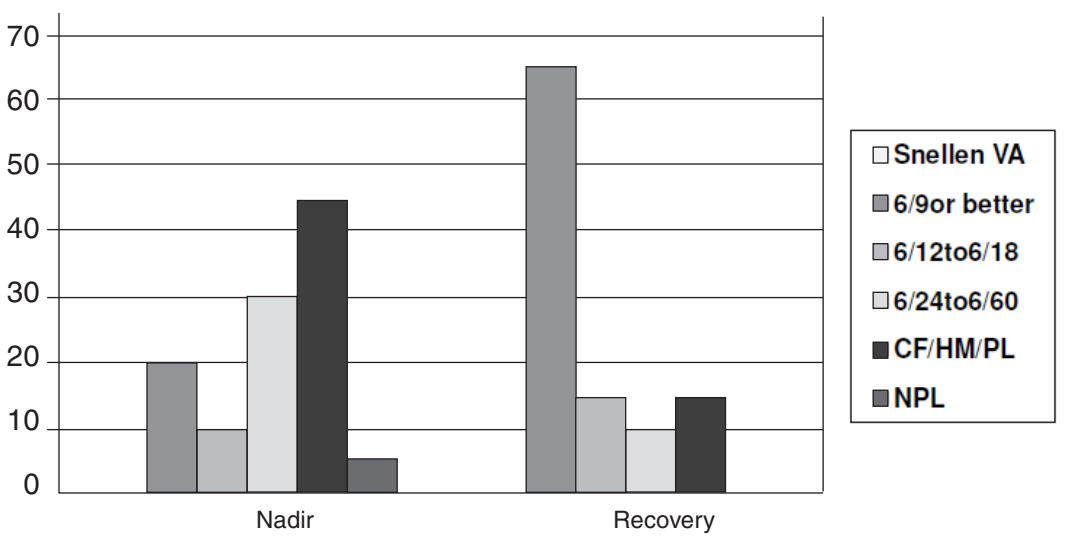


Figure 2. Final visual outcome

neuritis in the Asian context does not seem to be a different disease from unilateral optic neuritis.

The visual presentation of optic neuritis is also different in Asian patients compared to Caucasian patients. This has long been known to be the case for optic neuritis in African-American patients[23], but probably for the reasons stated above, has not been widely recognized for Asian patients. The current study determined that a greater proportion of male patients were affected (22.3%); this is in contrast to the usual female preponderance of 10:1.[24,25] The predominance of females with this condition was noted in 1995 when a male:female ratio of 1:1.22 was reported.[13] This finding was recently confirmed by Lin *et al*.[5] who had 46.8% male patients in their study.

Although in the current study visual acuity at nadir was severely affected in most of the patients a significant improvement was still observed. The majority of the patients had a final visual outcome of 6/12 or better. Most of the patients had no further events (88.5%) within the follow-up period, indicating that optic neuritis is usually a benign disease and does not bear a sinister prognosis. Of the 6 patients who had neurologic disease, 5 were found to have NMO and only 1 had classic MS. This is consistent with other reports that NMO is more common in Asian patients while classic MS is less common.[26,27] However, classic MS does exist in our population, and with the small numbers in this study we were unable to detect any predictive factors.

In terms of prognostic factors, it was surprising that neither bilateral optic neuritis nor a residual severe fixed visual defect, which were minor diagnostic criteria in the 1999 Wingerchuk criteria for NMO[15], were significant prognostic factors in our study. Rather, the strongest single risk factor for development of further episodes was severe visual loss (count fingers or worse) at presentation. Other nonsignificant risk factors included older age group (> 35 years), female gender and retrobulbar optic neuritis. The combination of severe visual loss in the setting of retrobulbar optic neuritis was statistically significant. (HR = 3.75, 95% CI 1.34 – 12.38, p = 0.020).

The primary limitation of this type of observational study is the lack of a standardised data collection protocol. Because optic neuritis is uncommon in the Asian population, the main priority was to collect sufficient patients to accurately study the long-term prognosis. As there are significant differences in the funding of investigations, including neuroimaging and serology, in the various countries studied, we were therefore unable to specify that any particular investigation be mandatory for study entry, without the introduction of selection bias towards patients from the higher socio-economic class (i.e. those able to self-pay for investigations). However, where financially possible, and consistent with good clinical practice, investigations including automated visual fields, neuroimaging and bloodwork for autoimmune, infective and nutritional conditions were obtained as mandated by local practice.

In conclusion, optic neuritis in Asian patients has significantly different presenting characteristics from the classic description, particularly with respect to a much higher proportion of bilateral optic neuritis, and a greater proportion of male patients, with severe visual loss at presentation. However, in the majority of the patients it is usually a benign disease, with good visual outcome and no further events. Severe visual acuity loss at onset was the most significant risk factor for developing further disease, followed by a trend towards retrobulbar neuritis, younger age, and female gender. The strongest risk factor was the combination of poor visual outcome and severe retrobulbar optic neuritis. Contrary to Wingerchuk *et al*.[15] bilateral optic neuritis and failure to recover vision were not risk factors for the development of subsequent disease. More research needs to be done to further clarify the interaction between these different factors.

Table 3. Prognostic factors

Risk factors	HR (95% CI)	P-value
Poor visual acuity	3.05 (1.04 – 8.97)	0.033
Older age (>35 years)	2.44 (0.88 – 6.74)	0.081
Female gender	0.26 (0.03 – 2.00)	0.164
Retrobulbar optic neuritis	3.38 (0.76 – 15.10)	0.170
Bilateral optic neuritis	0.46 (0.10 – 2.02)	0.430
Visual recovery	1.18 (0.26 – 5.40)	0.828

ACKNOWLEDGEMENTS

The authors would like to thank the following for their contribution to the manuscript: Jieh-Ren Jou, Department of Ophthalmology, National Taiwan University Hospital. 7, Chung-Shan South Road, Taipei, Taiwan; Dr. Nor Fadhilah Binti Mohamad, Department of Ophthalmology, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia.

DISCLOSURE

Financial support: The publication of this paper was financially supported in part by Merck Serono Singapore. The comments, views and conclusions set out in the manuscript represent those of the authors, independent of any influence from Merck Serono Singapore.

Conflict of interest: None

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