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The prevalence, clinical profile, and visual outcome of optic neuritis in Hospital Kuala Lumpur: a Malaysian perspective

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Abstract

Purpose: To study the clinical presentation, visual outcome, and predictors for both recurrence and poor visual recovery among optic neuritis (ON) patients in the Malaysian population.
Study design: Retrospective cohort study with longitudinal follow-up.
Methods: A total of 113 patients from the neuro-ophthalmology clinic fulfilling optic neuritis inclusion criteria within 4 weeks of onset were included. The study was conducted from May 2015 to June 2018. Demographic data, clinical findings, ophthalmological investigation, serological investigation, and imaging results were documented and tabulated. Patients were followed up to 1 year to assess the visual outcome and evidence of retinal nerve fibre layer (RNFL) thinning. Significant associative factors for recurrence and poor visual outcomes were identified using multivariate analysis.
Results: The age of the patients ranged from 13 to 71 years of age. The commonest age of presentation was 15–49 (67.3%) years of age. ON was predominant among Malays (65.5%), followed by Chinese (21.2%), and Indians (13.3%). The commonest form of ON was neuromyelitis optica spectrum disorder (NMOSD), which affected

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all ethnicities. Significant predictors for recurrence of ON were presentation within the 15–49 age group (p = 0.013) and presence of RNFL thinning following 1 year of treatment (p = 0.001). Indians had significantly lower odds of recurrence, 0.063 (p = 0.015). Significant variables associated with poor visual outcome > 6/18 were poor presenting vision > 6/18 (p < 0.001) and evidence of RNFL thinning following 1 year of treatment (p = 0.003). Females had better visual prognosis (p = 0.005) than males.
Conclusion: NMOSD was the commonest form of ON in our study population. The presenting age group of 15–49 along with the presence of RNFL thinning within 1 year of treatment were significantly associated with recurrence. Additionally, evidence of RNFL thinning and poor presenting vision > 6/18 were associated with a poor visual outcome. This group of patients will require regular monitoring and early access to treatment.

Keywords: Malaysia, optic neuritis, recurrence, visual outcome

Prevalen, profil klinikal dan ketajaman penglihatan selepas optik neuritis di Hospital Kuala Lumpur: perspektif dikalangan rakyat Malaysia

Abstrak

Objektif kajian: Bagi mengkaji manifestasi klinikal, ketajaman penglihatan, dan faktor ramalan kepada kemungkinan serangan ulangan dan ketajaman penglihatan yang kurang baik dikalangan pengidap optik neuritis (ON) di Malaysia
Reka bentuk: Kajian kohort retrospektif
Metodologi: Seramai 113 pesakit dari klinik neuro-oftalmologi yang memenuhi kriteria penyakit ON dalam tempoh 4 minggu penyakit ini bermula, tanpa mengira umur, bilangan pengulangan dan laterality mata telah direkrut antara Mei 2015 sehingga Jun 2018. Data demografi, penemuan klinikal, hasil ujian oftalmologi, ujian serologi dan hasil pengimejan telah didokumentasikan dan dijadualkan menurut kepelbagaian etnik. Pesakit disusuli selama setahun untuk menilai ketajaman penglihatan dan perubahan ukuran ketebalan lapisan gentian saraf retinal (RNFL). Faktor-faktor yang meramalkan keberulangan dan ketajaman penglihatan yang teruk telah dikenalpasti menggunakan analisis multivariasi.
Dapatan kajian: Kebanyakan pesakit kita tergolong di antara umur 15-49 (67.3%). Sebahagian besar penyakit ini melibatkan kaum Melayu (65.5%), diikuti kaum

Cina (21.2%) dan kaum India (13.3%). Neuromyelitis Optica Spectrum Disorder (NMOSD) merupakan punca utama ON dalam populasi kami dan penyakit ini melibatkan sebahagian besar kaum Cina. Faktor-faktor penting yang berkait dengan ramalan keberulangan ON adalah umur di antara 15-49 (p = 0.013), dan ukuran RNFL yang menjadi semakin nipis selepas setahun dalam rawatan (p = 0.001). Kaum India didapati berkemungkinan rendah untuk keberulangan penyakit ON (p = 0.015). Pesakit yang mempunyai kenipisan RNFLyang semakin rendah selepas rawatan dalam setahun (p = 0.001) serta penglihatan teruk >6/18 pada awalnya (p < 0.001) berpotensi tinggi untuk mendapat penglihatan yang teruk selepas setahun dalam rawatan. Majoriti pesakit perempuan didapati mempunyai penglihatan yang baik selepas setahun dalam rawatan (p = 0.005).
Kesimpulan: Penyakit NMOSD merupakan punca utama penyebab ON di kalangan masyarakat di Malaysia, terutamanya di kalangan kaum Cina. Kajian kita menunjukkan golongan pesakit berumur diantara 15-49 tahun dan ketebalan RNFL yang nipis selepas setahun dalam rawatan berisiko untuk mendapat penyakit ON berulang. Ketebalan RNFL yang nipis selepas rawatan serta datang dengan penglihatan teruk pada mulanya berisiko mendapat dengan hasil penglihatan teruk selepas setahun dalam rawatan. Golongan pesakit ini perlu pemantauan yang lebih kerap dan mendapat rawatan awal.

Kata kunci: kaum Melayu, keberulangan, ketajaman penglihatan, optik neuritis

Introduction

Optic neuritis (ON) is defined as an inflammation of the optic nerve, which can present in an acute or subacute manner.[1] It is a rare disease with an incidence rate of 5.1 in 100,000 per year in central Europe.[2] The results of the Optic Neuritis Treatment Trial (ONTT) were instrumental in the study of the presentation and treatment of ON. The landmark study later introduced a standardised treatment for ON that has been adopted widely to date, which is mainly applicable to clinically isolated syndrome (CIS) and multiple sclerosis (MS).[3]

The ONTT study was conducted in a Caucasian population, whereby the majority of ON cases were found to be associated with MS.[4] Other forms of demyelinating ON diseases and treatment responses were not well studied. The advancement of serological markers contributed to the discovery of new antibody-related ON, such as anti-aquaporin 4 (anti-AQP4) antibody and anti-myelin oligodendrocyte (anti-MOG) antibody, which have been recognised as a separate entity of demyelinating disease.[5] The demyelinating disease presentation is atypical of ON and does not respond well to the standard ONTT treatment regime. They are associated with treatment resistance, frequent recurrences, and poorer visual prognosis.[6,7]

We aim to determine the prevalence, clinical presentation of ON, identify predictors for recurrence of ON, evaluate the visual outcome after 1 year of treatment, and identify associative factors of poor visual outcome among our diversified population.

Methods

A retrospective cohort study was conducted on the prevalence and presentation of ON among the three different major ethnics in Hospital Kuala Lumpur's (HKL) Neuro-Ophthalmology Clinic from May 2015 to June 2018 with a 1-year minimum follow-up to assess the visual outcome. The study was approved by the Medical and Research Ethics Committee from Ministry of Health, Malaysia. In view of the rare nature of the disease, all patients that met the inclusion criteria were included in the study.

We included patients who presented with ON features for less than 4 weeks, all ages, and any number of attacks fulfilling all four criteria of optic neuritis. The criteria were unilateral or bilateral decreased visual acuity measured using Snellen chart, unilateral or bilateral impaired colour vision using Ishihara test, presence of relative afferent pupillary defect (unless there was bilateral involvement), and the presence of visual field defect as evident in Humphrey visual field test. This included ON patients with evidence of infectious and autoimmune serological presentations, cerebrospinal fluid, oligoclonal band positive, and positive radiological evidence of demyelinating lesion.

We excluded patients with poor media clarity, ON of other causes, and patients who were unable to complete a 1-year follow up. A total of 113 patients with ON fulfilling the inclusion criteria were recruited and assigned to an anonymous research number. Relevant data obtained included demographic data, history of clinical presentation, clinical examination findings, ophthalmological investigation results such as Humphrey Visual Field Analyzer 30-2 and Heidelberg Spectralis optical coherence tomography (OCT) of the retinal nerve fibre layer (RNFL). Relevant investigation results were venereal disease research laboratory (VDRL), Mantoux, antinuclear antibody (ANA), rheumatoid factor (RF), anti-AQP4 antibody, oligoclonal bands immunoglobulin G (IgG), and anti-MOG antibody. Radio-imaging findings based on magnetic resonance imaging (MRI) with a number of sites of involvement (spine, brain, optic nerve) were recorded.

Patients were categorised based on diagnosis of ON as defined in Table 1. ON diagnosis was further subcategorised into typical and atypical ON. CIS and MS were classified as typical ON, whereas the remaining types of ON were classified as atypical ON. This classification is in accordance with a review for typical and atypical ON.[8]

Data obtained were tabulated and analysed via Statistical Package for Social

Table 1. Aetiological definitions of optic neuritis

No	Diagnosis	Definition of disease
1	Multiple sclerosis (MS)	Demyelination of the central nervous system (CNS) disseminated in time and space (Mc Donald's revised criteria 2017)
2	Neuromyelitis optica spectrum disorder (NMOSD)	Inflammatory CNS syndrome associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) fulfilling the International Panel for NMO Diagnosis (IPND) criteria (IPND)
3	Clinically isolated syndrome (CIS)	First episode of neurologic symptoms lasting for 24 hours as a result of inflammation or demyelination of CNS (National MS Society)
4	Chronic relapsing inflammatory optic neuropathy (CRION)	Relapsing inflammatory optic neuritis with steroid dependency; diagnosis of exclusion (Lee HJ, 2018)
5	Acute disseminated encephalomyelitis (ADEM)	Non-infectious, acute, inflammatory demyelinating events of the CNS, fulfilling the International Paediatric Multiple Sclerosis Study Group updated consensus. A diagnosis of exclusion (Daniela Pohl, 2016)
6	Parainfectious	Follows the onset of a viral infection by 1–3 weeks, can occur as a postvaccination phenomenon (Myron Yanoff, 2009)
7	Myelin oligodendrocyte glycoprotein (MOG) optic neuritis	Antibody-mediated demyelinating disease of the CNS, distinct from other demyelinating processes of the CNS *e.g.*, MS or NMOSD (AAO – Eyewiki)

CNS: central nervous system

Sciences version 26.0. Following 1 year of treatment, vision was reassessed based on Snellen chart and best-corrected vision via refraction. RNFL measurement by OCT was performed by the same operator during the follow-up. Vision based on Snellen chart was converted into logMAR and categorised based on WHO categorisation of visual impairment. For the purpose of analysing the visual outcome, vision was further classified into good vision ≥ 6/18 and poor vision < 6/18 for presenting vision and final visual outcome. Visual categorisation was based on a study on ON by Hansapinyo *et al.* Demographic data were analysed using descriptive analysis. All categorical data associated with recurrence and poor visual outcome were analysed using Chi-square test. Statistically significant variables were further analysed using multivariate analysis via binary logistic regression. A p-value < 0.05 was accepted as statistically significant.

Results

Demographics and types of ON

A total of 159 eyes of 113 patients who completed the 1-year follow-up were studied. None of the patients dropped out of the study. In the year 2015, the prevalence was 3.8977 per 100,000 outpatients over a period of 6 months. As for the year 2016, the prevalence was 5.001 per 100,000 outpatients, followed by a slight increment to 5.012 per 100,000 outpatients in year 2017. Table 2 summarises the prevalence of ON from 2015 to 2017.

Forty-one (36.3%) were diagnosed with neuromyelitis optica spectrum disorder (NMOSD), followed by 23 (20.4%) patients with CIS, 21 (18.6%) patients with MS, 15 (13.3%) patients with infectious ON, 6 (5.3%) patients with parainfectious ON, 3 (2.7%) patients with chronic relapsing inflammatory optic neuropathy (CRION), 2 (1.8%) patients with anti-MOG ON, and 2 (1.8%) patients with other causes of autoimmune ON.

In terms of age, the majority of patients 76 (67.3%) were between the ages of 15 and 49 years. Seventeen (15%) patients were below the age of 15 years and 20 (17.7%) presented above 49 years of age. In general, there was female preponderance, with 82 (72.6%) female patients and 31 (27.4%) male patients. The predominant race in our study was Malay with 74 (65.5%) patients, followed by Chinese with 24 (21.2%), and Indian with 15 (13.3%).

Table 2. Prevalence of ON in Hospital Kuala Lumpur

Year	Total ON patients (*n*)	Total outpatients (*n*)	Population (*n*/100,000 population)
2015 (May–Dec)	32	820,992	3.8977
2016	42	839,731	5.001
2017	37	738,228	5.012

ON: optic neuritis

Racial distribution of ON

Table 3 illustrates the racial distribution and clinical profile of ON diseases among the different races. Within the Malay group, the commonest cause of ON was NMOSD with 22 (19.5%) patients, MS with 18 (15.9%) patients, and CIS with 16 (14.2%) patients. However, within the Chinese group, we noticed a significant proportion of NMOSD 15 (13.3%) patients, followed by a minority in infectious ON 5 (4.5%) patients, and CIS 2 (1.7%) patients. As for the Indian group, CIS was found in 5 (4.5%) patients, NMOSD was found in 4 (3.5%) patients, and MS was found in 2 (1.7%) patients. The commonest age of presentation was 15–49 years old ($p = 0.017$) for all three races. The Malay group demonstrated a tendency of presentation at an earlier age < 15 (12.4%) compared to Chinese (0.9%) and Indian (1.7%). Female preponderance was

seen among all races. Most patients presented as unilateral ON (59.3%). Most did not have a history of recurrence (67.3%), did not experience pain (69.9%), and did not have disc swelling (75.2%). More than half (57.5%) our patients did not manifest RNFL thinning following 1 year of follow-up.

Table 3. Racial distribution of optic neuritis clinical profile

Variables	**Total** ***n*** **(%)**	**Malay** ***n*** **(%)**	**Chinese** ***n*** **(%)**	**Indian** ***n*** **(%)**	**Univariate** ***P*****-value***
Diagnosis					
MS	21 (18.5)	18 (15.9)	1 (0.9)	2 (1.7)	0.141
NMOSD	41 (36.3)	22 (19.5)	15 (13.3)	4 (3.5)	
CIS	23 (20.4)	16 (14.2)	2 (1.7)	5 (4.5)	
CRION	3 (2.6)	3 (2.6)	0 (0)	0 (0)	
ADEM	2 (1.8)	2 (1.7)	0 (0)	0 (0)	
Parainfectious	6 (5.3)	4 (3.5)	1 (0.9)	1 (0.9)	
Anti-MOG	2 (1.8)	1 (0.9)	0 (0)	1 (0.9)	
Infection	15 (13.3)	8 (7.2)	5 (4.5)	2 (1.7)	
Age (years)					
< 15	17 (15.0)	14 (12.4)	1 (0.9)	2 (1.7)	0.017
15–49	76 (67.3)	53 (46.9)	14 (12.4)	9 (8.0)	
> 49	20 (17.7)	7 (6.2)	9 (8.0)	4 (3.5)	
Gender					
Male	31 (27.4)	21 (18.5)	7 (6.2)	3 (2.6)	0.784
Female	82 (72.6)	53 (47.0)	17 (15.0)	12 (10.6)	
Laterality					
Unilateral	67 (59.3)	42 (37.2)	14 (12.4)	11 (9.7)	0.489
Bilateral	46 (40.7)	32 (28.4)	10 (8.8)	4 (3.5)	
Recurrence					
Yes	37 (32.7)	28 (24.7)	8 (7.1)	1 (0.9)	0.064
No	76 (67.3)	46 (40.7)	16 (14.2)	14 (12.4)	
Pain					
Yes	34 (30.1)	23 (20.4)	8 (7.2)	3 (2.6)	0.644
No	79 (69.9)	51 (45.0)	16 (14.2)	12 (10.6)	
OD swelling					
Yes	28 (24.8)	19 (16.8)	5 (4.5)	4 (3.5)	0.878
No	85 (75.2)	55 (48.7)	19 (16.8)	11 (9.7)	

Variables	Total *n* (%)	Malay *n* (%)	Chinese *n* (%)	Indian *n* (%)	Univariate *P*-value*
RNFL thinning (at year 1)					
Yes	48 (42.5)	28 (24.7)	12 (10.6)	8 (7.1)	0.381
No	65 (57.5)	46 (40.7)	12 (10.6)	7 (6.2)	

MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; CIS: clinically isolated syndrome; CRION: chronic relapsing inflammatory optic neuropathy; ADEM: acute disseminated encephalomyelitis; ANTIMOG: myelin oligodendrocyte antibody; OD: optic disc; RNFL: retinal nerve fibre layer
*$P < 0.05$ is statistically significant (Chi-square test).

Comparing atypical with typical ON

As illustrated in Table 4, the common age group presenting with both typical and atypical ON was 15–19 years old. Atypical ON presented at near equal proportion for extreme age groups of < 15 years (14.2%) and > 49 years (15.0%) old. In contrast, typical ON rarely presented in the extreme age groups of > 49 years old (2.6%) and < 15 years old (0.9%). Atypical ON was shown to be predominantly affecting all the 3 major races. On the other hand, typical ON mostly affected the Malay group (15.9%) and rarely presented in the Chinese (0.9%) and Indian groups (2.6%). Female preponderance was still seen among both types of ON.

Table 4. Comparison of typical and atypical optic neuritis

Variable	Total (*n*) (%)	Typical ON (*n*) (%)	Atypical ON (*n*) (%)	Univariate	Multivariate	
				P-value	Odds ratio (95% CI)	*P*-value
Age						
< 15	17 (15.0)	1 (0.9)	16 (14.2)	0.259		
15–49	76 (67.3)	17 (15.0)	59 (52.3)			
> 49	20 (17.7)	3 (2.6)	17 (15.0)			
Race						
Malay	74 (65.5)	18 (15.9)	56 (49.5)	0.075		
Chinese	24 (21.2)	1 (0.9)	23 (20.4)			
Indian	15 (13.3)	2 (1.8)	13 (11.5)			
Gender						
Male	31 (27.4)	4 (3.5)	27 (23.9)	0.340		
Female	82 (72.6)	17 (15.0)	65 (57.5)			

Variable	Total (*n*) (%)	Typical ON (*n*) (%)	Atypical ON (*n*) (%)	Univariate	Multivariate	
				P-value	Odds ratio (95% CI)	*P*-value
Laterality*						
Unilateral	67 (42.1)	13 (8.1)	54 (34.0)	0.746		
Bilateral	92 (57.9)	16 (10.1)	76 (47.8)			
Recurrence*						
Yes	51 (32.1)	10 (6.3)	41 (25.8)	0.759		
No	108 (67.9)	19 (11.9)	89 (56.0)			
Pain*						
Yes	45 (28.3)	6 (3.8)	39 (24.5)	0.314		
No	114 (71.7)	23 (14.5)	91 (57.2)			
OD swelling*						
Yes	40 (25.2)	3 (1.89)	37 (23.2)	0.042		
No	119 (74.8)	26 (16.4)	93 (58.6)			
RNFL thinning (at 1 year)*						
Yes	67 (42.1)	11 (6.9)	56 (35.2)	0.612		
No	92 (57.9)	18 (11.3)	74 (46.6)			
Presenting vision*						
≤ 6/18	50 (31.4)	9 (5.7)	41 (25.8)	0.958		
> 6/18	109 (68.6)	20 (12.6)	89 (55.9)			
Visual outcome*						
≤ 6/18	111 (69.8)	25 (15.7)	86 (54.1)	0.033		
> 6/18	48 (30.2)	4 (2.5)	44 (27.7)		4.055 (1.264–13.009)	0.019
MRI sites*						
0	59 (37.1)	2 (1.3)	57 (35.8)	0.001		0.009
1	94 (59.1)	27 (17.0)	67 (42.1)		0.095 (0.021–0.425)	0.002
> 1	6 (3.8)	0 (0.0)	6 (3.8)			0.999

ON: optic nerve; OD: optic disc; RNFL: retinal nerve fibre layer; MRI: magnetic resonance imaging

$p < 0.05$ is statistically significant (univariate analysis = Chi square test; multivariate analysis = binary logistic regression).

*Calculated based on number of eyes.

Unilateral ON was the predominant presentation in both typical and atypical ON. Nevertheless, the fraction of bilateral ON presentation was slightly higher within the atypical ON group compared to the typical ON group. The majority of both typical and atypical ON did not have history of recurrence. However, as many as one-third of our ON patients had history of recurrence. Most of typical and atypical ON patients did not experience pain. Only one-fourth of our patients presented with pain, and the proportion of pain was greater in the atypical ON group compared to the typical ON group. In both typical and atypical ON, disc swelling was uncommon. Despite that, disc swelling was more frequently seen in the atypical ON group. In terms of presenting vision, both typical and atypical ON presented with nearly similar proportions of good vision ≤ 6/18 and poor vision > 6/18 within the respective groups. Good visual outcome, > 6/18 after 1 year of treatment was noted to be better in the typical ON group compared to the atypical ON group. Atypical ON, on the other hand, had a greater fraction of poor visual outcome ≤ 6/18 following 1 year of treatment. The presence of RNFL thinning at 1 year of follow-up was greater in the atypical ON group (35.2.%) compared to the typical ON group (6.9%). MRI lesions involving multiple sites (> 1) was only seen in atypical ON. Most typical ON had at least one MRI lesion. The proportion without MRI lesions was greater in the atypical ON group. From multivariate analysis, there seemed to be a significant association

Table 5. Positive laboratory results

Diagnosis	**Serology**					
	ANA	**RF**	**AntiSSARO**	**AntiAQP4**	**Oligoclonal band**	**ANTIMOG**
MS	1	0	0	0	2	0
NMOSD	1	2	2	26	0	0
CIS	0	0	0	0	0	0
CRION	0	0	0	0	0	0
ADEM	0	0	0	0	0	0
Parainfectious	0	0	0	0	0	0
ANTIMOG	1	0	0	0	0	2
Infectious	0	0	0	0	0	0
Total	3	2	2	26	2	2

MS: multiple sclerosis; NMOSD: neuromyelitis optica spectrum disorder; CIS: clinically isolated syndrome; CRION: chronic relapsing inflammatory optic neuropathy; ADEM: acute disseminated encephalomyelitis; ANTIMOG: myelin oligodendrocyte antibody; ANA: antinuclear antibody; RF: rheumatoid factor; AntiSSARO: anti–Sjögren's-syndrome-related antigen A autoantibodies; AntiAQP4: aquaporin 4 antibody

of poor visual outcome > 6/18 following 1 year of treatment within the atypical ON group ($p = 0.019$) with an odds ratio of 4.055. There was also a significant association between MRI lesions in only one site within typical ON ($p = 0.002$) and absence of MRI lesion within the atypical ON group ($p = 0.009$)

Serology results

As shown in Table 5, NMOSD had the most significant association with other autoimmune serology. More than half of NMOSD patients (26/41, 63.4%) were positive for anti-AQP4 antibody. Among patients with positive anti-AQP4 antibody, two NMOSD patients had overlapping syndrome with positive anti-SSARO antibody, while two patients were positive for RF, and one patient had positive ANA. We only had two MS patients: one with positive oligoclonal band and one with positive ANA. Two of our patients had MOG antibody and of them, 1 patient had ANA serology positive. Our patients with CRION and CIS did not display any evidence of other autoimmune associations.

Infectious and parainfectious ON aetiology

We had 15 patients within the infectious ON group. All patients tested positive for *Mycobacterium tuberculosis*. There were six patients who were treated as parainfectious ON with a history of preceding upper respiratory tract infection.

Analysis of recurrent ON

As shown in Table 6, there was a statistically significant association between the 15–49 age group ($p = 0.013$) and ON recurrence. Conversely, patients who presented with ON below the age of 15 years were associated with reduced recurrence ($p = 0.024$). The Malay group showed significant association with ON recurrence ($p = 0.038$). In contrast, the Indian group was significantly associated with having no ON recurrence ($p = 0.015$). Additionally, there was also a significant association between the presence of RNFL thinning following 1 year of treatment with ON recurrence ($p = 0.001$).

Analysis of poor visual outcome

As seen in Table 7, female gender was significantly associated with having a better visual outcome ≥ 6/18 ($p = 0.005$) following 1 year of treatment. Poor presenting vision > 6/18 was significantly associated with a poor visual outcome > 6/18 ($p < 0.001$). Additionally, the presence of RNFL thinning after 1 year of treatment was significantly associated with a poorer visual outcome ($p = 0.003$).

Table 6. Variables associated with optic neuritis recurrence

Variables	Total (*n*)	Recurrence		Univariate analysis	Multivariate analysis	
		Yes (*n*) (%)	No (*n*) (%)	*P*-value	Odds ratio (95% CI)	*P*-value
Age*						
< 15	23 (14.5)	4 (2.5)	19 (11.9)	0.013	-	0.024
15–49	109 (68.5)	43 (27.0)	66 (41.6)		8.142 (1.548–42.829)	0.013
≥ 50	27 (17.0)	4 (2.5)	23 (14.5)		2.903 (0.393–21.438)	0.296
Race*						
Malay	106 (66.7)	40 (25.2)	66 (41.5)	0.019	-	0.038
Chinese	34 (21.4)	10 (6.3)	24 (15.1)		0.520 (0.168–1.610)	0.257
Indian	19 (11.9)	1 (0.6)	18 (11.3)		0.063 (0.007–0.579)	0.015
Gender*						
Male	44 (27.7)	12 (7.5)	32 (20.1)	0.422		
Female	115 (72.3)	39 (24.5)	76 (47.9)			
Laterality*						
Unilateral	67 (42.1)	23 (14.5)	44 (27.7)	0.603		
Bilateral	92 (57.9)	28 (17.5)	64 (40.3)			
Pain*						
Yes	45 (28.3)	16 (10.1)	29 (18.2)	0.555		
No	114 (71.7)	35 (22.0)	79 (49.7)			
OD swelling*						
Yes	40 (25.2)	7 (4.4)	33 (20.8)	0.022	0.680 (0.234 – 1.975)	0.478
No	119 (74.8)	44 (27.7)	75 (47.1)		-	-
RNFL thinning*						
Yes	67 (42.1)	33 (20.8)	34 (21.4)	< 0.001	4.020 (1.735 – 9.315)	0.001
No	92 (57.9)	18 (11.3)	74 (46.5)		-	-

Variables	Total (*n*)	Recurrence		Univariate analysis	Multivariate analysis	
		Yes (*n*) (%)	No (*n*) (%)	*P*-value	Odds ratio (95% CI)	*P*-value
ANA*						
Yes	5 (3.1)	4 (2.5)	1 (0.6)	0.02	12.072 (0.819 – 177.962)	0.070
No	154 (96.9)	47 (29.6)	107 (67.3)		-	-
AntiAQP4*						
Yes	33 (20.8)	17 (10.6)	16 (10.1)	0.007	2.483 (0.840 – 7.340)	0.100
No	126 (79.2)	34 (21.4)	92 (57.9)		-	-
RF*						
Yes	2 (1.3)	2 (1.3)	0 (0)	0.038		0.999
No	157 (98.7)	49 (30.8)	108 (67.9)			
AntiSSARO*						
Yes	3 (2.0)	3 (1.9)	0 (0)	0.011		0.999
No	156 (98.0)	48 (30.2)	108 (67.9)			
Oligoclonal band*						
Yes	3 (2.0)	1 (0.6)	2 (1.3)	0.962		
No	156 (98.0)	50 (31.4)	106 (66.7)			
ANTIMOG*						
Yes	3 (2.0)	2 (1.3)	1 (0.6)	0.195		
No	156 (98.0)	49 (30.8)	107 (67.3)			
MRI sites*						
0	59 (37.1)	13 (8.2)	46 (28.9)	0.034	-	0.612
1	94 (59.1)	34 (21.4)	60 (37.7)		1.205 (0.476–3.054)	0.694
> 1	6 (3.8)	4 (2.5)	2 (1.3)		2.962 (0.342–25.659)	0.324
Presenting vision*						
≤ 6/18	50 (31.4)	10 (6.3)	40 (25.2)	0.027	1.221 (0.444–3.356)	0.699

Variables	Total (*n*)	Recurrence		Univariate analysis	Multivariate analysis	
		Yes (*n*) (%)	No (*n*) (%)	*P*-value	Odds ratio (95% CI)	*P*-value
> 6/18	109 (68.6)	41 (25.8)	68 (42.7)		-	-
Visual outcome*						
≤ 6/18	111 (69.8)	28 (17.6)	83 (52.2)	0.005	1.340 (0.470–3.821)	0.585
> 6/18	48 (30.2)	23 (14.5)	25 (15.7)			

ANTIMOG: myelin oligodendrocyte antibody; ANA: antinuclear antibody; RF: rheumatoid factor; AntiSSARO: anti–Sjögren's-syndrome-related antigen A autoantibodies; AntiAQP4: aquaporin 4 antibody; OD: optic disc; RNFL: retinal nerve fibre layer; MRI: magnetic resonance imaging

$P < 0.05$ is statistically significant (univariate analysis = Chi-square test; multivariate analysis = binary logistic regression).

*Calculated based on number of eyes.

Table 7. Variables associated with poor visual outcome

Variables	Total (*n*)	Vision after 1 year of treatment		Univariate analysis	Multivariate analysis	
		Vision ≥ 6/18 (*n*) (%)	Vision < 6/18 (*n*) (%)	*P*-value	OR (95% CI)	*P*-value
Gender*						
Male	44 (27.7)	25 (15.7)	19 (12.1)	0.027	1	-
Female	115 (72.3)	86 (54.1)	29 (18.1)		0.244 (0.091–0.653)	0.005
Age*						
< 15	23 (14.5)	19 (12.1)	4 (2.5)	0.295		
15–49	109 (68.5)	75 (47.1)	34 (21.4)			
≥ 50	27 (17.0)	17 (10.6)	10 (6.3)			
Race*						
Malay	106 (66.7)	76 (47.9)	30 (18.9)	0.507		
Chinese	34 (21.4)	21 (13.2)	13 (8.2)			
Indian	19 (11.9)	14 (8.8)	5 (3.0)			

Variables	Total (*n*)	Vision after 1 year of treatment		Univariate analysis	Multivariate analysis	
		Vision ≥ 6/18 (*n*) (%)	Vision < 6/18 (*n*) (%)	*P*-value	OR (95% CI)	*P*-value
Laterality*						
Unilateral	67 (42.1)	43 (27.0)	24 (15.1)	0.187		
Bilateral	92 (57.9)	68 (42.8)	24 (15.1)			
Recurrence*						
Yes	51 (32.1)	28 (17.6)	23 (14.5)	0.005	1.291 (0.507–3.288)	0.593
No	108 (67.9)	83 (52.2)	25 (15.7)		1	-
Pain*						
Yes	45 (28.3)	30 (18.9)	15 (9.4)	0.587		
No	114 (71.7)	81 (50.9)	33 (20.8)			
OD swelling*						
Yes	40 (25.2)	29 (18.2)	11 (6.9)	0.669		
No	119 (74.8)	82 (51.6)	37 (23.3)			
RNFL thinning*						
Yes	67 (42.1)	35 (22.0)	32 (20.1)	< 0.001	3.856 (1.567 – 9.489)	0.003
No	92 (57.9)	76 (47.8)	16 (10.1)		1	-
ANA*						
Yes	5 (3.1)	2 (1.3)	3 (2.0)	0.140		
No	154 (96.9)	109 (68.6)	45 (28.1)			
AntiAQP4*						
Yes	33 (20.8)	17 (10.7)	16 (10.1)	0.010	1.556 (0.557 – 4.344)	0.399
No	126 (79.2)	94 (59.1)	32 (20.1)		1	-
RF*						
Yes	2 (1.3)	1 (0.6)	1 (0.6)	0.539		
No	157 (98.7)	110 (69.2)	47 (29.6)			

Variables	Total (*n*)	Vision after 1 year of treatment		Univariate analysis	Multivariate analysis	
		Vision ≥ 6/18 (*n*) (%)	Vision < 6/18 (*n*) (%)	*P*-value	OR (95% CI)	*P*-value
AntiSSARO*						
Yes	3 (2.0)	2 (1.3)	1 (0.6)	0.905		
No	156 (98.0)	109 (68.5)	47 (29.6)			
ANTIMOG*						
Yes	3 (2.0)	2 (1.3)	1 (0.6)	0.905		
No	156 (98.0)	109 (68.5)	47 (29.6)			
Oligoclonal band*						
Yes	3 (2.0)	2 (1.3)	1 (0.6)	0.905		
No	156 (98.0)	109 (68.5)	47 (29.6)			
MRI sites*						
0	59 (37.1)	41 (25.9)	18 (11.4)	0.762		
1	94 (59.1)	65 (40.9)	29 (18.2)			
> 1	6 (3.8)	5 (3.0)	1 (0.6)			
Presenting vision*						
≤ 6/18	50 (31.4)	49 (30.8)	1 (0.6)	< 0.001	1	-
> 6/18	109 (68.6)	62 (39.0)	47 (29.6)		37.647 (4.728 –299.799)	< 0.001

ANTIMOG: myelin oligodendrocyte antibody; ANA: antinuclear antibody; RF: rheumatoid factor; AntiSSARO: anti–Sjögren's-syndrome-related antigen A autoantibodies; AntiAQP4: aquaporin 4 antibody; OD: optic disc; RNFL: retinal nerve fibre layer; MRI: magnetic resonance imaging

P < 0.05 is statistically significant (univariate analysis = Chi-square test; multivariate analysis = binary logistic regression).

*Calculated based on number of eyes.

Discussion

The prevalence of ON in our study population was 5.001–5.012/100,000 per year. A similar incidence of 5/100,000 per year has been reported in a study conducted in central Europe.[2] Our study compared the clinical profile of ON among the three main races (Malays, Chinese and Indians) in our diverse population. We found that the main causes of ON in our study population were NMOSD (36.3%), CIS (20.4%), and MS (18.6%). Similarly, Hansapinyo reported that the main cause of ON in Thailand was NMOSD (38.7%) as opposed to MS (15.3%).[9] Additionally, a Singaporean population based study by Lim *et al.* concluded that the incidence of MS-related ON is significantly lower in Singapore in comparison to the ONTT study.[10] Moreover, a recent systematic review and meta-analysis demonstrated that the prevalence of anti-AQP4- and anti-MOG-related ON antibodies were more common in Asian than Western populations.[11] Hence, our study supports the growing evidence that NMOSD might be more common in South East Asia compared to Western countries.

In our study, a greater proportion of Chinese patients had NMOSD. This appears to be consistent with a local neurology study reported by Viswanathan that their Chinese cohort had a greater NMOSD to MS ratio of 2:1 with significant seropositivity of anti-AQP4 antibody. It was postulated that the Chinese group is genetically susceptible to the disease.[12]

We found that the 15–49 age group tends to experience ON recurrence. This is consistent with a recent international outcome prediction study of NMOSD showing that the age group below 35 years has the tendency to present with ON at onset and is associated with frequent recurrences and higher incidence of blindness. On the other hand, the older age groups often presented with myelitis.[13] However, in our study, the association with blindness in the younger age group was insignificant. Female preponderance was seen throughout all races. Consistently, Woung reported female predominance of ON groups in both Asian and Western countries. It was postulated that the female gender is more susceptible to autoimmune disease.[14]

Our study demonstrated that most of typical and atypical ON manifested with common overlapping clinical features that can hardly be differentiated. The common age group for presentation of both typical and atypical ON was 15–49 years of age. Atypical ON was shown to be affecting the extreme ages of < 15 years (14.2%) and > 49 years (15.0%) more than typical ON. This finding is consistent with the ONTT 1992 study. Atypical ON was shown to be the predominant disease affecting all three major races. However, typical ON mainly affected the Malay group (15.9%) and was rarely present in the Chinese (0.9%) and Indian (2.6%) groups. MRI lesions involving multiple sites (> 1) was only seen in atypical ON. Most typical ON had at least one MRI lesion. The proportion without MRI lesions was greater in the atypical ON group. The atypical ON group was significantly associated with poor visual outcome > 6/18 following 1 year of treatment ($p = 0.019$).

Most patients in our study group (75.2%) did not have disc swelling (retrobulbar ON). Our finding is in concurrence with the ONTT 1992 study, which reported that the majority (64.7%) presented without disc swelling.[3] Patients who presented with optic disc oedema were mostly associated with infectious ON (80%) and parainfectious ON (33.3%).

Presentation of pain appeared to be lower in our study population (30.1%), in contrast to the ONTT group (92%).[3] A possible reason is that most of our ON patients consisted of atypical ON as compared to the ONTT study.

As for association with recurrence of ON, the 15–49 age group was more susceptible to recurrence (p = 0.013). In contrast, patients < 15 years were found to have a lower risk of recurrence (p = 0.024). The Indian group seemed to have a significant lower odds ratio of 0.063 for recurrence (p = 0.015). The presence of RNFL thinning following 1 year of treatment was also associated with a higher likelihood of recurrence (p = 0.001).

In terms of poor visual outcome analysis, the female gender was associated with a greater potential of a good visual outcome (p = 0.005). The presence of RNFL thinning following 1 year of tratment was associated with a poor visual outcome. Most of the RNFL thinning in our study was found in the NMOSD group. In consonance, Noval *et al.* reported that NMOSD was associated with severe RNFL thinning and a poorer visual prognosis.[15] Poor presenting vision was found to have a great odds ratio (37.647) of developing poor visual outcome (p < 0.001). In agreement with our findings, Hansapinyo *et al.* similarly reported male gender and poor presenting vision to be independent predictive factors of poor visual outcome.[9]

The limitation of our study is its retrospective design involving a single institution review and limited sample size. However, the neuro-ophthalmology clinic in HKL is the only tertiary governmental neuro-ophthalmology centre to which most of the cases are referred. Some of the cases could possibly be recurrent or poorly responding ON with guarded prognosis.

Conclusion

Our study is the first in Malaysia to compare the clinical profile of ON among the diversified races in our study population. NMOSD was the main cause of ON in our study population. A significant factor associated with poor visual outcome was presenting vision worse than 6/18. A factor significantly associated with recurrence was presentation between the ages of 15 and 49 years. Evidence of RNFL thinning following 1 year of treatment may also predict recurrence and poor long-term visual outcome. Our patients require regular and combined neuro-ophthalmology and neuro-medical follow-up and immediate access to treatment to attain a better visual prognosis.

Declarations

Ethics approval and consent to participate

The study was approved by the Medical and Research Ethics Committee from Ministry of Health, Malaysia.

Competing interests

None to declare.

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