Clinical Profile and Aetiology of Optic Neuritis in Hospital Universiti Sains Malaysia – 5 Years Review

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SUMMARY

Although few studies concerning optic neuritis (ON) in Asian countries have been reported, there is no report about ON in Malaysia particularly within the Malay population. We aimed to determine the clinical manifestation, visual outcome and aetiology of ON in Malays, and discussed the literature of ON studies in other Asian populations. This was a retrospective study involving 31 consecutive patients (41 eyes) with ON treated at Hospital Universiti Sains Malaysia commencing from July 2005 till January 2010 with a period of follow-up ranging from 18-60 months. The clinical features, laboratory results, possible aetiology, and visual acuity after one year were analysed. Females were the predominant group. The age of the patients ranged between 3-55 years and peaked between 21-30 years old. 67.7% of the patients had unilateral involvement. Pain on ocular movement was observed in 31.7% of the affected eyes. 73.3% of 41 involved eyes showed visual acuity equal 6/60 or worse on presentation. Paracentral scotoma was the most common visual field defect noted. Optic disc papillitis proved more widespread compared to the retrobulbar type of ON. The aetiology was idiopathic in more than 50%, while the risk of multiple sclerosis was extremely low (3.2%) in our series. 66.0% demonstrating visual acuity improved to 6/12 or better at one year after the attack. 16.1% showed evidence of recurrence during follow-up. In conclusion, the clinical profile and aetiology of ON in Malay patients are comparable to other ON studies reported by other Asian countries.

KEY WORDS:
Optic neuritis, Malay

INTRODUCTION

Optic neuritis (ON) is an inflammatory optic neuropathy, but most frequently indicates an acute disease of the optic nerve due to focal inflammation associated with demyelination[1]. As a rule, it usually affects patients between 15-45 years of age; women in particular. The diagnosis of ON is mainly clinical, based on the patient's history and clinical results, despite the availability of neuroimaging and laboratory findings.

Optic Neuritis Treatment Trial (ONTT) is a multi-centered randomized clinical trial conducted in the United States of America (USA) and has established a consistent treatment protocol for ON[2]. However, earlier reports concerning ON in Asian countries[3-9] have revealed different clinical profiles compared to Caucasian studies.

There is a limited data regarding ON in Malaysia with only few published case reports[10-16]. The attack of ON was attributed to hepatitis C infection[11], pansinusitis[12], varicella zoster infection[13] and systemic lupus erythematosus[14] in these reports. Thus, our study was aimed to determine the clinical manifestations, visual outcome and aetiology in patients with ON within the Malay population, and discussed the literature review of ON in Asian countries.

MATERIALS AND METHODS

A retrospective chart review was performed on 31 Malay patients (41 eyes) being treated with ON at Hospital Universiti Sains Malaysia beginning in the month of July 2005 until January 2010 with a follow-up period ranging from 18 to 60 months. The study was conducted according to the Declaration of Helsinki, and the study protocol was approved by the Research and Ethical Committee, School of Medical Sciences, Universiti Sains Malaysia.

Hospital Universiti Sains Malaysia is a teaching hospital in Malaysia equipped with neurology and neuro-ophthalmology services. It is located in the north-east of Peninsular Malaysia and serves as the main referral centre for neurology cases in the East Coast of Peninsular Malaysia. The states along the East Coast of Peninsular Malaysia include Kelantan, Terengganu and Pahang with a total estimated population of 3.8 million people in 2007. Kelantan, Terengganu and Pahang cover an area of about 63, 846 km^2. About 90% of our local population are Malay with the remaining deriving from Chinese, Siamese, Indian roots and the indigenous Orang Asli.

Patients who were included into our database fulfilled the following criteria:

(a) Acute loss of visual acuity or visual field, with or without eye pain.
(b) At least one of the following abnormalities; relative afferent pupillary defect, a nerve fibre bundle visual field defect, abnormal visual evoked potential.

Patients were excluded if they showed any evidence of compressive, vascular, toxic, metabolic, infiltrative, or

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hereditary optic neuropathy. We also excluded those who had retinal lesions or other causative ocular diseases.

The diagnosis of ON was made based on history and clinical examination findings. Onset and duration of the visual disturbances, presence of pain including pain on ocular movement and relevant neurological symptoms were documented. Other associated systemic symptoms including infection, connective tissue disorder and previous attacks were noted. Ocular examinations included visual acuity, pupillary response, anterior and posterior segment assessments, colour vision and visual field test. Visual acuity at one year after the attack was also recorded.

Laboratories and radiological results were recorded. These included Full Blood Picture, Erythrocyte Sedimentation Rate (ESR), Antinuclear Antibody (ANA), Venereal Disease Research Laboratory (VDRL), Rheumatoid Factor (RhF), Mantoux test and Magnetic Resonance Imaging (MRI) of the brain/orbit. The treatments received by the patients were carefully documented.

The Optic Neuritis Registry Forms were completed by the consultant Neuro-Ophthalmologist. The data was analysed using the Statistical Package for Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

We documented 32 patients that included 31 Malay and one Chinese patients[15] with ON who presented to our institution during the study period. We did not encounter any Indian, Siamese or indigenous Orang Asli with ON in our data base. However, the subsequent data analysis are confined to Malay patients only with ON.

Thirty one Malay patients with 41 eyes fulfilled the inclusion and exclusion criteria as described above. There were 21 females and 10 males with ages ranging from 3 to 55 years. Five patients (12.2%) were under 10 years of age, 10 patients (24.4%) between 11 to 20 years, 11 patients (26.9%) between 21-30 years, 9 patients (21.9%) between 31-40 years and 6 patients (14.6%) were above 40 years of age. 70.7% (29 eyes) suffered from papillitis attacks, whilst 29.3% (12 eyes) exhibited symptoms of acute retrobulbar ON.

Twenty one patients (67.7%) displayed unilateral involvement. Unilateral attacks were predominant in the retrobulbar group (10 eyes, 83.3%) while bilateral attacks outnumbered the papillitis group (18 eyes, 62.1%). Ocular pain was only present in 13 patients (31.7%) with ON. Paracentral scotoma was the most common visual field defect observed (12 eyes, 29.3%).

73.3% of the patients (30 eyes) have visual acuity 6/60 or worse during presentation. This included 70.0% (20 eyes) who suffered attacks of papillitis, and 83.4% (10 eyes) with signs of retrobulbar ON. All adult patients were treated with intravenous methylprednisolone and oral corticosteroid as recommended by the Optic Neuritis Treatment Trial[2], while the dose was adjusted accordingly in the paediatric patients. 66.0% (27 eyes) presented visual acuity improvement 6/12 or enhanced improvement at one year after the attack. This was attributed by 73.4% (21 eyes) of patients with papillitis attacks and 50% (6 eyes) with retrobulbar ON. 19.6% (8 eyes) had visual acuity 6/60 or worse at one year after the initial attack. This included 2.6% (one eye) who deteriorated to no perception of light at one year follow-up.

Recurrent attacks of ON was observed in five patients (16.1%). This included two patients with papillitis and three patients who displayed retrobulbar ON. The above information is summarized in Table I. Table II shows the visual acuities on presentation and at the one year follow-up.

51.7% (16 patients) had idiopathic ON in our series. There were 29.0 % (9 patients) who developed febrile illnesses within two weeks prior to the onset. Multiple sclerosis was observed in one patient (3.2%) and 12.9% (4 patients) displayed clinical signs of neuromyelitis optica. The remaining one patient (3.2%) had autoimmune disease.

Table III illustrates the demographic and clinical features of our patients with ON and in other Asian countries[3-9]. The possible aetiologies of our enrolled patients and other published Asian studies are summarized in Table 5[3-5,10]. Data from the ONTT is also included in Table III and IV for a wider scope of comparison.

DISCUSSION

Earlier reports from Singapore[3-4], India[5], China[6,10], Japan[7] and Taiwan[8-9] and have suggested that ON remains different in Asian patients in respect to its clinical profile, aetiology and association with multiple sclerosis. However, those reports were confined to mainly Chinese and Japanese patients with ON[3,4,6-10], while Jain *et al*[5] reported 42 patients with ON in India.

Unfortunately, there is minimal information available in the literature regarding ON within the Malay population. Lim *et al*[3] reported 10.5% of 55 ON patients in Singapore were Malay ethnicity. Thus in this report, we describe the clinical features, visual outcome and aetiology in a larger cohort of Malay patients suffering from ON attacks.

We enrolled all Malay patients with ON of identified and idiopathic aetiologies. Our study is fairly similar to Lim *et al*[3], Wang *et al*[4], Jain *et al*[5] and Zhang *et al*[10]. In contrast, the ONTT[2], Du *et al*[6], Wakakura *et al*[7], Bee *et al*[8] and Chang *et al*[9] described patients with idiopathic ON only. We are in agreement that a direct comparison with the above reports might not be appropriate owing to different inclusion and exclusion criteria.

The majority of our patients were females, and this runs parallel with Lim *et al*[3]. Female predominance was also reported by the ONTT[2] and other Asian studies[6-9] on idiopathic ON. In contrast, males were the most commonly affected group as reported by Wang *et al*[4] and Jain *et al*[5] in their series. Our patients ranged from 3 to 55 years of age, peaking between 21 to 30 years old (26.9%). There were 3 patients (5 eyes) aged below 10 years old included in our study. This is because we did not restrict any specific age in our inclusion criteria.

Table I: Demographic/clinical characteristics of ON patients, laboratory/neuroimaging results, and treatment received

Variables	Total n=41 eyes (%)	Papillitis ON n=29 eyes (%)	Retrobulbar ON n=12 eyes (%)
Gender			
Female	21 (67.7)*	22 (75.9)	9 (75.0)
Male	10 (32.3)*	7 (24.1)	3 (25.0)
Age at onset (years)			
0-10	5 (12.2)	5 (17.3)	0 (0.0)
11-20	10 (24.4)	7 (24.1)	3 (25.0)
21-30	11 (26.9)	8 (27.6)	2 (16.7)
31-40	9 (21.9)	6 (20.7)	3 (25.0)
41-50	3 (7.3)	0 (0.0)	3 (25.0)
More than 50	3 (7.3)	3 (10.3)	1 (8.3)
Laterality			
Unilateral	21 (67.7)*	11 (37.9)	10 (83.3)
Bilateral	10 (32.3)*	18 (62.1)	2 (16.7)
Ocular Pain	13 (31.7)	11 (37.9)	2 (16.7)
Visual Field Defect			
Diffuse depression	0 (0.0)	0 (0.0)	0 (0.0)
Altitudinal defect	4 (9.7)	3 (10.3)	1 (8.3)
Enlarged blind spot	1 (2.4)	1 (3.4)	0 (0.0)
Arcuate scotoma	1 (2.4)	0 (0.0)	1 (8.3)
Temporal wedge	0 (0.0)	0 (0.0)	0 (0.0)
Nasal wedge	0 (0.0)	0 (0.0)	0 (0.0)
Central scotoma	9 (22.0)	9 (31.1)	0 (0.0)
Paracentral scotoma	12 (29.3)	7 (24.1)	5 (41.7)
Not done	14 (34.2)	9 (31.1)	5 (41.7)
High ESR	9 (29.0)*	7 (22.6)*	2 (6.4)*
High CRP	0 (0.0)	0 (0.0)	0 (0.0)
Positive VDRL	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal ANA	0 (0.0)	0 (0.0)	0 (0.0)
Positive Rh Factor	0 (0.0)	0 (0.0)	0 (0.0)
MR Imaging			
Normal	11 (26.8)	9 (31.0)	2 (16.0)
Abnormal	29 (70.8)	20 (69.0)	9 (76.0)
Not done	1 (2.4)	-	1 (8.0)
Recurrence ON	5 (16.1)*	2 (6.4)*	3 (9.7)*
IV Corticosteroids			
Yes	31 (100.0)*	20 (100.0)*	11 (100.0)*
No	0 (0.0)	0 (0.0)	0 (0.0)

*calculated based on 31 patients

Table II: Visual acuity on ON patients on presentation and at one year after the initial attack

Variables	Total n=41 eyes (%)		Papillitis ON n=29 eyes (%)		Retrobulbar ON n=12 eyes (%)	
	On presentation	After one year	On presentation	After one year	On presentation	After one year
6/6 and better	1 (2.4)	15 (36.7)	1 (3.3)	12 (43.4)	0 (0.0)	3 (25.0)
6/7.5 - 6/12	2 (4.8)	12 (29.3)	2 (6.7)	9 (30.0)	0 (0.0)	3 (25.0)
6/15 - 6/57	8 (19.5)	6 (14.6)	6 (20.0)	4 (13.3)	2 (16.7)	2 (16.7)
6/60 - 6/240	7 (17.1)	4 (9.7)	5 (16.7)	4 (13.3)	2 (16.7)	0 (0.0)
Counting Fingers Or Hand Motion	19 (46.5)	3 (7.3)	14 (50.0)	0 (0.0)	5 (41.7)	3 (25.0)
Light Perception	4 (9.7)	0 (0.0)	1 (3.3)	0 (0.0)	3 (25.0)	0 (0.0)
No Light Perception	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)

Our study revealed that 73.3% had visual acuity 6/60 or worse during the presentation. However, 66.0% of our patients showed improved visual acuity 6/12 or better in the affected eye(s) at one year after the initial attack. One patient with neuromyelitis optica remained without any perception of light during the one year follow-up.

We observed that less than 40% of our patients suffered ocular pain during the attack, and this is in agreement with Jain *et al*[5]. In contrast, other Asian studies[3,4,6-9] reported more than 40% of their patients had symptoms of pain during the attack, while ONTT[2] reported 92% of patients experienced painful optic neuritis. In our study, we did not further classify pain severity as mild, moderate and severe as described in the ONTT.

Patients with papillitis type outnumbered the retrobulbar ON in our study, and this is consistent with other published ON studies from Singapore[3-4], India[5] and Taiwan[9]. Interestingly, Wakakura *et al*[7] from Japan reported an equal number of

Table III: Comparison of demographic and clinical features of patients with ON from Asian countries and the ONTT

Variables	Current study (Malaysia) n= 31 (%)	Lim *et al* (Singapore) n=55 (%)	Wang *et al* (Singapore) n= 31 (%)	Jain *et al* (India) n= 42 (%)	Du Y *et al* (China) n= 100 (%)	Wakakura *et al* (Japan) n= 70 (%)	Bee *et al* (Taiwan) n= 27 (%)	Chang *et al* (Taiwan) n= 43 (%)	ONTT (USA) n= 448 (%)
Sample size	31 patients	55 patients	31 patients	68 eyes	100 patients	70 patients	27 patients	43 patients	448 patients
Female	21 (66.7)	42 (76.3)	12 (38.7)	14 (33.0)	66 (66.0)	48 (69.0)	18 (66.7)	28 (65.1)	345 (77.0)
Age at onset (years)									
Range	3-55	12-70	11-67	The most common affected age group was 20-40 years old	18-74	14-55	13-54	U	15-46
Mean	U	U	39.1± 12.9		40.3 ± 13.3	U	35.8 ± 11.3	34.8 ± 11.9	31.8 ± 6.7
Bilateral	10 (32.3)	9 (16.4)	5 (19.2)	26 (62.0)	U	Half had bilateral disease	5 (18.5)	13 (30.2)	U (unilateral cases only)
Type									
Papillitis	21 (65.6)	31 (56.4)	17 (65.4)	38 (55.8)	U	35 (50.0)	12 (44.4)	24 (55.8)	157 (35.0)
Retrobulbar	11 (34.4)	22 (40.0)	9 (34.1)	20 (29.4)	U	35 (50.0)	15 (55.6)	19 (44.2)	291 (65.0)
Neuroretinitis	U	2 (3.6)	U	U	U	U	U	U	U
Ocular pain	13 (31.7)*	39 (70.9)	Half had retrobulbar discomfort	7 (16.7)	40 (40.0)	39 (56.0)	12 (44.4)	36 (64.3)	412 (92.0)
Optic disc									
Normal	12 (29.3)*	22 (40.0)	13 (41.9)	20 (29.4)	U	35 (50.0)	15 (55.6)	19 (44.2)	291 (65.0)
Swollen	29 (70.7)*	33 (60.0)	18 (58.1)	38 (55.8)	48 (48.0)	35 (50.0)	12 (44.4)	24 (55.8)	157 (35.0)
Pale	U	U	U	10 (14.7)	U	U	U	U	U
Visual field defect		U			U				
Diffuse depression	0 (0.0)*		U	17 (25.0)		27 (37.5)	11 (47.8)	22 (44.0)	186 (44.8)
Central scotoma	9 (22.0)*		3 (10.0)	13 (19.1)		4 (5.6)	4 (17.4)	U	16 (3.9)
Paracentral scotoma	12 (29.3)*		2 (6.7)	3 (4.4)		2 (2.8)	U	U	2 (0.5)
Cecocentral scotoma	0 (0.0)*		2 (6.7)	U		9 (12.5)	1 (4.3)	9 (18.0)	20 (4.8)
Altutidinal defect	4 (9.7)*		U	4 (5.7)		7 (9.7)	2 (8.7)	5 (10.0)	66 (15.9)
Enlarged blind spot	1 (2.4)*		1 (3.2)	4 (5.7)		6 (8.3)	1 (4.3)	4 (8.0)	6 (1.4)
Arcuate scotoma	1 (2.4)*		4 (13.6)	U		2 (2.8)	2 (8.7)	1 (2.0)	21 (5.1)
Temporal wedge	0 (0.0)*		1 (3.2)	U		U	1 (4.3)	4 (8.0)	U
Nasal wedge	0 (0.0)*		1 (3.2)	U		2 (2.8)	1 (4.3)	5 (10.0)	3 (0.7)
1 quadrant	U		1 (3.2)	3 (4.4)		U	U	U	27 (6.5)
3 quadrants	U		1 (3.2)	U		6 (8.3)	U	U	32 (7.7)
4 quadrants	U		2 (6.7)	U		U	U	U	U
Peripheral rim	U		4 (13.6)	U		1 (1.3)	U	U	16 (3.9)
Full fields	U		5 (16.7)	U		U	U	U	U
Hemianopic	U		U	1 (1.5)		3 (4.2)	U	U	19 (4.6)
Vertical step	U		U	U		U	U	U	1 (0.2)
Multiple foci	U		U	U		U	U	U	U
Not done / missing	14 (34.2)*		3 (10.0)	23 (34.0)		U	U	U	U
High ESR	9 (29.0)	U	2 (6.7)	U	U	U	3 (11.1)	8 (25.0)	U
High CRP	U	U	1 (3.2)	U	U	U	U	0 (0.0)	U
Positive VDRL	0 (0.0)	0 (0.0)	1 (3.2)	U	U	U	U	0 (0.0)	6 (1.4)
Abnormal ANA	0 (0.0)	U	U	U	U	2 (15.0)	3 (11.1)	0 (0.0)	73 (16.3)
Positive Rh Factor	0 (0.0)	U	1 (3.2)	U	U	U	U	0 (0.0)	U
Recurrence ON	5 (16.1)	16 (29.1)	U	U	Exclusion criteria	U	U	11 (57.9) in retro-bulbar group, 5 (20.8) in papillitis group	125 (28.0)

*calculated based on 41 eyes; U:unreported

Table IV: Aetiology of ON in Asian countries and the ONTT

Aetiology	Current Study (Malaysia)	Lim *et al* (Singapore)	Wang *et al* (Singapore)	Jain *et al* (India)	Zhang *et al* (China)	ONTT (USA)
	n= 31 (%)	n= 55 (%)	n= 31 (%)	n= 42 (%)	n= 113 (%)	n=448 (%)
Idiopathic	16 (51.7)	33 (60.0)	26 (83.9)	20 (47.9)	104 (92.0)	255 (56.9)
Multiple sclerosis	1 (3.2)	14 (25.5)	2 (6.5)	3 (7.1)	4 (3.5)	193 (43.1)
Neuromyelitis optica	4 (12.9)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	U
Infective causes						
Sinusitis	1 (3.2)	0 (0.0)	1 (3.2)	0 (0.0)	1 (0.9)	U
ADEM	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	U
Post viral	6 (19.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	U
Tuberculosis	1 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)	U
Syphilitic	0 (0.0)	0 (0.0)	1 (3.2)	1 (2.4)	1 (0.9)	U
Tonsilitis	0 (0.0)	U	0 (0.0)	1 (2.4)	0 (0.0)	U
Hepatitis	U	U	U	1 (2.4)	U	U
Not mentioned	U	5 (9.1)	U	U	U	U
Autoimmune disease	1 (3.2)	3 (5.5)	1 (3.2)	U	0 (0.0)	U
Anterior ischaemic optic neuropathy	U	U	U	4 (9.5)	U	U
Toxic	U	U	U	5 (11.9)	U	U
Alcohol poisoning	U	U	U	6 (14.9)	U	U
Diabetes mellitus	U	U	U	1 (2.4)	U	U

*Include possible, probable and definite MS, U:unreported

papillitis and retrobulbar ON in their series. On the other hand, ONTT[2] and Bee *et al*[8] reported a higher percentage of retrobulbar ON in comparison to papillitis type. However, the latter 3 studies were confined to patients with idiopathic ON only.

Our retrospective data analysis revealed that the most common field defect was paracentral scotoma (29.3%). Meanwhile, diffuse depression was documented as the highest by Lim *et al*[3] and Jain *et al*[5]. Wang *et al*[4] from Singapore reported a slightly differing pattern of visual field defect, where peripheral rim and full rim defects were the most common. The ONTT[2] and other idiopathic ON studies from Japan[7] and Taiwan[8-9] also reported diffuse depression as the most widespread field defect encountered in their patients.

None of our patients had previous history of ON during the enrolment. However, recurrence of ON was noted in 16.1% of our patients during follow-ups. Our data is extremely low compared to the 29.1% recurrence rate documented in Singaporean patients[3] with ON. The recurrence rate was 28.0% in the ONTT[2], while Chang *et al*[9] observed a higher percentage of recurrence, 57.9% and 20.8% in the retrobulbar and papillitis groups respectively.

In more than 50% of our patients, the cause of ON was not apparent. This remains parallel with ON studies from Singapore[3-4], India[5] and China[10]. Other identified aetiologies of ON in our study include post viral infection (19.4%), neuromyelitis optica (12.9%), sinusitis (3.2%)[12], tuberculosis (3.2%)[16], acute disseminated encephalomyelitis (ADEM), and autoimmune disease (3.2%).

There existed only 3.2% (one patient) who developed multiple sclerosis after the 6 months follow-up in our study. This supports the existing data of lower risk of multiple sclerosis in Asian patients[4,5,10] with ON compared to Western cohort. In contrast, Lim *et al*[3] reported 25.5% of their patients with ON had associated multiple sclerosis.

The prevalence of multiple sclerosis is estimated to 2/100,000 population in Malaysia[17]. Tan (1997) reviewed 38 cases of clinically definite multiple sclerosis seen in University Malaya Medical Centre[18]. 26% of his patients with multiple sclerosis presented with ON. However, 84% of his patients were Chinese, while Malay contributed 11% and Indian accounted for 5%.

Our study has several limitations. Firstly, this 5-year retrospective study might be biased due to missing data especially concerning the visual field results. Secondly, our findings reflect a single institution review and possibly left out important data pertaining to ON in Malaysia. Thus, multicenter involvement with a larger number of patients will be a future prospective. A multiethnic Malaysian population is another issue to address in future research.

CONCLUSION

The majority of Malay patients with ON attacks presented themselves with visual acuity 6/60 or worse. Papillitis was the most common type of ON documented. More than 50% were idiopathic, and multiple sclerosis was relatively rare. 66.0% had good visual recovery after one year. Our results are comparable with ON studies conducted in other Asian countries.

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