REVIEW ARTICLE

A Comparison of Optic Neuritis in Asian and in Western Countries

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ABSTRACT

Acute demyelinating optic neuritis is a common optic neuropathy in young adults. There is usually satisfactory visual recovery. However, some patients convert to multiple sclerosis (MS) with potential sequelae of neurological disability. The Optic Neuritis Treatment Trial in the United States was conducted prospectively for 15 years and provided valuable data about clinical course, efficacy of steroid treatment, and risk of conversion to MS. Compared to the many studies in Western countries, research concerning optic neuritis in Asia has so far not been extensive. However, cumulative evidence shows that various features of this disorder differ between patients of Caucasian and Oriental descent. In this article we review up-to-date studies on optic neuritis in Asia and compare the results with prior literature. Prospective and multi-centre studies are currently underway in these regions to increase our understanding of optic neuritis in Asia.

KEYWORDS multiple sclerosis, optic nerve, optic neuritis

INTRODUCTION

Optic neuritis is an acute inflammation of the optic nerve and also is a common optic neuropathy encountered in general practice. Although aetiologies of optic neuritis include infectious and autoimmune origins, demyelination is the most typical cause and by convention optic neuritis usually refers to demyelinating optic neuritis. Activation of T lymphocytes, and subsequently delayed-type hypersensitivity leading to the destruction of neuronal axons, is thought to be the pathophysiological mechanism of this disorder.¹

The Optic Neuritis Treatment Trial (ONTT) was a multi-centre cohort study in the United States from 1988 to 2006 that yielded critical information about clinical profiles, longitudinal visual course, and treatment outcomes for acute demyelinating optic neuritis.^{2,3} In that study, 85% of the participants were of white Caucasian ancestry. Japan was the first country in Asia to conduct large-scale studies on optic neuritis. The Optic Neuritis Treatment Trial Multicentre Co-operative Research Group (ONMRG)

enrolled 30 clinical centers throughout Japan from 1991 to 1996.⁴ In the recent studies of optic neuritis in certain Asian countries, the pattern of optic neuritis has been shown to differ in some aspects from those in Western countries.⁵ For instance, optic nerve involvement at the onset and during the course of multiple sclerosis (MS) was more common in Asia.^{6,7} Optic neuritis as the first manifestation was reported in 56% of patients with MS in Taiwan⁸ and 38.2% of those in China,⁹ in contrast to 20% in patients of European descent.¹⁰

A deeper understanding of the epidemiology and clinical manifestations of this disease is required for the development of appropriate treatments. Although the studies in Asia have been performed in only a limited number of countries so far, they have provided relevant information about this disease. Table 1 shows the basic data and study designs used by the various studies discussed in this article. Detailed comparisons between Western and Asian regions with regard to each characteristic of optic neuritis are provided in the sections that follow.

TABLE 1 Basic data from studies of optic neuritis in Asia and the Optic Neuritis Treatment Trial.

Countries and studies	Year	Sample size persons (eyes)	Study design	Major inclusion criteria
Japan				
Isayama <i>et al.</i> ¹¹	1969~1979	84 (122)	Retrospective, one centre	Without concomitant neurologic symptoms
Wakakura <i>et al.</i> ⁵	1991~1996	70 (70)	Prospective, 22 centres	14~55 years; symptoms <14 days; unilateral optic neuritis
Taiwan				
Yang and Hou ¹²	1957~1966	40 (67)	Retrospective, one centre	No
Liu and Ko ¹³	1967~1980	37 (56)	Retrospective, one centre	No
Woung and Ko ¹⁴	1967~1983	20 (34)	Retrospective, one centre	No
Chang and Ko ¹⁵	1972~1985	21 (31)	Retrospective, one centre	Subgroup analysis for final VA >0.5.
Lin <i>et al.</i> ¹⁶	1986~2003	109 (147)	Retrospective, one centre	Follow-up more than 1 year
Lin <i>et al.</i> ¹⁷	1990~1994	38 (38)	Retrospective, one centre	Acute monosymptomatic
Chang <i>et al.</i> ¹⁸	1991~2000	43 (56)	Retrospective, one centre	18~60 years, symptoms <10 days
Bee <i>et al.</i> ¹⁹	1992~2001	27 (32)	Retrospective, one centre	13~54 years, symptoms <14 days
Singapore				
Wang <i>et al.</i> ²⁰	1997~1999	31 (39)	Retrospective, one centre	No
Lim <i>et al.</i> ²¹	2002~2004	55 (64)	Prospective, population-based	Vision decreased <4 weeks
India				
Jain <i>et al.</i> ²²	1981	42 (68)	Retrospective, one centre	No
USA				
ONTT ²	1988~2006	448 (448)	Prospective, 15 centres	18~45 years; symptoms ≤8 days; unilateral optic neuritis; −6D < SE < 3D

D = dioptre; ONTT = the Optic Neuritis Treatment Trial; SE = spherical equivalent; VA = visual acuity.

CLINICAL PRESENTATIONS

Incidence

The annual incidence rate of optic neuritis in Olmsted County, Minnesota, in the United States is 5.1 per 100,000 person-years.²³ The annual incidence rate of optic neuritis in Japan according to the ONMRG study is around 1.62 per 100,000 person-years,⁴ approximately one third of that in the USA. Woung *et al.* utilized National Health Insurance data of Taiwan from 2000 to 2004 and found that the mean annual incidence of optic neuritis was 0.33 per 1000 person-years.²⁴

Age

Although optic neuritis can occur in children and the elderly, it usually occurs in young adults (Table 2). Optic neuritis presenting younger than 16 years of age is commonly seen following an infectious episode, and the visual recovery is generally good.^{25,26} The reports from Japan and Taiwan showed that the visual outcome in patients with childhood optic neuritis was similar to previous studies in countries outside Asia.^{27,28}

The risk of progression to MS following optic neuritis is lower in children than that in adults. The largest retrospective study enrolled 79 patients with childhood

optic neuritis in the United States and reported that the risk of MS was approximately 26% after 40 years.²⁹

Gender

Whether individuals are of Caucasian or Oriental descent, optic neuritis affects females more than males with a female:male ratio of about 2:1 (Table 2).³⁰ The exact pathomechanism is unclear, and is possibly related to gender dependent susceptibility to autoimmune diseases.

Ocular Pain

One of the presentations of optic neuritis that differs the most between patients with optic neuritis in Asia and those in Western countries is retrobulbar pain. Traction on the inflamed nerve by the rectus muscles on movement of the eye or associated inflammation of nearby meninges or sheaths of the optic nerve might contribute to this symptom. In contrast to the finding that 92% of patients had ocular discomfort in the ONTT,³¹ reports from Japan,⁵ Taiwan,^{12,16,18,19} and Singapore^{20,21} found that only about half of patients had this complaint (Table 2). Therefore, physicians cannot rule out the possibility of optic neuritis in suspicious cases due to lack of this symptom.

TABLE 2 Comparison of demographic and clinical features of optic neuritis in Asian studies and in the Optic Neuritis Treatment Trial.

Clinical presentations	Age, years Mean (range)	Female %	Ocular pain %	Papillitis %	Optic nerve swelling or enhancement %	MRI brain plaque %	Presence of MS %
Japan							
Isayama et al. ¹¹	33.7 (5~69)	59.5	NA	47.5	NA	NA	0
Wakakura et al. ⁵	36.3 (14~55)	69	56	50	30.0 (MRI)	14	5.6 [†]
Taiwan							
Yang and Hou ¹²	M 27.7; F 26.1 (4~56)	45	60	70	NA	NA	NA
Liu and Ko ¹³	NA (10~69)	62.2	NA	NA	NA	NA	NA
Lin et al. ¹⁶	41.2 (7~80)	53.2	58.7	53.2	70.2 (MRI); 47.8 (CT)	34.9	NA
Lin et al. ¹⁷	32.0 (7~49)	57.9	NA	NA	25.0 (CT)	33.3	NA
Chang et al. ¹⁸	34.8 (18~60)	65.1	64.3	55.8	48.8	16.7	NA
Bee et al. ¹⁹	35.8 (13~54)	66.7	44.4	44.4	43.5	7.4	3.7
Singapore							
Wang et al. ²⁰	39.1 (11~67)	38.7	50	65.4	31.8 (MRI)	4.5	NA
Lim et al. ²¹	NA (12~70)	76.3	70.9	60	80.0 (MRI; <i>n</i> = 15)	40.0 (<i>n</i> = 15)	20.0 (<i>n</i> = 15)
India							
Jain et al. ²²	NA	33	33.4	56	NA	NA	7.1
USA							
ONTT ²	31.8	77.2	92.2	35.3	NA	48.7	5.6

C = computed tomography; F = female; M = male; MRI = magnetic resonance imaging; MS = multiple sclerosis; *n* = sample size;

NA = non-applicable; ONTT = the Optic Neuritis Treatment Trial.

[†]Including probable and definite MS.

Retrobulbar Inflammation versus Papillitis

Retrobulbar optic neuritis was more common than anterior optic neuritis in the ONTT study (64.7%).² In contrast, anterior optic neuritis was predominant in Asian countries (Table 2). Since optic disc swelling has been identified with a lower risk of conversion to MS,³² the higher rate of papillitis in Asian patients with optic neuritis is compatible with the lower rate of developing MS in clinical studies.

VISUAL FUNCTION

Visual Acuity

Acute visual loss is the major complaint of patients with optic neuritis. Usually it progresses over several days. In approximately one third of eyes (35.9%) vision dropped to 20/200 or below in the ONTT at the onset.² This percentage was much lower than in other studies (Table 3). The discrepancy could be due to the criteria and designs of the different studies, since more severe cases were involved in retrospective studies at medical centres.

Visual dysfunction ranged from very mild impairment (10.5% with visual acuity 20/20 or better in the ONTT) to no light perception at all.² Vision usually improves spontaneously over weeks. Sixty-nine percent of patients in the ONTT had visual acuity (VA) of 20/20 at 1-year follow-up.³¹ The final visual acuity in patients with optic neuritis was generally good in the ONTT in that 82% of patients attained VA better than 20/20 over 15 years.³ However, residual deficits in visual acuity, colour sense, and contrast sensitivity

are not uncommon.^{33,34} In the Asian studies, the visual prognosis was not as good as in the ONTT regarding VA and visual field (Table 4).³⁵ Visual outcomes in patients without MS were better than those with MS³.

Colour Vision

The classic triad of optic neuritis consists of visual loss, ocular pain, and deficiency in colour discrimination. The severity of dyschromatopsia is out of proportion in patients with a mild visual deficit. The majority of affected eyes in Asian studies also showed this defect (Table 3). As vision recovered, most patients demonstrated an improvement in colour sense (Table 4).

Visual Field

All patients had abnormal visual field (VF) in affected eyes on presentation in both the ONTT and ONMRG studies.^{5,36} Any type of VF defect can be found following optic neuritis. In the ONTT study, 66.2% of VF defects were diffuse and 33.6% were localized (the most common types in order were arcuate and altitudinal defects).³⁶ However, in Japan, localized defects (62.5%) were more common.⁵ Caution has to be exercised in that the classification of VF defects was different in the various studies.

Other Functional Examinations

In addition to performing examinations with specific instruments, investigators have tried to find simple

TABLE 3 Comparison of visual functions of optic neuritis in Asian studies and in the Optic Neuritis Treatment Trial.

Visual functions	Initial visual acuity, %		Visual field defect, %	Abnormal VEP, %	Dyschromatopsia, %	Abnormal contrast sensitivity, %
	≤ 0.1	≥ 0.5				
Japan						
Isayama <i>et al.</i> ¹¹	71.3	8.2	91	NA	NA	NA
Wakakura <i>et al.</i> ⁵	61.0	10.0	100	NA	81	58.6
Taiwan						
Yang and Hou ¹²	86.6	6.0	62.7	NA	NA	NA
Liu and Ko ¹³	NA	NA	NA	66.7	NA	NA
Woung and Ko ¹⁴	NA	NA	NA	NA	NA	79.4
Chang and Ko ¹⁵	NA	NA	NA	80 [†]	47.8	NA
Lin <i>et al.</i> ¹⁶	NA	NA	91.8	77.8	NA	NA
Chang <i>et al.</i> ¹⁸	51.8	19.6	100	NA	NA	NA
Bee <i>et al.</i> ¹⁹	NA	NA	100	100	88.9	NA
Singapore						
Lim <i>et al.</i> ²¹	NA	17.2 [‡]	NA	NA	NA	NA
India						
Jain <i>et al.</i> ²²	NA	13.2	100	NA	NA	NA
USA						
ONTT ²	35.9	35.3	100	NA	88.2 (IS); 93.8 (FM)	98.2

FM = Farnsworth-Munsell 100-hue test; IS = Ishihara plates; NA = non-applicable; ONTT = the Optic Neuritis Treatment Trial; VEP = visual evoked potential.

[†]For patients with visual acuity >0.5.

[‡]Unilateral group.

TABLE 4 Comparison of visual outcomes of optic neuritis and the conversion rate to multiple sclerosis in Asian studies and in the Optic Neuritis Treatment Trial.

Countries and Studies	Mean duration of follow-up or range	Final visual acuity, %		Recovery of VF, %	Recovery of color vision, %	Recurrent rate, %	Conversion rate, %
		≤ 0.1	≥ 0.5				
Japan							
Isayama <i>et al.</i> ¹¹	5.2 Y	NA	94.3	NA	NA	17.9	8.3
Wakakura <i>et al.</i> ³⁶	1 Y	NA	NA	41.3	64.2	NA	NA
Taiwan							
Yang and Hou ¹²	Range 6 M~8 Y	35.8	47.8	NA	NA	100	15
Liu and Ko ¹³	2~11 Y	30.4	55.4	NA	NA	NA	7.2
Woung and Ko ¹⁴	7 Y	26.0	NA	NA	NA	NA	NA
Lin <i>et al.</i> ¹⁶	5 Y	NA	NA	NA	NA	33.9	14.3
Lin <i>et al.</i> ¹⁷	2 M~8 Y	NA	NA	NA	NA	NA	6.4
Chang <i>et al.</i> ¹⁸	5 Y	NA	NA	NA	NA	37.2	18.6
Bee <i>et al.</i> ¹⁹	4 Y	NA	48.1	NA	66.7	18.5	14.8
Singapore							
Wang <i>et al.</i> ²⁰	6 M	NA	83.9	NA	NA	NA	NA
Lim <i>et al.</i> ²¹	2 Y	NA	75.9 [†] (100.0 [‡])	NA	69	7.3	9.1
India							
Jain <i>et al.</i> ²²	NA	NA	44.0	NA	93	NA	NA
USA							
ONTT ³	15 Y	1.0	92.0	73	NA	NA	50

M = month; NA = non-applicable; ONTT = the Optic Neuritis Treatment Trial; VF = visual field; Y = year. [†]Unilateral group.

[‡]Bilateral group.

tests for the diagnosis of optic neuritis. Woung and Ko used Arden plates to examine the difference in contrast sensitivity between normal subjects and Taiwanese patients with optic neuritis.¹⁴ They found that 79.4% of eyes had abnormal findings at all spatial frequencies. Although the defects at the median frequency and at both the median and high frequencies are the most common in optic neuritis, the highest

sensitivity of the contrast sensitivity test for diagnosis of optic neuritis between the affected eye and unaffected eye is at high spatial frequency. The Visual Contrast Test System (Vistek Consultants, Dayton, OH, USA) was employed in the ONMRG study.⁵ The reduction in contrast sensitivity was found mainly at the median spatial frequency (98%) and least at the high frequency (80%).

Neuroimaging

Optic nerve swelling or contrast enhancement on computed tomographic (CT) or magnetic resonance imaging (MRI) scans can be recognized in some patients. Lin et al. found that the presence of optic nerve swelling or enhancement did not correlate with conversion to MS.¹⁶

The appearance of periventricular plaques (sharply demarcated, ovoid, greater than 3 mm) on MRI during an episode of optic neuritis has been demonstrated to indicate a high risk for conversion to MS.³² The 15-year ONTT study showed that 25% of patients with a normal brain MRI scan at baseline developed MS during follow-up compared with 72% of patients with one or more lesions.³⁷

In contrast to the ONTT report that 48.7% of patients have abnormal findings on brain MRI, patients with optic neuritis in Asia had a lower rate of similar lesions (Table 2). Whether this finding represents different disease entities across races requires further investigation for confirmation. However, it has been found that central nervous system imaging abnormalities remain a strong predictor for subsequent development of MS in patients with optic neuritis.^{15,18}

Cerebrospinal Fluid Analysis

Lumbar puncture was performed in only 31.5% of patients in the ONTT study. Current evidence indicates that a cerebrospinal fluid (CSF) test is not necessary for patients with typical optic neuritis, since its ability to predict further risk of MS is low.³⁸ However, it adds a predictive value (particularly when the baseline MRI is normal) in that the presence of unmatched oligoclonal bands in CSF doubles the risk for having a second attack in patients with a clinically isolated syndrome (CIS).³⁹

In a study by Lin et al. in Taiwan, an abnormal CSF immunoglobulin index was found in 9 patients (42.9%) and all of these patients developed MS during the study period. Five of 11 patients had positive oligoclonal bands (45.5%) and 4 of them eventually developed MS.¹⁶ The positive rate in CSF analysis was low in the ONMRG study⁵: among 42 patients who had a lumbar puncture test, 2 patients had elevated total protein, 1 had oligoclonal bands, and 2 had elevated myelin basic protein.

Manifestations in the Non-affected Eye

Visual function abnormalities were observed in the non-affected eye as well. In the ONTT study, visual acuity loss in the non-affected eye was noted in 13.8% of patients. In addition, abnormal contrast sensitivity in 15.4%; reading errors of Ishihara colour plates in 20.1%;

abnormal results of the Farnsworth-Munsell 100-hue test in 21.7%; and VF defect in 48.0% of the fellow eye of optic neuritis patients were observed.²

Similar findings were noted in a Japanese study in that 53% of non-affected eyes showed abnormal VF; 7.7% reading errors of Ishihara colour plates; and 14.6% reduced contrast sensitivity.⁵ Bee et al. reported that 21.7% of Taiwanese patients had a VF defect and 25% had a delayed VEP response in the non-affected eye.¹⁹

ASSOCIATION WITH MULTIPLE SCLEROSIS

Linkage and Conversion Rate to Multiple Sclerosis

It is well known that optic neuritis is the first clinical manifestation in approximately 20% of patients with MS.¹⁰ Optic neuritis can occur at any time in the life of a patient with MS.²³ In regions of high MS incidence, the majority of patients with optic neuritis have the condition in association with MS. The prevalence of MS exhibits a large variation with regard to both ethnicity and geographical area.⁴⁰ Prevalence rates can be as high as 200 cases per 100,000 in regions located at high latitude such as Scotland and Ireland.^{41,42} In general, the prevalence is about 0.22–8.6 per 100,000 across Asia. Within Asia the lowest prevalence is found in India at 0.22–0.6 per 100,000^{7,8,43,44}; and the highest prevalence is reported in Mediterranean populations (Jordan and Palestine, 20–42 per 100,000).⁴⁵ Based on the data from the Bureau of National Health Insurance, the prevalence of MS in Taiwan is 1.9 per 100,000 persons.⁴⁶

The report from the ONTT showed that MS had developed in 38% of patients at 10 years after optic neuritis and in 50% at 15 years.^{37,47} Optic disc swelling, lack of ocular pain, and mild abnormalities of VA were associated with a low risk of clinically definite MS (CDMS).³² The United Kingdom seems to have the highest conversion rate (59% over 10 years) in the world that has so far been reported.⁴⁸ The conversion rates were generally low in Asia with 8.3% in Japan at 5 years,¹¹ 9.1% in Singapore at 2 years,²¹ and 6.4–18.6% in Taiwan at 4–5 years^{12,13,16–19} (Table 4).

Optico-spinal Type of MS

Another feature of MS in Asia that differs from that in Western countries is the higher proportion of patients suffering lesions in the spinal cord. Longitudinally extensive transverse myelitis along with optic neuritis is the hallmark manifestation of neuromyelitis optica (NMO, also known as Devic disease). The recently discovered serum autoantibody (anti-aquaporin-4 or NMO-IgG) targeting an antigen on the aquaporin 4

water channel has a sensitivity of 75% and specificity of 90% in the diagnosis.⁴⁹ A study by Lin in Taiwan found nearly half (46.2%) of MS patients had significant lesions of the spine.¹⁶ Nearly 15–40% of cases of MS in Japan had selective lesions and severe damage of the optic nerve and spinal cord, the so-called “optico-spinal” variant of MS.⁴⁰ A study in India reported that the proportion of the optico-spinal form of MS was as high as 71.4%.⁷

TREATMENTS

There is no satisfactory treatment at this time that can completely prevent visual disability nor the development of MS in a case of optic neuritis. A meta-analysis of 12 randomised, controlled clinical trials conducted in Europe and in North America to evaluate the efficiency of steroid treatment (including any dosage, route of administration, and duration of treatment) for multiple sclerosis and optic neuritis has been carried out.⁵⁰ It demonstrated that this treatment paradigm accelerated visual recovery, but had no effect on final visual outcome. The protocol used in the ONTT study (intravenous methylprednisolone 250 mg every 6 hours for 3 days, followed by oral prednisolone 1 mg/kg per day for 11 days, and then 4-day prednisolone taper) can be considered for patients who need faster visual improvement.⁵¹ The studies in Asian countries showed the same results as the ONTT.^{16,35,52,53} However, these protocols may not be appropriate for non-MS cases: one recent study which used optical coherence tomography (OCT) measurements of retinal nerve fibre layer (RNFL) thickness as an outcome measure found that early high-dose intravenous methylprednisolone was effective in preserving RNFL thickness in patients with NMO.⁵⁴

The investigations on treatments shifted to disease-modifying drugs (DMDs) in recent years. The classic trials (multi-centre, randomised, and placebo-controlled) assessing the effects of interferon- β for patients with CIS in the disease course of MS and to MRI metrics are: the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) in North America,^{55,56} the Early Treatment of MS Study (ETOMS) in Europe,⁵⁷ and the Betaseron in Newly Emerging MS for Initial Treatment (BENEFIT) in Canada and Europe.⁵⁸ The above studies revealed that interferon treatment delays a second relapse, and reduces the cumulative probability of clinically definite MS.

The experiences in Japan and Taiwan with DMDs were not as favourable as in Western regions. Interferon treatment for patients with MS-associated optic neuritis led to early relapse of optic neuritis.⁵⁹ It also exacerbated MS in patients with severe optic nerve and spinal cord lesions.⁶⁰ However, another study conducted in Taiwan did not find an increased relapse rate of optic neuritis after interferon therapy.⁶¹

To date, no conclusive guidelines regarding the timing of treatment and the specific type of patients that should be considered for early treatments with DMDs have been established.

Findings from Optical Coherent Tomography (OCT)

The recent OCT device offers real-time, cross-sectional retinal images that allow repeated measurements easily. Since the eyeground is the only part of the body that can be observed in order to detect nerve fibers of the central nervous system in vivo, OCT data provide novel information on the course of optic neuritis. The thinning of the RNFL has been found to have an excellent correlation with visual function impairment.⁶² Reduction in the RNFL was observed in 74% of patients with optic neuritis within 3 months, suggesting axonal injury in the early stage.⁶³ This examination method has been utilised for patients with MS to monitor the progression of axonal damage.⁶³ One study in China that used OCT found that patients with optic atrophy following optic neuritis showed moderate reduction in the RNFL compared with those who had glaucomatous optic neuropathy.⁶⁴

CONCLUSION

A large body of evidence shows that the features of optic neuritis in Western studies cannot fully apply to patients with Oriental ethnicity. Clinicians should be aware of various presentations of this disease in order to provide an accurate diagnosis and appropriate management. Studies in Asia have provided increased understanding about optic neuritis. Efforts are continuing to achieve acute and long-term control of this disorder.

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