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Baseline Features of Idiopathic Optic Neuritis as Determined by a Multicenter Treatment Trial in Japan

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Background: An optic neuritis treatment trial was conducted at 30 clinical centers in Japan using the same protocol. Patient participation was based on: age range of 14–55 years; acute symptoms indicative of unilateral optic neuritis of unknown or demyelinating origin; visual symptoms of 14-day duration or less; relative afferent pupillary defect in affected eye; and normal or swollen optic disc of affected eye.

Cases: Initially, 102 patients qualified for participation; baseline data were obtained for analysis from 70 of these patients. Demographic characteristics of Japanese patients with optic neuritis were clarified and compared with those in a US study.

Observations: The incidence of ocular or periocular pain and the presence of periventricular plaques were noted to be lower, and the incidence of disc swelling higher, in the Japanese patients, suggesting racial differences in the characteristics of the disease. Such differences may possibly be related to the lower incidence of multiple sclerosis in Japanese patients. The results of visual function tests were virtually the same in both studies. The nonaffected eyes of more than half the patients showed abnormal mean deviation in Humphrey field analysis, as also noted in the US study.

Conclusions: The baseline clinical features of optic neuritis in the Japanese patients have been defined. Some racial differences in the characteristics of the disease may exist. **Jpn J Ophthalmol 1999; 43:127–132**

Key Words: Baseline features, demographic characteristics, multicenter treatment trial, multiple sclerosis, optic neuritis.

Introduction

Acute idiopathic optic neuritis (optic neuritis) is a very common optic nerve disease that is character-

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ized by acute onset and a higher incidence in young people. The annual rate of optic neuritis in Japan is approximately 1.62 per 100,000 adult population. More than 95% of patients with the disease are treated by systemic corticosteroid.[1]

The Optic Neuritis Multicenter Cooperative Research Group, comprised of members of 30 universities throughout Japan, is presently engaged in a clinical treatment trial of optic neuritis.[2] The purpose of the present study was to determine the clinical characteristics of this disease in Japan. Baseline data, such as initial symptoms, signs, and visual function of affected and nonaffected eyes, were analyzed.

Methods

This study was conducted as described previously.[2] Multicenters representing Ophthalmology Departments of University Hospitals throughout Japan participated in this study. All patients provided informed consent. Requirements for participation were: age range of 14–55 years; acute symptoms indicative of unilateral optic neuritis of unknown or demyelinating origin; visual symptoms of 14-day duration or less; relative afferent pupillary defect in the affected eye; and normal or swollen optic disc in the affected eye. Cases suspected of being other types of optic neuropathy with the following causes were excluded from the study: traumatic, toxic, ischemic, hereditary, compressive, or psychiatric causes. The major exclusion criteria are listed in Table 1.

A detailed history regarding visual symptoms; ocular or periocular pain; and past ocular, neurological, or systemic problems was recorded for each patient. Blood glucose and fluorescent treponemal antibody absorption (FTA-ABS) were determined and chest roentgenograms were obtained for all patients. Lumbar puncture was performed on 42 patients. Class I and II antigens of the human leukocyte antigens were determined in 14 and 11 patients, respectively. Magnetic resonance imaging (MRI) scans were taken and evaluated for 66 patients.

Following a standardized ocular examination, assessment was made of visual functions, including visual acuity, visual field, color vision, contrast sensitivity, and central critical flicker fusion frequency (CFF). Visual acuity was measured subsequent to full refractive correction using Landolt rings as the target at a viewing distance of 5 m, and the results were expressed as decimal acuity. Average visual acuity was determined based on finger counting, hand motion, and light perception as equivalent to 0.005, 0.001, and 0.0001, respectively. The category of no light perception was not recorded in this series.

The central 30° of the visual field was evaluated by perimetry using program 30-2 on the Humphrey field analyzer (HFA). When visual function was not sufficient to permit measurement by the HFA, the peripheral field as determined by Goldmann perimetry was used. The methods for visual field classification were the same as in the optic neuritis treatment trial in the United States.[3] When indexes (fixation losses, false positives, or false negatives) for HFA were exceeded in either eye, the measurement was repeated. The results were considered suitable for analysis when the above reliability indexes of the second measurement were not exceeded by 30% in either eye. In each patient, the visual field data by HFA and Goldmann perimetry was judged to be either normal or abnormal, this being based in the former on mean deviation, corrected pattern standard deviation, and foveal sensitivity. For statistical analysis, mean deviation less than −3.00 dB was regarded as abnormal.

The 38 Ishihara Pseudoisochromatic International Color Plates (Kanehara, Tokyo) were used for color vision evaluation. Normal reading was not possible for plates 18–21, 28, and 29, and thus only 32 plates were used for statistical analysis. A correct score was defined as the number of plates that could be read properly (maximal score, 32). A score of 32 was considered normal. Data for patients with congenital color blindness were not entered into the baseline analysis.

Table 1. Major Exclusion Criteria

Corticosteroid already administered for optic neuritis.
High risk for corticosteroid treatment in such conditions as diabetes mellitus, gastrointestinal ulcer, or pregnancy.
Evidence of optic disc pallor in affected eyes.
Previous optic nerve disease still existing with recovery.
Prior ocular disease, such as high myopia or amblyopia, that causes visual loss or further reduction in visual function in affected eye.
Systemic disease as a predisposing factor of ischemic optic neuropathy (eg, uncontrolled hypertension, moderate or severe heart disease, hyperlipidemia).
Present medication that would possibly give rise to retinal or optic nerve toxicity (eg, ethambutol, phenothiazine).
Possible alcoholism or addiction to thinner (eg, toluene, methylalcohol) with consequent toxic or nutritional optic neuropathy.

Table 2. Cases Dismissed After Start of This Study

	No. of Cases
Misdiagnosis (visual loss due to other causes)	17
Rhinogenic optic neuropathy	9
Brain tumor	3
Ischemic optic neuropathy	2
Leber hereditary optic neuropathy	1
Nutritional optic neuropathy	1
Age-related macular degeneration	1
Lost data	7
Under or over age	4
Eventual bilateral disease	2
Lack of cooperation (usually quick recovery)	2

The Visual Contrast Test System (VCTS, Vistek Consultants, Dayton, OH, USA) was used to measure contrast sensitivity at a testing distance of 1 m. The test chart comprised gratings with spatial frequencies of 1.5, 3, 6, 12, or 18 cycles per degree (CPD). The features of this test and evaluation have been reported.[4] Contrast sensitivity within the normal range indicated on the recording chart of VCTS at any of six frequencies was considered normal.

Average sensitivity was determined based on the maximal number of gratings at each spatial frequency judged visible as the contrast sensitivity. This number was converted to the real value of contrast sensitivity.

The instrument developed at Osaka University[5] (CFF Test Apparatus II; Matsumoto Medical Instruments, Osaka) or that produced at Kitasato University[6] (Handy Flicker HF; Neitz Instruments, Tokyo) was used to measure CFF in 56 patients. The latter device uses the yellow flicker value. Values less than 35 Hz were considered abnormal with either device, based on the normal values stipulated by the authors.

Results

Demographic and Systemic Characteristics

The present study was conducted over a 6-year period from March 1991 to December 1996, with 102 patients initially participating. For reasons such as misdiagnosis or poor patient cooperation (Table 2), 32 patients were dismissed so that finally, there were only 70 subjects from 22 institutions for the statistical analysis. On completion of the study, two 56-year-old women and one 58-year-old woman were found to have been inadvertently included among the patients. They were not eliminated because their data in all other respects fit the criteria for this study. The distribution of patients by age and sex is shown in Figure 1. Average age was 36.3 years with a standard deviation (SD) of 12.0 years; 69% of the patients were women. Ocular or periocular pain was reported by 56% of the patients: 57% noted the pain 1 week or more before visual onset; 27% at the onset, and 16% within 1 week after the onset. There was a positive history of presumed optic neuritis in the nonaffected eye in one patient whose corrected visual acuity was 1.2. Four cases (5.6%) had definite or probable multiple sclerosis, according to Poser's definition of at the onset of visual loss. Disc swelling was seen in 50% of the patients, and MRI showed

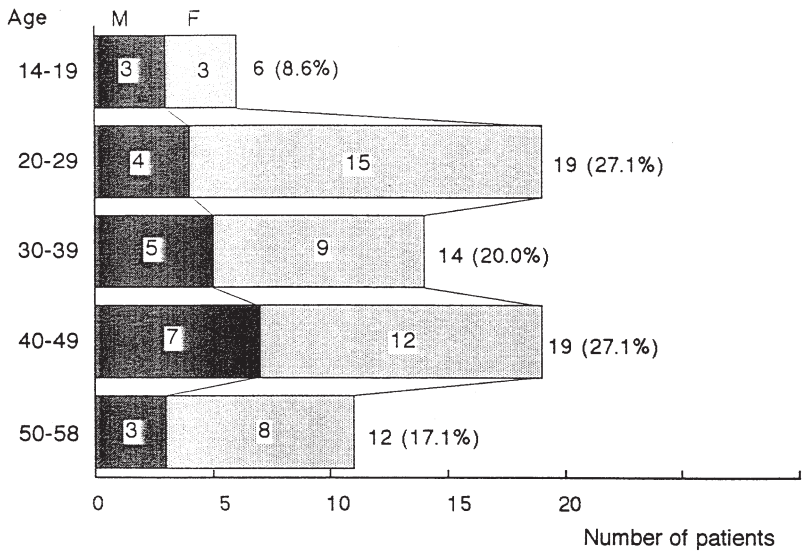

Figure 1. Distribution of patients by age and sex at start of this study.

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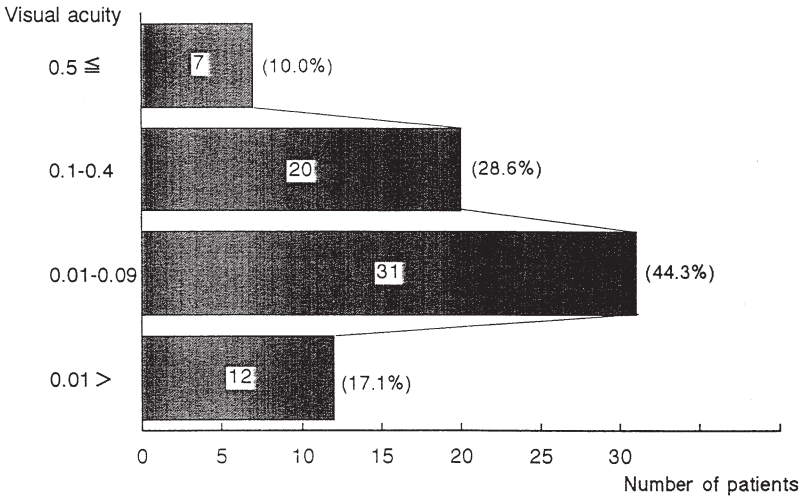

Figure 2. Distribution of corrected visual acuity of affected eyes at start of this study.

swelling of the optic nerve in the affected eye in 20 of 66 patients (30%). Periventricular plaques were evident in 9 patients (14%), 4 with three plaques or more and 5 patients with two plaques or less. FTA-ABS was negative and chest roentgenograms were unremarkable in all patients. No patient had had collagen vascular disease. High antinuclear antibody titer (>40) was detected in 2 of 13 patients (15%). In cerebrospinal fluid, leukocytosis (>10/3) was seen in 4 patients, elevation of total protein (>50 mg/dL) in 2 patients, positive oligoclonal bands in 1 patient, and elevated myelin basic protein (>0.5 ng/mL) in 2 patients. Human leukocyte antigen showed A24 in 10 (71%), CW1 in 7 (50%), and DR4 in 6 patients (55%).

Visual Function of Affected Eyes

Visual acuity was measured in all 70 affected eyes, but for some patients the visual function tests could not be conducted or the data were unreliable. Figure 2 shows the distribution of corrected visual acuity in the affected eyes at the start of this study. If the visual acuity was less than 0.1 it was rated as poor; this was found in 43 eyes (61%). Visual acuity was rated as relatively good when it was 0.5 or better, which was found in 7 eyes (10%). Average visual acuity was 0.037. Visual acuity in the affected eye of 1 patient was 1.2 before treatment, but dropped to only 0.7 during follow-up.

Forty-seven fields by HFA, 18 fields by Goldmann perimetry, and 3 fields by other perimetry were available for analysis. All 68 fields were judged abnormal. Average mean deviation in HFA was $-22.2 \pm 10/6$ dB (mean ± SD). Diffuse field defect was apparent in 37.5% of the cases. The centrocecal defect was the most frequent localized field defect, followed by altitudinal defect, enlarged blind spot, and three-quadrant defects (Table 3).

Forty-two of 52 eyes (81%) examined using the Ishihara pseudoisochromatic plates showed one or more reading errors. Average correct score was 9.7 (SD = 13.4).

Forty-one eyes showed reduced contrast sensitivity for at least one spatial frequency. Reduced sensitivity was evident mainly at 6 CPD (98%) and was least evident at 18 CPD (80%). The average sensitivity at each spatial frequency is shown in Figure 3 for the 41 eyes. Reduced fusion frequency of less than 35 Hz in CFF was noted in all affected eyes examined (n = 56). The average value was 12.8 Hz (SD = 8.8).

Table 3. Types of Visual Field Defects (n = 70)

	No. of Eyes	(%)
Diffuse	27	(37.5)
Localized	45	(62.5)
Arcuate	1	(1.3)
Altitudinal	7	(9.7)
Double arcuate	1	(1.3)
Enlarged blind spot	6	(8.3)
Central	4	(5.6)
Centrocecal	9	(12.5)
Paracentral	2	(2.8)
Nasal step	2	(2.8)
Quadrant	0	
Three quadrant	6	(8.3)
Hemianopic	3	(4.2)
Vertical step	0	
Peripheral rim	1	(1.3)
Multiple foci	3	(4.2)

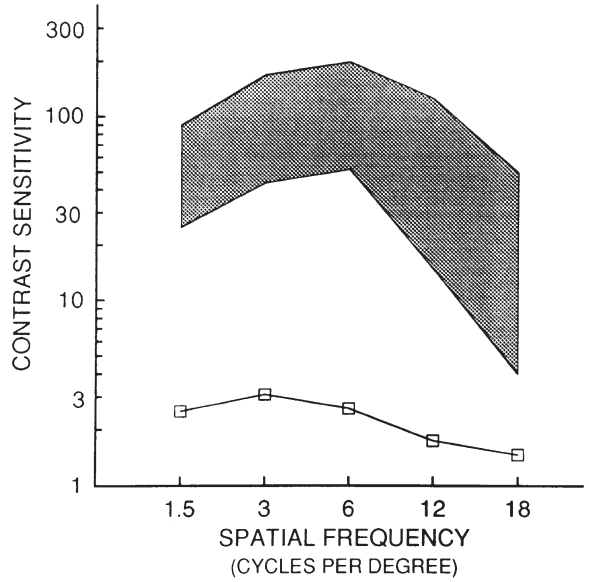

Figure 3. Average contrast sensitivity of affected eyes at start of this study.

Visual Function of Nonaffected Eyes

Visual acuity of nonaffected eyes was 1.0 or better in all cases, although anisometric amblyopia was noted in 1 patient. HFA was measured in 45 eyes. Average mean deviation was −4.54 dB (SD = 5.13). A mean deviation of less than −3.00 dB was noted in 53% of nonaffected eyes. Four of 52 eyes (7.7%) examined by Ishihara pseudoisochromatic plates showed one or more reading errors. In 6 of 41 eyes (14.6%), reduced contrast sensitivity was noted at one or more spatial frequencies. In CFF (n = 56), 16.1% of nonaffected eyes showed less than 35 Hz.

Discussion

A study of the baseline clinical characteristics of patients with optic neuritis in Japan indicated results that differed from those of the optic neuritis study in the USA,[7] with regard to certain demographic features. Ocular or periocular pain, usually noted before visual loss, and which worsened with eye movement, was detected in 56% of the present patients, whereas it was observed in 92% in the US study.[7] Pain was apparently a major factor in the diagnosis of optic neuritis in the predominately White US population, but this has not been considered so for Japanese cases. The present study shows major differences as compared with the study in the US. Swollen discs were noted in 50% of the present patients, as compared with only 35% in the US study.[7] The present Japanese study appears to be at variance with the generally held view that swollen discs in optic neuritis are encountered more frequently in young patients, whereas adults more often show the retrobulbar form of optic neuritis without swollen discs. The reason for this may be that fluorescein angiography, which readily detects even slight disc swelling, is often utilized in Japanese ophthalmology clinics. In US neuro-ophthalmology clinics, fluorescein angiography apparently is not generally conducted for patients with optic neuritis because such a procedure is considered necessary only for identifying retinal pathologies.[8] Thus, the lack of ocular pain and the presence of optic disc swelling appear to be characteristic features in Japanese optic neuritis patients, and possibly may be associated with the low risk of clinically definite multiple sclerosis.[9]

In contrast to 13% of patients with definite or probable multiple sclerosis at the start of the US study, there were only 6% in this study. The criteria for diagnosis may, in actuality, have differed from center to center, even though the diagnosis was based on Poser's definition for multiple sclerosis.[10] Thus, these figures would be of no use for valid comparison. A more accurate figure would be obtainable from MRI findings. Only 14% of our patients had periventricular plaques, in contrast to the very high US rate of 49%; the latter value is consistent with multiple sclerosis on MRI.[7] Most Japanese patients with optic neuritis are cases with no relation to multiple sclerosis. Regarding the association of optic neuritis to multiple sclerosis, the results of the two studies are seen clearly to differ. In the Japanese, multiple sclerosis is much less prevalent than in America, according to epidemiological studies,[11,12] as may also be said for optic neuritis. The annual incidence of optic neuritis in Olmsted County, Minnesota, USA, is 5.1 per 100,000.[13] Optic neuritis appears to occur three times more frequently in the US than in Japan.[1]

Despite demographic differences, the results of the baseline visual function tests were the same for the most part. CFF was conducted in our study but not in the US study. This test is frequently done at Japanese clinics because of its high sensitivity for detecting optic nerve disorders,[5,6] as was evident in the present study.

Nonaffected eyes of more than half the present patients showed abnormal HFA mean deviation; the results of other visual function tests were abnormal for only 7–16%. At least half the present cases apparently had bilateral disease, despite unilateral loss of visual acuity. Abnormalities of the visual field in

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the nonaffected eye was noted in 48% of patients in the US study.[14] It has yet to be determined whether fellow eye abnormalities have any value for predicting the development of multiple sclerosis.[14] Rather, bilateral involvement may be a common feature of optic neuritis, the detection of which should become more readily possible with the development of more sensitive testing apparatus.

The overlapping of the clinical features of optic neuritis and ischemic optic neuropathy is also an important factor in accurate diagnosis.[15] Visual function tests on nonaffected eyes should facilitate differential diagnosis because simultaneous bilateral disease is extremely rare in nonarteritic ischemic optic neuropathy.

In conclusion, the present study clarifies the baseline clinical features of Japanese patients with optic neuritis. Compared to the US study, the incidence of ocular pain was lower, the number of patients with optic disc swelling was higher and patients with MRI plaques were fewer. These characteristic features may be related to the low risk for Japanese patients for developing multiple sclerosis.

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