Pattern reversal visual evoked potentials in Japanese patients with multiple sclerosis

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SUMMARY Forty-seven Japanese patients with multiple sclerosis, 29 probable (clinically definite) and 18 possible, were studied by black-and-white checkerboard pattern reversal visual evoked potential and were compared with a control group of 20 healthy young adults. The major positive peak (P_{100}) was found to be abnormal in 70% of all cases, 90% of probable cases and 39% of possible cases. P_{100} was delayed in 38% of all cases and was absent in 23% of all cases. None of the eyes showing a flat pattern response was in the acute stage of optic neuritis. The percentage of cases with no response (23% of all cases) was greater than any of the previously reported series from Western countries, substantiating the previously reported clinical features of oriental multiple sclerosis. The pattern response was absent only when testing eyes with severe visual impairment, whereas delayed latency of P_{100} was seen regardless of the severity of visual impairment, suggesting the usefulness of P_{100} latency for detecting subclinical optic nerve lesions.

In 1972 Halliday *et al*¹ reported a delayed latency of the checkerboard pattern reversal visual evoked potential (VEP) in the affected eye of patients with optic neuritis even after visual acuity had returned to normal. Since then many investigators have confirmed the usefulness of pattern reversal VEP for detecting subclinical optic nerve lesions in optic neuritis and multiple sclerosis.^{2,3} A delayed pattern response has been regarded as highly characteristic of demyelinating diseases although it may not be specific.^{4,5} The amplitude of the pattern response was found to be correlated with the visual acuity at the time of recording and to recover in parallel with the improvement of visual acuity, while the latency did not correlate with the visual acuity.⁶

Oriental multiple sclerosis patients have been claimed to show acute and severe optic nerve involvement more frequently than Caucasian patients probably owing to the more common occurrence of axonal involvement in the former.⁷⁻¹⁵ The present study, therefore, was aimed at investigating whether Japanese multiple sclerosis patients show different features of pattern response abnormalities from Caucasians. This is the first report of pattern reversal VEP in oriental patients with multiple sclerosis.

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Received 10 July 1982.

Accepted 9 August 1982

Subjects and methods

Subjects for the present study were 49 consecutive Japanese patients with multiple sclerosis seen at Kyushu University Hospital from July 1979 to June 1981, 22 males and 27 females. Overall 58 recordings of pattern reversal VEP were made in these patients. Their age at the time of last recording ranged from 12 to 64 years, mean age 39 years ($SD = 12$ years). They consisted of 31 patients with "probable (clinically definite)" multiple sclerosis and 18 patients with "possible" multiple sclerosis according to the diagnostic criteria of the multiple sclerosis Research Committee of Japan.⁴ Duration of the illness from the onset to the time of last recording was 1 month to 30 years, mean 7 years ($SD = 7$ years).

Corrected visual acuity of each eye was tested just preceding VEP recording, and visual impairment of each eye was graded by the Minimum Scoring System of Multiple Sclerosis Disability proposed by the authors.¹² The visual impairment of each eye was categorised into five grades based on the corrected visual acuity: 0: none (1.0 or above), 1: slight (0.5 to 0.9), 2: moderate (0.1 to 0.4), 3: severe (0.08 or less), and 4: completely blind. Twenty healthy young adults, six males and 14 females, aged 18 to 33 years, served as normal controls. Corrected visual acuity was normal in all subjects.

The subject was seated in an arm-chair in a dark room. Pattern reversal VEP was recorded by stimulating each eye separately while the other eye was masked by a white bandage. Visual acuity was corrected by spectacles when necessary. Following Halliday's method,¹ the slide of a black-and-white checkerboard pattern was projected via a rotatable mirror onto the back of a translucent screen.

An electromechanical transducer enabled the mirror to be turned through a small angle, causing side-to-side movements of the pattern on the screen every 550 ms. The movement of the mirror took about 15 ms to complete. The repetitive movements through one square were used to produce an appearance of pattern reversal. The subject sat 80 cm in front of the screen, the whole stimulating field subtending 32° at the eye. The individual black-and-white squares subtended 45 minutes. The subject was instructed to fixate on a small red spot in the centre of the screen throughout the runs. A subject who could not see the spot was requested to keep looking straight ahead.

Six recording electrodes were placed on the occipital scalp; 5 cm and 2.5 cm above the inion (Oz' and Oz, respectively), 5 cm and 10 cm lateral to the Oz' electrode on a line joining Oz' to the external auditory meatus on each side. A reference electrode was placed at Fz (International 10-20 system). Electrode impedance was kept below 5 kΩ. Time constant used was 0.3 s, and the high frequency cut-off of the amplifier was 10% down at 2,000 Hz. EEGs were averaged by San-ei Signal Processor 7T08 time-locked to the onset of mirror movement. Analysis time was 280 ms with an ordinate period of 0.28 ms. 100 to 200 samples were averaged for one session and at least two runs were done for each eye. Measurement of the peak latency was carried out by computer cursoring. Data were plotted on an X-Y recorder. With respect to the peak latency of the response and its right-left differences, any value exceeding three standard deviations of the mean value of normal controls was judged abnormal.

Results

In normal subjects, the major positive peak (P100) was identified in all trials, being maximal at Oz' or Oz electrode. Its mean peak latency was 92.5 ms (table 1). Preceding P100, a positive peak was identified at a mean peak latency of 49.9 ms (P50) in 75% of eyes, and a negative peak was recorded at a mean peak latency of 67.8 ms (N70) in 95% of eyes (table 1). Following P100, a negative peak was recorded at a mean peak latency of 136.0 ms (N145) in 90% of eyes. The right-left differences of these peak latencies were very small (table 1).

Two patients with probable multiple sclerosis were unable to concentrate during recording session owing

Table 1 Peak latencies and their right (R)-left (L) differences of pattern reversal VEP in normal subjects (20 subjects, 40 eyes), measured at Oz' electrode

	P50	N70	P100	N145
Peak latency				
n	30	38	40	36
mean (ms)	49.9	67.8	92.5	136.0
SD (ms)	3.33	4.04	4.44	12.11
R-L difference of peak latency				
n	15	19	20	18
mean (ms)	0.2	0.7	-1.4	-4.3
SD (ms)	2.00	2.28	1.86	7.67

Table 2 Abnormalities of the major positive component (P100) of pattern reversal VEP in multiple sclerosis patients (number of cases)

(n)	Probable (29)	Possible (18)	Total (47)
No response	8 (27.6%)	1 (5.6%)	9 (19.1%)
one eye	5	1	6
both eyes	3	0	3
Delayed peak latency	13 (44.8%)	3 (16.7%)	16 (34.0%)
one eye	5	2	7
both eyes	8	1	9
No response in one eye and delayed latency in the other	1 (3.4%)	1 (5.6%)	2 (4.3%)
w-shaped waveform	2 (6.9%)	0 (0%)	2 (4.3%)
one eye	1	0	1
both eyes	1	0	1
Right-left difference of peak latencies	2 (6.9%)	2 (11.1%)	4 (8.5%)
Overall abnormalities	26 (89.7%)	7 (38.9%)	33 (70.2%)

to mental impairment. Among 47 cases who could co-operate, P100 was judged abnormal in 33 cases (70%). Among 29 cases with probable (clinically definite) multiple sclerosis, 26 cases (90%) showed some abnormalities in the P100 component in comparison with seven among 18 patients with possible multiple sclerosis (39%) (table 2). The most

Fig 1 Pattern reversal VEP in a 31-year-old male patient with multiple sclerosis showing predominantly progressive spastic form. Oz'-Fz derivations. 128 responses were averaged. The major positive peak (P100) for the right eye (dashed line) occurred 108.4 ms after the onset of pattern reversal, and that for the left eye (thick arrow) was 142.8 ms (upper normal limit 105.8 ms). No previous history of optic neuritis, and visual acuity was completely normal in both eyes at the time of recording

frequent abnormality was the delayed peak latency which was observed in 18 cases (38% of all cases) (fig 1). In cases showing delayed peak latency of P_{100} , all other recognisable components were also delayed. P_{100} was absent either in one eye or in both eyes in 11 cases (23% of all cases). In cases in whom P_{100} was not detectable, no other components were identified, either. Right-left difference of P_{100} peak latencies was a single abnormality in four cases (8.5% of all cases). Among 29 cases with probable multiple sclerosis, P_{100} was absent either in one eye or in both eyes in nine cases (31%), and was delayed in 14 cases (48%). Bilateral abnormalities were seen in 15 cases (32% of all cases).

With regard to clinical stage of the illness, 14 among 17 cases (82%) who were judged to be in exacerbation or in a chronic active (progressive) stage showed VEP abnormalities. Among 30 cases who were judged to be in remission or in a chronic stable stage, 19 cases (63%) showed VEP abnormalities. There was no significant difference in these two groups.

With regard to the relationship with previous history of optic neuritis, P_{100} of pattern reversal VEP was abnormal in 93% of cases with previous history of optic neuritis versus in 40% of cases without ($p < 0.002$, chi-square test) (table 3). Relationship between the peak latency of P_{100} and visual impairment of each eye at the time of recording is shown in fig 2. When stimulating the totally blind eyes, no response was obtained. Among 14 eyes with severe visual impairment, pattern response was absent in eight and markedly delayed in the remaining six eyes. Among 29 eyes whose visual acuity was mildly reduced, 10 eyes (34.5%) showed delayed peak latency of P_{100} , and w-shaped response was seen in two eyes. Among 58 eyes with normal visual acuity, P_{100} peak latency was delayed in 18 eyes (31%), and three other eyes showed w-shaped P_{100} component although the initial positive peak occurred within normal limits of latency.

In the 16 eyes which showed no pattern response at all, the time interval from the last attack of optic neuritis to the time of recording ranged from 2 months to 14 years, mean 3.0 years (SD = 3.2 years).

Table 3 Previous history of optic neuritis and abnormalities of P_{100} of pattern reversal VEP

	Optic neuritis		Total
	Present	Absent	
Abnormal	25 (92.6%)	8 (40.0%)	33 (70.2%)
Normal	2 (7.4%)	12 (60.0%)	14 (29.8%)
Total	27 (100%)	20 (100%)	47 (100%)

($\chi^2 = 10.05$, $p < 0.002$)

Fig 2 Peak latency of P_{100} and visual impairment at the time of recording for each eye. Visual impairment scale: 0, none (1.0 or above); 1, slight (0.5 to 0.9); 2, moderate (0.1 to 0.4); 3, severe (0.08 or less); 4, completely blind. Dashed lines indicate limit of normal range (mean $\pm$ 3 SD) of P_{100} latency, based on the control data. An open circle indicates an eye with no pattern response. A triangle; w-shaped P_{100} , plotted by using a latency of the initial positive peak

Discussion

A large number of studies on pattern reversal VEP in Caucasian multiple sclerosis patients have been reported from Western countries. Overall percentage of patients showing abnormal pattern responses ranged from 52 to 85%, and among patients with definite multiple sclerosis, 75 to 100% of those were reported to show abnormal pattern response.¹⁶⁻³³ The present study among Japanese multiple sclerosis patients, in fact the first study among orientals, demonstrated a similar percentage (70% of overall cases and 90% of probable (clinically definite) cases).

The usefulness of pattern reversal VEP for detecting subclinical optic nerve lesions in multiple sclerosis, as originally suggested by Halliday *et al*¹ and later by many other investigators, was reconfirmed in the present study (fig 2). Abnormalities of pattern response were significantly more frequent among patients with previous history of optic neuritis than among those without (93% versus 40%) (table 3). This finding is also in conformity with previous reports from Western countries.^{17 26 29 31 32} As in studies reported by other investigators, the most

Table 4 Percentage of patients with multiple sclerosis showing no pattern evoked response

Reference	Number of patients or eyes tested	No response (%)
Asselman <i>et al</i> 1975 (17)	100 eyes	2.0
Zeese 1977 (23)	30 cases	13.3
Nilsson 1978 (25)	38 cases	13.2
Shahrokhi <i>et al</i> 1978 (26)	51 cases of optic neuritis	13.7
	59 eyes of optic neuritis	13.6
Tackmann <i>et al</i> 1979 (29)	54 cases	20.4
Trojaborg and Petersen 1979 (30)	100 eyes	3.0
Kjaer 1980 (32)	100 cases	9.0
Wilson and Keyser 1980 (33)	100 cases	4.0
The present series	47 cases	23.4

common abnormality was a delayed latency of the major positive peak (P100).

The most conspicuous finding in the present study, however, was the complete absence of a pattern response either in one eye or in both eyes, which was seen in 23% of all cases or in 31% of probable multiple sclerosis cases. Although the amplitude of the pattern response has drawn much less attention as compared to the latency, several studies reported the percentage of multiple sclerosis patients showing no response (table 4). The percentage reported in the present study is greater than any of those reported from Western countries, and only the Basel series by Tackmann *et al*²⁹ reported a percentage similar to ours. Among their 54 multiple sclerosis cases, they found no response bilaterally in five cases and unilaterally in six cases.

Halliday *et al*¹ in their original report studied pattern reversal VEP in five patients with optic neuritis within a fortnight of the onset when a visual acuity was 6/60 or less, and recorded no response in the affected eye. Subsequent recordings in four of those patients showed responses of small amplitude, although with a much delayed peak latency, when vision was still impaired.¹ Sixteen eyes showing no pattern response in the present study had a time interval from the last attack of optic neuritis of 2 months to 14 years (mean 3 years), indicating that none of the eyes was in the acute stage of optic neuritis. In those reports listed in table 4, there is no information available as to whether the recording was made in acute or chronic stage of optic neuritis. Nonetheless, the present findings seem to support the previously reported clinical and pathological features of oriental multiple sclerosis that include more frequent occurrence of severe and non-remitting optic nerve involvement as compared to Caucasian cases.⁷⁻¹⁵

Concerning the correlation between the pattern

response abnormality and visual acuity, Halliday *et al*⁶ reported that visual acuity tested at the time of recording correlated significantly with the amplitude of the pattern response, but not with the latency. The present findings (fig 2) are in good agreement with their findings. All eyes with no pattern response had visual acuity of 0.08 or less, whereas delayed latency was seen regardless of the severity of visual impairment.

We are grateful to Dr AM Halliday, The National Hospital for Nervous Diseases, Queen Square, for his revision of this article.

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