Spatial tuning function of pattern visual evoked potentials in multiple sclerosis patients without optic neuritis history

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ABSTRACT

Aim To explore amplitude and latency-check size function in multiple sclerosis (MS) patients without optic neuritis history.

Methods Thirty-six MS patients and 21 control subjects were included. Pattern visual evoked responses to five check sizes (2°, 1°, 30', 15', and 7') were recorded.

Results P100 amplitudes were significantly reduced in 2°, 1° and 7' checks and, P100 latencies were significantly delayed in all checks in MS patients (p<0.05). Inter-ocular amplitude/latency differences were significantly higher in MS patients than control group (p<0.05). The P100 amplitudes for 2° check was somewhat higher than amplitudes for 1° check in MS and control groups. However, MS patients had flatter amplitude-check size function curve in large checks. In small checks, the slope of the amplitude-check size curves were similar for MS and control groups. The flattening of amplitude-check size function curve in large checks increased in MS patients with reduced P100 amplitudes. The P100 amplitudes for 2° check was lower than P100 amplitudes for 1° check in MS patients with reduced P100 amplitudes in contrast to normal subjects and MS patients with normal P100 amplitudes. Both groups had almost parallel P100 latency-check size curves in all checks. With respect to 95% confidence limit in control subjects in each check sizes, the number of eyes with delayed latency and reduced amplitude in MS patients were higher in large checks.

Conclusion This study showed that P100 amplitudes are reduced in MS patients without optic neuritis history, and responses to large checks are affected more than small checks.

Key words: multiple sclerosis, amplitude-check size function, check size
INTRODUCTION

Multiple sclerosis (MS) is an autoimmune-mediated neurodegenerative disease with characteristic inflammatory demyelination in the central nervous system. Visual dysfunction occurs in 80% of patients with MS during the course of their disease and is a presenting feature in 50% (1). Acute idiopathic demyelinating optic neuritis is frequently initial clinical manifestation. PVEP has been used as an indispensable part of examination of MS, and has been shown to detect subclinical optic nerve involvement in MS patients (1-4).

Pattern visual evoked potential (PVEP) is the cortical response to a counterphasing pattern stimulus. The response reflects the spatial and temporal processing properties of the visual pathway (5). The normal PVEP amplitude check size function curve has an inverted ‘U’ configuration peaking at intermediate to small check sizes (6,7). This shape may reflect that the human visual system is ‘tuned’ to certain spatial frequency ranges. Ohn and associates reported the flattening of the PVEP amplitude-check size function often observed in patients with optic nerve disease (8). Although, PVEP amplitude reduction and latency delay were shown in MS patients without symptoms of optic pathway involvement in previous studies (1-4), spatial processing properties of the cortical responses of that group of patients may be a useful tool in the diagnosis of optic pathway involvement.

This study aims to explore the spatial tuning function curves of MS patients without a history of optic pathway involvement.

PATIENTS AND METHODS

Subjects

Thirty-six patients with a diagnosis of definite MS were enrolled. They were under routine review by a single neurologist and ophthalmologists. Only the consecutively-selected MS patients who had no visual symptom or sign, and the best corrected Snellen visual acuity (VA) of at least 1.0 in both eyes during the follow-up were included. Mean duration from the diagnosis was 22.80±14.2 months. Mean expanded disability status scale (EDSS) was 2.8±1.7. All the patients had relapsing-remitting pattern of MS.

The research followed the tenets of Declaration of Helsinki and informed consent was obtained from the subjects after explanation and possible consequences of the study. The research was approved by the institutional review board. All the patients were specifically asked about visual complaints including vision blur, visual loss, diplopia, periorbital pain, and color vision disturbances (change in seeing traffic lights or in the brightness of colors in one or both eyes) throughout their life period. Complete ophthalmologic examination, including anterior segment biomicroscopy, applanation tonometry and indirect ophthalmoscopy including the examinations of the peripheral retina, was performed.

Control group comprised 21 healthy subjects who had no ophtalmic and systemic disease (including diabetes, systemic hypertension) in the past and at the time of study enrollment.

PVEP recordings

Monocular PVEPs were recorded with gold disc surface electrodes. On the basis of ISCEV (International Society for Clinical Electrophysiology of Vision) recommendations (9), active electrodes were placed on the scalp over the visual cortex at Oz, with the reference electrode at Fz. The ground electrode was placed on the forehead. The Roland Consult RETIScan System™ (Wiesbaden, Germany) was used. Refractions of the subjects were corrected with trial lenses before recordings were made. Each subject sat in a moderately lighted room one meter in front of a 20 cm × 30 cm black-and-white video display monitor. The checkerboard stimulus subtended a visual angle of 5.7° vertically and 8.5° horizontally on either side of the fixation. The responses to five check sizes (2°, 1°, 30’, 15’, and 7’) were recorded. Luminance was < 0.017cds/m2 (1cd/m2) for the black hexagons and 1.92cds/m2 (115cd/m2) for the white hexagons (contrast: 99%). Background light was dimmed (20cd/m2). The reversal rate was one reversal per second. The responses to 100 stimuli for each check were averaged. Subjects were instructed to fixate on a red marker at the center of the screen. If the cooperation of the subject was poor, the PVEP recording was repeated. Fixation stability, eye movements, and prolonged closing of the eye were monitored closely by an experienced electrophysiology technician throughout the entire testing period.
Statistics

The amplitude and latency of the first positive peak in PVEP response (P100 peak) were obtained for the statistical analyses. The amplitudes/latencies obtained at the five check sizes were plotted against the check sizes to obtain amplitude/latency-check size function curves. Only the right eyes of the patients were used for inter-group comparisons and both eyes were selected for inter-eye comparisons. Inter-ocular amplitude/latency differences were assessed by dividing the absolute difference for the P100 amplitudes/latencies between right and left eyes to the mean of both values. Using 95% confidence interval limit of P100 latency in control subjects, MS patients were classified into two groups: ‘MS-P100 delayed latency’ patients and ‘MS-P100 normal latency’ patients. Similarly, MS patients were again classified into two groups as ‘MS-P100 reduced amplitude’ and ‘MS-P100 normal amplitude’ patients with regard to 5% confidence interval limit of P100 amplitude in control subjects.

RESULTS

Age (MS patients: 35.4±7.9 years, control subjects: 36.8±6.5 years, p=0.365) and gender (male/female ratio: 13/23 in MS group, 8/13 in control group, p=0.915) distributions were similar between the groups.

Farnsworth-Munsell 100 Hue color vision test total error scores for MS and control subjects were 64.7±34.7 and 47.1±14.1, respectively (p=0.026). Humphrey visual field mean deviations for MS and control subjects were -1.9±1.3 and -1.1±0.7, respectively (p=0.087). All the patients had normal fundoscopic appearance with panfundoscopic examination.

Figures 1A and 1B represent examples of PVEPs, recorded from a control subject and an MS patient in response to stimuli of different spatial frequencies, respectively. In the control subject, P100 amplitudes are reduced sharply in 7’ check. However, in the MS subject, P100 amplitudes are reduced almost linearly with decrease in check size (Figure 1C). Regarding P100 latency, MS subject has almost equal and delayed P100 peak in all checks. However, in the control subject, P100 latencies are more delayed with smaller check sizes (Figure 1D).

Figure 1. Representative PVEP recordings from a control (1A) subject and a patient (1B). Legend: Amplitude check size curve and latency-check size curve for these recordings are seen in Figure 1C and 1D, respectively.

Figure 2. Latency-check size (above) and amplitude-check size (below) function curves in the groups.
The P100 latencies were significantly delayed for all check sizes and P100 amplitudes were significantly reduced in 2°, 1° and 7' checks, but insignificantly reduced in 30' and 15' checks in MS patients (Figure 2A, Figure 2B, respectively). Inter-ocular latency differences were significantly higher in all check sizes in MS patients. Similarly, inter-ocular amplitude differences were significantly higher in 2°, 30', 15' and 7', and insignificantly higher in 1° check in MS patients (Figure 3A, 3B).

Mean P100 latency for 2° was 104.5±6.4 ms in control subjects. Ninety-five percent confidence interval (95% CI) was 119.8 ms. The number of eyes of MS patients with delayed/normal P100 latencies and reduced/normal P100 amplitudes for each check sizes were investigated. It was seen that the highest number of eyes with a delayed P100 latency was observed in the responses to 1° check (52.8%). The highest number of eyes with reduced P100 amplitude was observed in the responses to 30° check (30.6%) in MS patients. The numbers of the eyes with reduced amplitude and delayed latency were higher in large checks (Figure 4A, 4B). The number of eyes with delayed latency was higher than the number of eyes with reduced amplitude in each check sizes (Figure 4A, 4B).

Both MS and control group amplitude-check size curves had almost ‘inverted U’ shapes (Figure 2B). In addition, both MS and control group latency-check size curves had ‘U’ shape. It should be emphasized that the highest amplitudes in MS group were apparently obtained in 15° check. In control subjects, however, the highest amplitudes were obtained in 1° check. In large checks, MS patients had somewhat flatter amplitude-check size function curve. In smaller checks, the slopes of the amplitude-check size curves were similar for MS and control groups (Figure 2B). Latency-check size curves in both groups showed that both MS patients and control subjects had

![Figure 3. Inter-ocular latency (above) and amplitude (below) differences in MS patients and controls. Legend: the values above the boxes show the inter-ocular statistical significance values (p).](image)

![Figure 4. The distribution of eyes with normal/delayed latency (left columns) and normal/reduced amplitude (right columns) and in multiple sclerosis patients and control subjects in each check sizes. Legend: the vertical lines in each box represent the 95% confidence interval limits for P100 latencies and 5% confidence interval limits for P100 amplitudes.](image)
the shortest P100 latencies in medium size check (30’) (Figure 2A). However, in larger and smaller checks, P100 latency was longer in both groups. Both MS and control groups had similar latency-check size curves (Figure 2A).

In comparison with the normal-latency MS, delayed-latency MS, and control subjects, latency-check size curves were similar in three groups (Figure 5A). However, amplitude-check size curves differed in shape in large checks. P100 amplitudes for 2° check was lower than P100 amplitudes for 1° check only in ‘MS-P100 reduced amplitude patients’. ‘MS-P100 normal amplitude’ patients and control subjects had higher P100 amplitudes for 2° check than for 1° check. In general, normal amplitude MS patients had a more harmonic curve with control subjects than for ‘MS-P100 reduced amplitude’ patients (Figure 5B).

**DISCUSSION**

Katsumi et al. analyzed the shape of the PVEP amplitude-check size function and suggested that the inverted-U shape is related to the number of pattern elements within the entire stimulus field (10). In pathologic conditions, this standard inverted-U shape function can change with the loss of inverted-U shape or the loss of spatial tuning characteristics. Two studies reported the shift of the peak check size to the larger checks in functional amblyopia (11,12). It is also noteworthy that there was no shift of the peak in PVEP amplitude-check size function in optic nerve disease compared with other pathologies, such as amblyopia in which the peak was reported to shift to the larger check sizes (6). To our knowledge this is the first study evaluating P100 amplitude and latency check size function curves in MS patients without a history of optic pathway involvement.

The present study was designed to evaluate the spatial tuning function of PVEP in MS patients without a history of optic neuritis. Our results have shown significantly delayed P100 latencies in all check sizes and significantly reduced P100 amplitudes in 2°, 1° and 7’ checks in MS patients as compared to control subjects. In addition, inter-ocular amplitude and latency differences were significantly higher in MS group than in the control group. This finding also implies the subclinical optic nerve involvement (2-4). It is noteworthy that similar to P100 parameters, MS patients had significantly increased total error scores. However, mean deviation increase with respect to control subjects in Humphrey visual field was insignificant. These findings emphasize the value of color vision assessment besides PVEP in detecting subclinical optic pathway involvement.

Previous studies suggested that VEP abnormalities may be dependent on the stimulus spatial frequency (13-17), with the responses at medium-high spatial frequencies being predominantly affected (15,16,18). This band-pass spatial tuning function is believed to reflect inhibitory centre-surround organization of the receptive fields of response generators (13). Different neuronal classes in the inner retina, which respond preferentially to different spatial characteristics of the stimulus, could dominate the VEP response (19,20). Regan et al. suggested that a dysfunction or loss of specific subpopulations of retinal ganglion cells with medium-sized receptive fields may contribute to psychophysical losses in MS (14).
In this study, almost ‘inverted U-shaped’ amplitude-check size function curves were obtained in both MS and control groups. However, in bigger checks (low spatial frequencies), MS patients had somewhat flatter amplitude-check size function curves. Latency-check size function curves were almost ‘U-shaped’ in both MS and control groups. These findings mean that P100 amplitudes in bigger checks are much more affected in MS patients than small checks. This finding is more obviously supported by another one in this study. P100 amplitudes for 2° check were higher than P100 amplitudes for 1° check in control subjects. In ‘MS-P100 normal amplitude’ patients, the same finding was found, but the amplitude difference was smaller. That is, the curve was flatter than in control subjects. However, in ‘MS-P100 reduced amplitude’ patients, the curve had a reversed angle, that is, P100 amplitudes for 2° were lower than P100 amplitudes for 1°. These findings may be a result of a decrement in the resolution capability of retina in bigger checks or a result of functional changes in the transmission of electrical activity in optic nerve axons in MS patients. Simultaneously recorded PVEP and PERG amplitude-check size function curves are needed to clarify this issue. As a result of these findings, it can be stressed that PVEP recording using big check sizes instead of small ones may explore the subclinical optic pathway involvement more definitely in MS patients.

Spatial tuning function of pattern electroretinogram (PERG) was also studied in MS patients. In human and animal studies (21-23), the amplitude of steady-state PERG was found to be maximum at intermediate spatial frequencies, and attenuation at lower and higher frequencies. However, there is evidence that the PERG tuning function has peak amplitude at a somewhat lower spatial frequency as compared with either VEPs or contrast sensitivity function (24). These differences may be related to the difference in source of electrical activity in retinal locations in these tests. While the PERG represents more uniformly the entire stimulus field (25), including those areas in which the response generators have larger receptive fields, PVEP reflects mainly foveal and parafoveal functions (13).

In conclusion, this study shows that analysis of PVEP as described in this paper appears to detect early or mild optic nerve dysfunction when the vision is relatively good. The amplitude-check size functions are affected especially in large checks in patients without a history of optic pathway involvement. Subclinical optic pathway involvement may be explored in a more consistent way by using large check sizes in PVEP recordings.

**FUNDING**

No specific funding was received for this study.

**TRANSPARENCY DECLARATIONS**

Competing interests: none to declare.

**REFERENCES**