Visual Evoked Potentials in Multiple Sclerosis Patients Treated with Interferon beta-1a

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Aim. To study pattern-reversal visual evoked potentials (VEP) in patients with relapsing-remitting multiple sclerosis on interferon beta-1a treatment.

Methods. In a randomized, prospective, non-blinded, placebo-uncontrolled study, VEP were studied in 9 patients (18 eyes) with relapsing-remitting multiple sclerosis treated with interferon. Three of them have had an episode of unilateral optic neuritis. VEP were first recorded before interferon treatment and then followed up for 12 months, at 3-month intervals, in the time when patients were receiving interferon, 11 µg twice weekly. All patients did not appear regularly at 3-months intervals follow-up, except for 6-month follow-up. P100 latency and P100 amplitude in responses to full field, right and left half-field stimulation were evaluated.

Results. For the group of 18 eyes, there was no statistically significant difference in P100 latency and P100 amplitude before and after 6 months of treatment. In individual cases P100 latency was delayed in 3 eyes of 3 patients with a history of optic neuritis before treatment. At follow-up, P100 latency remained delayed in 3 eyes with a history of optic neuritis. Further, in 3 eyes of two patients who have had normal P100 latency before treatment, P100 latency became delayed. Overall, P100 latency was at follow-up delayed in 6 eyes of 5 patients.

Conclusion. Interferon beta-1a therapy (22 µg per week) administered for 12 months during 1998/99 in Croatia showed no statistically significant VEP changes in the group of relapsing-remitting multiple sclerosis patients. However, VEP may reveal evidence for asymptomatic deterioration.

Key words: evoked potentials, visual; interferon-beta; multiple sclerosis, relapsing-remitting

The visual pathway is frequently involved sensory system in multiple sclerosis (MS). The spectrum of its involvement ranges from the changes demonstrated only by abnormal visual evoked potentials (VEP), concurrent with clinically normal visual acuity, normal fundi, normal visual fields and normal color vision, to the clinically evident visual dysfunctions, including optic neuritis. In MS patients, VEP latency prolongation is considered as evidence of demyelination in the visual pathway. In patients with no visual disturbance, delayed VEP is associated with clinically silent demyelinating lesions (1).

Nowadays, the use of magnetic resonance imaging (MRI) is leading in diagnosis and evaluation of treatment in MS patients. For that reason, there is a legitimate question of what additional information may VEP provide in demyelinating lesions of the visual system. Recent studies showed that VEP might distinguish between asymptomatic deterioration associated with a permanent axonal loss and/or demyelination or improvement associated with remyelination (2-4). Therefore, VEP continues to be unique in providing objective means of function along the visual pathway. VEP latency prolongation measures delay in conduction velocity and VEP amplitude reduction measures conduction block. As stated by Brigell et al (5), VEP is direct measure of demyelination, whereas MRI abnormalities indicate edema in acute optic neuritis and fibrosis in older lesions.

VEP recording could also be valuable in studying the effect of long-term treatment with interferon beta-1a or interferon beta-1b in patients with relapsing-remitting multiple sclerosis. The beneficial effect of interferon beta-1a on exacerbations in this form of MS has been demonstrated in clinical and MRI studies (6-10). There are only two studies, however, presenting VEP in patients with relapsing-remitting multiple sclerosis treated with interferon beta-1a (11) or interferon beta-1b (12). The aim of this study was to evaluate VEP in patients with relapsing-remitting multiple sclerosis during first 12 months of treatment with interferon beta-1a.

Patients and Methods

Patients

Twelve patients (10 women and 2 men) aged between 22 and 49 years (median age, 32 years on the first visit) were included in our randomized, prospective, non-blinded, pla-
cebo-uncontrolled electrophysiological study. Age matched group comparison was provided for VEP data. The study took place between January 1998 and February 1999, and included patients with clinically definite relapsing-remitting multiple sclerosis (13) of at least one-year duration with Expanded Disability Status Scale (EDSS) scores of 2.5-5.0 (14). They had experienced at least one relapse in the preceding 12 months, but not in the 6 weeks before the study. The use of corticosteroids in this period, as well as pregnancy, lactation or psychiatric illness were the exclusion criteria. During the study, acute optic neuritis was diagnosed in a single patient; he was treated with methylprednisolone 500 mg IV for five days, and was excluded from the study. In addition, two patients did not appear at follow-up. Of the final 9 patients, 3 have had unilateral optic neuritis before the start of study. The patients were examined before treatment and then followed up for 12 months, at 3-months intervals. Patients did not appear regularly for follow-up. We examined 4 patients at the 3 months of follow-up, all 9 at 6 months of follow-up, 2 at 9 months of follow-up and 6 at 12 months follow-up. At the time of our study all 9 patients did not complain about any visual problems. The local Ethics Board approved the study and all patients gave the informed consent.

All patients received interferon beta-1a (Rebif; Ares-Serono, Geneva, Switzerland) 6 million international units (MIU) twice weekly subcutaneously, which equaled to 22 µg on a mass basis (7), 11 µg twice weekly (this was the recommended dosage in Croatia at the time of this study). Two patients experienced depression but with out suicide attempts, (15,16) and were successfully treated by pharmacotherapy. One patient had myalgia with flu-like symptoms (17).

VEP Recording and Analysis

VEP to pattern-reversal stimulation was performed with a Neurosciences Brain Imager (Neuroscience Inc., San Jose, CA, USA). Checkerboard stimuli to full field, left half-field and right half-field were presented on a monitor subtending 13° horizontally and 10° vertically. The check size was 25. The luminance was 164 and 2 cd/m² for the white and black checks, respectively. Stimulus contrast was 98%. Stimulation rate was 1 Hz, frequency bandpass 0.8 Hz-100 Hz, and 256 responses were averaged. Each trial was repeated at least twice. Analysis time was 300 ms. For recordings, five Ag/AgCl electrodes were placed 5 cm above the inion, with the central electrode in the midline and the others 5 and 10 cm over the right and left hemisphere (Halliday’s montage, ref. 18), referred to Fz according to the 10-20 EEG (electroencephalogram) system. Impedance was below 5 kΩ.

Each patient was instructed to gaze at a dot in the center of the full field pattern and for the half-field at the same dot, this time on the edge of the pattern. During recordings, a technician checked the patient’s gaze fixation. First VEP was recorded in patients before treatment and further VEP recordings followed at 3, 6, 9, and 12 months of interferon beta-1a treatment, when all 9 patients were fully treated by pharmacotherapy. One patient had myalgia with flu-like symptoms (17).

The control group consisted of 22 healthy subjects (10 women and 12 men) aged between 19 and 44 years (median age, 30 years) with normal or corrected visual acuity. Mean values for P100 latency and upper normal limit, P100 amplitudes and their lower limit are presented in Table 1. The upper normal limit for P100 latency was the mean value + 2.5 SD, whereas the 5th percentile was the lower limit for P100 amplitude. There was no significant difference between the right and left eye, therefore we combined P100 latency and P100 amplitude values for both eyes (n=44 eyes).

For statistical analysis of P100 latencies and P100 amplitudes in full field, right half field, and left half field responses, one-way ANOVA was used.

Results

Figure 1. presents P100 latencies and P100 amplitudes in responses to full field, right half field, left half field stimulation from 9 relapsing-remitting multiple sclerosis patients (18 eyes), according to the limits of normality for females and males. Four patients at 3 month follow-up, 9 patients at 6 months, 2 patients at 9 months and 6 patients at 12 month follow-up were examined. There was no statistically significant difference in P100 latencies and amplitudes to full field, right half field and left half field before and after 6 months of interferon beta-1a treatment, when all 9 patients attended the VEP examination.

In individual cases, P100 latency was delayed before treatment in 3 eyes of 3 patients with a history of monosymptomatic optic neuritis (Table 2, patients

Table 2. P100 latencies (ms) before the interferon beta-1a treatment (0 months) and at 3, 6, 9, and 12 months follow-up in 3 patients with the history of optic neuritis as part of relapsing-remitting multiple sclerosis. Two patients with clinically silent demyelinating lesions are presented.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Eye</th>
<th>VEP*</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L</td>
<td>FF</td>
<td>110 130 112</td>
<td>110 130 112</td>
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<td>110 130 112</td>
<td>110 130 112</td>
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<td>110 130 112</td>
<td>110 130 112</td>
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<td>3</td>
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<td>110 130 112</td>
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<td>110 130 112</td>
<td>110 130 112</td>
</tr>
</tbody>
</table>

P100 latency (ms) at month of follow-up

Table 1. Visual evoked potential (VEP) normative data from the left and right eyes of 22 healthy subjects (10 women and 12 men)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>P100 latency (ms)</th>
<th>P100 amplitude (V)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>upper normal limit*</td>
<td>lower normal limit*</td>
</tr>
<tr>
<td>Full field: total</td>
<td>106.4±4.3</td>
<td>117</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>103.8±4.0</td>
</tr>
<tr>
<td></td>
<td>men</td>
<td>108.6±3.3</td>
</tr>
<tr>
<td>Right half-field: total</td>
<td>107.7±5.9</td>
<td>122</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>105.3±4.9</td>
</tr>
<tr>
<td></td>
<td>men</td>
<td>109.6±6.0</td>
</tr>
<tr>
<td>Left half-field: total</td>
<td>106.4±5.3</td>
<td>120</td>
</tr>
<tr>
<td></td>
<td>women</td>
<td>104.1±4.1</td>
</tr>
<tr>
<td></td>
<td>men</td>
<td>107.9±5.5</td>
</tr>
</tbody>
</table>

*The upper normal limit for P100 latency was the mean value + 2.5 SD, and the 5th percentile was the lower limit for P100 amplitude.
At follow-up, P100 latency remained delayed in 3 eyes with a history of optic neuritis. In 3 eyes of two patients with normal P100 latency before treatment, P100 became delayed after 6 months of treatment (Table 2, patients No. 2 and 3). As the patients had no concurrent visual acuity impairment, the observed delays demonstrate a subclinical, silent demyelinating lesions, indicating asymptomatic deterioration. In the patient No. 2, P100 latency delay was first evident in the left eye right half field and left half field responses at 6 and 9 months; at 12 months also in full field responses. In the patient No. 3, P100 latency delay was less consistent as it was observed from both eyes at 6, but not at 12 months. Therefore, after 6 months, when all 9 patients were tested, P100 latency was delayed in 6 eyes of five patients.

The normalization of P100 latency was not found in individual cases. Some degree of shortening was observed in patient 9 only in full field responses, from 146 ms before treatment to 140 ms after 12 months. P100 amplitude before treatment was reduced in 1 eye in full field responses and in 2 eyes in left half field responses. At follow up diminished P100 amplitudes were observed in half field responses, but not in full field responses. There was no tendency of decline in full field responses for P100 amplitude over one year follow-up (Fig. 1).

Discussion

With the mounting data supporting subclinical progression of destructive pathology in MS, the need for reliable and sensitive measure of tissue dysfunction has become most urgent (11). MRI changes are today considered the most sensitive marker for MS, although MRI reflects morphological abnormalities with poor correlation to clinical assessment (19,20). On the contrary, VEP monitors function along the visual pathway and VEP latency prolongation is a direct measure of demyelination. Although the hallmark of the disease is demyelination, results emerging from clinical and laboratory studies over the past few years have shown that axonal damage, primary or secondary to inflammation, occurs in the very early stages of MS (21,22). There is neuropathological evidence that remyelination does occur within a few weeks or months after the demyelination, so that the surviving oligodendrocytes start to proliferate and form new
myelin (23-25). Therefore, treatment early in the course of MS has been strongly supported (26,27). In this study, treatment with interferon beta-1a was found statistically non-significant for P100 latencies and amplitudes in a group of 9 patients after 6 months. There are only two studies concerning effect of interferon beta-1a (11) or interferon beta-1b (12) treatment on visual pathway in MS patients. The study of Weinstock-Guttman et al (11) showed that in 16 MS patients treated with interferon beta-1a P100 latency increased over the eight-year follow up. On contrary, the study by Anlar et al (12) reported that in 5 of 10 MS patients treated by interferon beta-1b P100 latency decreased after 2 years follow-up.

On the other hand, when individual patients were followed up to a year, VEP latency delay was observed in those with a history of optic neuritis, as well as in those with no evident visual problem (2). We were able to localize subclinical demyelinating process in the absence of any history of acute visual impairment. Recent prospective studies following-up optic neuritis patients for a period of 1, 2 or 3 years showed that VEP provides a sensitive tool for monitoring of the visual pathway improvement (remyelination), as well as progressive deterioration (demyelination and/or axonal degeneration) (2-4,28). During our study, P100 latency prolongation from previously normal to abnormal values was detected in 2 patients at no concurrent clinical visual deterioration. Therefore, the P100 latency prolongation presents electrophysiologic evidence of clinically asymptomatic demyelinating lesions and VEP deterioration. The findings may suggest that the demonstrated involvement, at the time clinically asymptomatic, could--in later stages progress into clinically manifested functional deterioration, including optic neuritis. On the other hand, in one of the patients with a history of optic neuritis, P100 latency shortening of 6 ms was observed between baseline recording and at 6, 9, and 12 months follow-up, eventually suggesting recovery because of remyelination. VEP amplitude deterioration is probably associated with permanent axonal loss, a process that may start early in the course of the disease, but may be masked by remyelination for some time (2-4). In our study we also observed diminished P100 amplitudes in some patients but we did not observe progressive amplitude decline over one year follow-up.

Low dose of interferon beta-1a used in our study is in accordance with another study (7). Patients’ data, however, suggest that lower doses of interferon beta-1a may compromise efficacy when compared with a higher dose regimen (8). At years 3 and 4 extension study on 167 patients per group, authors demonstrated the 44 µg three times weekly (t.i.w.) doses subcutaneously superior to 22 µg t.i.w. Relapse rates for 4 years were 1.02 (crossover), 0.80 (22 µg, p<0.001), and 0.72 (44 µg, p<0.001). The 4-year data also demonstrated that disability progression, relapses, and MRI activity is lowest in patients who had received interferon beta-1a 44 µg t.i.w. throughout the trial (9).

In another study of 618 patients receiving 22 µg or 44 µg of interferon beta-1a or placebo subcutaneously thrice weekly for 3 years, the relapse rate was significantly reduced (p<0.001) from 0.71 per year with placebo to 0.50 per year with both treatment doses (29). However, the concept of dose and frequency-response is not surprising. Biologic markers are less influenced by once-a-week rather than twice a week dosing (30), and blood levels of interferon beta-1a fall rapidly within 24 hours of administration (31), highlighting the importance of dose frequency (32). The OWIMS study suggested that, although low doses of interferon have some clinical effect, this benefit was small and may be delayed, only becoming manifest a year or more after initiation of the therapy (7). The results of our study may suggest that in relapsing-remitting multiple sclerosis patients, interferon beta-1a administered subcutaneously twice weekly in doses of 11 µg, between January 1998 and February 1999 seems not being effective enough in the visual pathway. Also, obtained only on a small group of patients, our results have rather limited value. Despite the fact that in the majority of eyes (15 out of 18) VEP were normal before treatment, the low-dosage interferon beta-1a therapy was most likely not sufficient, because in two of our patients VEP became delayed during the therapy. According to other studies, the therapy with higher and more frequent doses of anti-inflammatory interferon is recommended as early as possible in order to prevent the axonal damage (4,21,22).

We conclude that the sensitivity of serial VEP in revealing demyelinating lesions, could be relevant in monitoring progression/regression of the demyelinating disease in the visual pathway, and thus also in the assessment of therapeutic efficiency. VEP, in addition to the well-accepted clinical (Expanded Disability Status Scale) and radiological (MRI) evaluation, may provide sensitive functional evaluation of visual pathway and identify patients with higher risk for disease progression.

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References


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