Cognitive Dysfunction Evaluation in Multiple Sclerosis Patients Treated with Interferon Beta-1b: An Open-Label Prospective 1 Year Study

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Key words: interferon beta-1b, cognition, P300, multiple sclerosis

Abstract

Background: The cognitive impairment (frontal, parietal) in many patients with multiple sclerosis does not correlate with the degree of neurological disability and disease duration. Frontal/prefrontal cognitive impairment requires neuropsychological diagnostic tools.

Objectives: To evaluate the clinical effect of IFNβ-1b (Betaferon®) treatment on cognitive function and event-related potential as compared to the clinical course (EDSS) in MS patients during 1 year of follow-up.

Methods: This prospective open-label design study included 16 consecutive patients with relapsing forms of MS attending the MS outpatient clinic. Mean EDSS score was calculated prior to starting treatment. Parietal lobe event-related potential P300 was elicited using an auditory physical stimulus to an alert subject. Mean P300 amplitude and latency were calculated for the group before treatment. The Wisconsin Card Sorting Test, which measures frontal lobe functions, was performed before the treatment. After 1 year of treatment a second P300 and Wisconsin test were performed and the mean change between visit 1 and baseline was calculated for each parameter. Correlation between the change in P300 and the Wisconsin test score at baseline was measured using the paired *t*-test.

Results: There was a significant reduction in P300 amplitude and latency after 1 year of treatment with IFNβ-1b: from 20.3 ± 8.3 μv to 13.1 ± 10.6 μv ($P = 0.026$) for amplitude, and from 312.9 ± 15.6 msec to 302.0 ± 17.0 msec ($P = 0.002$) for latency. The Perseverative Response (raw score) and the Perseverative Response U.S. Census age-matched standard score showed a significant improvement – from 20.7 ± 30.7 to 13.1 ± 10.6 ($P = 0.001$) and 96.7 ± 15.7 to 100.1 ± 11.1 ($P = 0.0025$) respectively – after 1 year of treatment. A mild but not significant improvement was observed on the EDSS after 1 year of treatment: 2.9 ± 0.5 to 2.8 ± 1.1.

Conclusions: A cognitive decline in MS patients may have a negative impact on the quality of life, affecting all active daily living domains. IFNβ-1b, a disease-modifying therapy, has demonstrated a positive therapeutic effect on cognitive dysfunction, unrelated to its effect on the EDSS score and course of the disease.

IMAJ 2007;9:457–459

Cognitive impairment in multiple sclerosis may manifest as a mild or moderate decline in some functions. It is present in about 45% to 65% of patients and can occur as the first sign of MS. It may involve executive functions, attention, recent memory, speed of information processing, and visuospatial perception. It can have a profound effect on activities of daily living, and requires neuropsychological diagnostic tools and possibly rehabilitation. In many cases it does not correlate with the degree of neurological disability and disease duration [1-3].

Studies on event-related potentials demonstrated a possible relationship between cognitive impairment and prolonged latencies in cognitive P300 auditory or optic evoked potentials [4,5]. Cognitive evoked potentials of the parietal lobe represent a longer latency component reflecting a higher level of cognitive processing; it reflects the activity of the neurochemical mediators involved in cognitive processes – cholinergic neurons, which are involved in generating these potentials. The P300 is an event-related potential that is elicited either by an auditory stimulus in the auditory pathway, or an optic stimulus in the optic pathway [4,5]; it is the third positive waveform and occurs at 300 msec after the stimulation, with a maximal amplitude over parietocentral scalp locations. It may reflect attention and memory process. The origin of P300 is still controversial although hippocampal and inferior parietal sites may be critical; some neural generators have also been identified in the frontal cortex and in subcortical sites affecting the thalamus and basal ganglia [6-9].

In the last decade several medications were introduced in the treatment of relapsing MS [10]. One of them, interferon beta-1b, led to a decrease in relapse rate, an increase in the number of relapse-free patients, and a decrease in the formation of new active enhanced lesions as demonstrated on magnetic resonance imaging [11]. Neuropsychological outcome assessment was inadequate in most of the trials [11-13]. In the present open-label prospective study we investigated the effect of 1 year treatment with IFNβ-1b (Betaferon®) on frontal and parietal cognitive performances in 16 MS patients as measured by the Wisconsin Card Sorting Test, which reflects frontal lobe white matter lesions and impaired conceptual reasoning skill [13,14], and the ERP P300 latency which represents the parietal cortex activity in various cognitive domains.

Patients and Methods

The study group comprised 16 patients, 11 females and 5 males aged 22–52 years (mean 37.6 ± 8.9), suffering from clinically definite relapsing MS [15] for 1–15 years (mean 6.2 ± 5.4), with at

MS = multiple sclerosis
IFNβ = interferon beta
EDSS = Expanded Disability Status Scale
ERP = event-related potential

least two relapses in the 2 years prior to entering the study and an Expanded Disability Status Scale of 3 to 4. The patients had 8–16 years of education (mean 12.3 ± 3.2), and provided informed consent to participate in this open-label prospective study.

The event-related potential P300 was performed using an auditory physical stimulus to an alert subject. The stimulus is a non-target and target mission in which the subject has to be awake and count silently only the target clicks. The outcome is a positive 300 msec wave. The P300 was recorded by silver disk electrodes from F_z C_z P_z and a recording electrode placed above the eye (to prevent eye movement). One ear electrode was used as a reference and the second ear electrode served as the "earth". Stimulus was set on audio pip through earphones, 70 db HI on both sides, at the rate of 0.5 pps; stimulus frequency was 1 kHz.

Before starting treatment we performed a neuropsychological test – the Wisconsin Card Sorting Test – and the Perseverative Response Score, which measures abstract-conceptual reasoning skills/functions involving frontal lobes. IFNβ-1b (Betaferon®) 8 MIU was administered subcutaneously on alternate days. After 1 year of treatment, a second ERP P300 and Wisconsin test were performed. The clinical course using EDSS and relapse rate were evaluated before starting the treatment and after 1 year of follow-up.

Table 1. Mean values before and after 1 year treatment with IFNβ-1b

	Before treatment (baseline)				After 1 year (visit 1)				
	Mean	SD	Min	Max	Mean	SD	Min	Max	*P*
Perseverative Response (raw score)	20.7	30.7	4	111	13.1	10.6	4	37	< 0.01
Perseverative Response age & education-corrected standard score	96.5	17.6	55	113	99.9	15.6	76	127	NS
Perseverative Response U.S. Census age-matched standard score	96.7	15.7	57	113	100.1	11.1	80	113	< 0.005
P300 (uv)	20.3	8.3	6	38	13.1	7.5	6	31	< 0.026
P300 msec	312.9	15.6	294	339	302.0	17.0	278	328	< 0.002
EDSS	2.9	0.5	3	4	2.8	1.1	2	6	NS

Statistical analysis

The mean change between visit 1 and baseline was calculated for each parameter. The correlation between the change in P300 and the Perseverative Response Score at baseline was measured using the paired *t*-test

Results

Table 1 displays the mean standard deviation, minimum and maximum of all parameters at baseline and at visit 1 (after 1 year of treatment with Betaferon®). The statistical analysis revealed a significant reduction in P300 μv amplitude, and P300 msec latency parameters. Although P300 amplitude (μv) decreased from 20.3 ± 8.3 μv at baseline to 13.1 ± 10.6 μv at visit 1 (P = 0.026), we did not consider this decrease clinically significant. P300 latency (msec) decreased from 312.9 msec at baseline to 302.0 ± 17.0 msec at visit 1 (P = 0.002).

The Perseverative Response (raw score) and the Perseverative Response U.S. Census age-matched standard score demonstrated a significant improvement (P = 0.001 and P = 0.0025 respectively) after 1 year of treatment. Perseverative Response score corrected for age and education was not significant. The improvement in neurological disability, as measured by EDSS at baseline and after 1 year of treatment, was not significant.

Discussion

Cognitive impairment is a common problem encountered in the "naive course" of MS. It may be present even in the early stages of the disease when physical disability is still mild. The degree of involvement of any cognitive domain in an MS patient is highly variable; 45–65% of patients in whom no mental disturbances are found on neurological examination may present cognitive deficits on neuropsychological tests [5,8].

The main cognitive function that may be impaired in MS patients is memory: working-memory, long-term memory and recognition memory. MS patients demonstrate impaired visuospatial processing, motor speed and reaction time. In many aspects, MS patients exhibit a general delay of cognitive processes [16,17]. Tests dealing with abstract or conceptual reasoning (Wisconsin Card Sorting Test) demonstrate that MS patients have perseveration errors. They are distracted easily from tasks that involve learning and memory [18].

The relationship between cognitive decline and disease duration, disability accumulation or course of disease is still controversial. Usually there is only a weak correlation between cognitive deficits and the degree of disability, course of disease and affective disorder [5,8].

Recent studies of MRI and MR spectroscopy have demonstrated a correlation between the burden of disease on proton density-weighted MRI and on magnetization transfer and selective cognitive functions. These studies found an association between cognitive impairment and the total lesion area, size of corpus callosum, and ventricular brain ratio [19].

ERP studies demonstrated a relationship between cognitive decline and prolonged latencies in cognitive P300 auditory evoked potentials. This test is considered to be sensitive for evaluating cognitive decline, confirming that demyelinating changes in MS can markedly alter the patients' cognitive functions [20,21].

Although cognitive dysfunction is common and frequently found in MS patients, even at the early stages of the disease, only a few studies have evaluated the effects of the new disease-modifying medications on the cognitive impairment [12]. In a recent study with IFNβ-1a (Avonex®), neuropsychological tests showed that patients on medication performed better on information processing and learning (recent memory domain), and on visuospatial and executive functions. In another study on IFNβ-1b (Betaferon®), after 1 year of treatment there was a slight difference in the latency of P300 in favor of the treated patients, and a significant improvement on the neuropsychological test – SRT (Spatial Recall Test) [22,23]. In another study, P300 laten-

cies to visual stimuli were found to be normal in patients who had recordable P300 [5].

In our study there were significant differences in the P300 latencies and amplitudes, with improvement of those parameters in the treated patients (P = 0.002 and P = 0.026 respectively). The neuropsychological test (Wisconsin Card Sorting Test) demonstrated a significant improvement after 1 year of treatment with INFβ-1b for the Perseverative Response (raw score) and the Perseverative Response U.S. Census age matched score (P = 0.001 and P = 0.0025 respectively). In contrast, no significant improvement was observed in the patients' clinical course during the 1 year of treatment, as shown by the EDSS score. The discrepancy in the effect of INFβ-1b on the cognitive measures and the clinical physical measures found in our patients shows that there is no linear relationship between these two parameters.

Since the demyelinating process observed in MS is involved with metabolic changes causing a significant reduction in metabolism of the white and gray matter, it is assumed that in MS patients with impaired cognition the demyelinating process has a disruptive metabolic effect on deep cortical and subcortical structures.

In summary, cognitive decline in MS patients may have a negative impact on the quality of life. It may affect all domains of activities of daily living, causing a decrease in patients' working capacity and difficulties in house-holding tasks and they become dependent for most of these tasks.

MRI and MR spectroscopy, considered excellent tools for evaluating disease activity including cognitive decline, are expensive and not always available. The use of simple and inexpensive means such as various neuropsychological tests and evoked related potentials (P300) may detect early cognitive impairment, helping to determine their remaining abilities and adapting the work setting. Once cognitive decline is detected, active treatment with disease-modifying therapy and cognitive rehabilitation may slow down the accumulation of cognitive dysfunction and improve cognitive function. Finally, it may be concluded that patients with cognitive decline may benefit from INFβ-1b treatment, irrespective of their clinical physical course.

Acknowledgment. We are thankful to our much-loved neuropsychologist Mrs. B. Mildorff PhD, who passed away during preparation of the manuscript.

The study was supported partially by a grant from Schering Ltd.

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