

Clinical and electrophysiological follow-up of modafinil treatment for multiple sclerosis patients with fatigue symptom

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ABSTRACT

Objectives: In our study, we investigated the effects of modafinil therapy on clinical and neurophysiological tests of multiple sclerosis (MS) patients with fatigue.

Methods: The study was performed on 18 MS patients (16 females, 2 males) at Uludağ University School of Medicine, Department of Neurology, who are followed up according to Mc Donald's criteria, who had 36 points or above based on the fatigue assesment scala (FAS), whose Beck depression inventory points were 16 and below, whose thyroid, liver and renal functions were evaluated as normal, and who had no systemic disorder. All patients had neurological examination and their expanded disability status scale (EDSS), fatigue impact scala (FIS) and multiple sclerosis quality of life (MSQoL-54) were evaluated. Somatosensory evoked potential (SEP), visual evoked potential (VEP), brainstem auditory evoked potential (BAEP), visual event related evoked potential (visual P300) were performed in our neurophysiology laboratory. After that the patients were given modafinil 100 mgr 1x1 (morning) for 1 week, the following weeks 2x1 (morning and noon). At the end of the 6 weeks of therapy the patients were called to the neurology polyclinic, and their neurological examinations, EDSS, FIS, MSQoL-54, SEP, VEP, BAEP and visual P300 were repeated.

Results: When the patients' previous and subsequent FIS and MSQoL-54 total scores were compared, a significant statistical difference was found. When all 3 subgroups of FIS (consciousness, physical and social) were evaluated after the modafinil therapy, a significant statistical decrease in previous and successive scores were found. It is found out that modafinil therapy improves life quality which is evaluated due to MSQoL-54 ($p < 0.05$). A significant statistical relation between the number of MS disease attacks and the three subgroups of MFIS was not figured out ($p > 0.05$). There were no statistically significant relation between the FAS, EDSS and Beck depression inventory scores before the modafinil therapy had been applied ($p > 0.05$). There was a statistically correlation between Beck depression inventory score and FIS's social subgroup ($p = 0.017$). When the patient's SEP, VEP, BAEP, visual P300 average test values before and after the modafinil therapy were compared, a statistically significant difference was not observed.

Conclusions: In our study, it is found that modafinil therapy, which is used against fatigue, one of the MS disease's most common symptom, has a positive impact on MS life quality and patients' clinical symptoms of fatigue, although it has no effect on patients' evoked potential methods (BAEP, SEP, VEP, visual P300) performed in neurophysiology laboratory.

Keywords: multiple sclerosis, fatigue, modafinil, evoked potential, fatigue severity scala

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Although multiple sclerosis (MS) is a clinically heterogeneous neurological disease, it is difficult to diagnose the disease due to the diversity of its symptoms, its fluctuating nature, and its heterogeneity [1]. Despite its disadvantages in the evaluation of cognitive deterioration and upper extremity functions as demonstrated in clinical MS studies, the expanded disability status scale (EDSS) is used as the primary measurement method of disability in MS [2].

Fatigue is today recognized as the most prevalent symptom of MS. MS-derived fatigue is different from the usual fatigue that follows strenuous activities, and it is believed that such fatigue is specific to MS. Freal *et al.* [3], who were the first to study fatigue complaints of MS patients, reported that 75-90% of the patients included in their sample complained about fatigue.

The symptoms and consequences associated with fatigue include physical fatigue, mental fatigue, absence of motivation, concentration difficulty, incapability of fulfilling tasks, sense of depression, sense of anxiety, tiredness after sleep, general and specific muscle weakness, diminished performance at home and/or at work, pain and/or physical ailments, and sleep disorders [4].

This study aims to investigate the qualitative effect of modafinil treatment on fatigue assessment scales and on the quality of life scale, and the quantitative effect of the said treatment on the measurement of evoked potentials and on clinical and neurophysiological tests. To the best of the researchers' knowledge, this is the first study to analyze the effect of modafinil treatment administered for MS-related fatigue, on somatosensory evoked potential (SEP), visual evoked potential (VEP), brainstem auditory evoked potential (BAEP), and all of the event-related endogenous potentials.

METHODS

A total of 18 patients (16 females and 2 males), who had received follow-up care for 6 months at Uludağ University School of Medicine, Department of Neurology due to MS diagnosis, were included in the study after they had given their informed written consent to participate. The study was approved by the local ethics committee. To be included in the study,

patients had to have no systemic disease, no pathology according to thyroid function tests, liver function tests, and kidney function tests, and they had to have complaints about fatigue and scores of ≥ 36 and ≤ 16 on the fatigue assessment scale (FAS) and Beck's Depression Inventory, respectively. Patients who had started to undergo antidepressant treatment within the last 3 months and/or who had had a seizure within the last 4 months were excluded from the study.

The results from the EDSS, the fatigue impact scale (FIS), and the MS Quality of Life Scale-54 (MSQoL-54) of the patients included in the study were evaluated as part of the neurological examination. The modafinil treatment of the patients started with the administration of a 100 mg dose of 1x1 tablet (morning) in the first week and a 100 mg dose of 2x1 tablet (morning and noon) in the weeks that followed. Prior to the modafinil treatment, SEP, VEP, BAEP and visual event-related endogenous potential (Visual P300) were applied on the patients in the neurophysiology laboratory. At the end of week 6 of the treatment, the patients visited the outpatient department and underwent a neurological examination again based on the assessment of EDSS, FIS, MSQoL-54, SEP, VEP, BAEP, and Visual P300.

Disability Assessment

The participants' level of neurological impairment was assessed using the Kurtzke EDSS. Impairment in 8 functional systems is measured with this scale, with most of the scores in the functional system being assessed in a range from 0 to 6, where 0 showing normal neurological examination, whereas 10 indicates MS-related death [2].

Fatigue Assessment Scale (FAS)

Fatigue symptoms were scaled with FAS, which is a nine-part scale used to evaluate the overall effect of fatigue on daily activities. Each part is scored according to a seven-point Likert-type scale, where 1 is never agree and 7 is completely agree. The FAS score is calculated by summing up or averaging out the scores of the nine parts. FAS is effective for distinguishing patients with fatigue complaint who need treatment and those who do not require treatment. Moreover, it is used to detect the effects of the treatment administered to patients with fatigue symptoms [5].

Fatigue Impact Scale (FIS)

The FSS, which evaluates physical, psychological, and cognitive functions, is more detailed than FAS. There are 10 items under the cognitive component, 10 items under the physical component and 20 items under the psychosocial component. Responses to each item range from 0-3 (0: no problem, 3: very big problem) [6].

Quality of Life Scale (MSQoL-54)

For this scale, 18 MS-related questions were added to the original 36-Item Short Form Health Survey Questionnaire (SF-36), which was developed from the Medical Outcome Study and is used for all chronic diseases (10). SF-36 includes 36 items under 8 scales. Of these 36 items, 10 are related to physical function, 4 to the role of physical function, 2 to body pain, 5 to general health, 4 to liveliness, 2 to social function, 3 to the role of emotional function, and 5 to mental health. Vicrey *et al.* [7] added 18 items to this scale, of which 4 are related to health-related stress, 4 to sexual function, 1 to satisfaction in sexual function, 2 to quality of life, 4 to cognitive function, 1 to energy, 1 to pain, and 1 to social function.

Electrophysiological Procedures

The patients' SEP, VEP, BAEP, and P300 were recorded at room temperature (22 °C) in the Uludağ University School of Medicine, Neurophysiology Laboratory. A Medelec/TECA "Sapphire" brand device was used to conduct these measurements after performing a complete skin cleansing process. Electrode impedances were kept below 5 kOhm in all of the applications.

The waves that emerged in the first 10 ms were recorded with BAEP following an 80-85 dB monoaural click stimulus. The click was applied 60 decibels above the threshold of hearing to one, while the other ear was masked by noise. Active electrode and reference electrode were placed on point CZ and ipsilateral mastoid (M1 and M2), respectively, during recording. Analysis duration was set as 100 ms, with the polarity alternans and frequency limits placed at 100-200 Hz.

Recording was performed on the occipital by stimulating the eyes with VEP through a checkerboard-pattern reversible stimulus. The color of the black-white checkerboard-pattern squares on the

screen changed every 20 ms. The patients were seated 90 cm from a TV screen, whereon the stimuli, activated 3 cycles per second, were watched. Superficial electrodes were used for recording. Active electrode and reference electrode were put on point OZ and point FZ, respectively. Frequency limits were set to 1-100 Hz, while the analysis duration was set as 250 ms. The middle part of the screen was marked to ensure visual fixation. The whole screen was able to be seen at a 23° angle, while a square on the screen was able to be seen at a 1° angle. As one eye was stimulated, the other eye was closed with an eye patch. Median SEP (mSEP) was obtained through electrical stimulation of the right and left median nerve. The electrical stimulation was applied at a frequency of three 50 ms per second using a sensitivity just over the motor threshold. The records were attained from the C3 contralateral cortex region.

Tibial SEP (tSEP) was obtained with the electrical stimulation of n. tibialis posterior from ankle. Successive electrical stimulation was applied at a frequency of four 100 ms per second using a sensitivity just over the motor threshold. Recordings were performed in the foot region (Cz). Frequency limits were set as 10-2000 Hz, while the analysis duration was set as 100 ms.

Event-related endogenous potentials are a type of evoked potential that forms as a response to an event outside or a stimulus. It occurs when a person distinguishes two stimuli of different qualities whose recurrence intervals are variable (target and non-target) when he/she pays attention to the stimuli. P300, which was used to assess the mental functions, is the most well-known wave with respect to event-related endogenous potentials [8]. During P300 assessment, the target stimulus was sent to both eyes at various intervals following the routine stimulation repeated once a second. Active recording was performed based on point Pz. The duration of routine stimulations and target stimulations were 2 ms and 30 ms, respectively. Routine stimulations constituted 85% of all stimulations, while target stimulations constituted 15% of all stimulations. The average analysis duration was 1 s, and the lower and upper frequencies were applied within a range of 0.1-50 Hz.

Depression Assessment

The patients were assessed with Beck's

Table 1. Demographic and MS-related information

Number of patients (n)	18
Female/male, n (%)	16 (88.9) / 2 (11.1)
Mean age (mean ± SD) (years)	40.5 ± 10.4
Mean age of onset of disease (mean ± SD) (years)	32.3 ± 8.4
Clinical type of MS, n (%)	
Relapsing remitting	15 (83.3)
Secondary progressive	2 (11)
Rrelapsing progressive	1 (5.6)
Mean duration of disease (mean ± SD) (years)	8.1 ± 5.9
Mean EDSS score (mean ± SD)	1.8 ± 1.1

MS = multiple sclerosis, EDSS = expanded disability status scale, SD = standard deviation

Depression Inventory to ascertain their depressive symptoms. Beck's Depression Inventory consists of 21 items, with each item having four response options. Every item is scored from 1 to 4, and scores ≥ 17 are evaluated as indication of depression [9]. The patients who received scores of ≥ 17 were excluded from the study .

Statistical Analysis

Statistical assessment of the study data was performed with SPSS programme for Windows. A post hoc power analysis was conducted using a medium effect size, based upon findings of the present study. A medium effect size was obtained by comparing mean Physical dimension scores which were calculated from before treatment (14.1 ± 4.6) and after treatment (8.5 ± 6.3) terms for 18 participants. Using this effect size (d = 0.75) with a sample size of 18 participants, achieved power was estimated as 81%

at the significance level of α= 0.05. The median (minimum-maximum) was calculated for all data in cases where the mean standard deviation (mean ± SD) was needed. Paired t-test and Wilcoxon signed-rank test were used to compare the pre-treatment and post-treatment scale scores. Correlation analyses were conducted for the correlations between the scale scores and Pearson or Spearman correlation coefficients were reported. A significance level of p < 0.05 was set for all statistical analyses.

RESULTS

The mean age of the patients was 40.5 ± 10.4 years (males: 317 years; females 41.6 ± 10.3 years). The mean age of onset of MS symptoms was 32.3 ± 8.4 years, while the mean duration of disease was 8.1 ± 5.9 years. In terms of the clinical type of MS, 15

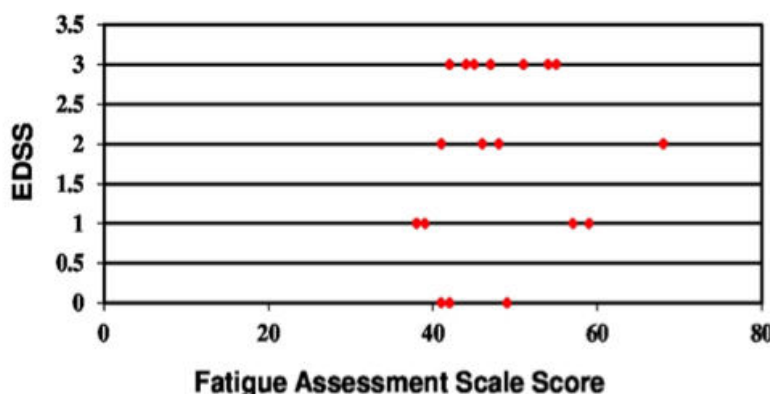


Fig. 1. Relationship between the expanded disability status scores and fatigue assessment scores of the patients.

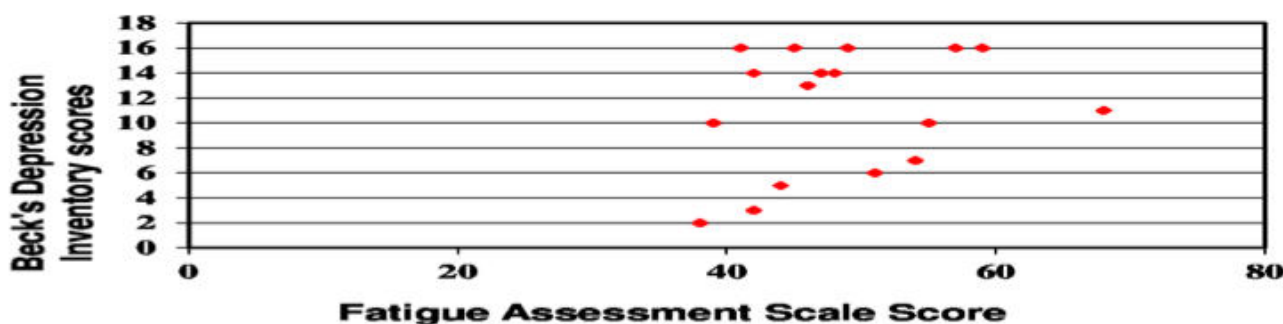


Fig. 2. Relationship between the scores on Beck's Depression Inventory and Fatigue Assessment Scale.

patients had relapsing remitting, 2 patients had secondary progressive, and 1 patient had relapsing progressive. The mean EDSS of the patients was 1.8 ± 1.1 (Table 1).

Among the patients included in the study, 15 (83.3%) were using an immunomodulator, while 3 (16.7%) were not; of the 15 patients who were using an immunomodulator, 5 (27.8%) had been on it for one year, 5 (27.8%) for two years, 2 (11.1%) for three years, 2 (11.1%) for four years, and 1 (5.6%) for five years. Seven patients were using beta interferon 1 b 0.3 MG (9.6 MIU) subcutaneous every other day, 3 patients were using beta interferon 1a 44 mcg (12 MIU) subcutaneous three times a week, 4 patients were using glatiramer acetate 20 mg subcutaneous every day, and 1 was using interferon beta 1 a 30 mcg (6 MIU) intramuscular once a week.

Nine patients had been on antidepressants for at least for three years, while nine patients had not been taking antidepressants. Regarding MS onset symptoms, 4 patients had optic neuritis, 8 patients had pyramidal signs, 2 patients had cerebellar signs, 2 patients had cerebellar and pyramidal signs, and 2 patients had sensual signs. Regarding relapses, 2 patients had one, 6 patients had two, 4 patients had

three, 3 patients had four, 1 patient had five and 2 patients had 6. Within the last two years, 6 of the patients did not have any relapse, while 10 patients and 2 patients had one and two relapses, respectively.

There was a negative correlation between age and the pre-treatment score on the Beck's Depression Inventory (Spearman correlation coefficient = -0.716, $p = 0.001$). No statistically significant relationship was found between the pre-treatment scores on the FAS and the EDSS (Spearman correlation coefficient = 0.210, $p > 0.05$). (Fig. 1). No statistically significant relationship was found between the pre-treatment scores on the FAS and the Beck's Depression Inventory (Spearman correlation coefficient = 0.369, $p > 0.05$) (Fig. 2).

According to the Wilcoxon rank-sum test, the difference between the pre-treatment scores and post-treatment scores on Beck's Depression Inventory was statistically significant, with the Beck's Depression Inventory scores of the patients being significantly lower after the treatment. ($p < 0.001$) (Table 2). The mean total FAS score of all 18 patients after the treatment (32.7 ± 9.2) was statistically significantly lower than that before the treatment (48.1 ± 7.9). The difference between the total FAS scores was found to

Table 2. Beck's Depression Inventory scores

	Before modafinil treatment	After modafinil treatment	p value
Beck's Depression Inventory Score			
Mean \pm SD	10.7 \pm 5.0	4.7 \pm 4.43	< 0.01*
Median	12	4	
Minimum-maximum	2-16	0-12	

*According to Wilcoxon rank-sum test, SD = standard deviation

Table 3. Relationship between the sub-dimensions of fatigue impact scale before the treatment and after the treatment

	Before the treatment	After the treatment	<i>p</i> value
Cognitive dimension			
Mean ± SD	12.8 ± 4.4	8.8 ± 7.5	0.014*
Median	12.5	11	
Minimum-maximum	6-20	0-20	
Physical dimension			
Mean ± SD	14.1 ± 4.6	8.5 ± 6.3	0.007*
Median	14	8.5	
Minimum-maximum	5-21	0-21	
Social dimension			
Mean ± SD	30.1 ± 12	16.8 ± 12.5	0.001*
Median	28.5	18.5	
Minimum-maximum	13-55	0-38	

*Wilcoxon rank-sum test, SD = standard deviation

be statistically significant to the highest degree (Matched-pair t-test, *p* < 0.001).

No statistically significant correlation between age and FAS values was detected (Pearson correlation coefficient = 0.153, *p* > 0.05).

Significantly lower values in the cognitive, physical, and social dimensions of FIS were determined during the post-treatment measurement based on the Wilcoxon rank-sum test. There were

significant (+) correlations between cognitive, physical, and social dimensions to the highest degree following the treatment (after the treatment, Spearman coefficients for the relationship between cognitive and physical dimensions = 0.744 (*p* < 0.001), for relationship between cognitive and social dimensions = 0.685 (*p* = 0.002) and for relationship between physical and social dimensions = 0.814 (*p* < 0.001)). No statistically significant relationship was found

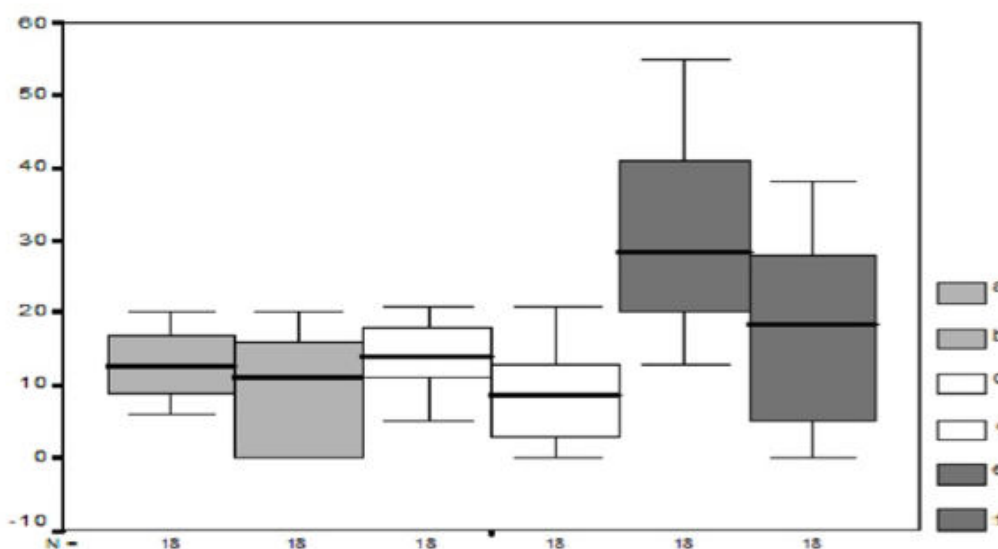


Fig. 3. The relationship between sub-dimensions of the Fatigue Impact Scale. (a) pre-treatment cognitive dimension, (b) post-treatment cognitive dimension, (c) pre-treatment physical dimension, (d) post-treatment physical dimension, (e) pre-treatment social dimension, (f) post-treatment social dimension.

Table 4. Relationship between the sub-dimensions of MS Quality of Life Scale (MSQoL-54) before the treatment and after the treatment

MS Quality of Life Scale (MSQoL-54)	Before the treatment	After the treatment	p value
Physical health	52.30 ± 13.01	72.23 ± 13.06	< 0.001
Cognitive health	54.25 ± 19.33	69.79 ± 16.39	0.001
Change in health	58.33 ± 25.72	73.61 ± 18.13	0.005
Sexual function	54.16 ± 21.43	68.05 ± 23.95	0.008

between the number of MS relapses and the 3 dimensions on the FIS ($p > 0.05$) (Table 3) (Fig. 3). There was a statistically significant moderate correlation between the score on the Beck's Depression Inventory and the social dimension of the FIS (Spearman correlation coefficient 0.553, $p = 0.017$).

A statistically significant difference was found

between pre-treatment values and post-treatment values on the four sub-dimensions of the MSQoL-54. According to the matched-pair t-test, pre-treatment values on physical health and cognitive health were significantly lower than their respective post-treatment values (p values based on matched-pair t-test: physical health; $p < 0.001$, cognitive health; $p = 0.001$). When pre-treatment values and post-treatment values related

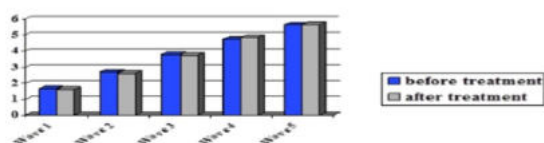


Figure 4a: Left BEAP

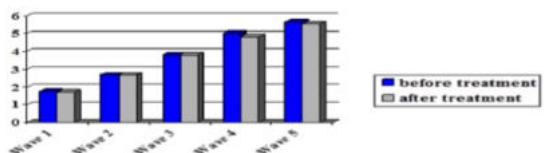


Figure 4b: Right BEAP

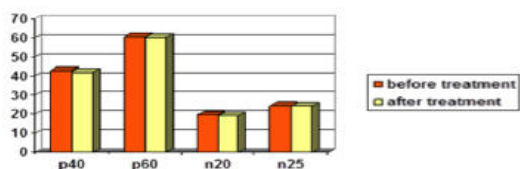


Figure 4d: Left SEP

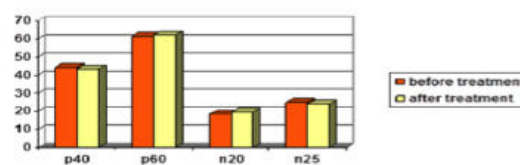


Figure 4e: Right SEP

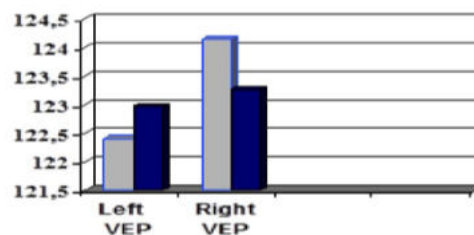


Figure 4c: VEP

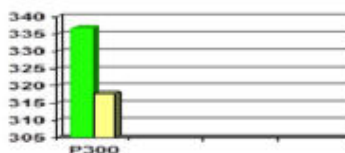
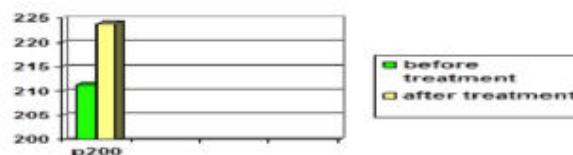


Figure 4f,g: p200,p300

Fig. 4. Evoked potential values attained before the treatment and after the treatment. (a, b) BAEP = brainstem auditory evoked potential, (c) VEP = visual evoked potential, (d, e) SEP = somatosensory evoked potential, (f, g) P200, P300 = visual event related evoked potential..

to the sub-dimensions of change in general health and in sexual functions in one year were compared, post-treatment values were found to be significantly lower (According to Wilcoxon rank-sum test: change in health; $p = 0.005$, sexual function; $p = 0.008$) (Table 4).

Mean right and left VEP values, mean right and left BAEP values, mean lower and upper SEP values, and mean p200 and p300 values of the patients obtained before the treatment and after the treatment were matched. When the evoked potential values were statistically compared based on the matched-paired t-test, no significant difference was observed (Fig. 4).

DISCUSSION

The relationship between the clinical type of MS, physical disability and depression of the patients, and fatigue has been discussed for many years. Neurological impairment and fatigue affect the quality of life of MS patients adversely, as does fatigue and depression, as demonstrated by results from the EDSS [10]. While some studies have shown there to be no relationship between age, gender, duration of disease and fatigue [11-13], others have reported that fatigue increases in parallel with age and longer duration of disease [14-16]. In the present study, no statistically significant relationship was detected between scores on the FSS and the frequency of seizures.

Depression is a symptom which usually accompanies MS, having a prevalence of above 50% [17, 18]. Inconsistent results have been reported in studies examining the relationship between depression and fatigue. Several studies have revealed there to be a moderate [19, 20] or strong [21] relationship, whereas others have found there to be no relationship [22, 23]. For example, in a study by Flachenecker *et al.* [24], which included 151 diseases, the FAS scores of the patients with depression were significantly higher than those of the patients without depression. Although depressive and anxious patients complained about fatigue more, only a weak linear correlation between fatigue and depression and anxiety was revealed [13]. As fatigue is regarded as a feature of depression, overlapping is to be expected. On the other hand, this point emphasizes the importance of defining fatigue clearly. In the present study, no statistically

significant relationship was observed between the pre-treatment scores obtained on the Beck's Depression Inventory and the FAS. Treatment of depression in MS may not lead to a reduction in the complaints about fatigue. Mohr *et al.* [25] reported a significant improvement only in global fatigue severity among the four sub-dimensions (global fatigue severity, situation-specific fatigue, results of fatigue, responsiveness to rest and sleep) of the fatigue assessment instrument following a 16-week treatment with sertraline. The relationship between fatigue and depression remains unclear [26].

Studies have presented inconsistent results about the correlation between fatigue and EDSS as well. Several studies have determined there to be a positive correlation between these two variables [27, 28], some [11, 24, 29] have found there to be a weak correlation [30, 31] and others have reported there to be no correlation [32, 33]. The differences in the results found in these studies could have resulted from cohort features, the assessment tools used in fatigue measurement, change in neurobehavioral findings with medication, or differences in the designs applied by these studies [34]. In the present study, there was no statistically significant relationship found between fatigue and EDSS, the results of which could be attributed to the low number of patients in the study and the similar EDSS scores of the patients.

Fatigue is worse in progressive MS and worsens apparently when ambulation is affected. However, it should be noted that fatigue is a cause of morbidity, even among patients who do not complain about fatigue [13]. Studies have demonstrated that patients with progressive MS experience fatigue more frequently than patients with relapsing remitting MS [15, 35]. In the present study, an evaluation of the relationship between clinical type of MS and fatigue could not be conducted due to the low number of patients and to the fact that a majority of the patients had relapsing remitting MS.

Fatigue is explicitly related to physical and psychological functional disruption. It has been found that fatigue rises dramatically when walking ability is affected [13]. Detection of high levels of physical fatigue plays a role in predicting an increase in disability in three years [36].

Analyses on quality of life sub-dimensions indicated that both fatigue and depression have a

strong relationship with quality of life due to emotional problems and pain, and that depression has importance in predicting emotional well-being, cognitive function and health distress, regardless of the physical disability and fatigue levels of the patients [10]. Merkelbach *et al.* [37] argue that psychological symptoms are more important than physical disability with respect to fatigue.

Modafinil, amantadine, 4 aminopyridine, antidepressants, and L-carnitine are used for the treatment of MS-related fatigue. In the present study, comparison of the mean total Beck's Depression Inventory and FAS scores of the patients obtained after a 6-week modafinil treatment for overcoming their complaints about fatigue to their initial scores showed that the former were statistically significantly lower. These results implicitly indicate that the treatment of the fatigue symptoms seen in the patients reduced their depressive symptoms as well. The post-treatment values on the four sub-dimensions (physical health, cognitive health, change in health, sexual function) of the MSOL- 54 were significantly lower than the pre-treatment values of these dimensions, thereby supporting that modafinil treatment was useful for the patients. This outcome suggests that fatigue symptom affects the quality of life of MS patients adversely, and that the treatment of fatigue symptom improves their quality of life. Rammohan *et al.* compared the scores attained on fatigue scales after placebo with the scores found after a 2-week modafinil treatment administered as 200 mg/day and reported there to be an apparent improvement in fatigue symptom following modafinil treatment [38]. A double blind study that comparatively analyzed the use of placebo and modafinil for 8 weeks among MS patients with fatigue determined that administration of modafinil improved not only fatigue symptoms but also attention and manual skill performances [39].

To the best of the present researchers' knowledge, there is no study examining the effect that modafinil treatment for MS-related fatigue has on evoked potentials in MS patients, where the aim is to measure the treatment results quantitatively. The closest study found, in terms of similarity to the present one, was the one conducted by Sangal *et al.*, where a visual P300 evoked potential procedure was implemented to detect the response of narcolepsy patients to modafinil treatment; it was reported that such neurophysiological

tests are not effective for detecting the response to modafinil treatment earlier [38]. In the analysis conducted in the present study, where BEAP, SEP, VEP, and visual P300 evoked potential methods were used before and after the modafinil treatment of the patients, it was observed that the well-being of the patients after the treatment, which was determined with subjective methods, did not affect the neurophysiological tests.

According to a study which evaluated visual and brainstem auditory-evoked potentials of MS patients on the basis of the presence and severity of fatigue, P100 latency (interocular latency difference) increased significantly when the patients with high fatigue severity were compared to MS patients without fatigue symptom [40]. The same study revealed BAEP anomalies (prolonged interlatency between BAEP 1-3-5 components) among MS patients with moderate and severe fatigue. This result indicates that there are conduction disturbances inside the brain stem, which suggests that the progression rate and disability of these sub-groups are extremely high.

CONCLUSION

Fatigue is a very frequently-seen symptom in MS patients and affects their quality of life. When modafinil, whose use in narcolepsy treatment was approved by the FDA, was administered to the MS patients, it was observed that their fatigue symptoms declined and their quality of life improved as compared to the pre-treatment period. However, the modafinil treatment had no effect on evoked potential procedures when it was applied to treat MS-related fatigue symptoms. Further studies involving more patient groups are required to determine the effect of evoked potential parameters on fatigue symptoms of MS patients and to detect the importance of certain parameters, like electrophysiological reagents.

Conflict of interest

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