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ORIGINAL ARTICLE

# The Effects of Demographic, Clinical, and Radiological Parameters of Multiple Sclerosis on Quality of Life and Fatigue

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## Abstract

**Introduction:** Multiple sclerosis is a progressive disease involving the central nervous system, usually starting between 20 and 40 years of age and causing recurrent dysfunction. There may be differences in physical, social and psychological effects depending on the degree of the disease. Fatigue is a common symptom of MS, which can be seen in different disease degrees and affects quality of life. The relationship between clinical and radiological findings and fatigue and quality of life remains unclear. Therefore, the purpose of the research is to evaluate the relationship between disease markers such as age, mood, physical disability, laboratory findings, and fatigue and quality of life.

**Methods:** The study included 100 patients who met the 2010 McDonald's criteria, had an Expanded Disability Status Scale (EDSS) score of <6.5 and had no episodes in the last month. Oligoclonal band (OCB), autoimmune thyroid antibody values and cranial and spinal magnetic resonance images of the patients were examined to evaluate the laboratory and radiological findings. Beck depression inventory and Fatigue Impact Scale were engaged for mood and fatigue assessment. The MS Functional Composite and 36-item short-form survey (SF-36) included to evaluate cognitive and physical impairment related to MS.

**Results:** There was a low but significant correlation between fatigue and EDSS (p=0.041), 9 hole test (dominant hand) (p=0.005) and timed 25 walk (p=0.020) tests. There was no significant relationship between fatigue and SF-36 scores and thyroid auto-antibodies and OCB scores. In addition, there was a significant relationship between fatigue and cranial (p=0.049) and spinal (p=0.025) MR results.

**Discussion and Conclusion:** This study showed that an increase in lesion burden in MS patients also increased their fatigue. In addition, this positive correlation between lesion burden and fatigue was not observed between laboratory results such as OCB and autoimmune thyroid antibodies.

**Keywords:** Cognition; depression; fatigue; multiple sclerosis; quality of life.

Multiple sclerosis (MS) is a chronic progressive disease of the central nervous system, which usually starts between the ages of 20 and 40 years and presents disabilities with recurrent dysfunctions[1,2]. The disease usually occurs in early adulthood and causes disability. Various problems arise in the professional and social life of the patient depending on this disability. As a result, physical, social and psychological effects caused by illness significantly impair the quality of life and cause fatigue[3,4].

The most commonly used scale to measure disability affecting the quality of life in patients with MS is the Expanded Disability Status Scale (EDSS)[5,6]. In this scale, the score obtained from ambulatory skills is the key factor in calculating disability. Patients with a score of 4 or higher

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fall into the category of disability linked to MS. However, EDSS is insufficient to evaluate upper extremity and cognitive functions. Therefore, The MS Functional Composite (MSFC) was developed to eliminate these deficiencies with three subscales[7,8].

In MS, fatigue also affects the quality of life, regardless of disability. Most patients describe fatigue as the worst symptom they experience, that affects their daily activities and occupational status negatively[3]. The aim of this study is to investigate the relationship between age and duration of the disability, number of relapses, mood, laboratory findings, radiological features using 36-item short-form survey (SF-36) quality of life scale and fatigue ımpact scale (FIS) fatigue scale.

## Materials and Methods

### Patient Selection

A total of 100 patients diagnosed with definitive MS according to 2010 McDonald criteria, were included in the study[5]. Furthermore, patients with an EDSS ≤6.5, not having an MS relapses or pseudo relaps in the past 4 weeks are recruited. The study was approved by the Institutional Review Board and signed consents were obtained from all patients.

### Laboratory Investigations

To eliminate non-MS-related factors that can affect the quality of life and induce fatigue, forced expiratory volume, thyroid function tests, B12, folic acid levels, and total blood cells count investigations were evaluated. Patients with hyperthyroidism and anemia (with a level of fatigue that could affect the quality of life) were excluded from the study. Five patients with a low B12 value were included in the study after one month of B12 treatment to eliminate the possibility of cognitive impairment. Oligoclonal band (OCB) and autoimmune thyroid antibody examinations were performed as laboratory parameters.

Patients underwent cranial and spinal magnetic resonance imaging (MRI) examination with the 3-Tesla Siemens Trio scanner (Siemens, Erlangen, Germany), using a contrast agent. Cranial MRI findings were classified as <4 lesions (mild), 4–10 lesions (moderate), and >10 lesions (severe involvement). In spinal MRI: 1 lesion corresponded to mild, 2 lesions to moderate, and more than 2 lesions to severe involvement. Lesions that were hyperintense on T2-weighted and FLAIR sequences and isointense or hypointense on T1-weighted sequences were considered as MS lesions[5].

A detailed clinical evaluation of the cases was made by calculating the EDSS scores and the MSFC score. The SF-36 questionnaire was used to evaluate the quality of life. The existence and level of fatigue were determined by FIS[9]. The presence and degree of depression were demonstrated using the Beck's depression ınventory (BDI)[10]. The SF-36 questionnaire was developed by Rand Corporation in 1992, and the reliability and validity studies of the Turkish version were performed by Kaya and Icagasioglu[11]. The scale consists of 36 items and provides the measurement of 8 dimensions: Physical function (10 items), social function (2 items), role physical (4 items), role emotional (3 items), mental health (5 items), vitality (4 items), bodily pain (2 items), and general health (5 items). The last 4 weeks of the patient are taken into account when evaluating the scale[12].

### Fatigue Impact Scale (FIS)

Is used to measure the impact of fatigue on daily life quality and daily living activities. It was developed by Fisk et al.[13] for clinical and experimental studies. Turkish version of the scale was performed by Armutlu et al.[9] in patients with MS. The scale is a Likert-type scale consisting of 40 questions and a score of 0–4. The maximum total score is 160.

### Statistical Analysis

Data obtained from the study were analyzed in SPSS 20. Descriptive tests were performed for means and standard deviation. Parametric tests were used in statistical evaluations since the data were normal distribution. The relationship between the two groups was evaluated by independent sample t-test and the relationship between more than two groups was evaluated by one-way analysis of variance. Pearson's correlation test was used for correlation of numeric data. 95% significance level was taken as the statistical significance level.

## Results

### Clinical Characteristics of Patients

Of the 100 participants, 69 were female and 31 were male. The mean age of these participants was 38.2±9.5. The mean education length was 9.2±3.6 years. The age of onset of the illnesses of the participants was also included in the study and the mean age was 29.1±9.0. The mean disease duration of the participants was found 8.9±6.4 years.

### Quality of Life and Fatigue Assessments

During MSFC evaluation, EDSS scores were determined

and Pasat 3" (3 s), time to walk 25 feet (TW25), and 9 hole peg test (9-HPT) tests were performed. The EDSS scores of the patients ranged between 0 and 6.5. The EDSS score was above four in 27 patients. EDSS of 73 patients were found to be four or less. The mean EDSS score was 2.9±1.82. PASAT, 9-HPT and TW25 tests were performed to evaluate the disability. The mean score of the PASAT 3" test of the participants was 34.2±12.6. The mean of timed 25 walk test in which the lower extremities were evaluated was found to be 9.17±5.7. The mean 9-HPT where upper extremities were evaluated was 14.1±3.6 for the dominant hand and 17.3±10.8 for the non-dominant hand. The mean and standard deviation of the FIS scores was 42.7±43.1 in women, 33.6±36.6 in men, and 40.0±41.3 in all patients.

## Relationship between Fatigue Level and Laboratory Findings

Initially, the relation between fatigue and disability scales was investigated. A significant but low correlation was found between EDSS, 9-HPT (Dominant), T25-FW, and FIS scores (Table 1). There was a positive but low correlation between EDSS (p=0.041), 9-HPT (Dominant) (p=0.005) and T25-FW (p=0.020) with FIS total value. In other words, patients with higher fatigue levels showed trends toward exhibiting increased EDSS scores and prolonged 9-HPT (dominant) and T25-FW durations. There was no relationship between PASAT and 9-HPT (non-dominant) duration and fatigue. There was no significant relationship between FIS and duration of disease, age of onset, and the number of relapses (Table 1).

**Table 1.** Correlation between FIS (total) and disease characteristics/MSFC

| Characteristics | Fatique ımpact scale (total) | |
|---|---|---|
| | R | p |
| Duration of Disease | 0.117 | 0.365 |
| Age of Onset | 0.046 | 0.521 |
| Number of Relapses | 0.186 | 0.170 |
| MSFC | | |
| EDSS | 0.368 | 0.041** |
| 9-HPT (Dominant) | 0.328 | 0.005** |
| 9-HPT (Non-dominant) | 0.085 | 0.090 |
| T25W | 0.251 | 0.020** |
| Pasat 3' | 0.127 | 0.256 |

FIS: Fatigue impact scale; T25-FW: Timed 25 Foot Walk; MSFC: The Multiple Sclerosis Functional Composite; EDSS: Expanded disability status scale; 9-HPT: 9 hole peg test disability status scale; 9-HPT: 9 hole peg test; * p<0.05; ** p<0.001.

In this study, autoimmune thyroid antibody levels were evaluated to evaluate subclinical hypothyroidism. Autoimmune thyroid antibodies were positive in 13 patients and negative in 87 patients. The FIS score was found to be 38.25 in the positive and 41.5 in the negative patients. Autoimmune antibody positivity did not have a significant effect on fatigue level. The mean FIS score was found at 37.8 in 82 OCB (+) patients and 47.1 in 13 OCB (-) patients. There were no significant differences in OCB groups (p>0.05). In addition, no statistically significant difference was found between SF-36 quality of life subscales and thyroid autoantibody and OCB groups (p>0.05) (Table 2).

The presence and level of depression were determined with BDI. The FIS total score increased with the increasing BDI scores. As a result, the presence of depression increases fatigue levels in MS patients. Out of 100 participants; the mean FIS score of the patients without depression (n=65) was 23.04±27.5. The mean FIS score of the patients for mild depression (n=20) was 59.3±43.3, moderate depression (n=5) was 90.25±24.1, and severe depression (n=10) was 105.5±40.2. According to these results, the increase in the level of depression is correlated with the increase in fatigue.

All subscales of the SF-36 and MSFC showed a negative correlation with FIS scores suggesting that the increase in EDSS score affects the quality of life negatively. The most affected parameter with EDSS is physical function. The least affected parameter is mental health. A significant positive correlation was found between the MSFC subtest PASAT and the role-physical (19.9%). PASAT does not affect the SF-36 subscales except for role-physical. There is a significant relationship between 9-HPT (Non-dominant Hand) and role-physical and physical function. As the 9-HPT duration increases, the SF-36 scores decrease and the quality of life worsens. There is also a significant relationship between T25-FW duration and SF-36 subscales other than mental health. As a result, the quality of life is affected by the deterioration of the least cognition and the maximum duration of T25-FW (Table 3).

In cranial MRI; 4 lesions correspond to mild, 4–10 lesions to moderate and more than 10 lesions to moderate and more than 2 lesions to severe involvement. Increased lesion burden on cranial and spinal MRI causes an increase in FIS score (Table 4). The relationship between the level of depression and SF-36 subscales was evaluated. As the degree of depression increases, the whole subscale score of SF-36 decreases. Quality of life deteriorates as the presence and severity of depression increase (Table 5).

**Table 2.** Relationship between SF-36 and laboratory ınvestigations

| Tyroid auto-antibody | Physical function | Role-physical | Bodily pain | General health | Vitality | Social function | Role emotional | Mental health | p |
|---|---|---|---|---|---|---|---|---|---|
| Negative (-) | 71.7±34.5 | 56.7±48.1 | 68.8±27.0 | 58.8±19.9 | 45.0±23.7 | 69.9±31.1 | 73.2±42.5 | 58.7±20.2 | 0.416 |
| Positive (+) | 68.8±31.0 | 42.3±46.1 | 73.8±23.3 | 62.1±16.1 | 48.5±16.9 | 76.2±21.4 | 59.0±49.4 | 61.5±15.1 | |
| OCB | | | | | | | | | |
| Negative (-) | 71.9±38.4 | 53.8±51.9 | 67.9±30.2 | 65.4±21.4 | 38.8±25.2 | 65.6±36.4 | 61.5±46.9 | 56.0±15.6 | 0.122 |
| Positive (+) | 70.6±33.7 | 53.8±47 | 68.6±26.2 | 58.9±19.0 | 46.4±22.8 | 71.0±29.1 | 72.9±42.8 | 59.9±20.2 | |

SF-36: 36-item short-form survey; OCB: Oligoclonal band.

**Table 3.** Relationship between SF-36 subcales versus EDSS, FIS and MSFC

| SF-36 subcales | EDSS | Pasat 3' | 9-HPT (Dominant) | 9-HPT (Non-Dominant) | TW25 | Fatique impact scale (Total) |
|---|---|---|---|---|---|---|
| Physical Function | −0.814 | 0.122 | −0.518** | −0.354* | −0.765** | −0.435 |
| Role-Physical | −0.613 | 0.199 | −0.452* | −0.202* | −0.506* | −0.619 |
| Bodily Pain | −0.339 | 0.062 | −0.178 | 0.024 | −0.257* | −0.488 |
| General Health | −0.346 | 0.012 | −0.222* | −0.064 | −0.380* | −0.577 |
| Vitality | −0.303 | 0.090 | −0.297* | −0.111 | −0.197* | −0.754 |
| Social Function | −0.428 | 0.069 | −0.295* | −0.119 | −0.376* | −0.645 |
| Role Emotional | −0.339 | 0.118 | −0.245* | −0.140 | −0.249* | −0.731 |
| Mental Health | −0.154 | 0.079 | −0.079 | −0.014 | −0.083 | −0.669 |

*p<0.05; **p<0.001; FIS: Fatigue ımpact scale; MSFC: The MS Functional Composite; EDSS: Expanded disability status scale; 9-HPT: 9 hole peg test.

**Table 4.** Relationship between FIS and cranial/spinal MRI ınvolvement

| MRI Features | Fatique ımpact scale (Total) mean±S.D. | p |
|---|---|---|
| Cranial MRI | | |
| Mild | 35.1±40.5 | 0.049 |
| Moderate | 36.9±29.9 | |
| Severe | 48.2±43.4 | |
| Spinal MRI | | |
| Unaffected | 34.9±37.4 | 0.025 |
| Mild | 36.0±37.5 | |
| Moderate | 51.9±40.8 | |
| Severe | 55.6±51.9 | |

FIS: Fatigue ımpact scale; MRI: Magnetic resonance imaging.

## Discussion

MS has a chronic and progressive nature and affects the quality of life of patients, especially in young adults because of its disability. Therefore, health-related quality of life scales have been gained importance in clinical studies, drug studies and determining the health status of patients in the evaluation of MS disease in the past 20 years[14].

In 1992, Rudick et al.[15] for the first time showed that lower quality of life due to MS is higher than inflammatory bowel disease and rheumatoid arthritis. In the next 20 years, many studies were conducted to evaluate the quality of life in MS. They showed that health-related quality of life scales can be used to measure the positive and negative effects of MS and evaluate the development of the disease and its response to treatment. In our study, we analyzed the quality of life and the factors that affect the quality of life of the patients by using the SF-36 scale which includes general health concepts which have been validated by Koçyiğit et al.[16]

Eight subscales of SF-36 including; physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health were evaluated in 100 cases for the study. Considering the Turkish population, our results have demonstrated a significant downtrend in eight subscales. When the factors affecting the quality of life were investigated, no significant correlation was found between age, age of onset, gender, educational status, and SF-36. This was similar to the results of Fernández et al.[17] It has been seen that prolongation of disease duration worsened physical functioning and role-

**Table 5.** Relationship between SF-36 and BDI

| SF-36 subcales | Unaffected (n=65) | Mild Depression (n=20) | Moderate Depression (n=5) | Severe Depression (n=10) | p |
|---|---|---|---|---|---|
| Physical Function | 79.6±30.7 | 65.7±30.4 | 37.5±21.0 | 29.3±32.8 | 0.000 |
| Role-Physical | 79.1±28.5 | 44.0±30.5 | 28.1±22.9 | 22.6±27.5 | 0.025 |
| Bodily Pain | 80.0±23.0 | 70.3±25.6 | 69.4±22.9 | 34.7±28.1 | 0.000 |
| General Health | 59.8±11.8 | 54.9±13.2 | 52.2±10.2 | 43.6±14.8 | 0.006 |
| Vitality | 53.8±17.9 | 39.8±18.0 | 17.1±12.8 | 21.8±16.0 | 0.000 |
| Social Function | 79.1±25.7 | 64.8±26.4 | 53.1±25.7 | 35.9±30.2 | 0.000 |
| Role Emotional | 89.3±17.3 | 62.3±26.3 | 62.5±25.0 | 28.1±33.9 | 0.012 |
| Mental Health | 65.2±13.4 | 54.5±16.9 | 45.0±12.2 | 29.3±14.2 | 0.000 |

physical problems from SF-36 subscales. The mental functioning was not significantly affected by the extension of disease duration. These results suggest that the physical functions may be affected more due to the prolongation of the duration and the increase in disability as a result of the increased physical function. There was no effect on the sub-scales in which mental functions were evaluated. This can be explained by the prolonged disease period, the nature of the disease, and increased disease acceptance[18].

İdiman et al.[19] reported a positive correlation between disease duration and physical and mental health subscales of the MSQOL-54 quality of life scale. However, Rudick et al.[15] reported no significant relationship between duration of illness and quality of life score. In our study, EDSS was evaluated in relation to MSFC scales. The increase in EDSS scores adversely affected all subscales of SF-36 except mental health. Although other subscales are affected, the reason for not affecting mental health may be the increase in the duration of the disease and the acceptance of the disease in parallel with the increase in disability. The most affected parameter in parallel with the increase in EDSS score is physical functionality. The reason for this increase may be that EDSS is a scale that evaluates physical function, especially ambulation. In the literature, there are studies showing the correlation of EDSS with the physical function subunit of SF-36[20,21].

The correlation between MSFC and SF-36 was also investigated. No significant correlation was found between PASAT 3" and SF-36. The increase in PASAT 3" score minimally deteriorates the scale of the role physical. The reason for the decrease in quality of life despite the deterioration of the PASAT 3" score may be the nature of frontal lobe disorders. A deterioration in the frontal lobe causes daily life problems only in its severed stages. A significant correlation was found between the length of the T25-FW, 9HPT (dominant hand) and the SF-36 parameters including physical components. The reason for not affecting mental health is the inadequacy of these tests in evaluating mental functions similar to EDSS. T25-FW is sensitive to ambulation as well as the quality of life. Eventually, quality of life is most affected by the loss of function of lower extremities[19,22].

In our study, it was observed that fatigue and depression affected the quality of life more than disability. Depression can be related to the problems experienced in the occupation, social, and home life caused by disability in MS and related to the pathology of the disease. The presence of depression affected all subscales of SF-36. The reason why depression affects the quality of life may be because depression, in addition to disability in MS patients, causes psychomotor deceleration as a result of neurotic findings and widespread body pain. Similar results were found in studies by Emel Koçer et al.[23] and Kaya et al.[24]

The increase in lesion load in cranial and spinal MRI seems to influence SF-36 subscales, especially Physical Functionality, Role Physical. There was no significant deterioration in mental function. This may be explained by the increase in the burden of lesion causing disability. Besides, no correlation was found between the presence of autoimmune antibodies in cerebrospinal fluid (CSF)[2].

Fatigue is one of the most common symptoms of MS, such as depression. Although fatigue is not associated with conventional MRI lesions and atrophy, it is associated with a decrease in glucose metabolism in the bilateral frontal cortex and basal ganglia. Fatigue is a subjective experience. It prevents daily activities, creates problems in work, family life, and prevents social activities[3].

## Conclusion

In this study significant relationship between disability status, lower/upper extremities and fatigue was encountered.

However, this relationship was not seen between fatigue and cognition. In studies showing that disability increases fatigue in MS patients, the common opinion is peripheral fatigue except for central fatigue. Accordingly, it can be said that MS patients use their muscles more to compensate for the spastic walking pattern and muscle weakness. Intensive use of muscles can cause peripheral fatigue. This view explains the EDSS score and the increase in disability in patients due to disability. In our study, depression was the most important cause of fatigue. Similar to cognition, no significant correlation was observed between autoimmune antibody levels evaluated in CSF and total cell count and fatigue. When the relationship between radiological findings and fatigue was evaluated, there was no significant difference between cranial MRI findings and mild and moderate fatigue. The level of fatigue has increased in the severe effect. In spinal MRI, fatigue level increased with the increase in lesion load.

**Ethics Committee Approval:** This study was approved by the Haydarpaşa Numune Training and Research Hospital clinical research ethics committee (Date: 09/12/2010, decision no: 2010/110). The study was carried out following the International Helsinki and other declarations.

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