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Original Article / Özgün Araştırma

Cognitive Impairment in Young Multiple Sclerosis and Essential Tremor Patients: A Comparative Study

Genç Multipl Skleroz ve Esansiyel Tremor Hastalarında Kognitif Bozulma: Bir Karşılaştırmalı Çalışma

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Summary

Objective: In multiple sclerosis (MS); memory, attention, information processing speed, and executive function deficits associated with cortical demyelination and atrophy can be seen in the early phases. In essential tremor (ET) cognitive impairment associated with cerebral-thalamocortical pathway dysfunction, which is characterized by visuospatial functions, verbal memory, and executive functions were seen. We aimed to evaluate cognitive impairment in patients with MS and ET, and to compare the features of impairment.

Materials and Methods: Thirty patients ET (mean age 27.7±6.8 years), 30 patients with MS (mean age 32.4±6.6 years) and 20 healthy controls (mean age 28.81±7.3 years) were recruited for the study. For assessing cognitive impairment, the Montreal Cognitive Assessment (MoCA) test was applied to all participants. For grading the disease, the Fahn-Tolosa-Marin Tremor Rating Scale was used in the ET group, and the Expanded Disability Status Scale was used in the MS group.

Results: The total MoCA mean scores in patients with MS was 22.4±4.34, 25.8±2.7 in patients with ET, and 28.2±1.8 in controls. When we compared the patients with the controls, the patients' mean score was lower than in the controls. Cognitive impairment in patients with MS was more apparent than in patients with ET. Naming, attention, language, and delayed recall subgroups in patients with MS were more affected than in patients with ET.

Conclusion: In this present study, we determined cognitive impairment can be seen in both group of patients, and MS can cause more prominent deficit than ET. In addition, our study confirms that cognitive impairment in MS and ET can be detected using the MoCA test.

Keywords: Multiple sclerosis, essential tremor, cognitive impairment, Montreal Cognitive Assessment test

Öz

Amaç: Multipl sklerozda (MS) kortikal demiyelinizasyon ve atrofi ile ilişkili bellek, dikkat, bilgi işleme hızı ve yönetici işlev bozuklukları hastalığın ilk dönemlerinden itibaren görülmektedir. Esansiyel tremorda (ET) ise serebello-talamo-kortikal yol disfonksiyonunu ile viziospasyal fonksiyonlar, verbal hafıza ve yine yürütücü işlevlerin bozulması ile karakterize kognitif etkilenmenin olduğu gösterilmiştir. Çalışmamızda MS ve ET hastalarında kognitif bozukluğunun değerlendirilmesini ve özellikleri açısından karşılaştırılmasını amaçladık.

Gereç ve Yöntem: Çalışmamıza 30 ET (27,7±6,8), 30 MS (32,4±6,6) ve 20 sağlıklı gönüllü (28,81±7,3) dahil edildi. Katılımcılara kognitif fonksiyonları değerlendirmek amacıyla Montreal Kognitif Değerlendirme Ölçeği (MoCA) testi, hastalık derecesini değerlendirmek amacıyla ET grubuna Fahn Tolosa Marin-Tremor Değerlendirme Ölçeği ve MS grubuna Genişletilmiş Özürlülük Durum Ölçeği uygulandı.

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Bulgular: MoCA toplam skor ortalaması MS hastalarında 22,4±4,34, ET hastalarında 25,8±2,7 ve kontrol grubunda 28,2±1,8 olarak saptandı. Hasta gruplarının skorları kontrol grubu ile karşılaştırıldığında düşük olarak bulundu. MS hastalarıyla ET hastaları karşılaştırıldığında MS hastalarında kognitif bozulmanın daha fazla olduğu; adlandırma, dikkat, lisan ve gecikmeli hatırlama alt gruplarının ET hastalarına göre daha belirgin etkilendiği görüldü.

Sonuç: Bu çalışmada her iki hastalık grubunda erken dönemde dahi kognitif bozukluğun görülebileceği ve bu bozulmanın MS hastalarında daha belirgin olduğu tespit edildi. Bununla birlikte MoCA testinin bu hastalık gruplarında kognitif bozulmanın gösterilebilmesi amacıyla kullanılabileceği saptandı.

Anahtar Kelimeler: Multipl skleroz, esansiyel tremor, kognitif bozulma, Montreal Kognitif Değerlendirme Ölçeği

Introduction

Multiple sclerosis (MS), which is among the leading causes of physical disability in young adults with non-traumatic neurologic diseases, is a chronic, demyelinating, inflammatory disease (1). The disease has a wide range of variability in terms of clinical features, course, prognosis, pathogenesis, and anatomic features (2). Sensory symptoms, visual disturbances, muscle weakness, depression, cognitive impairment, coordination, and speech disorders, severe fatigue, balance problems, and pain are among the symptoms of the disease (3). Cognitive impairment affects 40% to 65% of patients and is a major cause of disability associated with the disease (4). The most affected cognitive functions in patients with MS are attention, learning, visuospatial functions, memory, information processing speed, and executive functions (5).

Although essential tremor (ET) has been described as a monosymptomatic, slowly progressive, benign motor system disease characterized by tremors during voluntary movements, an increasing number of studies in recent years have shown that the disease also has non-motor symptoms and that a subgroup of this disease may be neurodegenerative in nature (6). Besides motor symptoms such as tremor, bradykinesia (mild), cerebellar dysfunction, postural instability, smelling and hearing disorders, non-motor symptoms such as mild cognitive impairment, neuropsychiatric symptoms, and sleep disorders are defined with successively increasing rates (7). In several studies, findings suggesting cerebral-thalamocortical tract dysfunction were found in patients with ET. Mild cognitive impairment characterized by impairment of visuospatial functions, verbal memory, and executive functions has been shown in young patients (8,9,10,11,12,13).

The Montreal Cognitive Assessment Scale (MoCA) has become one of the most widely used tests by physicians for rapidly assessing cognitive impairment. It is an alternative to the Standardized Mini-Mental State Examination (SMMSE) for the evaluation of cognitive functions, besides, it is more comprehensive and more sensitive (14,15). The time required for implementation of the SMMSE is about 5-10 minutes. Short-term memory, visuospatial function, executive function, attention, concentration, working memory, language, and orientation can be evaluated using the MoCA test. Its sensitivity in the detection of mild cognitive impairment is 90% (16).

In our study, we aimed to evaluate cognitive functions in young adults with MS and ET, and to compare the characteristics of cognitive impairment between the two groups.

Materials and Methods

Among the follow-up patients in Erzurum Regional Training and Research Hospital neurology outpatient clinic between November 2012 and October 2013, 30 patients with relapsing-remitting MS diagnosed in accordance with the revised McDonald 2010 criteria, and 30 patients with ET diagnosed as per the Bain P. diagnostic criteria were included in our study. Twenty healthy participants with similar characteristics (age, sex, and education level) were recruited as the control group (17,18). The principles of the study were presented to all participants and volunteer consent forms were obtained. The study was approved by the ethics committee of our hospital. The exclusion criteria for patients with MS were as follows: neurologic disease other than MS, duration of disease less than a year, previous attack in the last 6 weeks, and steroid therapy. The exclusion criteria for patients with ET were neurologic diseases other than ET, and use of drugs that could cause tremor. Illiterate patients, patients with history of drugs that could affect cognitive function, patients with low blood count or vitamin B12 levels, and patients with thyroid dysfunction in both groups were excluded from the study. All patients in the ET group were evaluated for Wilson's disease. Patients were referred to the ophthalmology clinic and screened for Kayser-Fleischer ring. The socio-demographic characteristics of all participants were recorded. The MoCA test was used to evaluate cognitive functions. The Fahn-Tolosa-Marin tremor rating scale (FTM-TRS) and Expanded Disability Status Scale (EDSS) were used for grading ET and MS, respectively.

MoCA: Memory (recall and delayed recall-5 points), visuospatial abilities (clock-drawing task: 3 points, and a three-dimensional cube copy: 1 point), executive functions (trail-making task: 1 point), phonemic fluency task (1 point) and two-item verbal abstraction task (2 points), attention, concentration and working memory (serial subtraction task: 3 points, digits forward and backward: 1 point each), language (a three-item animal naming task: 3 points, repetition of two syntactically complex sentences: 2 points) and finally, orientation to time and place were evaluated (6 points). The minimum and maximum scores are 0 and 30 points, respectively (19). Values higher than 26 points were considered normal in this study (20).

FTM-TRS: This scale used to assess resting, postural, and action tremor. It is a 5-point scale that rates tremor severity from 0 to 4. Increasing scores indicate increased severity (21).

EDSS: This method is used to quantify neurologic disability caused by MS through examination of eight different systems (pyramidal, cerebellar, brainstem, sensory, bowel, and bladder). Disability scores range from 0 to 10 (22).

Statistical Analysis

Data analyses were performed using SPSS version 21.0. Discrete numeric variables are expressed as mean±standard deviation (SD) and categorical variables as number of cases and percentage (%) in the descriptive statistics. The cross-table method was used for

comparison of means. The difference between groups and the significance of differences in terms of means were analyzed using the independent samples t-test. The effects of duration of disease and severity of disease on cognitive impairment were analyzed using multiple regression analysis.

Results

The mean ages of patients with ET and MS were 27.7±6.8 and 32.4±6.6 years, respectively. The mean age of the control group was 28.8±7.3 years (mean±SD). The demographic features of the participants are shown in Table 1. The mean disease duration was 5.1±4.4 years in patients with ET and 5.3±4.7 years in patients with MS. The mean FTM-TRS score was 10.1±3.9 in the ET group, and the mean EDSS score was 1.2±1.7 in the MS group (mean±SD). Both disease groups had relatively short disease duration and low disease severity.

Cognitive impairment was found in 53.3% of patients with MS. This rate was 30.0% in patients with ET. The mean total MoCA score was 22.4±4.34 in MS group, 25.8±2.7 in the ET group, and 28.2±1.8 in the control group (mean±SD). The scores of the patient groups were found lower than the control group when compared using the independent samples t-test (p=0.001 for ET, p<0.001 for MS).

When comparing the subgroup scores of patients with MS and the control group, dysfunction was observed in all areas except abstract thinking and orientation. Similar results were observed in all areas except visuospatial abilities and delayed recall in the subgroup comparison between the ET and control group. Compared with patients with ET, more cognitive impairment was observed in patients with MS (p=0.001). When the mean subgroup scores were compared using the independent samples t-test, naming (p=0.03), attention (p=0.004), language (p=0.007), and delayed recall (p=0.012) subgroups were more affected in patients with MS than in patients with ET. Tables 2 and 3 show the comparison of the means of the total MoCA score and subgroup scores in patients with MS and ET with the control group.

Table 1. The demographical features of the participants

	Patients with MS (n=30)	Patients with ET (n=30)	Control group (n=20)	p value
Age	32.4±6.6	27.7±6.8	28.8±7.3	0.12-0.50*
Gender				
Female	18 (60.0%)	18 (60.0%)	14 (70.0%)	0.72**
Male	12 (40.0%)	12 (40.0%)	6 (30.0%)	
Education level				
Primary school	13 (43.3%)	11 (36.7%)	6 (30%)	0.91**
High school	5 (16.7%)	5 (16.7%)	4 (20%)	
University	12 (40.0%)	14 (46.7%)	10 (50%)	

MS: Multiple sclerosis, ET: Essential tremor, *Independent samples t test. The first value shows the comparison between patients with multiple sclerosis and healthy control group, and the second value shows the comparison between patients with essential tremor and healthy control group, **Cross-table method

Disease duration and EDSS score were found to have no effect on cognitive impairment in patients with MS in the multiple regression analysis. When evaluated using the same method, disease duration and FTM-TRS scores were found to have no effect on cognitive impairment in patients with ET. The effects of disease duration and disease severity on cognitive functions are shown in Table 4.

Discussion

Demyelinating diseases and neurodegenerative disorders are among the neurologic diseases that may lead to cognitive impairment at young ages. MS is the most common disease among demyelinating diseases. Neurodegenerative diseases with cognitive loss at young age are relatively rare. In recent years,

Table 2. The comparison between patients with multiple sclerosis and healthy control group in terms of Montreal Cognitive Assessment total score and subgroup scores

	Patients with MS (n=30)	Control group (n=20)	p value*
MoCA total score	22.43±4.39	28.20±1.88	<0.001
Subgroups			
Visual-spatial functions	3.90±1.24	4.60±0.59	0.02
Naming	2.33±0.51	2.90±0.30	<0.001
Attention	5.66±0.56	5.85±0.36	0.002
Language	1.63±1.12	2.60±0.68	0.001
Abstract thinking	1.43±0.72	1.75±0.44	0.09
Delayed recall	2.63±1.47	4.50±0.60	<0.001
Orientation	5.90±0.30	6.00±0.00	0.08

MS: Multiple sclerosis, MoCA: Montreal Cognitive Assessment, *Independent samples t test was used

Table 3. The comparison between patients with essential tremor and healthy control group in terms of total Montreal Cognitive Assessment score and subgroup scores

	Patients with ET (n=30)	Control group (n=20)	p value*
MoCA total score	25.76±2.73	28.20±1.88	0.001
Subgroups			
Visual-spatial functions	3.90±1.09	4.60±0.59	0.01
Naming	2.73±0.44	2.90±0.30	0.15
Attention	5.60±0.62	5.85±0.36	0.11
Language	2.33±0.76	2.60±0.68	0.21
Abstract thinking	1.56±0.50	1.75±0.44	0.19
Delayed recall	3.53±1.19	4.50±0.60	0.002
Orientation	5.90±0.31	6.00±0.00	0.15

ET: Essential tremor, MoCA: Montreal Cognitive Assessment, *Independent samples t test was used

there have been both anatomic and clinical studies that support the neurodegenerative nature of ET. In young patients, ET and MS are more commonly seen in our daily clinical practice compared with other diseases.

In this study, it was aimed to assess cognitive functions at early stages in young patients with MS and ET using the MoCA test, and to compare and evaluate the characteristics of the observed cognitive impairment in both groups. Our study demonstrated that both groups had cognitive impairment and that this impairment was more prominent in patients with MS. When MoCA test subgroups were evaluated, impairment in visuospatial abilities, naming, attention, and delayed memory functions were observed in patients with MS, whereas impairment was only observed in visuospatial abilities and delayed memory in the ET group. Impairment in naming, attention, language and delayed recall sub-groups were significantly higher in patients with MS compared with patients with ET.

Nearly 30 years ago, it was thought that cognitive impairment was up to 3% in patients with MS and that this impairment occurred in the later stages of the disease (23). Today, however, we know that cognitive impairment is much more common and can also be observed in early stages of the disease (24). In a review on this subject, forty previously published articles were evaluated and it was shown that cognitive impairment in memory, information processing speed, executive functions, attention, and concentration were more prominent (5). Our study also showed that there was impairment in many areas and that this could be detected even by using the MoCA screening test. Cognitive impairment is one of the important reasons for disease-associated disability (25). Cognitive impairment in MS has become the focus of attention by physicians because it affects sexuality and routine activities, in addition to emotional, social and work activities, and significantly decreases the quality of life, even in patients with mild physical disability (26,27,28,29). Cognitive impairment, which is mostly ignored in our daily clinical practice, can be detected with a precise and fast test such as MoCA. Studies that used MoCA as a screening test in the past few years showed that even mild cognitive impairment could be determined with this test, which supports our results (30,31,32).

The results of studies that showed a relationship between cognitive disturbances and EDSS are conflicting. In the studies by Aksoy et al. (19) and Dagenais et al. (30), there was no relationship between the two variables in a similar way to our study. However, in a recent study, EDSS was identified as a strong predictor of cognitive impairment. Also, cognitive impairment was found in 31% of patients with low EDSS (32). This can be explained by the very low mean EDSS score in our study.

Table 4. Multiple regression analysis demonstrating the effects of disease duration and disease severity on Montreal Cognitive Assessment total score

MS	**p value***	**OR**	**Confidence interval**
Disease duration	0.06	-3.50	-0.71-0.01
EDSS score	0.53	-3.09	-1.3-0.69
ET	**p value***	**OR**	**Confidence interval**
Disease duration	0.69	0.05	-0.21-0.31
EDSS score	0.43	-0.11	-0.40-0.18

EDSS: Expanded Disability Status Scale, ET: Essential tremor, MS: Multiple sclerosis, OR: Odds ratio, *Multiple regression analysis

The presence of cognitive impairment in patients with ET is relatively new. Studies on this subject showed cognitive impairment with affected visuospatial abilities, verbal memory, executive functions, verbal fluency, naming and working memory in ET (12,33,34,35,36). Moreover, in a limited number of studies conducted with young patients, this condition has been proved to be present even at early stages (6,13). In our study, we also found that visuospatial abilities and delayed recall functions were significantly impaired compared with the controls.

Although Kim et al. (37) found a significant relationship between the severity of tremor and cognitive impairment, no statistically significant relationship was determined in our study, even though there was a negative correlation.

Study Limitations

The limitations of our study are the small number of patients, lack of exclusion of undiagnosed conditions such as depression and sleep disorders, which could cause cognitive impairment in patients and controls, and lack of questioning about substance abuse although drug use was questioned. The strengths of this study are that the study groups included young patients, and the paucity of a similar studies in the literature.

Conclusion

Our study showed that MS and ET could cause cognitive impairment even at early stages of the disease in patients of young ages. Impairment was more pronounced in patients with MS and included multiple functions in both groups. Besides remarkable motor symptoms, early-stage mild cognitive impairment is easily overlooked in daily practice and this causes significant deterioration in the patient's quality of life. Cognitive rehabilitation in the early stages is important. Therefore, it is necessary to evaluate cognitive function in young-aged patients at the early stages of disease.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Şişli Etfal Training and Research Hospital (19.03.2013, 2013/4-1, Erzurum Training and Research Hospital), Informed Consent: Consent forms were completed by all participants.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Design: Yıldızhan Şengül, Hulki Forta, Hakan Serdar Şengül, Data Collection or Processing: Yıldızhan Şengül, Selma Yücel, Hakan Serdar Şengül, Analysis or Interpretation: Yıldızhan Şengül, Hakan Serdar Şengül, Literature Search: Yıldızhan Şengül, Writing: Yıldızhan Şengül, Hakan Serdar Şengül.

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