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RESEARCH ARTICLE

The Multiple Sclerosis Functional Composite (MSFC) for Determining Disease Progression: A Methodological Study

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Abstract

Objective: The methods used in monitoring the progression of multiple sclerosis (MS) and evaluating the effectiveness of disease-modifying treatments are insufficient. Data obtained from the expanded disability status scale (EDSS), annual relapse rate, or magnetic resonance imaging methods lead to the understanding of symptoms such as cognitive involvement only in the late disease phase. Therefore, this study aimed to compare the relationship between a tool that also evaluated cognitive involvement, such as the multiple sclerosis functional composite (MSFC), which is not widely used in every MS clinic, and a traditional method such as the EDSS.

Materials and Methods: A total of 121 patients with relapsing-remitting MS [female, n=82 (67.8%); male, n=39 (32.2%)] were included in the study. Three (baseline, year 1, and year 2)-year changes in the EDSS scores of these patients within 1 year were visually categorized as both ≥0.5 or ≥1.0. Changes in MSFC components were recorded numerically. The relationship between the changes in 1 year and the EDSS categories was analyzed by repeated-measures analysis of variance (ANOVA). P values <0.05 were considered significant.

Results: According to the results of repeated measures ANOVA, timed 25-foot walk (T25-FW) values were significantly correlated with EDSS changes of ≥1.0 point between both baseline to year 1 [F (1,118) = 6.532; p=0.012] and year 1 to year 2 [F (1,118)=10.222; p=0.002]. When the 3-year change between the baseline and year 2 was considered, the paced auditory serial addition test (PASAT) 3" was found to be significantly correlated with EDSS changes of ≥1.0 points [F (2,118) = 4.204; p=0.043].

Conclusion: MSFC results demonstrated disease progression in line with the EDSS categories designed for the study. T25-FW is effective in predicting changes of ≥1.0 points in the EDSS at 1-year intervals. The PASAT 3" was effective in predicting changes of ≥0.5 points and ≥1.0 points, considering the 2-year change. Accordingly, MSFC components can be used in clinics as an alternative method to determine the treatment endpoint and to monitor cognitive involvement.

Keywords: Multiple sclerosis functional composite, evidence of disease activity, Expanded Disability Status Scale, Paced Auditory Serial Addition Test

Introduction

Multiple sclerosis (MS) is a heterogeneous disease with various challenges in monitoring patients during clinical practice and evaluating the results of their pharmacological interventions. In addition, new disease-modifying therapy options have recently increased in the treatment of the disease, and the concept of "no evidence of disease activity" (NEDA) has become a significant MS progression concept (1).

To date, many different evaluation methods have been developed for disease progression and follow-up. Of these, Kurtzke's (2) expanded disability status scale (EDSS) has been the most widely used method for assessing disease progression in MS clinics for the past 50 years. Similarly, the annual relapse rate (ARR), which is useful for determining regression in the relapsing MS and testing the efficacy of new anti-inflammatory drugs in phase 3 studies, has been widely used together with EDSS in disease follow-up since the 1990s (3). Besides EDSS and ARR, magnetic resonance imaging (MRI) is one of the most common methods of evaluating disease progression and treatment efficacy. Giovannoni et al. (4) highlighted the usefulness of MRI for both fluid-attenuated inversion recovery, T2, and Gd+ T1. If the patient has an increase in Gd+ T1 lesions that will indicate

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a subclinical recurrence and disease progression, changing treatment could be an option.

Moreover, recent developments in imaging methods and in the biomedical field reveal the unparalleled situations between NEDA-3 (EDSS, ARR, and lesion activity on MRI) and progression, especially in cognition. The insufficiency of NEDA components in evaluating cognitive involvement has brought different assessment tools and batteries such as the multiple sclerosis functional composite (MSFC), brief repeatable battery of neuropsychology (BRB-N), (5) and brief international cognitive assessment for MS (BICAMS) (6) to the agenda. According to a meta-analysis by Meyer-Moock et al. (7), in which they included a total of 50 EDSS and 9 MSFC studies, the use of MSFC as disability level and treatment endpoint is recommended as a quantitative assessment tool for cognitive functions. Although MSFC is criticized as the primary or secondary treatment endpoint, it appears to be used in different drug phase studies (8). However, the use of EDSS and MSFC as endpoints should not disregard factors such as limited inter-rater reliability, application of standard protocols, and learning. Specifically, one of the most important handicaps of MSFC is the learning effect seen in the paced auditory serial addition test (PASAT) and the nine-hole peg test (9HPT). According to Rudick et al. (9), MSFC was also correlated with deterioration due to gray matter, white matter, and whole-brain atrophy observed over 6 years. In this study, the 4-year gray matter atrophy rates were parallel to MSFC, but not significantly correlated with EDSS.

Thus, the present study aimed to examine the association of disability, determined according to different EDSS changes, with the MSFC subtotal and total scores over time. This can ensure the consistency between the existing evaluation tools and the creation of alternative evaluation methods.

Materials and Methods

Patient Selection

Initially, 121 patients with relapsing-remitting MS followed in the Multiple Sclerosis Unit of the University of Health Sciences Haydarpasa Numune Training Hospital were considered for the study. Patients with RRMS who had a disease duration of at least 2 years, aged <50 years, had an EDSS score of ≤4, had no relapse in the last 6 months, and had no inflammatory or psychiatric disease other than MS were included in the study. The retrospective data of the patients who did not sign the informed consent form were not evaluated.

Disease Activity Data Conversion

Disease activity was determined visually in Excel in two ways. Within the scope of the study, EDSS changes were recorded from baseline to year 1 and from year 1 to year 2, taking into account ≥0.5 and ≥1 score ranges. If the EDSS score increased by 0.5 and ≥1 point within a year, it was determined as "increased disease activity (IDA)." Similarly, if the EDSS score decreased, it was determined as "decreased disease activity (DDA)." If there was no change in the EDSS score within 1 year, it was defined as "stable disease activity (SDA)." The relationship between sequential disease activities and 1-year recurrent dominant, non-dominant upper extremity, lower extremity, cognition, and MSFC overall score data were included in the analysis.

Calculation of the Overall MSFC Score

According to Fischer et al. (10), the patient's scores on the lower, upper extremity, and cognitive subtests were calculated according to the following formula:

- Z_{leg} = (Mean T25-FW-9.5353)/11.4058

- Z_{arm} = [Mean (1/9HPT)-0.0439]/0.0101

- Z_{cog} = (PASAT3"-45.0311)/12.0771

In the above formula, 9.5353 is the "mean reference cohort of T25-FW," and 11.4058 is the "standard deviation reference cohort of T25-FW." The reference cohorts for 9 HPT and PASAT 3" were also determined by Fischer et al. (10). The composite score was obtained by taking the arithmetic average of the Z values calculated according to the above formulas:

- $Z_{MSFC} = (Z_{arm} - Z_{leg} + Z_{cog})/3$

Statistical Analysis

As a result of the analysis made with the G* Power 3.1 (11), 168 participants should be included in the study; however, only 121 participants were included because a sufficient number could not be reached due to the aforementioned reasons. Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24.0 (IBM Corp., Armonk, NY, USA). Variables were expressed as apercentage and mean ± standard deviation. Age, number of relapses, disease duration, and age of disease onset were evaluated as both numerical and ordinal data. The ratio of ordinal or nominal data to each other was evaluated using the chi-square test. Changes in dominant (9HPT-D), non-dominant upper extremity (9HPT-ND), lower extremity (T25-FW), multi-tasking skills (PASAT 3"), and overall MSFC scores over 2 years were analyzed using the one-way repeated-measures ANOVA. The two-way repeated-measures ANOVA test was applied to evaluate the effect of ordinal variables such as age and number of relapses on repeated measures over time. Those with a p value <0.05 were considered significant.

Results

Demographic Features of the Patients

In this study, the mean age of the 121 patients with RRMS [female, n=82 (67.8%); male, n=39 (32.2%)] was 37.92±9.10 [minimum (min)=20, maximum (max)=50] years, and the mean age of onset was 28.81±8.50 (min=10, max=46) years. When the clinical features of the patients were examined, the disease

duration was 9.14±5.99 (min=2, max=28), and the number of relapses was 5.57±3.80 (min=2, max=20) (Table 1).

Relationship Between Clinical Features and Disease Activity

Ordinal variables such as age, sex, education level, number of relapses, disease duration, age of disease onset, first disease symptom, presence of Gd+ T1 and T2 hyperintense lesions, and 0.5 and 1.0 changes in the EDSS level were evaluated separately by the chi-square method. Hence, variables other than the presence of lesion were not associated with the progression determined using EDSS (p>0.05).

In addition, a significant correlation was found between disease progression determined using an EDSS change of 0.5 and the presence of T2 hyperintense lesions [$\chi 2$ (2, N=121) =11.581; p=0.003]. Specifically, a significant correlation was noted between 0.5 EDSS changes in disease progression of patients with ≥9 T2 hyperintense lesions.

Another similar significant relationship was observed between disease progression determined using an EDSS change of 1.0 and the presence of Gd+ T1 lesions [$\chi 2$ (2, N=121)=6.367; p=0.041]. The results of the chi-square test indicated that the fixed disease activity and presence of Gd+ T1 lesion were highly correlated.

Relationship Between Disease Activity and Possible Assessment Methods

Changes in MSFC and its four components (9HPT/D, 9HPT/ND, timed 25-foot walk [T25-FW], and PASAT 3") over 1 year were measured by repeated-measures ANOVA. Accordingly, changes in 9HPT/D, 9HPT/ND, and PASAT 3" results between baseline and year 1, year 1 and year 2, and baseline and year 2 were not significant when considering both EDSS ≥0.5 and ≥ 0.1 (p>0.05).

Considering the ≥0.5 changes in EDSS, only the timed 25-foot walk change between baseline and year 1 was significant [$F_{\text{Timed 25-Foot Walk}}(1,118) = 6.532$; p=0.012] (Table 2, Figure 1). However, this change was not significantly distributed among the groups (p>0.05).

Similarly, the timed 25-foot walk scores between year 1 and year 2 were significant when evaluated considering the change in EDSS value of ≥1.0 [$F_{\text{T25-FW}}(1,118) = 10.222$; p=0.002] (Table 3). When the significance of the distribution was evaluated between the groups, this change was significant [$F_{\text{T25-FW*disease activity(≥1.0)}}(2,118)=5.523$; p=0.005] (Figure 1). However, according to the post-hoc test results, it could not be observed from which groups the difference originated (p>0.05).

In the evaluation of cognitive functions, the PASAT 3" results changed significantly, which was valid for both half-point [$F_{\text{PASAT 3"}}(1,118)=5.849$; p=0.017] and 1-point [$F_{\text{PASAT 3"}}(2,118) = 4.204$; p=0.043] changes (Table 4, Figure 2). Still, this change was not significantly distributed between the groups. In the case where the EDSS change is ≥1.0, the change in the MSFC overall score between year 1 and year 2 is significant at the trend level [$F_{\text{MSFC}}(1,118) = 3.068$; p=0.082] (Table 3). However, this change was not significantly distributed among the groups (p>0.05).

Relation of Significant MSFC Components and Clinical Factors

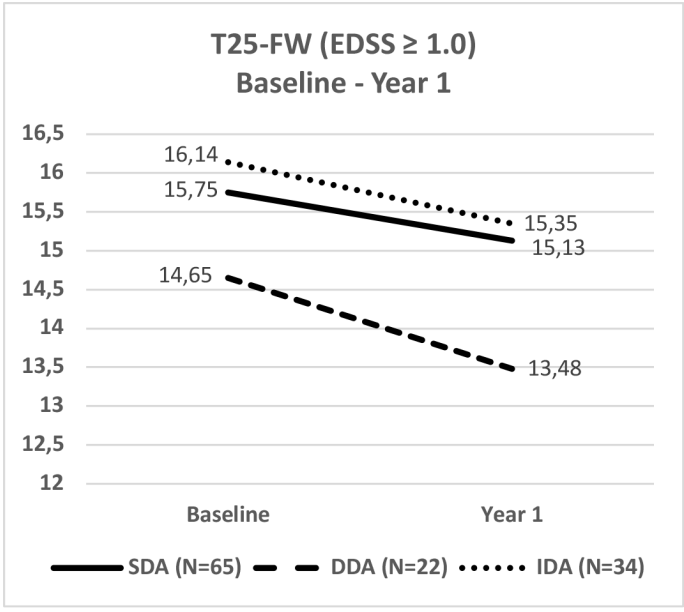
In the evaluations made with two-way repeated-measures ANOVA, no relationship was found between clinical factors and recurrent MSFC components (p>0.05).

Discussion

The primary aim of this study is to evaluate whether there is a relationship between the disability levels recorded over 1- and

Table 1. Demographic features of the patients

		N	%
Age	**<29**	32	26.4
	30-39	33	27.3
	40-49	38	31.4
	>50	18	14.9
Gender	**Female**	82	67.8
	Male	39	32.2
Education	**Elementary/ middle school**	32	26.4
	High school	38	31.4
	Undergraduate/ graduate	51	42.1
Number of relapse	**<4**	44	36.4
	4–6	43	35.5
	>6	34	28.1
Disease duration	**<5**	26	21.5
	5-10	57	47.1
	>10	38	31.4
Age of onset	**<20**	16	13.2
	20-24	31	25.6
	25-29	23	19.0
	30-34	15	12.4
	35-39	15	12.4
	>40	21	17.4
First symptom	**Supratentorial**	31	25.6
	Optic pathway	29	24.0
	Cerebellum	32	26.4
	Spinal cord	29	24.0
Gd+ T1 lesions	**–**	97	80.2
	+	24	19.8
T2 hyperintense lesions	**3-8**	25	20.7
	9+	96	79.3



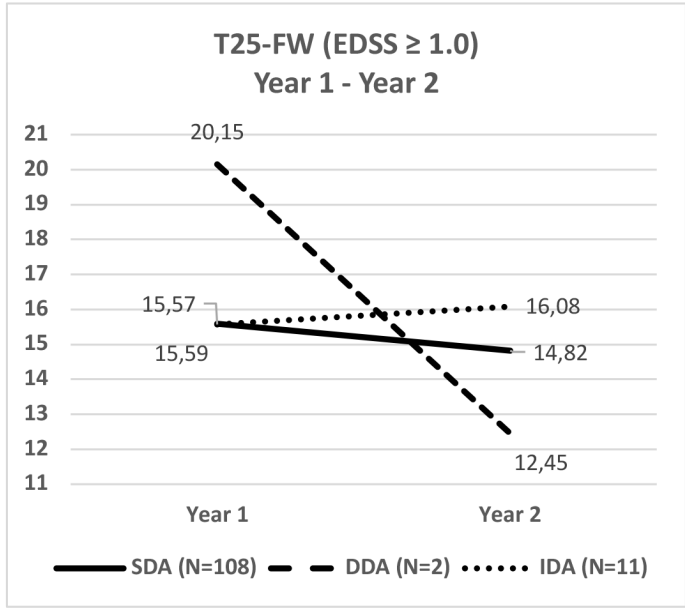
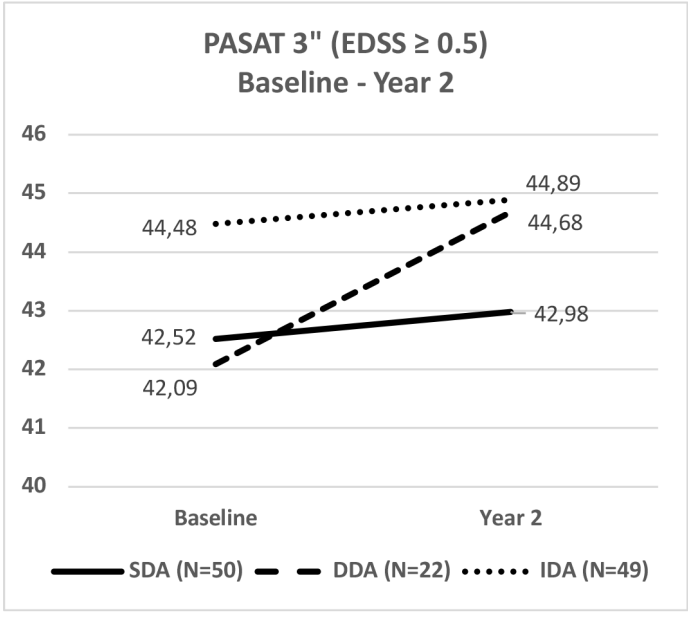


Figure 1. T25-FW Change Over Time According to EDSS
EDDS: Expanded disability status



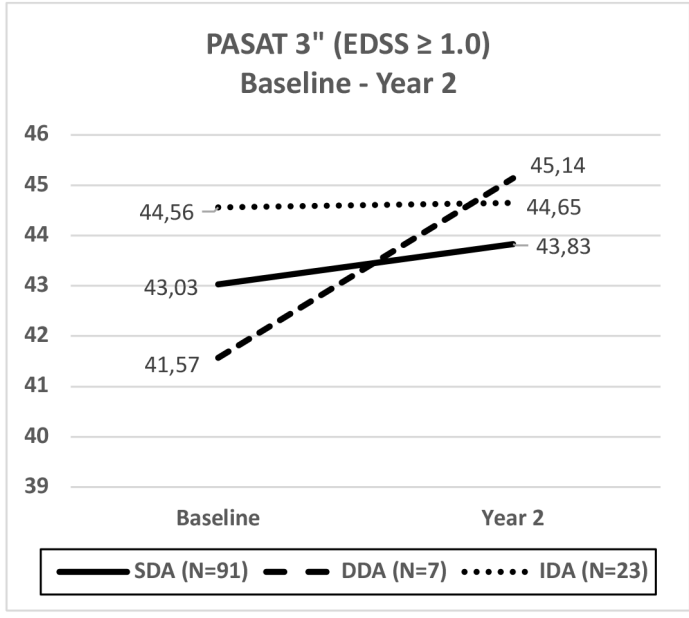


Figure 2. PASAT 3" Change Over Time According to EDSS
EDDS: Expanded disability status

2-year periods and the MSFC components. Within the scope of the study, MSFC components were analyzed considering both 0.5 and 1.0 point changes over two time periods. Therefore, EDSS changes of ≥0.5 were not associated with any MSFC component. However, a change of ≥1.0 in disability over 1 year is consistent with the change in the T25-FW test. In addition, the level of disability is significantly correlated with the change of 0.5 and ≥1.0 observed in 2 years from the PASAT 3." According to these results, lower extremity evaluations made in 1 year and cognitive evaluations made in 2 years may be useful in determining the disability levels and "evidence of disease activity" of patients.

Unlike existing studies, we described the changes in EDSS scores as increasing (IDA), decreasing (DDA), and stable (SDA) forms, not numerically. Existing studies have considered EDSS scores as numerical (12) or basal limits (13,14). During our literature review, we only encountered two studies (15) that are similar to our research method. Since EDSS is an ordinal variable, it was not used numerically in the study, and it was taken into account as 0.5- and 1.0-point changes. In addition, our study covers disability or functionality assessments for 3 years and is similar to Kragt's dissertation in terms of the components and duration it examined. Kragt (15) evaluated the relationship between EDSS, Guy's Neurological Disability Scale (GNDS), and MSFC

Table 2. Changes in MSFC components between baseline and year 1 according to the stages of progression											
		EDSS ≥0.5						EDSS ≥1.0			
	N	Baseline	Year 1	F	p		N	Baseline	Year 1	F	p
		Mean (SD)	Mean (SD)					Mean (SD)	Mean (SD)		
SDA	63	21.89 (4.64)	22.20 (3.87)	1.257	0.265	SDA	65	21.01 (3.91)	21.83 (3.74)	1.607	0.207
DDA	20	22.67 (5.01)	21.48 (3.47)			DDA	22	21.56 (3.22)	22.21 (4.16)		
IDA	38	21.88 (4.31)	21.58 (3.15)			IDA	34	21.85 (3.19)	22.59 (3.88)		
9 HPT/D											
SDA	63	24.78 (8.68)	23.74 (4.72)	1.037	0.311	SDA	65	23.32 (4.60)	23.20 (4.55)	2.442	0.121
DDA	20	23.02 (5.95)	22.62 (3.57)			DDA	22	23.25 (4.44)	24.49 (5.49)		
IDA	38	22.69 (3.57)	22.22 (3.19)			IDA	34	22.50 (2.88)	23.05 (4.64)		
9 HPT/ND											
SDA	63	15.78 (3.61)	15.30 (2.80)	1.213	0.273	SDA	65	15.75 (3.91)	15.13 (4.15)	6.532	**0.012**
DDA	20	14.76 (2.95)	14.94 (2.69)			DDA	22	14.65 (3.44)	13.48 (2.47)		
IDA	38	15.11 (2.86)	16.63 (4.90)			IDA	34	16.14 (3.07)	15.35 (3.16)		
Timed 25-foot walk											
SDA	63	43.30 (11.29)	43.04 (11.43)	2.661	0.105	SDA	65	41.98 (11.47)	42.36 (11.13)	0.532	0.467
DDA	20	42.25 (12.79)	43.20 (11.37)			DDA	22	45.31 (9.35)	45.54 (9.91)		
IDA	38	43.65 (9.25)	45.28 (9.35)			IDA	34	46.20 (9.86)	46.35 (10.73)		
PASAT 3"											
SDA	63	0.045 (0.48)	0.033 (0.46)	1.440	0.233	SDA	65	0.016 (0.43)	0.046 (0.43)	0.005	0.945
DDA	20	0.041 (0.43)	0.096 (0.39)			DDA	22	0.140 (0.46)	0.114 (0.43)		
IDA	38	0.085 (0.36)	0.131 (0.36)			IDA	34	0.143 (0.36)	0.135 (0.40)		
MSFC Overall											

MSFC: Multiple sclerosis functional composite, EDDS: Expanded disability status, DDA: Decreased disease activity, SD: Standard deviation

scores in patients with secondary progressive MS and designed the changes in EDSS values as 0.5 and 1.0. Unlike our study, the study of Kragt (15) found a consistent relationship between EDSS and MSFC components only in the upper extremity. This situation was seen only in patients with severe disability (EDSS ≥6.0) with a 0.5-point EDSS change. The study of Coles et al. (16), using the EDSS method, is closely related to our study and similar in terms of progression level. In the study in which the effects of alemtuzumab and interferon beta 1-a were evaluated in patients with early-stage MS, the patients were evaluated in the 1st, 12th, and 24th months, and 1.0- and 1.5-point changes in EDSS scores were taken into account. Since MSFC results were not used in this study, they are similar to our study only in terms of method.

The association between MSFC components and disability is mostly seen in drug efficacy studies. Only methodically similar, Ozakbas et al. (14) evaluated the effect of methylprednisolone in 30 days, although the research durations were different. Accordingly, T25-FW, one of the MSFC components, was found to be the strongest test to correlate with EDSS scores. These results are also in line with the work of Patzold et al. (17). Unlike our study, the MSFC component, which evaluated the upper extremities, also significantly separated the groups, which included a 20-day treatment period. The weakest aspect of our study is the effect of the drugs used by the patients. These data were not included in the study because the drugs used vary, and they may affect the results negatively. However, none of the study patients received acute-relapse (corticosteroid) treatment during follow-up.

In a study in which EDSS scores differed from our study (≤5.5, 6.0-7.0, and >7.5) and lesion burden and MSFC Z score were compared, the precision of different assessment algorithms was evaluated (18). Basically, it aimed to measure the relative precision of progression in patients grouped according to different lesion burdens. Accordingly, MSFC was found to be more effective in observing an increase in T2-hyperintense lesions than EDSS. As seen in Section 3.2., these results are inconsistent with our study. The burden of Gd+ T1 lesions, especially T2 hyperintense lesion burden, was not significantly associated with MSFC scores, but with 0.5-point changes in EDSS.

In the study, the PASAT 3" was the MSFC component that was significant with both EDSS changes. The PASAT 3," which

Table 3. Changes in MSFC components between year 1 and year 2 according to the stages of progression

	EDSS ≥ 0.5						EDSS ≥ 1.0				
	N	Year 1st Mean (SD)	Year 2nd Mean (SD)	F	p	N	Year 1st Mean (SD)	Year 2nd Mean (SD)	F	p
SDA	96	22.06 (4.54)	21.92 (3.65)	0.138	0.711	108	21.76 (3.65)	21.94 (3.91)	0.248	0.619
DDA	9	22.38 (4.26)	21.73 (3.40)			2	22.90 (4.80)	20.30 (1.27)		
IDA	16	21.52 (2.79)	21.76 (3.45)			11	22.93 (2.58)	24.13 (2.78)		
9 HPT/D										
SDA	96	24.31 (7.70)	23.31 (4.35)	0.002	0 .967	108	23.07 (4.17)	23.45 (4.70)	0.873	0.352
DDA	9	21.85 (3.15)	23.73 (3.54)			2	22.60 (7.91)	19.25 (3.46)		
IDA	16	22.08 (2.85)	21.31 (2.65)			11	23.18 (3.68)	23.57 (5.33)		
9 HPT/ND										
SDA	96	15.55 (3.53)	15.45 (3.35)	2.085	0.151	108	15.59 (3.56)	14.82 (3.70)	10.222	**0.002**
DDA	9	15.24 (2.07)	14.87 (2.69)			2	20.15 (9.12)	12.45 (0.07)		
IDA	16	14.63 (2.10)	17.35 (5.08)			11	15.57 (3.00)	16.08 (3.47)		
Timed 25-Foot walk										
SDA	96	42.87 (10.94)	43.30 (11.10)	1.446	0.232	108	43.92 (10.91)	44.15 (11.00)	0.181	0.671
DDA	9	42.66 (11.88)	43.88 (9.47)			2	37.50 (17.67)	37.50 (17.67)		
IDA	16	45.75 (10.31)	46.56 (9.52)			11	43.45 (8.89)	44.36 (9.23)		
PASAT 3"										
SDA	96	0.036 (0.45)	0.058 (0.44)	0.036	0.849	108	0.085 (0.41)	0.091 (0.43)	3.068	0.082
DDA	9	0.072 (0.42)	0.064 (0.32)			2	-0.157 (1.04)	0.126 (0.69)		
IDA	16	0.173 (0.38)	0.179 (0.29)			11	0.014 (0.37)	0.000 (0.39)		
MSFC Overall										

MSFC: Multiple sclerosis functional composite, EDDS: Expanded disability status, DDA: Decreased disease activity, SD: Standard deviation

measures information processing speed or multiprocessing skills, was found to be compatible with disease progression. This is significant in terms of reviewing classical methods (such as EDSS and GNDS) that are inadequate in assessing cognitive progress. Different studies also support that the PASAT 2" or 3" is important in determining cognitive findings (18,19). In addition, studies have found that different tools such as the Symbol Digit Modalities Test (SDMT), which measures information-processing speed, are more useful than the PASAT in longitudinal evaluations (20-21). Drake et al. (22) conducted disease prediction research with different MSFC components including SDMT and PASAT 3" on 400 patients with MS and 100 controls. Accordingly, the change in the PASAT 3" score between baseline and follow-up was more significant. In addition to their usefulness in understanding disease progression, SDMT and PASAT have limitations, such as the learning effect. Sonder et al. (23) analyzed the reliability of SDMT and PASAT 3" over time. As a result of the test-retest, SDMT was found to be more reliable over time than the PASAT 3," and there was a significant ceiling and learning effect in the PASAT 3." As seen in Figure 2, the EDSS change of 0.5 observed in 2 years in the PASAT 3" appears to be a learning effect. In addition, although the score increase in patients with DDA at 1.0 EDSS change appears to be above the learning effect, it would be useful to control these results with an advanced analysis method.

In line with these results and the literature, 9HPT-D/ND, which evaluates the upper extremities, and MSFC Z score, which evaluates all activities, were not sufficient to predict disease progression. Specifically, PASAT 3" scores were found to be effective in comprehending 0.5-point changes. Cognitive impairment (CI) in MS is insidious and shows only severe losses in routine neurological examinations such as the standardized minimental test (24). Since the evaluation of CI in EDSS scoring is subjective, it may not be detected clinically. For this reason, it would be useful to observe cognitive involvement by expanding assessment tools such as MSFC.

Study Limitations

Comparative evaluations with the current SDMT could not be obtained in the study. This is because not every patient has SDMT scores during this period. Adding studies such as volumetric-based morphometry (VBM) to the study, where we can determine the location of Gd+ T1 and T2 hyperintense lesions rather than the number, will strengthen the research. We could not benefit from these data because we had standardized MR images. In addition, it is possible to add the effect of

Table 4. Changes in MSFC components between baseline and year 2 according to the stages of progression

		EDSS ≥ 0.5						EDSS ≥ 1.0			
	N	Baseline	Year 2	F	p		N	Baseline	Year 2	F	p
		Mean (SD)	Mean (SD)					Mean (SD)	Mean (SD)		
SDA	50	21.37 (4.16)	21.21 (3.44)			**SDA**	91	21.77 (4.17)	21.79 (3.68)		
DDA	22	23.45 (5.91)	23.16 (4.43)	0.004	0.947	**DDA**	7	24.75 (7.08)	22.34 (4.08)	0.522	0.472
IDA	49	22.04 (3.48)	22.56 (3.82)			**IDA**	23	22.16 (3.73)	23.30 (4.32)		
9 HPT/D											
SDA	50	24.63 (9.17)	23.01 (4.87)			**SDA**	91	23.98 (7.37)	23.35 (4.97)		
DDA	22	24.56 (6.47)	24.58 (4.86)	0.269	0.605	**DDA**	7	24.82 (9.35)	23.31 (3.36)	0.242	0.623
IDA	49	22.69 (4.15)	23.25 (4.57)			**IDA**	23	22.96 (4.71)	23.60 (4.32)		
9 HPT/ND											
SDA	50	16.03 (3.70)	14.96 (3.77)			**SDA**	91	15.54 (3.49)	14.66 (3.77)		
DDA	22	14.77 (3.12)	13.77 (2.54)	2.518	0.115	**DDA**	7	15.62 (2.91)	14.77 (2.50)	0.148	0.701
IDA	49	15.04 (2.83)	15.34 (3.93)			**IDA**	23	14.79 (2.49)	15.88 (3.51)		
Timed 25-Foot Walk											
SDA	50	42.52 (11.74)	42.98 (12.05)			**SDA**	91	43.03 (11.12)	43.83 (11.43)		
DDA	22	42.09 (12.88)	44.68 (11.58)	5.849	**0.017**	**DDA**	7	41.57 (13.36)	45.14 (9.82)	4.204	**0.043**
IDA	49	44.48 (8.94)	44.89 (9.32)			**IDA**	**23**	**44.56 (9.41)**	**44.65 (9.16)**		
PASAT 3″											
SDA	50	0.038 (0.48)	0.095 (0.49)			**SDA**	91	0.053 (0.44)	**0.093 (0.45)**		
DDA	22	-0.016 (0.47)	0.047 (0.42)	1.638	0.203	**DDA**	7	-0.063 (0.49)	0.098 (0.37)	1.345	0.248
IDA	49	0.109 (0.37)	0.087 (0.36)			**IDA**	23	0.106 (0.39)	0.040 (0.36)		
MSFC Overall											

MSFC: Multiple sclerosis functional composite, EDDS: Expanded disability status, DDA: Decreased disease activity, SD: Standard deviation

research drugs, but since we did not have drug-free values of the patients, these data would only negatively affect the results.

Conclusion

T25-FW, which evaluates the lower extremities, and PASAT 3″ results, which evaluate the multiprocessing capacity, are thought to indicate disease progression, consistent with EDSS. While the T25-FW is useful in predicting 1.0-point changes in EDSS, the PASAT 3″ can be used as an effective examination method in terms of both 0.5- and 1.0-point changes. These results also suggest that both the PASAT 3″ and T25-FW test may be a possible treatment endpoint or NEDA.

Ethics

Ethics Committee Approval: The research protocol was approved by University of Health Sciences Turkey Hamidiye Scientific Research Ethics Committee (decision number: 22/15, date: 14.01.2021)

Informed Consent: The retrospective data of the patients who did not sign the informed consent form were not evaluated.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.T., Concept: E.A., N.B., S.P., R.T., Design: E.A., R.T., Data Collection or Processing: E.A., N.B., S.P., R.T., Analysis or Interpretation: E.A., Literature Search: E.A., R.T., Writing: E.A.

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