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Utilization of the multiple sclerosis functional composite in follow-up: relationship to disease phenotype, disability and treatment strategies

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Abstract

As multiple sclerosis (MS) has a dynamic process, monitoring of the disability is important in the remission period. The main aim of the present study was to investigate the usefulness of MSFC instead of EDSS in the follow-up period of MS. In addition, evaluation of the effect of immunomodulatory therapy, and the difference among the type of MS in follow-up was purposed. One hundred and eighty-three patients with definite MS were enrolled in the present study. Patients were diagnosed as having relapsing–remitting (RR) MS (n=149) or secondary progressive (SP) MS (n=34). Fifty-eight out of 149 RRMS patients who had at least two relapses in the last 2 years have received any of the immunomodulator agents. The Multiple Sclerosis Functional Composite (MSFC) and Expanded Disability Status Scale (EDSS) were performed at baseline and after 2 years to assess disability. Patients who were under disease modifying therapy were assessed before the treatment and 2 years after starting the treatment. Cross-sectional correlations between MSFC and EDSS score at baseline and follow-up were studied. Patients were divided into three subgroups: (1) RRMS patients who did not receive disease modifying therapy (DMT)—non-DMT group, (2) RRMS patients who received DMT—DMT group, (3) SPMS patients who did not receive DMT—SPMS group. EDSS and MSFC scores got worsened significantly at the end of the second year. Decreases in either EDSS or MSFC scores were more prominent in SPMS group. The most significant worsening was found in T25WT. The most prominent and significant decrease was in PASAT of SPMS group. Moderately strong cross-sectional correlations were found between MSFC and EDSS scores at baseline and follow-up. The most prominent correlation was between EDSS and T25WT scores with an excellent correlation. We concluded that the MSFC assesses aspects of neurological function not measured by the EDSS, suggesting that it is more sensitive to detect change over time and better able to demonstrate a therapeutic effect. The pattern of correlations among the MSFC, its components, and the EDSS supported the validity of MSFC.

Keywords: Multiple sclerosis; Expanded disability status scale; Multiple sclerosis functional composite; Immunomodulation; Follow-up; Remission

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by a relapsing nature and progressive disability. It has a dynamic process, which addresses here the existence of progression even in the remission period of the disease. This situation makes monitoring the disability significantly important in the remission period especially for the treatment strategies. The Expanded Disability Status Scale (EDSS) has been used as a primary outcome measure for neurological impairment and disability in clinical trials of MS [1], despite its well-recognized disadvantages such as being a poor measurement of cognitive and upper limb function, and having a poor reproducibility. The Multiple Sclerosis Functional Composite (MSFC) which includes quantitative tests of leg function (Timed 25-Foot Walk—[T25W]), arm function (9-Hole Peg Test—[9-HPT]), and cognitive function (Paced Auditory Serial Additional Test—[PASAT-3 min version]) has been developed by The Clinical Outcomes Assessment Task Force [2–5]. Previous observations suggest that the MSFC might be more sensitive to change in clinical aspects than the EDSS [2,4,6]. Furthermore, change in MSFC correlated with change in the EDSS [4]. The clinical

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Outcome Task Force reported that MSFC change preceded EDSS change during a 2-year follow-up period [4]. Rudick et al. found that MSFC scores in patients with relapsing–remitting MS (RRMS) predicted the level of disability [7]. The aims of the present study were (1) to investigate the change in MSFC between MS patients who were treated with an immunomodulator and who were not, prospectively, (2) to show the difference between patients with RRMS and secondary progressive MS (SPMS), in follow-up period, (3) to investigate the correlation between EDSS and each of the three tests of MSFC, and (4) to test the usefulness of MSFC instead of EDSS in the follow-up period of MS.

2. Material and methods

2.1. Patients

One hundred and eighty-three patients with definite MS on the basis of McDonald's criteria [8] were enrolled in the present study. Patients were diagnosed as having relapsing–remitting (RR) MS (n=149) or secondary progressive (SP) MS (n=34). Fifty-eight out of 149 RRMS patients who had at least two relapses in the last 2 years have received one of the immunomodulator agents (i.e., interferon beta 1b, interferon beta 1a [subcutaneous form] or glatiramer acetate [GA]). Secondary progressive course was accepted as progression for at least 6 months with or without occasional relapses, minor remissions or plateau after an initial relapsing–remitting disease course. All patients had stable disease course without any relapse for at least previous 3 months. Characteristics of samples were shown in Table 1.

2.2. The EDSS and MSFC

The EDSS is the most widely used instrument for evaluating patients with MS in clinical trials as a primary clinical outcome. The EDSS score is determined both by a physician interview and a neurological examination. It is a 20-step scale, with a best score of 0 (normal neurological examination), and a worst score of 10 (death due to MS); in-between are 0.5-step intervals. The scoring of EDSS was clearly designed to reflect the pattern of worsening of MS. The EDSS scores 1.0 to 4.0 were designed to reflect the Functional Systems (FS), especially the severity on individual FS. From EDSS scores 4.0 to 8.0, the scale was designed to reflect difficulty with ambulation. There are some drawbacks to the EDSS [9]: (1) in the lower range of EDSS, the definitions for the functional systems scales gradations are subjective, (2) in the mid-range of the scale, the EDSS is almost entirely an ambulation instrument, (3) in the upper range, EDSS steps represent such large changes as to be almost useless as a rating scale, (4) at any range of the scale, cognition is poorly assessed, even though cognitive impairments are common in MS patients, (5) in the range, from 4.0 to 6.5 the EDSS is insensitive to arm impairment.

Table 1
Characteristics of patients

Patients (n)	183
Male	41
Female	142
Course of disease (%)	
Relapsing–remitting	81.4
DMT group (Betaferon [n=29], Rebif [n=20] Copaxone [n=9])	31.7
Non-DMT group	49.7
Secondary progressive	18.6
Mean age	38.6±11.97 (18–51)
Mean age at onset	29.87±10.71
Mean duration of disease	6.61±2.76 (2–15)

The MSFC was administered to patients as described in the standardized protocol [10]. The T25WT was administered twice and mean time (in seconds) was used for analysis. The 9-HPT was administered twice for each hand; the mean of these four trials was used. For PASAT, 61 single-digit numbers were named on a tape at a rate of 1 every 3 s. The score was the total correct numbers (out of 60 possible). The score on each assessment was converted to a Z score and the composite score was then computed according to the standardized formula, which was recommended in the 'Administration and Scoring Manual for the Multiple Sclerosis Functional Composite Measure' [11]. The MSFC score is higher when patients have better scores on these components compared to the means, and is lower when patient have worse scores compared to the means of the reference population. The components of MSFC were administered by two trained neurologists. Training procedure included standardized didactic description of the MSFC background and testing protocol, viewing of a training videotape, and an interactive MSFC administration practice session.

The MSFC and EDSS were performed at baseline and after 2 years to assess disability. Patients who were taking disease modifying therapy were assessed before the treatment and 2 years after starting the treatment. The different groups were exposed to the MSFC the same number of times before baseline.

2.3. Analysis

Cross-sectional correlations between MSFC and EDSS score at baseline and follow-up were studied. Longitudinal correlations were studied between changes in MSFC (ΔMSFC) and EDSS (ΔEDSS) as well as between changes in MSFC components and the EDSS subcategories. When analyzing changes in the individual MSFC components we used the change in Z score of T25WT, 9-HPT and PASAT.

Patients were divided into three subgroups: (1) RRMS patients who did not receive disease modifying therapy (DMT)—non-DMT group, (2) RRMS patients who received DMT—DMT group, (3) SPMS patients who did not receive DMT—SPMS group.

2.4. Statistics

We studied the cross-sectional correlations between MSFC and EDSS score at baseline and follow-up and longitudinal correlations between ΔMSFC and ΔEDSS and between ΔMSFC and the ΔEDSS subcategories using the Spearman rank correlation coefficient (r). We considered p values<0.01 as significant and <0.05 as trend only. The strength of correlation was labeled as follows: correlation <0.40 as weak to marginal; 0.40–0.60 as moderate; 0.60–0.80 as good; and >0.80 as excellent.

Changes in the EDSS score of the patients on days 0 and 730 (at the end of the second year) was assessed by Friedman's ANOVA. For analyzing changes on overall MSFC score and its components on days 0 and 730, repeated measurements ANOVA was performed. Changes in the EDSS and MSFC scores and its components in the non-DMT group, DMT group and SPMS group on days 0 and 730 were also analyzed.

3. Results

There were no significant differences between non-DMT and DMT groups on the basis of EDSS, MSFC and MSFC components, at the entry. Scores on MSFC, MSFC components and EDSS at baseline and follow-up were summarized in Table 2 for the DMT, non-DMT and SPMS groups. EDSS and MSFC scores worsened significantly at the end of the second year. Worsening in either EDSS or MSFC scores was more prominent in SPMS group then DMT group. When analyzing the components of MSFC, the most prominent and significant decrease was in PASAT of SPMS group. DMT group did not show any difference on EDSS, overall MSFC and 9-HPT; deteriorations in T25WT and PASAT were not significant but trend only in DMT group.

Moderately strong cross-sectional correlations were found between MSFC and EDSS scores at baseline (r=−0.765, p<0.001) and follow-up (r=−0.73, p<0.001). The most prominent correlation was between EDSS and T25WT with an excellent correlation (r=0.804, p<0.001). The 9-HPT moderately correlated with the EDSS (r=0.56). Correlation between PASAT and EDSS was found very weak (r=−0.24). The correlations between MSFC and 9-HPT, MSFC and T25WT, and MSFC and PASAT were moderate (r=0.49, r=−0.56, and r=−0.50, respectively).

Correlation between change over time in MSFC (ΔMSFC) and EDSS (ΔEDSS) score, however, was weaker (r=−0.64 to −0.43, p<0.001 to 0.01). When analyzing the correlation between change over time in the EDSS and the MSFC components, change in the T25WT was the one most correlated with the EDSS (r=0.81). Change in the 9-HPT was correlated with change in the EDSS, as well (r=0.45). There was no correlation between the changes in the EDSS and the PASAT. There was not any correlation (even trend)

Table 2
Scores on MSFC, MSFC components and EDSS at baseline and follow-up for the DMT, non-DMT and SPMS groups (P_1—statistical significance between non-DMT and DMT groups, P_2—statistical significance between non-DMT and SPMS groups)

	Non-DMT	DMT	P_1	SPMS	P_2
	n=58 (Mean±SD)	N=91 (Mean±SD)		n=34 (Mean±SD)	
Mean attack rate (biennial)					
Day 0	0.76±1.04	2.27±1.54	0.003	0.14±1.10	0.007
Day 730	0.64±0.99	0.71±1.40	>0.05	0.08±0.78	0.002
P	>0.05	**0.0002**		>0.05	
EDSS					
Day 0	2.64±1.26	2.49±1.87	>0.05	4.16±2.21	0.001
Day 730	3.42±1.56	2.60±2.08	0.003	4.99±2.08	0.004
P	**0.003**	>0.05		**0.002**	
MSFC					
Day 0	1.47±0.67	1.33±1.01	>0.05	1.19±1.29	0.003
Day 730	1.06±0.56	1.19±0.98	0.006	0.59±1.44	0.004
P	**0.006**	**0.018**		**0.003**	
9-HPT (s)					
Day 0	21.10±3.40	21.71±5.01	>0.05	24.34±4.32	0.003
Day 730	23.91±4.81	22.63±4.66	0.005	26.68±6.18	0.003
P	**0.004**	**0.009**		**0.005**	
T25WT (s)					
Day 0	6.11±3.00	5.94±2.61	>0.05	7.01±4.70	0.019
Day 730	7.94±2.86	6.76±3.15	0.004	8.67±4.18	0.012
P	**0.002**	**0.040**		**0.006**	
PASAT					
Day 0	40.72±13.69	41.20±14.55	>0.05	37.13±17.49	0.004
Day 730	38.26±15.04	39.42±12.14	0.023	33.04±16.10	0.0002
P	**0.001**	**0.031**		**0.0003**	

SD—standard deviation.

between ΔMSFC and Δvisual, Δbrainstem and Δmental functional systems ($p>0.05$).

As expected, the mean attack rate for SPMS group was the lowest. The DMT group had the highest attack rate at the beginning of the study. The rate declined on day 730 after 2 years disease modifying therapy (Table 2).

4. Discussion

The MSFC, which has been introduced as a sensitive, valid and reliable new outcome measure in patients with MS [4,5,11–13] reflects major clinical manifestations of MS including hand (arm) and cognitive functions. It is now absolutely known that these are the main drawbacks to the EDSS [9]. Previous studies have shown that the MSFC correlated with the EDSS [4,7,13], which has been the most widely used measure of the neurological disability in MS clinical trials. It was also demonstrated that MSFC was more sensitive in detecting therapeutic effect [6]. In our previous study, we showed significant correlations between the EDSS, the MSFC and Multiple Sclerosis Quality of Life (MSQoL)—54 measures [14], in the exacerbation period, indicated that the EDSS and MSFC reflected the severity of MS as perceived by patients [6]. Both EDSS and MSFC scores reflected physical health status more than mental health. This finding was more prominent for MSFC [6]. The novel result in that study was the significant correlation between the changes in MSFC scores and MSQoL-54 on day 30 compared with day 0 [6]. These results were supported by the present study, which demonstrated the moderate correlation between EDSS and MSFC. This might be concluded as a support of the convergent validity (the correlation with another measure of neurological disability) and divergent validity (measurement of aspects of MS not covered by the EDSS) of the MSFC. The correlations among the MSFC, its components and the EDSS were not similar to those previously reported [4,15]. Cohen et al. found the correlations among the three components of the MSFC modest. They concluded that the T25WT, 9-HPT and PASAT3 clearly measure independent clinical dimensions [15]. Although this is a very attractive conclusion, our results revealed a moderate correlation, as we found in the previous study [6].

It was not surprising that among the components of MSFC, the T25WT correlated best with the EDSS. It was also demonstrated in the Cohen's study [15]. It might be concluded that walking speed and distance were related.

As expected, the EDSS deteriorated significantly in non-DMT group at the end of the second year, when compared to the baseline. The DMT group did not show any statistically significant change in EDSS, in the same period. But there was remarkable difference in the MSFC, which had a trend to be deteriorated after 2 years follow-up. The present results demonstrated that MSFC might be more sensitive in detecting changes in function than the EDSS. These results may also support the concept which suggests the use of early immunomodulatory therapy in MS.

Secondary Progressive MS group had a significant decline in functions scored by EDSS and MSFC. Another interesting result in the SPMS group was the change in PASAT. Decline in PASAT was most marked in SPMS group. Moreover, decline in PASAT appeared to be more prominent in SPMS group than non-DMT (RRMS) group. Our data might suggest a prominent difference between SPMS and RRMS regarding changes in cognitive decline. Although we have not collected these data, it would have been interesting if we had included more extensive cognitive tests, in our analyses. It must be kept in mind that PASAT is the most common test, which has been used for screening cognitive function in brief office visits.

In conclusion, our results indicated that the MSFC includes aspects of neurological function not well measured by the EDSS, such as cognitive function, suggesting that it is more sensitive to detect change over time and better able to demonstrate a therapeutic effect. The pattern of correlations among the MSFC, its components, and the EDSS supported the validity of MSFC.

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