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Correlations between multiple sclerosis functional composite, expanded disability status scale and health-related quality of life during and after treatment of relapses in patients with multiple sclerosis

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Abstract

The measurement of the clinical manifestations of multiple sclerosis (MS) is difficult. In the present study, we examined the changes in measurement of functions during and after pulse methylprednisolon (MP) treatment of MS exacerbations using the MSFC and EDSS. Correlation between multiple sclerosis quality of life (MSQoL)-54, EDSS and MSFC were studied. Thirty-six clinically definite MS patients were included in this study. Because of MSFC's repeating feature, we administered the tests to a control group to exclude practise effects. All patients received 1000-mg intravenous MP for 5 days, followed by tappering dose of 100-mg oral prednisolone. All three scales were assessed on day 0. EDSS and two components of MSFC (nine HPT and T25WT) were administered on the other days of pulse MP treatment. PASAT was not applied before the day 5 to exclude the practise effect. MSQoL-54 was assessed again on day 30. Mean EDSS values significantly decreased after the day 2. MSFC score improved from 0.03 ± 1.71 on day 0 to 0.79 ± 1.51 on day 5. Improvement continued on day 30. The mean physical health composite score increased from 66.50 ± 9.3 on day 0 to 74.34 ± 8.9 on day 30. Mental health composite had also a significant improvement on day 30. Correlation between the baseline overall MSFC and the EDSS was moderately strong. T25WT correlated most strongly with EDSS. Significant positive correlation was found between MSFC and both components of MSQoL-54. It is more prominent for the MSFC and physical health composite correlation. The same correlation was found for the EDSS and MSQoL-54 composites. Changes in EDSS and MSFC scores and MSQoL-54 were found significantly correlated for the overall score on day 30 compared with day 0. In conclusion, MSFC seems to be more sensitive in detecting changes in function than the EDSS. Hence, EDSS is still useful for daily routine practise. When these results combined with the significant correlation between MSFC and MSQoL-54 measures, which indicated the MSFC reflects the severity of MS as perceived by patients, MSFC seems to be the most useful scale for clinical trials.

Keywords: Multiple sclerosis; Functional composite; EDSS; Health-related quality of life; MSQoL-54; Relapse; Treatment

1. Introduction

Multiple sclerosis (MS) is a clinically heterogeneous neurological disease. Not only because of its heterogeneity but also fluctuating nature and diversity of its symptoms, the measurement of the clinical manifestations of MS is difficult. Traditionally, the Expanded Disability Status Scale (EDSS) [1] has been used as a primary outcome measure for neurological impairment and disability in clinical trials of MS, despite its well-recognized disadvantages such as a poor cognitive decline and upper limb function, and a poor reproducibility. In 1994, MS Functional Composite (MSFC) was developed by The Clinical Outcomes Assessment Task Force in an international workshop entitled 'Outcomes Assessment in Multiple Sclerosis Clinical Trials', which was sponsored by the US National Multiple Sclerosis Society [2–5]. The MSFC 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 sec version).

It is generally accepted that health-related quality of life (HRQoL) data are not correlated with the measures of disease severity [6]. However, it has been demonstrated that there was a significant correlation between clinical and HRQoL data [7,8]. In a cross-section study determining clinical significance of MSFC by analyzing its relationship with a HRQoL measurement, Miller et al. [15] found a

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strong correlation between MSFC scores and self-reported quality of life.

In a very recent study, Patzold et al. [9] examined the measurement changes in function during and after treatment of acute relapses in MS patients using MSFC and EDSS. They found that correlation between EDSS and MSFC scores had not been statistically significant, and they concluded, as the underlying reason, that both measures contained different information. Another conclusion of their study was that MSFC seemed to be more sensitive than EDSS in identifying changes in functions during treatment of acute exacerbation. Our experiences about detecting the differences of functions during and after pulse steroid treatment on the base of EDSS and MSFC have not been parallel with the results of Patzold et al. In the present study, we examined the changes in measurement of functions during (everyday) and after pulse methylprednisolon (MP) treatment of MS exacerbations using the MSFC and EDSS. Correlation between EDSS and every three tests of MSFC, and correlation between multiple sclerosis quality of life-54 (MSQoL-54) of Vickrey, EDSS, and MSFC were studied.

2. Materials and methods

2.1. Patients and controls

Thirty-six patients (28 were female and 8 were male) were included in this study. All were clinically definite on the base of Poser's criteria [10]. Patients were diagnosed as relapsing-remitting (RR) ($n=30$) or secondary progressive (SP) ($n=6$) MS. Because of MSFC's repeating feature, we administered the tests to a control group to exclude practise effects. Control group consisted of 17 patients (12 were female and 5 were male) with a clinically definite MS. They all had stable disease course (in remission period) for at least previous 6 months. All patients were in an objective acute exacerbation, which was defined as the appearance of new symptom(s) or worsening of existing symptom(s). Symptom(s) should have lasted at least 48 h. Patients who had infectious diseases causing fever and patients (or controls) who had an experience with any tests of MSFC were excluded. Patients were also excluded if they had optic neuritis as a current attack, and patients (and controls) who were not able to perform any part of MSFC were excluded. Demographic and clinical features are summarized in Table 1.

All patients received 1000-mg intravenous (i.v.) MP for 5 days, followed by tappering dose of 100-mg oral prednisolone for 25 days. The MSFC, EDSS and MSQoL-54 were assessed during the period of 30 days. All three scales were assessed on day 0, before the first administration of corticosteroid. EDSS and two components of MSFC (nine HPT and T25WT) were administered on the other days of pulse MP treatment. PASAT, as a cognitive test, was not applied before the day 5 to exclude the practise effect. MSQoL-54 was assessed again on day 30, after corticosteroid treatment was finished. Applying days of scales were shown in Table 2.

Table 1
Demographic features of patients and controls

	Patients	Controls
N	36	17
Males	8	5
Females	28	12
MS category	clinically definite MS	clinically definite MS
Disease course *n* (%)		
Relapsing-remitting (RR)	30 (83.3)	14 (82.3)
Secondary progressive (SP)	6 (16.7)	3 (17.7)
Mean age, years (± S.D.)	30.41 ± 7.83	29.82 ± 6.65
Mean duration of MS, years (± S.D.)	5.87 ± 2.98	6.05 ± 3.12
Time to treatment from relapse onset, days (± S.D.)	9.14 ± 4.45	

Assessment of EDSS and administration of three components of MSFC and MSQoL-54 were at the same time of the day, i.e. at 5 and 6 p.m. in the afternoon. Same test protocol was used for control group.

2.2. The MSFC and MSQoL-54

The MSFC was administered to patients using a standardized protocol [5]: (1) T25WT (trials 1 and 2), (2) 9HPT (trials 1 and 2 for dominant hand, and trials 1 and 2 for nondominant), (3) PASAT3 (3-s interstimulus interval). The MSFC is based on the concept that scores for these three dimensions are combined to create a single score that can be used to detect the change over time in a group of MS patients. This was done by creating *z*-scores for each component of MSFC, and averaging them to create an overall composite score. MSFC *z*-scores were calculated as recommended in the 'Administration and Scoring Manual for the Multiple Sclerosis Functional Composite Measure' [11] using standardized formula:

$$\begin{aligned}\text{MSFC Score} = \{&(\text{Average}(1/9\text{HPT}) \\ &- \text{Baseline Mean}(1/9\text{HPT}) \\ &/\text{Baseline Standard Deviation(S.D.)} \\ &\times (1/9\text{HPT}) - (\text{Average T25WT} \\ &- \text{Baseline Mean T25WT}) \\ &/\text{Baseline S.D. T25WT} \\ &+ (\text{PASAT3} - \text{Baseline Mean PASAT3}) \\ &/\text{Baseline S.D. PASAT3}/3.0\end{aligned}$$

The number of correct sums given in the PASAT3 (out of 60 possible), the mean time of 2 T25WT and mean time across four 9HPT trials (in seconds) (2 with the dominant hand and 2 with the nondominant hand) were used for analysis. The components of MSFC were administered by

Table 2
Applying days of EDSS, MSFC, subtests of MSFC and MSQoL-54

Days	0	1	2	3	4	5	30
Scales							
EDSS	+	+	+	+	+	+	+
PASAT	+					+	+
9 HPT	+	+	+	+	+	+	+
25 TWT	+	+	+	+	+	+	+
MSFC	+					+	+
MSQoL-54	+						+

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 practise session.

The MSQoL-54 developed by Vickrey et al. [7] consists of 54 items. Eighteen MS-related specific questions were added to the original Medical Outcome Study 36-Item Short Form Health Survey (SF-36) [12]. SF-36 consists of 36 items divided into 8 scales: physical functioning (10 items), role-physical functioning (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional functioning (3 items) and mental health (5 items). Vickrey et al. added 18 items on the original SF-36 which address: health distress (4 items), sexual function (4 items), satisfaction with sexual function (1 item), overall quality of life (2 items), cognitive function (4 items), energy (1 item), pain (1 item) and social function (1 item). The MSQOL-54 instrument contains 52 items distributed into 12 scales and 2 single items. The patients and controls were interviewed in the neurologist's office. They were given a brief explanation of the objective of the study and were asked to complete the scale after reading the instruction.

In summary, the same physician, at each study site, administered the MSFC (or MSQoL54) to a given patient at each study visit. All examining technicians were trained neurologists, and each neurologist was blinded to the other results of tests or questionnaire. The physician assessing EDSS score of patients was blinded to control results and vice versa.

2.3. Statistics

Changes in the EDSS score of the treated patients and control group on days 0, 1, 2, 3, 4, 5 and 30 and changes in MSQoL-54 score were assessed by Friedman's ANOVA. For analyzing changes on overall MSFC score on days 0, 5, 30 and its components on days 0, 1, 2, 3, 4, 5 and 30 repeated measurements ANOVA was performed. Spearman rank correlations were constructed to assess correlations between EDSS, MSFC and its component, and MSQoL54.

3. Results

Thirty-one of 36 treated patients reported improvement on day 5 and all patients have subjective improvement on day 30. The mean EDSS value, overall MSFC and components of MSFC scores, and values of MSQoL-54 were shown in Table 3.

Mean EDSS was 4.72 ± 2.34 on day 0. EDSS values significantly decreased after the day 2 ($p < 0.05$). All patients, except two, had an improvement with a decrease at least 0.5 points on days 5 and 30. Those two patients had secondary progressive course. So, all 30 patients (100%) with relapsing-remitting course and 4 (66%) with secondary progressive course had a significant improvement on day 5 which pulse MP treatment had been finished. There was a statistically significant difference between these two groups of disease course, regarding to response to the treatment, on the base of EDSS ($p < 0.01$). So, SPMS patients had a worse outcome than RRMS patients.

MSFC score improved from 0.03 ± 1.71 on day 0 to 0.79 ± 1.51 on day 5 after the pulse MP treatment was completed. Change in MSFC score was statistically significant ($p = 0.005$). Improvement continued on day 30: MSFC score was 0.95 ± 1.52 ($p = 0.002$). Detailed list of MSFC components is shown in Table 3. All 31 patients reported improvement on day 5 had also a significantly better MSFC score. The two patients, who did not have an improvement on EDSS, did not have a better MSFC score either. The other four patients had no change in MSFC score. Mean 9HPT time was decreased from 25.70 ± 3.70 on day 0 to 24.28 ± 2.84 on day 1 ($p < 0.01$) and 22.46 ± 3.09 on day 5 ($p < 0.001$). Hence, statistically significant improvement of 9HPT was observed on day 1. Mean T25WT score was improved from 6.50 ± 1.53 on day 0 to 5.61 ± 1.00 on day 1 ($p < 0.01$) and 5.43 ± 0.95 on day 5 ($p < 0.001$). Mean numbers of correct responses in PASAT were 34.22 ± 12.68

Table 3
Results for EDSS, overall MSFC, MSFC components and MSQoL-54 of 36 treated patients between pre-treatment period and 30 days after treatment

Days	EDSS	9HPT	T25WT	PASAT	MSFC	MSQoL-54 composites	
						Physical	Mental
Day 0	4.72 ± 2.34	25.70 ± 3.70	6.50 ± 1.53	34.22 ± 12.68	0.03 ± 1.71	66.50 ± 9.3	67.44 ± 11.6
Day 1	4.55 ± 2.09	24.28 ± 2.84	5.61 ± 1.00				
Day 2	4.11 ± 3.01	24.50 ± 4.26	5.50 ± 0.96				
Day 3	3.72 ± 2.56	22.95 ± 2.75	6.64 ± 1.04				
Day 4	3.27 ± 2.77	22.85 ± 3.39	5.44 ± 0.77				
Day 5	3.11 ± 2.32	22.46 ± 3.09	5.43 ± 0.95	36.16 ± 14.17	0.79 ± 1.51		
Day 30	2.94 ± 3.01	22.20 ± 3.21	5.40 ± 1.12	36.98 ± 10.08	0.95 ± 1.52	74.34 ± 8.9	78.04 ± 10.93

on day 0. It was improved to 36.16 ± 14.17 on day 5 ($p < 0.05$). PASAT score remain unchanged on day 30. 9HPT, T25WT and overall MSFC score improved on day 30, just as EDSS score.

For patients in this study, the mean physical health composite score increased from 66.50 ± 9.3 on day 0 to 74.34 ± 8.9 on day 30. This improvement was statistically significant ($p < 0.05$). Mental health composite had also a significant improvement from 67.44 ± 11.6 on day 0 to 78.04 ± 10.93 on day 30 ($p < 0.05$).

3.1. MSFC-EDSS, MSFC-MSQoL-54 and EDSS-MSQoL-54 correlations

Correlation between the baseline overall MSFC and the EDSS was moderately strong ($r = -0.61$). As EDSS scores increased, progressive decrease was found in the MSFC scores, indicating poorer performance on the functional measures within MSFC. The three components of MSFC correlated with the overall MSFC. As expected, T25WT correlated most strongly with EDSS ($r = 0.84$). The 9HPT moderately correlated with the EDSS ($r = 0.51$). Correlation between PASAT and EDSS was found very weak ($r = -0.31$). Changes in EDSS and MSFC scores were found significantly correlated for the overall score on day 30 ($r = -0.54$) compared with day 0. Correlation was again at the utmost with T25WT ($r = 0.77$). Change in the 9HPT was correlated with change in the EDSS, as well ($r = 0.47$). There was no correlation between the changes in the EDSS and the PASAT ($r = -0.11$).

Significant positive correlation was found between MSFC and both components of MSQoL-54. It is more prominent for the MSFC and physical health composite correlation ($r = 0.67$). The Spearman correlation coefficient (0.53) indicated a moderate correlation between the MSFC and the mental health composite of the MSQoL-54. The same correlation was found for the EDSS and MSQoL-54 composites ($r = -0.69$ and $r = -0.49$, respectively). Changes in EDSS and MSFC scores and MSQoL-54 were found significantly correlated for the overall score on day 30 compared with day 0. *r*-values were 0.61 for changes in MSFC-physical health composite and 0.48 for mental health composite. Changes in EDSS and composites of MSQoL-54 was also significant ($r = -0.51$ and $r = -0.39$, respectively).

3.2. Control group

In this group, the mean EDSS score (3.1 ± 1.2) remained unchanged during all seven trials (3.2 ± 0.9 on day 30 and no statistically significant difference). The mean MSFC score at baseline was 0.99 ± 1.02. It was 0.98 ± 0.96 on day 5 and 1.02 ± 1.11 on day 30. There was no significant difference between the MSFC scores on days 0, 5 and 30. Physical and mental health composites of MSQoL-54 scores were 76.56 ± 10.89 and 75.43 ± 13.07, respectively. Physical health composite score was measured 75.98 ± 11.1 and mental health composite was 73.99 ± 8.76 on day 30. The differences between MSQoL-54 scores on days 0 and 30 were not statistically significant.

4. Discussion

Because of its marked heterogeneity, quantitative assessment of impairment is difficult in patients with MS. The EDSS has been the most widely used clinical outcome measure in therapeutic trials of MS, but three main limitations have been well identified, e.g. poor assessment of cognition and upper limb, and poor reproducibility. The MSFC was proposed as a new outcome measure for MS clinical trials [4,5,13,14]. The present study is the second one detecting the changes in EDSS and MSFC during and after pulse MP treatment. Patzold et al. [9], in their study, examined the possibility to measure the changes in function during and after treatment of relapses in 27 patients with MS using the MSFC and EDSS. They assessed the EDSS and MSFC on day 0 (before treatment),—not the other days but—on day 5 (after the last course of i.v. MP) and on day 20 (after the last dose of oral prednizolon). One of the main differences of our study is the frequency of tests: EDSS and two components of MSFC (nine HPT and T25WT) were administered on days 0 (before treatment), 1, 2, 3, 4, 5 (after the last course of i.v. MP) and 30 (after the last dose of oral prednizolon). This design was taught to be good for detecting the first day of effect of MP not only by EDSS but also by MSFC. The other difference in study design was adding HRQoL assessment. HRQoL refers to an individual's assessment of how a health problem and its treatment affect patients' ability to perform activities and roles that he/she values. In MS, as a disease not affecting mortality but produce morbidity, one important goal of treatment should be to reduce impact of the disease on patients' lives. Such patient-derived data are gaining increasing acceptance as an important assessment domain. MSQoL-54, as one of these HRQoL instruments, was used in our study.

Both EDSS and MSFC was found useful to show the effect of MP on the treatment of acute relapse of MS. The differences between the scores measured before and during the treatment of MS attack with pulse MP were statistically significant not only for the overall MSFC and its three components but also for EDSS. This result was the main difference of our study from Patzold's [9]. In their study, EDSS had no effect to show how MP affects MS attack. They found that the mean EDSS scores were not different on the day treatment had been finished from the baseline. It is very interesting and needed explanation. The reason may be the time from relapse onset to treatment. Time to treatment in their group was prominently late than ours (19.29 ± 22.28 and 9.14 ± 4.45, respectively). The other important difference in the feature of groups was mean EDSS score in the baseline

visit. Mean EDSS value was significantly higher in our study than Patzold's group. This difference might affect the results of the effect of MP on EDSS. Regarding the MSFC and its components, our results seem to be parallel. It is found a significant correlation between EDSS and MSFC in our study. The correlation remained unchanged on the base of changes in the EDSS and in the MSFC scores. But, as expected, possibly because of no change in EDSS during the treatment period, Patzold et al. [9] could not find any correlation between changes in the EDSS and MSFC. The weakest correlation was shown between EDSS and PASAT. These results may confirm the knowledge of poor assessment of cognitive decline of EDSS. Similarly, EDSS and 9HPT were moderately correlated. This may be the cause of known disadvantage of EDSS in the assessment of upper limb function.

Significant correlations between the EDSS, the MSFC and MSQoL-54 measures indicate that not only EDSS but also MSFC reflect the severity of MS as perceived by patients. Both EDSS and MSFC scores reflect physical health status more than mental health. This finding is more prominent for MSFC. Similar results were found in previous studies [15]. Miller et al. [15], in their study, found a significant correlation between MSFC scores and MSQoL measure. The results are correlated with our study. The novel result in our study is the significant correlation between the changes in MSFC scores and MSQoL-54 on day 30 compared with day 0.

Are improvements in MSFC score or changes in MSQoL-54 measures because of practise effect? All measurements were done for control group and systematic trend suggesting practise effect could not be observed.

In conclusion, because of statistically significant correlation between EDSS and MSFC, and well-recognized disadvantages such as a poor reproducibility and a poor assessment upper limb function and cognitive state of EDSS, MSFC might be used for detecting any treatment effect instead of EDSS. MSFC seems to be more sensitive in detecting changes in function than the EDSS. On the other hand, EDSS seems to be—not as much as MSFC—sensitive in identifying changes in functions, and MSFC is a time-spending process. Hence, EDSS is still useful for daily routine practise. But the results of our study and suggestion of Cutter et al. that patients who show MSFC worsening are at significantly higher risk of EDSS worsening in the next year [3] indicate that MSFC is better for clinical trial than EDSS. When these results combined with the significant correlation between MSFC and MSQoL-54 measures, which indicated the MSFC reflects the severity of MS as perceived by patients, MSFC seems to be the most useful scale for clinical trials.

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