A Study Validating Changes in the Multiple Sclerosis Functional Composite

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Objective: To prospectively characterize the relation between 1-year changes in neurologist ratings of abnormalities as measured by means of the Expanded Disability Status Scale (EDSS) and changes in observations of functional impairment as measured by means of the Multiple Sclerosis Functional Composite (MSFC) in the clinical assessment of multiple sclerosis (MS).

Methods: One hundred twenty patients with MS were recruited at our outpatient clinic. Impairment and disability at baseline and follow-up were assessed using the EDSS and MSFC. We studied correlations between change (Δ) in the EDSS, MSFC, and MSFC components for the total population and different subgroups and analyzed the contribution of change in MSFC components to change in the EDSS and MSFC.

Results: Median EDSS score at baseline was 4.5; at follow-up, 5.0. Mean MSFC score at baseline was −0.00; at follow-up, −0.04. Good cross-sectional correlations were found between the EDSS and MSFC at baseline (−0.72) and follow-up (−0.73). Only weak correlations were found between ΔEDSS and ΔMSFC. Although ΔEDSS showed the strongest correlations with change in leg function and weak or no correlation with change in cognitive function or arm function, ΔMSFC showed the highest correlation with change in arm function and cognitive function.

Conclusion: Our longitudinal data indicate that the MSFC reflects change from different dimensions of neurologic functions, which is a favorable characteristic when compared with the EDSS.

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Neurologic impairment and disability in patients with multiple sclerosis (MS) can be measured in several ways. The often-used primary outcome measure in clinical trials is the Expanded Disability Status Scale (EDSS). The EDSS ranges from 0 (normal) to 10 (death due to MS), based on results of a neurologic examination of 8 functional systems (visual, brainstem, sensory, cerebellar, sphincter, cerebral, and others) and the ability of patients to walk. The EDSS, however, fails to fulfill requirements for a reliable outcome measure. The major problems are related to standardization, resulting in suboptimal interrater reliability, marginal sensitivity to change, and bias toward locomotor function. Some of these problems are related to the fact that the EDSS is an ordinal scale.

The Multiple Sclerosis Functional Composite (MSFC) was introduced recently as an alternative to the available MS clinical rating scales. The MSFC is a clinical outcome measure that includes quantitative tests of arm and hand function (9-hole peg test [9-HPT]), cognitive function (3-second version of the Paced Auditory Serial Addition Test [PASAT]), and leg function and ambulation (7.62-m Timed Walk Test [TWT]). At development, quantitative tests were assumed to be more sensitive to change over time than traditional ordinal measures.

Previous studies from our center performed cross-sectional comparisons between the EDSS and MSFC. In these studies, good correlations were shown between the scales, mainly because of the importance of spinal cord–related neurologic functions, and the construct validity of the MSFC was confirmed and extended in different subgroups of MS.

To our knowledge, only 2 studies have reported data on longitudinal measurements of the MSFC. Cutter et al showed correlations between changes in the MSFC and EDSS, and Fisher et al showed correlations between changes in the MSFC and brain parenchymal fraction.

The aim of the current study was to prospectively characterize the relation between 1-year change in neurologist rating...
PATIENTS AND METHODS

PATIENTS

One hundred twenty patients with MS were recruited at our outpatient clinic to undergo longitudinal examinations using the EDSS and MSFC. Diagnoses included relapsing-remitting (n = 40), secondary progressive (n = 37), and primary progressive (n = 43) MS. The group was also stratified by disability strata, on the basis of whether the EDSS score was mainly derived from the underlying functional systems or from ambulatory function, as mildly disabled (baseline EDSS score, ≤ 4.0 [n = 37]) and more disabled (baseline EDSS score, > 4.0 [n = 63]).

TEST PROCEDURES

Patients underwent EDSS and MSFC examinations at baseline and after 1 year to assess impairment and disability. Data from the EDSS and MSFC were collected in the same visit under carefully standardized conditions by well-trained physicians (including E.L.J.H. and N.F.K.), as described previously. Full assessment of both tests required 30 to 40 minutes (15-20 minutes for the EDSS and 15-20 minutes for the MSFC). Inability to perform a test of the MSFC because of MS-related symptoms was scored with the maximum time allowed for the 9-HPT (300 seconds) and TWT (180 seconds) and with the worst possible score for the PASAT (0). If patients refused to participate in a test, results were scored as missing.

ANALYSIS

To calculate the MSFC score, z scores were created for the 9-HPT, PASAT, and TWT. These z scores were obtained using means and SDs of an external reference population consisting of a wide range of patients with MS. The composite score was calculated by adding the z scores and dividing the sum by 3, as seen in the following equation:

MSFC = \left( \frac{Z_{9\text{-HPT}}\text{average}}{3} \right) - \frac{Z_{\text{TWT}} + Z_{\text{PASAT}}}{3}

The MSFC score becomes higher when patients have better scores and lower when patients have worse scores on the MSFC components compared with the reference population.

Results were analyzed in several ways. We studied cross-sectional correlations between baseline EDSS and MSFC scores and between follow-up EDSS and MSFC scores, and longitudinal correlations among ΔEDSS, ΔMSFC, and changes in MSFC components (Δ9-HPT, ΔPASAT, and ΔTWT) for the total population and for the different disability strata and subtypes of MS. For change in MSFC components, we used the relative change in actual measurements of 9-HPT, PASAT, and TWT.

Since this analysis incorrectly assumes that the EDSS is a continuous variable, we also studied the total number of patients showing significant change on the EDSS by quartile of change on the MSFC. A significant change on the EDSS was defined as a change of 1.0 point or more at EDSS levels of less than 5.5, or a change of 0.5 point or more at EDSS levels of at least 5.5. Quartiles of change were defined by the amount of change in the MSFC.

STATISTICS

Cross-sectional correlations between EDSS and MSFC scores at baseline and follow-up and correlations between ΔEDSS, ΔMSFC, and ΔMSFC components were calculated using the Spearman rank correlation coefficient (r). We considered P values of less than .01 as significant and P values of less than .05 as a trend only. We analyzed the contribution of Δ9-HPT, ΔPASAT, and ΔTWT for ΔEDSS and ΔMSFC in the total population by using a stepwise multiple linear regression method (P to enter .05), with ΔEDSS or ΔMSFC as the dependent variable and the changes in the MSFC components as predictors.

Patient characteristics and scores on the EDSS and MSFC at baseline and follow-up are summarized in Table 1 for the total population, different MS subtypes, and disability strata. Mean age at baseline was 47.1 years (SD, 12.1 years); 37% of the patients were male and 63% were female. Average time from baseline to follow-up measurement was 1.1 years (SD, 0.2 year). Data were incomplete for 5 patients who refused to undergo the PASAT and 2 patients who refused to undergo the TWT.

The EDSS showed a bimodal distribution in the total population, with EDSS baseline peak scores of 4.0 and 6.5 and follow-up peak scores of 4.0 and 6.0. Median EDSS score at baseline was 4.5; at follow-up, 5.0. Mean MSFC score at baseline was −0.00; at follow-up, −0.04.

Cross-sectional correlations between EDSS and MSFC scores at baseline (r = −0.72, P < .01) and follow-up (r = −0.73, P < .01) were strong. Correlations were also found between ΔEDSS and ΔMSFC for the total population and for the more disabled patients; these correlations, however, were weak and not statistically significant (Table 2).

The Figure shows the number of patients with a significant ΔEDSS by quartile of ΔMSFC. The first quartile of ΔMSFC contains patients in whom the MSFC score worsened most in 1 year (ΔMSFC, ≤ −0.16); the second quartile, ΔMSFC from greater than −0.16 to −0.014; the third quartile, ΔMSFC from greater than −0.014 to 0.14; and the fourth quartile, ΔMSFC improved most in 1 year (MSFC score increased > 0.14). In total, 30 patients...
showed a significant worsening and 19 patients a significant improvement in EDSS score.

Table 2 shows correlations of ΔEDSS with ΔMSFC, Δ9-HPT, ΔPASAT, and ΔTWT for the total population, different MS subtypes, and disability strata. No significant correlation was found between ΔEDSS and ΔPASAT, and only a trend was found between ΔEDSS and Δ9-HPT. Moderate correlations were found between ΔEDSS and ΔTWT for the total population (r = -0.39), the different disability strata (mild, r = -0.19; more disability, r = -0.48), relapsing-remitting subtype (r = -0.35), and primary progressive subtype (r = -0.44).

Table 3 shows the correlations of ΔMSFC with its components for the total population and different subgroups. Correlations were strong with Δ9-HPT in the total population (r = 0.65), both disability strata (mild, r = 0.71; more disability, r = 0.62), relapsing-remitting subtype (r = 0.74), and secondary progressive subtype (r = 0.65). Significant correlations of ΔPASAT with ΔMSFC were seen in all subpopulations. For the TWT only, significant correlations were found for both progressive MS subtypes and more disabled patients. No significant correlations were found in mildly disabled patients or the relapsing-remitting MS subtype.

Stepwise multiple linear regression analysis using ΔEDSS as the dependent variable and Δ9-HPT, ΔPASAT, and ΔTWT as independent variables showed no valuable contribution for predicting ΔEDSS (data not shown).

When using ΔMSFC as the dependent variable, ΔPASAT disclosed the most valuable predictor for ΔMSFC (adjusted R² = 0.13); when Δ9-HPT was also included, the adjusted R² was 0.23. No valuable contribution of ΔTWT was seen for predicting the ΔMSFC.

To our knowledge, only one other study has reported on the relation between ΔMSFC and ΔEDSS scores. That study was retrospective and based on compiled data sets.
Our prospective study demonstrates the concurrent validity of 1-year ΔMSFC by comparing it with ΔEDSS. In addition, we tried to understand the background of the ΔMSFC and ΔEDSS by relating them to changes in the actual measurements of cognition, arm function, and leg function that form the basis of the MSFC.

Analysis of the number of patients showing a significant ΔEDSS by quartiles of ΔMSFC showed that patients in the lowest quartile (most MSFC worsening) were about 2 times more likely (11 vs 6 patients) to have a significant worsening on the EDSS and 2 to 3 times less likely (3 vs 8 patients) to have a significant improvement on the EDSS when compared with patients in the highest MSFC quartile (most MSFC improvement).

Our finding on longitudinal ΔMSFC is, to our knowledge, the first independent and prospective confirmation of the observations in the original data by Cutter et al. The Spearman rank correlation coefficient between ΔMSFC and ΔEDSS is also very comparable in both studies ($r = 0.22$ vs $r = 0.24$), although indicative of only a weak correlation between the changes in both measures.

Our study clearly indicates why this correlation is weak. Although ΔEDSS is especially correlated to changes in leg function (and not or marginally to changes in cognition and arm function), ΔMSFC is strongly correlated to changes in arm function and cognition and to a lesser degree—in patients with greater disability or in the progressive phase of the disease—to change in ambulatory function.

The correlation found between ΔEDSS and ΔTWT is in line with the fact that the EDSS is heavily biased to locomotor function. Our data do not show any correlation between ΔEDSS and ΔPASAT, which is in line with previous findings that results of a cognition test (PASAT) do not contribute to the EDSS. Our correlation between ΔEDSS and Δ9-HPT ($r = 0.24$) is comparable to that reported by Cutter et al ($r = 0.27$).

Correlations between ΔMSFC and changes in the underlying measurements were not reported in the study by Cutter et al. However, in that report, the correlations between ΔMSFC and ΔEDSS are somewhat better in more disabled patients.

These longitudinal data confirm the impression obtained from previous cross-sectional studies that the MSFC has favorable characteristics, especially being more multidimensional, when compared with the EDSS. Before proposing the MSFC as the preferred outcome measure for clinical trials, however, we advocate that more of its characteristics, including sensitivity to change and differential weighting of changes in actual measurements on z scores, be prospectively investigated in larger cohorts of patients with a wide range of disability.

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### REFERENCES