The effect of fatigability on Expanded Disability Status Scale components in multiple sclerosis

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SUMMARY

Introduction The Expanded Disability Status Scale (EDSS) is the most widely used disability measure in multiple sclerosis (MS). The effect of fatigability on EDSS components has been underreported to date.

Objective We investigated daytime variability in EDSS score and EDSS components – functional scores (FS) and walking distance (WD) up to 500 m, in MS patients who underwent a standardized fatiguing exercise.

Methods Twenty-four patients with relapsing-remitting MS (n = 7), secondary-progressive MS (n = 8) and primary-progressive MS (n = 9) were included. Exclusion criteria were as follows: current MS relapse, infection/fever/flu-like symptoms, conditions prohibiting safe exercise testing, current medication affecting fatigue. One trained examiner performed baseline (BL) and follow-up (FU) assessments (FU1 after a standardized fatiguing exercise, FU2 after rest) over a single day. EDSS score change of ≥1 point if BL EDSS score was <5.5 or of ≥0.5 point if BL EDSS score was ≥5.5 were considered clinically meaningful.

Results In progressive MS subtypes, WD decreased at FU1, but recovered at FU2, more so in secondary-progressive MS subgroup with the highest BL EDSS score. Although BL EDSS scores (median, 5.0; range 4.0–6.5) and FS remained relatively stable over repeated assessments in the total group, a clinically meaningful transitory post-exercise EDSS score increase was observed in three patients with progressive MS.

Conclusion WD seems to be more influenced by fatigability than the total EDSS score, more so in patients with progressive MS and higher disability. WD should be assessed after rest and this strategy should be implemented into protocols of clinical trials recruiting patients with progressive MS phenotypes.

Keywords: multiple sclerosis; disability evaluation; Expanded Disability Status Scale; walking distance; fatigability

INTRODUCTION

An increasing number of clinical trials are testing new therapeutic compounds in multiple sclerosis (MS) [1]. However, outcome assessment in MS remains challenging due to diversity and fluctuating nature of MS symptoms [2], whose transitory worsening could be underlain by several factors including fatigability [1]. Many trial designs have no standardized interval between previous physical activity and clinical examinations. Expanded Disability Status Scale (EDSS) is the most widely used clinical scale in MS, but has been debated because of low sensitivity [1, 3]. Daytime variability in EDSS components has been rarely investigated, but the influence of physical exercise on these outcomes has not been addressed at all except for sensory symptoms [4, 5].

OBJECTIVE

The aim of the study was to investigate daytime variability in EDSS score and EDSS components – functional scores (FS) and walking distance (WD) up to 500 m in MS patients exposed to a standardized fatiguing exercise.

METHODS

Patients

MS patients who had scheduled visits at the MS Clinic, Department of Neurology, Innsbruck Medical University Hospital, were screened for participation in the study. Inclusion criteria were as follows: MS according to the McDonald criteria [6], EDSS score 3.5–6.5, and no current medication affecting fatigue. Exclusion criteria were the following: current MS relapse, interferon-beta-related flu-like symptoms, current infection or fever or other condition prohibiting safe exercise testing.

To detect a difference of 0.5 EDSS points with a standard deviation of 0.3 and a power of 80% at an alpha level of 0.025 (multiple testing), a sample size of 24 patients was calculated and patients were recruited until this sample size was reached. Twenty-four MS patients with relapsing-remitting (RR) MS, secondary-progressive (SP) MS, and primary-progressive (PP) MS were included (female/male ratio, 1.19:1) (Table 1).

All study participants gave written consent prior to entering the study, which was approved by the Innsbruck Medical University Ethics Committee.
Study procedures

All included patients were admitted for study purposes to the hospital at 08:00 a.m. and were examined at 09:00 a.m. (baseline, BL), at 11:00 a.m. without delay following fatiguing exercise (follow-up, FU1), and at 05:00 p.m. (FU2) following rest in a hospital area.

All patients underwent standardized physical exercise before FU1 on a standard bicycle ergometer at a heart rate of 100–120 beats/minute for 30 minutes, but were allowed to stop the exercise if they subjectively reached maximal exertion. Time to maximal perceived exertion in seconds (s) and maximal exercise mechanical power output in Watts (W) were recorded (Table 1). All study procedures were performed in a hospital area with stable ambient temperatures (average, 21°C).

To avoid inter-rater variability [4], neurological disability level was assessed in all patients by one trained examiner (SD), according to EDSS grading using Kurtzke FS, along with WD assessment up to 500 m [7, 8]. EDSS score change of ≥1 point in patients with BL EDSS score <5.5 or of ≥0.5 point change if BL EDSS score was ≥5.5 were considered clinically meaningful [9].

Statistical analysis

The Kolmogorov–Smirnov test was used to determine normality of data distribution. The significance of changes over time was tested by repeated measures analysis of variance (ANOVA) with Tukey’s posttest or Friedman’s test with Dunn’s posttest while the differences between subgroups were assessed by one-way ANOVA (with Tukey’s posttest) or Kruskal–Wallis test (with Dunn’s posttest). Spearman’s or Pearson’s model were used for correlations. P-values <0.05 were considered significant. We used GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) for statistical analyses and Power and Sample Size Calculation (PS, downloaded from: http://ps-power-and-sample-size-calculation.software.informer.com) software for sample size calculation.

RESULTS

Tables 2 and 3 summarize all the results. In the total group, EDSS score and single FS did not change significantly over repeated assessments (Table 2), although clinically meaningful post-exercise EDSS deterioration was observed in three patients (two SPMS and one PPMS) (12.5% of all the patients). WD decreased following fatiguing exercise and improved after rest in SPMS and PPMS, but not in RRMS patients (Table 3). A post-exercise decrease in WD was statistically significant in SPMS patients, a subgroup with the highest BL EDSS score (Table 3).

The total EDSS score was significantly driven by pyramidal and cerebellar FS as well as by WD (Table 2).

Performance on any scale did correlate, not significantly though, with age and disease duration. BL–FU1 changes

### Table 1. The characteristics of multiple sclerosis (MS) patients with exercise parameters

<table>
<thead>
<tr>
<th>MS subgroup</th>
<th>Number of patients (%)</th>
<th>Agea (years)</th>
<th>Disease durationb (years)</th>
<th>Maximal exercise power outputb (W)†</th>
<th>Time to maximal perceived exertiona (s)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>RRMS</td>
<td>7 (29.2)</td>
<td>38.3 ± 7.2* (31.6–45.0)</td>
<td>9 (3–22)</td>
<td>60 (30–80)</td>
<td>615.9 ± 142.0 (484.5–747.2)</td>
</tr>
<tr>
<td>SPMS</td>
<td>8 (33.3)</td>
<td>51.9 ± 8.8 (44.5–59.2)</td>
<td>18 (9–27)**</td>
<td>40 (20–70)</td>
<td>453.8 ± 226.9 (215.7–692.0)</td>
</tr>
<tr>
<td>PPMS</td>
<td>9 (37.5)</td>
<td>54.3 ± 11.7 (45.4–63.3)</td>
<td>7 (2–17)</td>
<td>50 (25–75)</td>
<td>550.0 ± 178.8 (412.5–687.5)</td>
</tr>
<tr>
<td>Total MS</td>
<td>24 (100)</td>
<td>48.8 ± 11.6 (43.9–53.7)</td>
<td>12 (2–27)</td>
<td>50 (20–80)</td>
<td>544.7 ± 185.1 (462.7–626.8)</td>
</tr>
</tbody>
</table>

RRMS – relapsing-remitting MS; SPMS – secondary-progressive MS; PPMS – primary-progressive MS; † mean with standard deviation (95% confidence interval of the mean); * median with range; † no statistically significant difference between subgroups; ** significantly lower than in SPMS or PPMS (one-way ANOVA p = 0.0083, Tukey’s posttest); ** significantly longer than in RRMS or PPMS (one-way ANOVA p = 0.0140, Tukey’s posttest)

### Table 2. Expanded Disability Status Scale (EDSS) components over three repeated assessments and their correlation with the overall EDSS score at baseline; values are given in median (ranges) unless otherwise stated

<table>
<thead>
<tr>
<th>EDSS component</th>
<th>BL</th>
<th>FU1</th>
<th>FU2</th>
<th>P*</th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>FS: Visual</td>
<td>1 (0–2)</td>
<td>1 (0–3)</td>
<td>1.5 (0–3)</td>
<td>0.03*</td>
<td>-0.28</td>
</tr>
<tr>
<td>FS: Brainstem</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>2 (1–3)</td>
<td>n.s.</td>
<td>0.18</td>
</tr>
<tr>
<td>FS: Pyramidal</td>
<td>3 (3–4)</td>
<td>3 (3–4)</td>
<td>3 (2–4)</td>
<td>n.s.</td>
<td>0.52*</td>
</tr>
<tr>
<td>FS: Cerebellar</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>3 (2–4)</td>
<td>n.s.</td>
<td>0.66*</td>
</tr>
<tr>
<td>FS: Sensory</td>
<td>3 (1–4)</td>
<td>3 (2–4)</td>
<td>3 (1–4)</td>
<td>n.s.</td>
<td>0.33</td>
</tr>
<tr>
<td>FS: Bowel/bladder</td>
<td>1 (0–4)</td>
<td>1 (0–4)</td>
<td>1 (0–4)</td>
<td>n.s.</td>
<td>0.05</td>
</tr>
<tr>
<td>FS: Cerebral</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>0 (0–2)</td>
<td>n.s.</td>
<td>0.02</td>
</tr>
<tr>
<td>WD m</td>
<td>305.0 (175.0–500.0)</td>
<td>235.0** (128.8–487.5)</td>
<td>372.5 (178.8–500.0)</td>
<td>0.007</td>
<td>-0.82*</td>
</tr>
<tr>
<td>EDSS score</td>
<td>5.0 (4.0–6.5)</td>
<td>5.2 (4.0–6.5)</td>
<td>4.5 (4.0–6.5)</td>
<td>n.s.</td>
<td>---</td>
</tr>
</tbody>
</table>

FS – functional score; WD – walking distance up to 500 m; BL – baseline; FU – follow-up assessment; r – Spearman’s correlation coefficient (with EDSS score at BL); n.s. – not significant; * p-values obtained by Friedman test between BL, FU1 and FU2 assessment, except repeated-measures ANOVA for WD; ** Dunn’s post-hoc multiple comparison test revealed no statistically significant difference; * median (interquartile range); * statistically significant correlation with EDSS score at BL; ** statistically significant difference from BL.
Higher sensitivity could offer improved precision to detect assessing individual treatment response in clinical routine. This would be advantageous for designing clinical trials but also for predicting long-term disability in a shorter time. This would strongly correlate with the EDSS such as WD—being strongly sensitive to detect daily functional fluctuations in MS and progressive MS by Zhang et al. [13].

The EDSS remains a robust clinical score designed to cover the life span of MS patients and therefore insensitive to short-term changes even after fatiguing exercise. In contrast to the total EDSS score, WD seems to be more sensitive to detect daily functional fluctuations in MS and progressive MS phenotypes.

Table 3. Expanded disability status scale (EDSS) scores and walking distance up to 500 m (WD) over three repeated assessments in multiple sclerosis (MS) phenotype strata

<table>
<thead>
<tr>
<th>Disability measure</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>FU1</td>
<td>FU2</td>
</tr>
<tr>
<td>EDSS</td>
<td>4.0 (4.0–5.5)</td>
<td>4.0 (4.0–5.5)</td>
<td>4.0 (4.0–5.5)</td>
</tr>
<tr>
<td>WD (m)</td>
<td>500.0 (420.0–500.0)</td>
<td>500.0 (450.0–500.0)</td>
<td>500.0 (365.0–500.0)</td>
</tr>
</tbody>
</table>

RRMS — relapsing-remitting MS; SPMS — secondary-progressive MS; PPMS — primary-progressive MS; BL — baseline; FU — follow-up assessment; * median (range); † median (interquartile range); †† significantly lower than in SPMS (Kruskal–Wallis test p = 0.0146, Dunn’s posttest); ‡ significantly longer than in SPMS (one-way ANOVA p = 0.0184, Tukey’s posttest); * change from BL was statistically significant (repeated-measures ANOVA p = 0.0155, Tukey’s posttest)

in studied scores did not correlate significantly with maximal exercise power output or time to maximal perceived exertion (data not shown).

DISCUSSION

Decades ago, Kurtzke [10] indicated that one good reason for quantitative schemes in MS was to document changes. In contrast to the total EDSS score, WD in our study showed a significant daily variability induced by fatigability, more so in patients with progressive MS phenotypes and higher disability. Considering also day-to-day variability of maximum walking distance [11], our results further necessitate WD assessment in non-fatigued MS patients.

Similarly to previous reports [3], BL EDSS score was predominantly determined by FS mainly affecting walking performance (pyramidal, cerebellar) and WD, but significant daily WD changes were not followed by significant changes in the EDSS score. Although being stable at the total group level, a clinically meaningful transitory post-exercise EDSS score increase occurred in 6.25% of our patients who had progressive MS phenotypes. Such short-term variations should be considered when evaluating disease progression and designing trial outcomes since measurement of changes smaller than the variation intrinsic to the tool might be inappropriate [12]. Additionally, EDSS variability before randomization might limit treatment discovery in MS, as recently shown in primary progressive MS by Zhang et al. [13].

Since a two-year EDSS change might predict later EDSS progression [14], more sensitive outcome variables that strongly correlate with the EDSS such as WD—being metric rather than ordinal measures—might be able to predict long-term disability in a shorter time. This would be advantageous for designing clinical trials but also for assessing individual treatment response in clinical routine. Higher sensitivity could offer improved precision to detect even subtle disability changes and would increase study power / decrease sample sizes in clinical trials [15]. More sensitive disability measures might also provide more clinically relevant information than relapse rates, which are poorly predictive of the long term outcome [14, 16]. However, the validity of WD as a separate assessment tool still has to be investigated in longitudinal studies on a larger sample size.

The phenomenon of fatigability, which contributes to the more general complaint of fatigue in MS [17], has been assumed to be partly due to impaired membrane excitability after a fatiguing exercise [18]. In this context, our results could represent a clinical correlate of neurophysiological findings showing intracortical excitability to be altered at higher EDSS scores and different across disease subtypes as we found motor fatigability to be more pronounced in patients with progressive MS and higher disability [19]. This is in line with results showing the complex paradigm of fatigue to be more frequent in MS patients with progressive MS and higher disability [20, 21, 22].

Our study was powered to detect minor EDSS changes, which probably has not introduced a bias regarding the sensitivity of WD to detect changes, but correlations done in our study might have been underestimated.

CONCLUSION

The EDSS remains a robust clinical score designed to cover the life span of MS patients and therefore insensitive to short-term changes even after fatiguing exercise. In contrast to the total EDSS score, WD seems to be more sensitive to detect daily functional fluctuations in MS and is influenced by fatigability, more so in patients with progressive MS course and higher disability. WD should be assessed after rest and this strategy should be implemented into protocols of MS clinical trials recruiting patients with progressive MS phenotypes.

REFERENCES


Kratka sadržaja
Uvod Procena onosposobljenosti u multiploj sklerazi (MC) najčešće se vodi proširenom skalom unoseosobljenosti (EDSS). Uticaj onosposobljenosti na sve komponente EDSS skale nije do sada analiziran. 

Člja radaj Va radaj je bio da analizira uticaj onosposobljenosti na ukinutu EDSS skor i komponente EDSS skale – funkcionalne skorove (FS) i distanca hoda (DH) do 500 m kod boljesnika s MC koji su podvrgnuti standardizovanom fizikom opterećenju.

Metode radia u studiju su uključena 24 boljesnika s relapsirajuće-remitirajućim MC (n = 7), sekundarno-progresivnom MC (n = 8) i primarno-progresivnom MC (n = 9). Isklučujući kriterijum su bili: aktuelni relaps MC, postojanje infekcije/fefirilnosti/симптомa na liku, utroba lekova sa potencijalnim uticajem na zamor, kontinuiranoj onosposobljenosti. Komponente EDSS skale su pročeni vane od strane jednog procenjivača u toku istog dana: pre opterećenja, po izlaganju standardizovanoj opterećenju

i naktom odmora. Klincni znakom je smanjena učenja EDSS skora za ≥1 ukoliko je ćas EDSS skor <5,5 ili za ≥0,5 ukoliko je ćas EDSS skor ≥5,5. 

Rezultati DH je u podgrupu sa progressivnom MC bila umanjena nakon zamara, izraženije u podgrupi sekundarno-progresivne MC, u kojoj je ćas EDSS skor bio najveći. U ukinutoj grupe bolesnika ćas EDSS skor (mediana, 5; raspon 4–6,5) i FS nisu se značajno mešali tokom ponavljanih procena, ali je klincni znak po lani porast EDSS skora nakt od ćesana u zaležen bed kod tri bolesnika sa progressivnim formama MC.

Klucne reči: multijla skleraza; prošireno onosposobljenost; prošireno skalna unoseosobljenost; distanca hoda; zamor

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