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Does the Modified Fatigue Impact Scale offer a more comprehensive assessment of fatigue in MS?

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Background: As a symptom of multiple sclerosis (MS), fatigue is difficult to manage because of its unknown etiology, the lack of efficacy of the drugs tested to date and the absence of consensus about which would be the ideal measure to assess fatigue. Objective: Our aim was to assess the frequency of fatigue in a sample of MS patients and healthy controls (HC) using two fatigue scales, the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS) with physical, cognitive and psychosocial subscales. We also studied the relationship fatigue has with depression, disability and interferon beta. Methods: Three hundred and fifty-four individuals (231 MS patients and 123 HC) were included in this cross-sectional study. Fatigue was assessed using the FSS and MFIS. Depression was measured by the Beck Depression Inventory (BDI), and disability by the Expanded Disability Status Scale (EDSS). A status of fatigue was considered when the FSS ≥ 5, of non-fatigue when the FSS ≤ 4, and scores between 4.1 and 4.9 were considered doubtful fatigue cases. Results: Fifty-five percent of MS patients and 13% of HC were fatigued. The global MFIS score positively correlated with the FSS in MS and HC (r = 0.68 for MS and r = 0.59 for HC, p < 0.0001). Nonetheless, the MFIS physical subscale showed the strongest correlation score with the FSS (r = 0.75, p < 0.0001). In addition, a prediction analysis showed the physical MFIS subscale to be the only independent predictor of FSS score (p < 0.0001), suggesting other aspects of fatigue, as cognition and psychosocial functions, may be explored by the FSS to a lesser extent. Depression also correlated with fatigue (r = 0.48 for the FSS and r = 0.7 for the MFIS, p < 0.0001) and, although EDSS correlated with fatigue as well, the scores decreased after correcting for depression. Interferon beta showed no relationship with fatigue. Conclusions: Fatigue is a frequent symptom found in MS patients and clearly related with depression. Each fatigue scale correlates with one another, indicating that they are measuring similar constructs. Nevertheless, spheres of fatigue as cognition and psychosocial functions are probably better measured by the MFIS, although this hypothesis will need to be confirmed with appropriate psychometrical testing.

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Key words: fatigue; Fatigue Severity Scale (FSS); Modified Fatigue Impact Scale (MFIS); MS

Introduction

Fatigue is often found in patients with multiple sclerosis (MS) and frequently becomes a very life limiting symptom.1 The US National Multiple Sclerosis Society (NMSS) defines fatigue as ‘a subjective lack of physical and/or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities’.2 Several aspects seriously factor in on the difficult management of the symptom. The unknown etiology of fatigue, the lack of efficacy of the various drugs tested to date, together with the lack of consensus about which is the ideal measure to assess it, increase such difficulty. Because of the subjectivity in describing fatigue as a symptom, self-report instruments are probably the most useful tools that can be used to assess it. Nowadays, there are several scales that quantify fatigue. However, to assume that these scales actually measure the symptom is still to be fully elucidated.3 After reviewing the literature, there are two scales we believe it is worth looking into, namely, the Fatigue Severity Scale (FSS) and the Modified Fatigue Impact Scale (MFIS). The FSS was proposed by Krupp et al. in 1989,4 it consists of nine items and is probably the most widely used. Although the FSS has been classified as a unidimensional scale5 with a capacity to analyse the impact of fatigue in the daily living of patients, three items are related to physical exercise, three items to the psychosocial environment and the remainder three are more generic.5 The MFIS, derived from the original 40-item Fatigue Impact Scale,6 is a 21-item scale recently developed by the US NMSS. It has been classified as multidimensional scale and is intended to analyse different aspects of fatigue by assessing impact on physical, cognitive and psychosocial functioning. The combination of nine items for physical status (pMFIS), ten items for cognitive status (cMFIS), and two items for psychosocial function status (psMFIS), renders the global score of the MFIS.5

A description of other fatigue scales frequently used can be found in a paper by Comi and colleagues.3 The FSS has...
been chosen to measure fatigue in many MS studies and clinical trials. In contrast, there is little information in the literature as for the MFIS; in 2002, Flachennecker and colleagues studied different rating scales in a sample of MS patients and, for the first time in the literature, the MFIS was used in a comparative analysis. Relevant information derived from this work was, in the first place, the good correlation found between the FSS and the MFIS, plus the ideal cut-off values of 4.6 for the FSS and 38 for the MFIS to better discriminate fatigued from non-fatigued patients. These results, however, have yet to be reproduced.

We conducted a large cross-sectional study. The primary objective was to assess fatigue in our MS and healthy control (HC) populations. We also studied the impact on fatigue from the clinical course of MS, depression and disability. Immunomodulatory treatment intake was also recorded. We then compared two fatigue scales, the FSS and the MFIS, in MS patients and HC.

Subjects and methods

Over a period of eight months, MS patients not involved in any clinical trial at the time, who believed themselves capable to answer questionnaires without external aid, and HC (represented by patients’ relatives or caregivers without psychiatric disorders or history of other major medical illness) were invited to participate in the study at our outpatient MS clinic. On the visit day, they were given questionnaires to be filled in while in a non-private, waiting room environment, although with no communication between participants. Questionnaires from patients found to be in relapse after completion were excluded from analysis. Fatigue was assessed using two scales, the FSS and the MFIS; depression was quantified with the Beck Depression Inventory (BDI). All scales used were translated versions from source language into Spanish. The questionnaires were always completed in the same order starting with the FSS, then the MFIS, and finally the BDI; at the same appointment, we assessed the EDSS. Demographics and clinical data such as disease duration, activity in terms of number of relapses, and immunomodulatory treatment intake were recorded.

Based on earlier studies, we considered a status of ‘fatigue’ when the FSS score was ≥5, and a status of ‘non-fatigue’ when the score was ≤4, and scores between 4.1 and 4.9 were considered ‘doubtful fatigue’. We considered presence of depression when the BDI score was above 13 and major depression when the score was ≥30.

Statistics

Statistical analysis was performed with the SPSS package (SPSS Inc, Chicago, IL) v.11.5 for MS-Windows. None of the variables, tested in a Kolmogorov Smirnov test, followed a normal distribution. Comparison between phenotypes was done using a Mann–Whitney U test. Because of the abnormal distribution of the scales, for study correlations we used the Spearman rank coefficient (r). A multiple regression analysis using the forward stepwise method was used to analyse the predictive value of each MFIS subscale for the FSS as well as the relation between fatigue and clinical variables as EDSS, BDI, and disease duration. Level of significance was set at p < 0.05.

Results

Two hundred and forty-seven MS patients and 123 HC agreed to participate in the study and filled in the questionnaires.

After the follow-up visit, 16 patients were excluded from analysis because of a concomitant relapse. Hence, 354 individuals were finally included (231 patients and 123 HC). The patient group comprised 223 individuals with clinically definite MS according to the Poser Criteria and eight patients with a first attack suggestive of demyelinating disease. The MS course was relapsing–remitting (RRMS) in 164 patients, secondary progressive (SPMS) in 47, and primary progressive (PPMS) in 12. The small number of PPMS patients included was due to the fact that at the time most in our patient population were enrolled in a clinical trial. As for immunomodulatory treatment, 117 patients were on interferon beta and the remainder 114 were untreated. Table 1 summarizes demographic and clinical data.

**Table 1** Demographic and clinical data

<table>
<thead>
<tr>
<th>Overall patients (n = 231)</th>
<th>HC (n = 123)</th>
<th>RRMS (n = 164)</th>
<th>SPMS (n = 47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (W/M, %)</td>
<td>69.2/30.7</td>
<td>55.3/44.7</td>
<td>74.4/25.6</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>37.1 ± 10</td>
<td>39.3 ± 12.2</td>
<td>35.0 ± 9.7</td>
</tr>
<tr>
<td>EDSS (median, range)</td>
<td>2.0 (0–8.5)</td>
<td>1.5 (0–6.5)</td>
<td>6.0 (4.0–8.5)</td>
</tr>
<tr>
<td>Relapse rate (2 years)</td>
<td>0.44</td>
<td>–</td>
<td>0.48</td>
</tr>
<tr>
<td>Disease duration (mean, SD)</td>
<td>9.6 ± 7.2</td>
<td>–</td>
<td>8.5 ± 6.6</td>
</tr>
</tbody>
</table>

N.B. PPMS patients and CIS were included in the overall patient group. W, women; M, men; HC, healthy controls; RRMS, relapsing remitting MS; SPMS, secondary progressive MS.
Median FSS score was 5.2 (range 1.2–7.4) and the median MFIS score was 33.0 (range 0–82). Depression was found in 67 patients (68.7%) and major depression was found in 5 (2.6%). Fatigue was significantly more frequent in progressive than in relapsing forms of MS. Fatigue was observed in 51% of the RRMS patients and the median FSS score was 5.0 (range 1.2–7.4); 74.5% of the SPMS patients were fatigued and the median FSS score was 5.8 (range 1.8–7.0). Statistical differences in depression were also found between secondary progressive and relapsing forms, showing that the SPMS group had higher BDI scores. Table 2 summarizes fatigue and depression scores in the MS and HC groups.

Fatigue and depression scores did not differ between patients on interferon beta and untreated patients.

HC group
Fatigue was present in 16 individuals (13%) and absent in 86 (70%). The remaining 17% had doubtful fatigue. Median FSS score was 3.3 (range 1–6.7) and median MFIS score was 11.0 (range 0–58). Depression was found in 9.7% of the individuals.

Correlation studies
Correlation between the global MFIS and the FSS scores was strong ($r = 0.68$, $p < 0.0001$). MFIS subscales also correlated with the FSS as follows: $p$MFIS $r = 0.75$, $c$MFIS $r = 0.44$, and $ps$MFIS $r = 0.62$; $p < 0.0001$.

Fatigue positively correlated with depression. Global MFIS showed stronger correlation scores with depression than the FSS ($r = 0.70$ for the MFIS and $r = 0.48$ for the FSS). Taken separately, each MFIS subscale showed higher correlation scores with the BDI than did the FSS. When controlling for EDSS, correlations between fatigue and depression remained positive; EDSS showed mild correlations with fatigue scales ($r = 0.45$ for the FSS and $r = 0.33$ for the MFIS, $p < 0.0001$). When controlling for BDI, correlation scores between fatigue and EDSS decreased ($r = 0.30$, $p < 0.0001$ for the FSS and $r = 0.15$, $p = 0.02$ for the MFIS). Results are summarized in Table 3.

Prediction studies
Multiple linear regression analysis between FSS as a dependent variable and each MFIS subscale as independent variables showed the $p$MFIS, but not the $c$MFIS or the $ps$MFIS, as an independent predictor of the FSS score (Beta 0.82, $p < 0.0001$). Additional analyses considering depression, EDSS and disease duration as independent variables identified EDSS (Beta 0.30, $p < 0.0001$) and BDI (Beta 0.37, $p < 0.0001$) scores as independent predictors of the FSS score ($p = 0.001$). As regards the MFIS, we identified the EDSS, the BDI and disease duration as independent predictors of all the MFIS subscales: $p$MFIS (EDSS: Beta 0.14, $p = 0.01$; BDI: Beta 0.57, $p < 0.0001$; and disease duration: Beta 0.16, $p = 0.003$); for the $c$MFIS (EDSS: Beta $-0.12$, $p = 0.03$; BDI: Beta 0.61, $p < 0.0001$; and disease duration: Beta 0.19, $p = 0.001$); for the $ps$MFIS (EDSS: Beta 0.14, $p = 0.01$; BDI: Beta 0.52, $p < 0.0001$; and disease duration: Beta 0.14, $p = 0.01$).

Discussion
In the present work, we report the results of a large study conducted with the aim of analysing different aspects of fatigue in MS patients and HC. Our major finding was that the two fatigue scales, the FSS and the MFIS, strongly correlated with one another, indicating that they are both measuring related features.

We found that 55% of MS patients had fatigue. These results are in agreement with previous studies using the same FSS cut-off point.7,19 Additionally, also similarly to other studies, we found higher levels of fatigue in SPMS than in RRMS.5,13

Concerning aspects that can impact fatigue, we analysed depression, disability and treatment with interferon beta. The role depression and disability play in the development of fatigue remains a controversial issue. Although many studies have shed some light on this, the fact that each used a different measuring scale for the same objective makes comparisons between different studies unfeasible. Depression has been positively correlated with fatigue in several studies, but other authors have obtained opposite results.4,8,22 Our study reveals a clear relationship between fatigue and depression. Although the MFIS showed a slightly stronger relation than the FSS, we can assert that the two fatigue scales are taking depression into consideration. On the other hand, few authors have found disability to be related with fatigue, although most report weak correlation scores when controlling for other variables as depression, age or disease duration.12,13 Our results show that fatigue is slightly

Table 2 Median scale scores and comparison between groups

<table>
<thead>
<tr>
<th>Scales</th>
<th>All patients (n = 231)</th>
<th>HC (n = 123)</th>
<th>p</th>
<th>RRMS (n = 164)</th>
<th>SPMS (n = 47)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>8.0 (4.0–14.0)</td>
<td>5.0 (2.0–8.0)</td>
<td>&lt;0.0001</td>
<td>8.0 (3.3–5.8)</td>
<td>10.5 (7.0–16.0)</td>
<td>0.009</td>
</tr>
<tr>
<td>FSS</td>
<td>5.2 (3.7–6.0)</td>
<td>3.3 (2.6–4.2)</td>
<td>&lt;0.0001</td>
<td>5.0 (1.2–7.4)</td>
<td>5.8 (5.0–6.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>MFIS</td>
<td>33.0 (16.0–45.0)</td>
<td>11.0 (5.0–21.5)</td>
<td>&lt;0.0001</td>
<td>32.0 (13.0–45.5)</td>
<td>37.5 (28.0–54.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>$p$MFIS</td>
<td>18.0 (9.0–25.0)</td>
<td>5.0 (1.0–9.2)</td>
<td>&lt;0.0001</td>
<td>17.0 (7.0–24.0)</td>
<td>22.0 (17.0–28.0)</td>
<td>0.001</td>
</tr>
<tr>
<td>$c$MFIS</td>
<td>10.0 (4.0–20.0)</td>
<td>5.0 (2.0–10.0)</td>
<td>&lt;0.0001</td>
<td>10.0 (4.0–20.0)</td>
<td>9.5 (5.75–21.5)</td>
<td>0.4</td>
</tr>
<tr>
<td>$ps$MFIS</td>
<td>3.0 (1.0–5.0)</td>
<td>1.0 (1.0–3.0)</td>
<td>&lt;0.0001</td>
<td>3.0 (1.0–5.0)</td>
<td>5.0 (3.0–7.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

N.B. PPMS patients and CIS were included in the all patients group. Interquartile ranges (25–75%) are in brackets.
BDI, Beck Depression Inventory; FSS, Fatigue Severity Scale; MFIS, Modified Fatigue Impact Scale; $p$MFIS, physical MFIS subscale; $c$MFIS, cognitive MFIS subscale; $ps$MFIS, psychosocial MFIS subscale.
related to disability and when controlling for other potentially confounding variables as depression, correlations between fatigue and disability were even weaker. Concerning interferon beta, several studies have pointed to fatigue as a treatment side-effect. However, as the MFIS panel has already pointed out, despite the expert consensus applied to the development of the scale, it had never been previously used in large trials and its clinical relevance remained to be fully tested.

Recently, for the first time, Flachenecker and colleagues conducting a large study have demonstrated how the new MFIS correlates with the well known FSS. We have also tested both scales and confirm the earlier results. Since the FSS score strongly correlates with the global MFIS score, it can be said that both scales are measuring similar constructs. Interestingly, taking into account that the physical MFIS subscale showed the strongest correlation score with the FSS and that the linear regression analysis revealed that the physical MFIS subscale was the only independent predictor as to the FSS score, we argue that, first, the FSS is basically analysing the impact of fatigue on physical aspects of the daily living and that, secondly, the psychosocial and cognitive aspects of fatigue are probably better analysed by the MFIS than the FSS. Nonetheless, to confirm these hypotheses, the analysis of the psychometrical properties of each scale is mandatory.

The cognitive aspect of fatigue may occasionally be one of the most limiting spheres in the management of the symptom, but there is little knowledge about it and specific literature is scarce. Whilst earlier studies using different neuropsychological batteries found no differences in cognitive fatigue between patients and HC, other studies did find differences. Krupp et al. showed significant differences over the testing session between patients and HC, but neuropsychological measure scores between both groups did not differ at baseline. Our results, based on self-report measures (cognitive MFIS subscale), show statistical differences on cognitive fatigue between patients and HC (Table 1). However, to our knowledge this cognitive subscale of fatigue has not as yet been psychometrically tested to correctly interpret data concerning cognitive fatigue.

We have assessed fatigue according to the scale scores and, although it could represent a study limitation as it would have also been relevant to approach the subjective feeling of fatigue, it has been proven that the Visual Analogue Scale, which quantifies the subjective feeling of the symptom, correlates with the FSS. On the other hand, the main limitation of our study derives from the methodology used. The fatigue scales used here were directly translated from the source language into Spanish, with no formal validation and no psychometrical testing. Because it is highly suspected that even validated scales are probably not assessing the actual subjective symptom of fatigue, in our study we realize the method used made appropriate analysis of the symptom even more difficult. The interpretation of the results is thus limited.

In conclusion, the results of our study show that fatigue is a frequent symptom in MS patients, though more so in progressive than in relapsing forms of the disease. Moreover, we show that depression and, to a lesser degree, disability but not immunomodulatory treatment are related to the presence of fatigue. As repeatedly pointed out, fatigue seems to be a multidimensional symptom in which different aspects play different roles to a varying degree depending on the scenario. Thus, the study of fatigue needs to be dealt in a more comprehensive manner, as different spheres of this symptom may need different therapeutic approaches. Although the MFIS subscales have not been independently or fully studied as yet, it seems that the MFIS could offer more detailed information about the psychosocial and cognitive spheres of fatigue. Nevertheless, the study of the psychometrical properties of the scales will be needed to confirm this.

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References