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Assessment of Global Fatigue in Multiple Sclerosis: A Spanish Language Version of the CGI and PGI Fatigue Scales

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ABSTRACT

Background: Fatigue is often identified as weakness following muscular exertion in patients with multiple sclerosis (MS) but may be associated with other physical, cognitive and emotional symptoms. **Objective:** Develop a Spanish language global impression of fatigue scale to evaluate symptoms of fatigue distinct from a particular disease. **Methods:** 50 ambulatory patients with MS attending a clinical institute in Argentina consented to participate in this reliability study. The Spanish language version of the Clinical and Patient Global Impressions of Fatigue (CGI-S-F and PGI-S-F) instruments were administered with the Massachusetts General Hospital cognitive and physical functioning questionnaire (MGH-CPFQ). **Results:** The CGI-S-F and PGI-S-F scores were well correlated with each other ($p < 0.00005$). The mean CGI-S for fatigue was 2.28 ± 1.07 (SD) and PGI-S for fatigue was 2.30 ± 1.16 (p = ns) reflecting borderline to mild perception of fatigue. The total MGH-CPFQ was 16.68 ± 4.32. Both CGI-S-F and PGI-S-F measures were correlated with the MGH-CPFQ: CGI-Severity ($r = 0.632$; $p < 0.00005$); PGI-Severity ($r = 0.717$; $p < 0.00005$). **Conclusions**: In this study, the Spanish language versions of the CGI-S-F and PGI-S-F were reliable measures in an MS population and can be useful and easily applied metrics in a busy clinical practice.

Keywords: Reliability; Multiple Sclerosis; Spanish; Global Assessment; Fatigue; Psychometrics; Treatment Response

1. Introduction

Approximately 50% to 60% of patients with Multiple Sclerosis (MS) describe fatigue as one of their most troubling symptoms, regardless of their disease course or level of disability [1]. Fatigue symptoms are often presented as part of the symptom cluster of MS and have been associated with regional cerebral brain atrophy in these patients [2-4]. In MS, fatigue is often experienced as weakness following muscular exertion (muscular fatigue) and may precede the other evolving symptoms of the disease [5]. In addition, Krupp and Elkins [6] found that following continuous effort, MS patients performed worse than control subjects on tests of visual and verbal memory reflecting the impact of mental fatigue. MS patients with symptoms of fatigue may have greater work and/or social performance difficulties and develop more health problems than less fatigued patients [7,8]. In the United States, the Social Security Administration recognizes fatigue as a significant cause of unemployment among people with MS [1].

The perception of fatigue may reflect different issues including muscular weakness, lassitude, daytime sleepiness, and/or the inability to focus [9-12]. Arnold [13] delineated three distinct categories of fatigue related to physical, cognitive, and emotional symptoms. The physical symptoms of fatigue include reduced activity, low energy, tiredness, decreased physical endurance, increased effort to do physical tasks, general weakness, heaviness, slowness or sluggishness, non-restorative sleep, and sleepiness. Clearly, many patients with MS experience these symptoms. However, additional cognitive and emotional symptoms may also be associated symptoms of fatigue. The cognitive symptoms include decreased concentration, decreased attention, decreased mental endurance, and slowed thinking. The emotional (affective) symptoms of fatigue include decreased motivation or initiative (apathy), decreased interest, feeling overwhelmed, feeling bored, aversion to effort, and feeling low. Therefore, the subjective experience and differential description of fatigue symptoms may differ markedly between patients.

In clinical practice, the evaluation and treatment of fatigue may be complicated because it is often part of the symptom cluster of MS, but can also be a symptom of another disorder distinct from MS, or a side effect of the medications used in the treatment of MS [10,11]. Furthermore, adding additional medications to treat the identified symptoms of fatigue adds risk because of the possibility of inducing additional adverse symptoms as a consequence of the intervention.

There are several instruments used to assess fatigue including the 9-item self-report fatigue severity scale (FSS), more comprehensive instruments examining vitality and inertia, and performance-based measures specifically related to MS [5,14-16]. The 11-item fatigue questionnaire has been used in clinical trials to assess symptoms of fatigue, and the fatigue descriptive scale (FDS) distinguishes fatigue at rest, during exercise, and worsening with exertion [15-17]. Alternatively, Schwid and colleagues [14] developed a quantitative, performance-based measure of motor fatigue using three exercise protocols to distinguish fatigue from weakness in individual muscles. Bakshi *et al.* [18] used the FSS and expanded disability status scale (EDSS) [19] to study fatigue and examine its relationship to depression and disability in 71 patients with multiple sclerosis. They reported that fatigue was significantly correlated with depression in these MS patients but was not associated with physical disability as measured by the EDSS.

Although useful in many instances, these aforementioned rating tools may be too time consuming for use in a busy clinic or limited in scope to either the clinician's or subjects personal interpretation (e.g., FSS). In a busy clinical setting, it would be helpful to have a simpler, faster, yet reliable metric tool that can quickly assess both the clinician's and subject's independent assessment of fatigue symptoms. The Clinical Global Impression of severity scale (CGI-S) and related patient version (PGI-S) are easily understood, single score metrics that can be useful for this purpose [20,21]. Targum *et al.* [22] developed and validated a modified form of the CGI and PGI severity scales to specifically assess the severity of symptoms of fatigue in central nervous system (CNS) populations. This modified CGI severity scale for fatigue (CGI-S-F) provides specific "targeted" symptoms of fatigue to facilitate specific symptom identification and adds scoring anchors to improve the precision needed to assess these symptoms [23]. For this study, we translated these companion global assessment instruments into Spanish and assessed the utility and reliability of the Spanish-version CGI-S-F and PGI-S-F in an ambulatory clinic population of patients with MS.

2. Methods and Materials

2.1. Study Description and Subject Population

50 ambulatory patients with MS consented to participate in the assessment of a newly developed, Spanish-language global assessment scale for fatigue. All subjects were attending the Institute of Cognitive Neurology (INECO) located in Buenos Aires, Argentina, and were randomly selected to participate in the study between August 2011 and January 2012.

Clinicians administered the CGI-S-F scale to all subjects who independently completed the PGI-S-F and the Massachusetts General Hospital Cognitive and Physical Functioning Scale (MGH-CPFQ). The MGH-CPFQ is a 7-item patient-rated instrument that has been shown to be both valid and reliable in clinical trials [24].

2.2. Description of the Instruments

Both the CGI-S-F and PGI-S-F were designed as anchored instruments rated from 1 to 7 with increasing severity of fatigue based upon the last 7 days [22]. The descriptive anchors specifically focus on the identified symptoms of fatigue. For instance, a global severity score of 3 reflects mild fatigue whereas a severity of 4 reflects moderate fatigue. Both instruments include the same generic, yet "targeted" descriptors of possible symptoms that may be associated with fatigue in any medical condition, including MS.

For instance, the PGI-S descriptor refers to the individual (patient) completing the self-rating instrument and reads as follows in English:

Symptoms of fatigue may include effects on your ***physical wellbeing*** (*such as low or decreased energy*, *tiredness*, *decreased physical endurance or ability to sustain physical activity*, *general weakness*, *heaviness in the arms or legs*, *general heaviness*, *slowness or sluggishness*, *sleepiness*, *increased effort with physical tasks*) *on your* ***mood state*** (*decreased motivation or interest*, *decreased effort or initiative*), *or your* ***cognitive abilities*** (*such as decreased concentration*, *decreased attention*, *slowed thinking*, *reduced mental sharpness*).

The English versions of the CGI-S-F and PGI-S-F were translated into Spanish by one of the authors (FM) and cross-validated back into English prior to its use in the current study.

The MGH-CPFQ is a validated patient-rated scale scored from 1-6 with increasing severity that individually evaluates 7 distinct items: Motivation/Enthusiasm, Wakefulness/Alertness, Energy, Focus/Attention, Recall, Ability to find words, and Sharpness/Mental acuity.

2.3. Statistical Analyses

Statistical analyses included intra-class correlations, Pearson's correlation coefficient, and paired t-test comparisons. The MGH-CPFQ was used to validate the PGI and CGI fatigue instruments.

3. Results

3.1. Demographics

50 subjects attending an outpatient clinic for multiple sclerosis consented to participate in this study. There were 12 men and 38 women. The mean age of the group was 41.6 ± 11.6 (SD) years.

3.2. Reliability

Both PGI-S and CGI-S were reliable measures of fatigue in this MS population. The mean scores for the PGI-S and CGI-S revealed borderline to mild fatigue although the scores ranged from 1 (normal) to 5 (marked fatigue). There were no statistically significant differences between the patient-rated and clinician-rated global measures of fatigue. The mean PGI-S score was 2.30 ± 1.16 (SD) and the mean CGI-S was 2.28 ± 1.07 ($t = 0.89$; $df = 98$; p = ns). The intra-class correlation between the clinician-rated CGI-S and patient-rated PGI-S was r = 0.9465 ($p < 0.0001$).

3.3. Validation of the Global Impressions Instrument

The MGH-CPFQ was included in this study to assess the validity of the CGI-S and PGI-S for fatigue. The mean MGH-CPFQ score was 16.68 ± 4.48. Most subjects perceived mild cognitive or physical symptoms although the scores ranged from 1 to 5 in this ambulatory population. Most of these MS subjects did not equate the experience of fatigue related to their illness with any impairment of motivation, alertness, energy, focus, or their cognitive abilities.

The Pearson's correlation with the total MGH-CPFQ score was 0.6316 for the PGI-S and 0.7173 for the CGI-S. Both CGI-S and PGI-S scores were highly correlated with the total MGH-CPFQ (p < 0.001) and each of the individual 7 items.

Table 1 reveals the mean CGI-S scores and the Pearson's correlation for each of the individual CPFQ items.

Table 1. Pearson Correlation: CGI-S Fatigue with individual MGH-CPFQ items in an MS population (n = 50).

Comparison	MGH-CPFQ Score (mean ± SD)	Pearson's correlation	*p*-value
CGI-S to Motivation	2.40 ± 1.07	0.560	<0.005
CGI-S to Wakefulness	2.40 ± 0.86	0.521	<0.005
CGI-S to Energy	2.76 ± 1.04	0.501	<0.005
CGI-S to Focus	2.36 ± 0.88	0.609	<0.005
CGI-S to Recall	2.44 ± 0.86	0.528	<0.005
CGI-S to Ability	2.22 ± 0.58	0.456	<0.005
CGI-S to Sharpness	2.10 ± 0.58	0.480	<0.005

4. Discussion

In this study, a Spanish language version of a validated global assessment instrument (the PGI and CGI for severity of fatigue) was both reliable and valid when administered to a population of ambulatory patients with MS. Each of the seven items of the MGH-CPFQ was highly correlated with the CGI-S and PGI-S for fatigue reflecting the validity of the instrument.

Fatigue symptoms often present as part of the symptom cluster of MS as weakness following muscular exertion and/or cognitive deficits [5,6]. However, in this study the majority of MS subject's perceived their global fatigue as only borderline or mild severity (mean PGI-S score of 2.30). These global scores were essentially equivalent to the scores obtained from a healthy, comparison group (mean PGI-S = 2.39), and substantially lower than the scores for subjects with psychiatric disorders (mean PGI-S score = 3.92) examined in the United States [22]. The MGH-CPFQ scores submitted by the MS patients were also similar to the healthy controls in the US study [22]. Therefore, these MS subjects did not equate the fatigue often related to their illness with impairment of motivation, energy, focus, or with their cognitive abilities. Although this finding may be due to cultural or geographical differences related to fatigue perception, it is more likely due to the specific, relatively stable patients making routine visits to this specific ambulatory clinic and the broad diversity of fatigue symptom severity observed in MS patients. The extremely high correlation noted between the PGI-S and CGI-S scores ($r = 0.9465$) suggests that the patient perceptions were at least consistent with the independent clinical judgment of the clinician.

Fatigue symptoms can impact productivity, interpersonal relations, and the sense of well bring across the CNS spectrum including patients with depression, multiple sclerosis, and schizophrenia [5,7-9,12,13].

Our objectives in this study were to develop a Spanish language version of the validated CGI fatigue scale and apply it in a different CNS population. A limitation of this study is that we did not compare our CGI fatigue instrument with other commonly used, but longer fatigue instruments, like the FSS or the revised 11-item fatigue questionnaire [5,17]. In addition, we did not include the EDSS [19] as an independent measure of disability distinct from fatigue. Our intent was not to replace these tools but to design a simple, reliable single item metric that would be applicable for both clinician's and patients. The PGI-S and CGI-S instruments that we have developed does provide a single item, overall impression that assesses three distinct categories of fatigue related to physical, cognitive, and emotional symptoms. Both the English and Spanish language versions offer detailed descriptors of these three categories to facilitate symptom identification and customized scoring anchors to facilitate accurate scoring.

We have now employed the CGI fatigue instrument in American psychiatric patients (Major Depressive Disorder and schizophrenia) and healthy controls, and in a second study of Latin patients with multiple sclerosis. In each group, there was a high correlation between the CGI-S and PGI-S as well as high correlations with the MGH-CPFQ providing a validation of the instrument. In both studies, the CGI-S and PGI-S were easily understood and administered by both the clinic staff and consenting subjects. Consequently, we believe this instrument can be a meaningful metric when applied in a busy clinic setting to reliably gauge symptoms of fatigue *distinct* from the specific CNS disorder being treated.

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