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Clinical Study

Apathy in multiple sclerosis: gender matters

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ABSTRACT

Apathy has been recognized as a frequent symptom in multiple sclerosis (MS) but uncertainty remains about its prevalence and clinical correlates. Therefore, the objective of this work was to assess the prevalence of apathy in patients with MS and to identify clinical and demographic correlates. A case-control study with 30 patients and 30 healthy controls matched for age, gender and education was performed. Apathy diagnosis was established using *Robert et al.'s* criteria. Additionally, apathy was assessed using the 10-item short version of the clinical-rated Apathy Evaluation Scale (AES-C-10). The Beck Depression Inventory (BDI), Modified Fatigue Impact Scale (MFIS), and Montreal Cognitive Assessment (MoCA) were used to evaluate depression, fatigue and cognitive impairment, respectively. Apathy prevalence in MS patients was 43.3%. Patients with MS had higher AES-C-10 scores than controls (13.9 vs. 12.0, $p = 0.015$). Patients with apathy presented a higher proportion of males (53.8% vs. 11.8%, $p = 0.02$), lower educational level (53.8% vs. 11.8% of patients with up to 9 years of education), higher scores on cognitive dimension of MFIS (18.0 vs. 8.0, $p = 0.048$) and BDI (13.0 vs. 7.0, $p = 0.035$) and worse performance on MoCA (24.0 vs. 26.0, $p = 0.028$). Gender was the only independent predictor of apathy, with men presenting a higher risk compared to women (OR: 9.62; 95%CI: 1.02–90.61; $p = 0.048$). In conclusion, apathy is a common neuropsychiatric disorder in MS and it is probably underdiagnosed. Male patients seem to have an increased risk of apathy, and this finding may be related to the generally more unfavorable course of MS in men.

1. Introduction

According to Marin [1], apathy is defined as lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress. This author structured the clinical expression of apathy around the concepts of reduced goal directed behavior (lack of initiative), reduced goal directed cognition (lack of plans and goals and lack of concern about one's own health) and reduced emotional concomitants of goal directed behaviors (flattened affect and emotional indifference) [1,2]. The concept of apathy has undergone changes over the ages and there is still no consensus on whether apathy should be considered primarily a disorder of drive and motivation, a disorder of emotions, or both [3]. Modern conceptualizations reflect efforts to reconcile the cognitive, motor and behavioral dimensions of apathy [4].

While cognitive dysfunction is well documented in multiple sclerosis (MS), apathy and other behavioral syndromes have received less attention and are generally not a part of the health status assessment of patients with MS [5].

The results of a meta-analysis including 23 studies revealed that apathy was one of the most common behavioral symptoms in MS, with a prevalence rate of 22% [5]. However, Chiaravolloti et al. [6] reported an apathy prevalence of 35% in their study.

The aetiology of the neuropsychiatric manifestations of MS is poorly understood. Figved et al. [7] proposed that pathophysiological changes affecting frontal-subcortical circuits and limbic structures contribute to apathy in patients with MS. More specifically, apathy has been related to damage of the medial frontal-anterior cingulate circuit, the so-called motivational circuit [8].

The aim of this study was to assess the prevalence of apathy in patients with MS and to identify clinical and demographic variables associated with its occurrence.

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2. Methods

2.1. Subjects and controls

We recruited 30 consecutive patients with a diagnosis of MS according to the 2010 revised McDonald criteria regularly followed in our department. Patients were excluded from the present study on the basis of the following criteria: primary progressive MS; history of relevant head trauma, medical, psychiatric or neurological disorder (other than MS); severe depression; illiteracy, language impairment, severe dementia or physical disability preventing cognitive assessment; alcohol, drug, or substance abuse; and relapse or steroid pulse treatment within 4 weeks preceding evaluation.

Thirty healthy controls were randomly selected from a convenience sample, matched for age, gender and education. All the patients and controls gave their written informed consent to participate in the study, which was approved by the local Ethics Committee.

2.2. Demographic and clinical assessment

We collected information about demographic aspects (age, gender, level of education) in all subjects and clinical data in MS patients, namely MS subtype, disease duration, age of onset, age at diagnosis, number of relapses in the previous year, current disease-modifying therapy and neurological disability measured by Expanded Disability Status Scale (EDSS).

2.3. Assessment of apathy

An interview based on Robert et al.'s criteria [4] was used for clinical diagnosis of apathy. According to these criteria, apathy is a disorder of motivation that persists over time and should meet the following requirements: firstly, diminished motivation must be present for at least four weeks; secondly, two of the three dimensions of apathy (reduced goal-directed behavior, goal-directed cognitive activity, and emotions) must also be present; thirdly, there should be functional impairments attributable to the apathy; and finally, symptoms and states that mimic apathy must be excluded.

To further assess apathy, the 10-item version of the clinical-rated Apathy Evaluation Scale (AES-C-10) was administered to all subjects. AES-C-10 was validated for the Portuguese population by Caeiro and Ferro [9]. AES-C uses a 4 point, Likert-type scale: "Not at all characteristic" (4 points), "Slightly characteristic" (3 points), "Somewhat characteristic" (2 points) or "Very characteristic" (1 point). AES-C ratings are based on the clinician's best judgment of the subject's "thoughts, feelings and actions" during the past 4 weeks [10]. To carry out this assessment, verbal and non-verbal data must be evaluated. Results range from a minimum of 10 points to a maximum of 40 points, with higher scores indicating more severe apathy. The clinician rater followed the Guidelines for coding severity of apathy, developed by the original author of the AES [11]. According to these specific instructions, the four response options are defined as follows: *not at all characteristic* (none, no examples given); *slightly characteristic* (trivial, questionable, minimal, for example: "I guess so", "May be a little"); *somewhat characteristic* (moderate, definite, for example "Yes", "Definitely", "I enjoy playing bridge and dancing"); *Very characteristic* (a great deal, strongly, for example: "Oh yes, absolutely, I love it.", or non-verbal evidence of intensity such as vigorous head nodding; raising amplitude or frequency of speech).

2.4. Assessment of cognitive status, depression and fatigue

Global cognitive status was evaluated by the Portuguese version of the Montreal Cognitive assessment (MoCA) [12], the presence of clinically relevant depressive symptoms was determined by the Portuguese version of Beck Depression Inventory (BDI) [13] and the presence of fatigue was assessed using the Portuguese version of the Modified Fatigue Impact Scale (MFIS) [14].

The BDI is a measure of self-reported depression severity consisting in 21 multiple choice questions. Results range from 0 to 63, and cut-offs are applied as follows: 0–14 indicates no depression, 15–19 dysphoria, 20–29 mild depression, 30–45 moderate depression and >45 severe depression.

The MFIS measures the impact of fatigue in quality of live as perceived by the subject. The test contains 21 items and comprises three levels of fatigue: physical (MFISphy), cognitive (MFIScog) and psychological (MFISpsy). The global score (MFIStotal) ranges from 0 to 84, with higher scores indicating more fatigue. The cut-off score beyond which the subject can be considered fatigued is 38.

2.5. Statistical analysis

The level of statistical significance was set at $p < 0.05$ for all analyses.

Variables were checked for normality using Kolmogorov–Smirnov and histogram inspection. Qualitative variables are reported as absolute (n) and relative frequencies (%), quantitative variables with normal distribution as mean and standard deviation (SD), and not normally distributed variables as median, first and third quartiles.

Comparisons between two groups (patients versus controls and patients with apathy versus patients without apathy) were made using independent-samples *T*-test for normally distributed variables, Mann–Whitney U-test for quantitative variables not normally distributed and chi-square (χ^2) test or Fisher exact test (when appropriate) for categorical variables.

A stepwise backward binary logistic regression model (entrance criterion $p < 0.05$ and exit criterion $p = 0.10$) was used to determine which demographic or clinical characteristics were predictors of apathy as defined by Robert et al.'s criteria. Only significant variables in the univariate comparisons were carried forward into the regression analyses.

Pearson's correlation (or Spearman correlation if normality was not assumed) was used to assess the correlation between AES-C-10 score and quantitative clinical variables. For categorical variables, as gender and educational level a Mann–Whitney *U*-test was performed.

3. Results

There were no significant differences in age, gender distribution and level of education between MS patients and healthy control groups. The demographic characteristics of the whole sample are shown in Table 1.

Regarding the clinical characteristics, 28 patients (93.3%) presented relapsing-remitting MS and 2 (6.7%) secondary progressive MS. The mean age at onset of MS was 32.4 years (SD ± 9.1) and the mean age at diagnosis was 34.6 years (SD ± 9.5). The mean disease duration was 12.3 (SD ± 7.8) and the median number of relapses in the previous year was 0 (0–1). The median EDSS was 2.5 (1.5–4.2).

The prevalence of apathy (based on Robert et al.'s criteria) in patients with MS was 43.3%. Moreover, MS patients scored significantly higher in AES-C-10, BDI and MFIS compared to