Clinical Study

Apathy in multiple sclerosis: gender matters

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Article info

Article history:
Received 21 October 2015
Accepted 7 February 2016

Keywords:
Apathy
Male gender
Multiple sclerosis
Neuropsychiatric disorders

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.

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 fronto-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.

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].

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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.
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 the apathy; 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.

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 life 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 ($\chi^2$) 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
Comparison of demographic and clinical data between MS patients with apathy and without apathy (based on Robert’s et al diagnostic criteria)

1stQ = first quartile, 3thQ = third quartile.

Median AES-C-10, MFIS, MoCA and BDI scores in patients and controls

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 30)</th>
<th>Controls (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) Median</td>
<td>44.0</td>
<td>51.0</td>
<td>0.169</td>
</tr>
<tr>
<td>[1stQ; 3thQ]</td>
<td>[37.8; 52.2]</td>
<td>[44.8; 53.5]</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>21 (70.0%)</td>
<td>17 (56.7%)</td>
<td>0.284</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9 years</td>
<td>9 (30.0%)</td>
<td>5 (16.7%)</td>
<td>0.222</td>
</tr>
<tr>
<td>&gt;9 years</td>
<td>21 (70.0%)</td>
<td>25 (83.3%)</td>
<td></td>
</tr>
</tbody>
</table>

P < 0.05 was considered statistically significant. 1stQ = first quartile, 3thQ = third quartile.

Table 2

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients</th>
<th>Controls</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AES-C-10</td>
<td>13.0 [12.0; 17.0]</td>
<td>12.0 [10.8; 14.0]</td>
<td>0.015</td>
</tr>
<tr>
<td>MFIS_total</td>
<td>35.5 [17.0; 51.0]</td>
<td>6.0 [4.0; 18.8]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MFIS_phy</td>
<td>19.0 [10.0; 26.0]</td>
<td>4.0 [1.0; 9.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MFIS_cog</td>
<td>4.0 [1.0; 5.0]</td>
<td>0.5 [0.0; 2.0]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MFIS_aps</td>
<td>10.5 [5.5; 19.3]</td>
<td>1.5 [0.0; 8.3]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MoCA</td>
<td>25.0 [23.8; 27.0]</td>
<td>27.0 [25.0; 29.0]</td>
<td>0.020</td>
</tr>
<tr>
<td>BDI</td>
<td>8.0 [4.0; 15.3]</td>
<td>5.0 [2.0; 7.0]</td>
<td>0.006</td>
</tr>
</tbody>
</table>

1stQ = first quartile, 3thQ = third quartile, AES-C-10 = 10-item short version of the Apathy Evaluation Scale, MFIS = cognitive dimension of Modified Fatigue Impact Scale, MFISphy = physical dimension of Modified Fatigue Impact Scale, MFIScog = cognitive dimension of Modified Fatigue Impact Scale, MFISTotal = global score of Modified Fatigue Impact Scale, MoCA = Montreal Cognitive Assessment, BDI = Beck Depression Inventory.

Table 3

Comparison of demographic and clinical data between MS patients with apathy and without apathy (based on Robert’s et al diagnostic criteria)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients with apathy (n = 13)</th>
<th>Patients without apathy (n = 17)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>51.0 [39.5; 53.0]</td>
<td>40.0 [36.0; 45.5]</td>
<td>0.094</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (53.8)</td>
<td>2 (11.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9 years</td>
<td>7 (53.8)</td>
<td>2 (11.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;9 years</td>
<td>6 (46.2)</td>
<td>15 (88.2)</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>13.0 [3.5; 22.0]</td>
<td>12.0 [7.0; 15.5]</td>
<td>0.934</td>
</tr>
<tr>
<td>Age at onset</td>
<td>37.0 [26.0; 42.5]</td>
<td>31.0 [26.0; 33.0]</td>
<td>0.229</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>39.0 [26.5; 44.0]</td>
<td>32.0 [26.0; 37.5]</td>
<td>0.385</td>
</tr>
<tr>
<td>Number of relapses</td>
<td>1.0 [0.0; 1.5]</td>
<td>0.0 [0.0; 1.0]</td>
<td>0.229</td>
</tr>
<tr>
<td>EDSS</td>
<td>3.5 [2.2; 6.5]</td>
<td>2.0 [1.5; 4.8]</td>
<td>0.157</td>
</tr>
<tr>
<td>MFIS_total</td>
<td>45.0 [22.5; 56.5]</td>
<td>28.0 [16.0; 43.0]</td>
<td>0.103</td>
</tr>
<tr>
<td>MFIS_phy</td>
<td>22.0 [12.5; 26.5]</td>
<td>18.0 [9.0; 26.0]</td>
<td>0.457</td>
</tr>
<tr>
<td>MFIS_cog</td>
<td>4.0 [2.0; 5.5]</td>
<td>4.0 [0.0; 4.0]</td>
<td>0.183</td>
</tr>
<tr>
<td>MFIS_aps</td>
<td>18.0 [8.0; 24.5]</td>
<td>8.0 [4.0; 16.0]</td>
<td>0.048</td>
</tr>
<tr>
<td>MoCA</td>
<td>24.0 [22.0; 25.5]</td>
<td>26.0 [24.5; 27.5]</td>
<td>0.028</td>
</tr>
<tr>
<td>BDI</td>
<td>13.0 [7.0; 22.0]</td>
<td>7.0 [3.0; 12.0]</td>
<td>0.035</td>
</tr>
</tbody>
</table>

1stQ = first quartile, 3thQ = third quartile, BDI = Beck Depression Inventory, EDSS = Expanded Disability Status Scale, MFIScog = cognitive dimension of Modified Fatigue Impact Scale, MFISphy = physical dimension of Modified Fatigue Impact Scale, MFISaphy = psychological dimension of Modified Fatigue Impact Scale, MFISTotal = global score of Modified Fatigue Impact Scale, MoCA = Montreal Cognitive Assessment, MS = multiple sclerosis.
Interestingly, we found an important gender effect on the occurrence of apathy in patients with MS. In fact, gender was the only independent predictor of apathy with an almost ten-fold higher risk in men as compared to women. Likewise, men presented higher AES-C-10 scores. Despite the lack of published data on the prevalence of apathy by gender in MS, male gender was previously reported as a risk factor for apathy in other diseases, namely Parkinson’s Disease [16], Alzheimer’s Disease [17] and Vascular Dementia [18]. Nevertheless, the underlying pathophysiology of this gender effect remains unknown.

In MS, one can hypothesize that the higher prevalence of apathy in males may be related to the generally more unfavorable course of MS in this group [19,20]. Furthermore, a recent study showed that both deep gray matter atrophy and cognitive dysfunction were worse in males [21]. A proposed explanation is that estrogen may serve as a protective factor in MS, as suggested by animal models [22]. In addition, the gender variation reported in healthy controls regarding neuroanatomy [23] and functional network properties [24] may contribute to different cognitive and neuropsychiatric manifestations of MS. However, this gender effect on apathy in MS patients has not been reported so far and needs validation.

The differences found among the educational groups, with the higher educated patients having lower prevalence of apathy, may be related to the well-known concept of the cognitive reserve. The greater intellectual enrichment attenuates the negative effect of disease burden on cognitive and motivational status [25], and, theoretically, may have the same effect on neuropsychiatric manifestations as apathy.

Finally, we found an association between apathy and cognitive fatigue, depression and cognitive impairment. In 1994, Marin et al. [26] highlighted the importance of differentiating between apathy as one symptom comprising part of a larger syndrome, such as depression or dementia, from apathy as a primary disorder. Our findings are in line with more recent studies that define apathy as a specific and independent neuropsychiatric syndrome distinct from depression, fatigue or cognitive impairment, even though these symptoms co-occur in some patients [27,28]. An attempt to better define the relationships between apathy, depression and cognitive performance in MS is expected to generate greater knowledge about the pathophysiology of these conditions. On the other hand, from a clinical point of view, distinguishing these syndromes is important, since it has therapeutic implications.

Finally, in this study apathy was not related with age of onset, age of diagnosis, disease duration or EDSS. This finding has important clinical implications by suggesting that apathy should be suspected even in earlier stages of the disease or in mildly disabled patients, as it might have a significant impact on the daily routines of MS patients.

There are some limitations to this study to be considered. Firstly, the cross-sectional design and the small sample size might have prevented to fully examine the influence of the clinical and demographic variables on apathy. Secondly, the patients presented relatively mild disability and most of them had a relapsing-remitting subtype of MS. Therefore, the results of the current study are not fully applicable to all MS patients, especially to those with a more disabling form of the disease and with a secondary progressive subtype of MS. Therefore, these results should be replicated in a larger sample of patients with MS. Lastly, the relationship between apathy and treatment with different disease modifying drugs was not explored.

5. Conclusions

Apathy is a common neuropsychiatric syndrome in MS and it is probably underdiagnosed. Therefore, we propose that the use of screening and diagnostic tools for apathy should be a part of the health status assessment in patients with MS.

Moreover, this is the first study reporting that male gender is associated with an increased risk of apathy in MS. Future studies analyzing the influence of the different MS disease modifying therapies on apathy and studies with MRI techniques are required in order to better understand the pathophysiology underlying apathy in MS, which eventually may lead to the development of specific treatment strategies.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

References

References: