Clinical Study

Apathy in multiple sclerosis: gender matters

Ana M. Novo [a],[1], Sonia Batista [a],[b],[*],[1], Joana Tenente [b], Carla Nunes [a], Carmo Macário [a], Lívia Sousa [a],[b], Freire Gonçalves [a],[b]

[a] Department of Neurology, Centro Hospitalar e Universitário de Coimbra, Praceta Mota Pinto, 3000-075 Coimbra, Portugal
[b] Faculty of Medicine, University of Coimbra, Coimbra, Portugal

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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.

* Corresponding author. Tel.: +351 239 400 448; fax: +351 239 822 637.
  E-mail address: soniarmbatista@huc.min-saude.pt (S. Batista).
[1] These authors have contributed equally to the manuscript.

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

Table 1
Demographic characteristics of patients with multiple sclerosis and healthy controls

	Patients (n = 30)	Controls (n = 30)	P
Age (years) Median [1stQ; 3thQ]	44.0 [37.8;52.2]	51.0 [44.8;53.5]	0.169
Female, n (%)	21 (70.0%)	17 (56.7%)	0.284
Education, n (%)			
⩽9 years	9 (30.0%)	5 (16.7%)	0.222
>9 years	21 (70.0%)	25 (83.3%)	

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

Table 2
Median AES-C-10, MFIS, MoCA and BDI scores in patients and controls

	Patients Median [1stQ; 3thQ]	Controls Median [1stQ; 3thQ]	P
AES-C-10	13.0 [12.0;17.0]	12.0 [10.8;14.0]	0.015
MFIS$_{total}$	35.5 [17.0;51.0]	6.0 [4.0;18.8]	<0.001
MFIS$_{phy}$	19.0 [10.0;26.0]	4.0 [1.00;9.3]	<0.001
MFIS$_{psy}$	4.0 [1.0;5.0]	0.5 [0.0;2.0]	<0.001
MFIS$_{cog}$	10.5 [5.5;19.3]	1.5 [0.0;8.3]	<0.001
MoCA	25.0 [23.8;27.0]	27.0 [25.0;29.0]	0.020
BDI	8.0 [4.0;15.3]	5.0 [2.0;7.0]	0.006

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

healthy controls (p = 0.015, p = 0.006 and p < 0.0001, respectively), suggesting the presence of more apathy, more depression and more fatigue in patients. MS patients had worse cognitive performance than controls (significantly lower MoCA scores, p = 0.020). Table 2 summarizes the performance of each group in all tests.

Compared to non-apathetic MS patients, MS patients with apathy presented a higher proportion of male gender (53.8% vs. 11.8%, p = 0.02) and lower educational level (53.8% vs. 11.8% of patients with up to 9 years of education). Moreover, patients with apathy presented significantly higher scores in MFIScog (p = 0.048) and BDI (p = 0.035) and significantly lower scores in MoCA (p = 0.028), corresponding to higher indexes of cognitive fatigue

and depression, and to worse cognitive performance, respectively. On the other hand, we found no statistically significant differences for the other clinical variables such as age, disease duration, age at onset, age at diagnosis, number of relapses, EDSS and the total, physical or psychosocial dimensions of fatigue (Table 3).

Regarding the AES-C-10 score, we found that it was correlated positively with scores on BDI (p = 0.025) and on cognitive subscale of MFIS (p = 0.028), and negatively correlated with scores on MoCA (p = 0.005). The other clinical and demographical variables were not significantly correlated with the scores on AES-C-10 (Table 4).

Gender was also associated with AES-C-10 score, with male patients presenting significantly higher scores (17.0 vs. 12.0, p = 0.004) (Fig. 1).

On the other hand, we found no association with education level (up to 9 years: median score of 16.0; >9 years: median score of 12.0, p = 0.164).

In the multivariate analysis, gender was the only variable retained as an independent predictor of apathy, with men presenting a significantly higher risk compared to women (OR:9.62; 95% CI: 1.02–90.61; p = 0.048).

The frequency of apathy in male patients was 77.8% compared to 28.6% in female patients (p = 0.02).

4. Discussion

In the present study, the prevalence of apathy in patients with MS was 43.3%, which is higher than previously reported in literature [5,6]. This finding is particularly striking considering that the study population was composed mainly by patients with relapsing-remitting MS subtype, with relatively mild disability and short disease duration. The discrepancy in the reported prevalence of apathy in MS can be partially explained by the fact that in most of the previous studies, patients are assessed simultaneously for a wide range of neuropsychiatric disorders using multi-symptom assessment methods, such as the Neuropsychiatric Inventory and the Frontal Systems Behavior Scale. To our knowledge, there was only one study that explored specifically the occurrence of apathy in MS patient using AES as a tool [15]. We might speculate that the use of specific criteria for apathy and validated scales would allow to increase sensitivity for diagnosing apathy in patients with MS, and that this neuropsychiatric symptom might be more frequent than previously reported.

Table 3
Comparison of demographic and clinical data between MS patients with apathy and without apathy (based on Robert's et al. diagnostic criteria)

Variables Median [1stQ; 3thQ], except for gender and education	Patients with apathy (n = 13)	Patients without apathy (n = 17)	p
Age	51.0 [39.5;53.0]	40.0 [36.0;45.5]	0.094
Male, n (%)	7 (53.8)	2 (11.8)	0.02
Education, n (%)			
⩽9 years	7 (53.8)	2 (11.8)	0.02
>9 years	6 (46.2)	15 (88.2)	
Disease duration	13.0 [3.5;22.0]	12.00 [7.0;15.5]	0.934
Age at onset	37.0 [26.0;42.5]	31.0 [26.0;33.0]	0.229
Age at diagnosis	39.0 [26.5;44.0]	32.0 [26.0;37.5]	0.385
Number of relapses	1.0 [0.0;1.5]	0.0 [0.0;1.0]	0.229
EDSS	3.5 [2.2;6.5]	2.0 [1.5;4.8]	0.157
MFIS$_{total}$	45.0 [22.5;56.5]	28.0 [16.0;43.0]	0.103
MFIS$_{phy}$	22.0 [12.5;26.5]	18 [9.0;26.0]	0.457
MFIS$_{psy}$	4.0 [2.0;5.5]	4.0 [0.0;4.0]	0.183
MFIS$_{cog}$	18.0 [8.0;24.5]	8.0 [4.0;16.0]	0.048
MoCA	24.0 [22.0;25.5]	26.0 [24.5;27.5]	0.028
BDI	13.0 [7.0;22.0]	7.0 [3.0;12.0]	0.035

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, MFISpsy = psychological dimension of Modified Fatigue Impact Scale, MFIStotal = global score of Modified Fatigue Impact Scale, MoCA = Montreal Cognitive Assessment, MS = multiple sclerosis

Table 4
Correlation between AES-C-10 scores and clinical variables

	AES-C-10	
	r	p
Disease duration	0.133	0.482
Age at onset	−0.012	0.951
Age at diagnosis	−0.085	0.654
Number of relapses	0.350	0.058
EDSS	−0.043	0.821
MFIS$_{total}$	0.280	0.134
MFIS$_{phy}$	0.099	0.604
MFIS$_{psy}$	0.276	0.140
MFIS$_{cog}$	0.401	0.028
MoCA	−0.499	0.005
BDI	0.408	0.025

AES-C-10 = 10-item short version of the clinical-rated Apathy Evaluation Scale, 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, MFISpsy = psychological dimension of Modified Fatigue Impact Scale, MFIStotal = global score of Modified Fatigue Impact Scale, MoCA = Montreal Cognitive Assessment
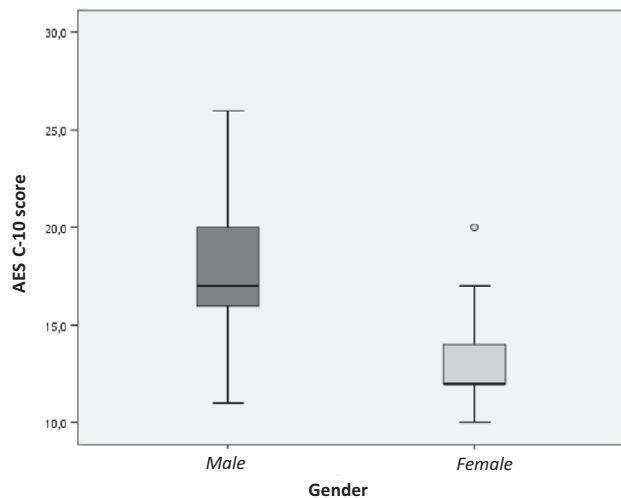
Fig. 1. Scores on AES-C-10 according to gender in multiple sclerosis patients. Male patients presented higher median scores in AES-C-10 compared to female patients, indicating more severe apathy. AES-C-10 = 10-item short version of the clinical-rated Apathy Evaluation Scale.

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 Parkinsońs Disease [16], Alzheimeŕs 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]. The hypotheses that there is a shared biological substrate for these disorders has already been put forward [29]. 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

[1] Marin RS. Apathy: a neuropsychiatric syndrome. J Neuropsychiatry Clin Neurosci 1991;3:243–54.

[2] Marin RS. Apathy: concept, syndrome, neural mechanisms, and treatment. Semin Clin Neuropsychiatry 1996;1:304–14.

[3] Starkstein SE, Leentjens AFG. The nosological position of apathy in clinical practice. J Neurol Neurosurg Psychiatry 2008;79:1088–92.

[4] Robert P, Onyike CU, Leentjens AF, et al. Proposed diagnostic criteria for apathy in Alzheimer's disease and other neuropsychiatric disorders. Eur Psychiatry 2009;24:98–104.

[5] Rosti-Otajarvi E, Hamalainen P. Behavioural symptoms and impairments in multiple sclerosis: a systematic review and meta-analysis. Mult Scler J 2012;19:31–45.

[6] Chiaravalloti ND, DeLuca J. Assessing the behavioral consequences of multiple sclerosis: an application of the Frontal Systems Behavior Scale (FrSBe). Cogn Behav Neurol 2003;16:54–67.

[7] Figved N, Klevan G, Myhr KM, et al. Neuropsychiatric symptoms in patients with multiple sclerosis. Acta Psychiatr Scand 2005;112:463–8.

[8] Cummings JL. Frontal-subcortical circuits and human behavior. Arch Neurol 1993;50:873–80.

[9] Caeiro L, Silva T, Ferro JM, et al. Metric properties of the Portuguese version of the Apathy Evaluation Scale. Psicologia Saúde Doenças 2012;13:266–82.

[10] Marin RS, Fogel BS, Hawkins J, et al. Apathy: a treatable syndrome. J Neuropsychiatry Clin Neurosci 1995;7:23–30.

[11] Marin RS, Guidelines for Apathy Evaluation Scale. Available from (URL): <http://www.dementia-assessment.com.au/symptoms/AES_Guidelines.pdf> (last accessed on July 15, 2015).

[12] Freitas S, Simões MR, Santana I, et al. Montreal Cognitive Assessment (MoCA): Versão 1. Coimbra: Faculdade de Psicologia e de Ciências da Educação da Universidade de Coimbra (2013).

[13] Vaz Serra A, Pio Abreu JL. Aferição dos quadros depressivos. I – Ensaio de aplicação do Inventário Depressivo de Beck a uma amostra portuguesa de doentes deprimidos. Coimbra Médica 1973;20:623–44.

[14] Gomes, LR. Validação da versão portuguesa da escala de impacto da fadiga modificada e da escala de severidade da fadiga na esclerose múltipla. Dissertação de mestrado integrado em Psicologia (área de especialização em Psicologia da Saúde). 2011. Universidade do Minho.

[15] Raimo S, Trojano L, Spitaleri D, et al. Apathy in multiple sclerosis: a validation study of the apathy evaluation scale. J Neurol Sci 2014;347:295–300.

[16] Pedersen KF, Alves G, Brønnick K, et al. Apathy in drug-naïve patients with incident Parkinson's disease: the Norwegian ParkWest study. J Neurol 2010;257:217–23.

[17] Ott BR, Tate CA, Gordon NM, et al. Gender differences in the behavioral manifestations of Alzheimer's disease. J Am Geriatr Soc 1996;44:583–7.

[18] Xing Y, Wei C, Chu C, et al. Stage-specific gender differences in cognitive and neuropsychiatric manifestations of vascular dementia. Am J Alzheimers Dis Other Demen 2012;27:433–8.

[19] Bergamaschi R, Berzuini C, Romani A, et al. Predicting secondary progression in relapsing-remitting multiple sclerosis: a Bayesian analysis. J Neurol Sci 2001;189:13–21.

[20] Koch M, Kingwell E, Rieckmann P, et al. The natural history of secondary progressive multiple sclerosis. J Neurol Neurosurg Psychiatry 2010;81:1039–43.

[21] Schoonheim MM, Popescu V, Rueda Lopes FC, et al. Subcortical atrophy and cognition: sex effects in multiple sclerosis. Neurology 2012;79:1754–61.

[22] Gosselin D, Rivest S. Estrogen receptor transrepresses brain inflammation. Cell 2011;145:495–7.

[23] Cosgrove KP, Mazure CM, Staley JK. Evolving knowledge of sex differences in brain structure, function, and chemistry. Biol Psychiatry 2007;62:847–55.

[24] Douw L, Schoonheim MM, Landi D, et al. Cognition is related to resting-state small-world network topology: an magnetoencephalographic study. Neuroscience 2011;175:169–77.

[25] Sumowksi JF, Leavitt VM. Cognitive reserve in multiple sclerosis. Mult Scler 2013;19:1122–7.

[26] Marin RS, Firinciogullari S, Biedrzycki RC. Group differences in the relationship between apathy and depression. J Nerv Ment Dis 1994;182:235–9.

[27] Levy ML, Cummings JL, Fairbanks LA, et al. Apathy is not depression. J Neuropsychiatry Clin Neurosci 1998;10:314–9.

[28] Caeiro L, Ferro JM, Figueira ML. Apathy in acute stroke patients. Eur J Neurol 2012;19:291–7.

[29] Figved N, Benedict R, Klevan G, et al. Relationship of cognitive impairment to psychiatric symptoms in multiple sclerosis. Mult Scler 2008;14:1084–90.