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Apathy in multiple sclerosis: A validation study of the apathy evaluation scale

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ABSTRACT

Background: Apathy is defined as lack of motivation affecting cognitive, emotional, and behavioral domains and is usually assessed by standardized scales, such as the Apathy Evaluation Scale (AES). Recently, apathy has been recognized as a frequent behavioral symptom in multiple sclerosis (MS).
Objective: To evaluate applicability and clinical-metric properties of AES in MS and the agreement between patients' and caregivers' evaluation of apathy.
Materials and methods: Seventy non-demented MS patients underwent a thorough clinical and neuropsychological assessment, including evaluation of apathy according to established clinical criteria. All patients also completed the self-report version of AES (AES-S).
Results: AES-S was easy to administer and acceptable, and showed fair internal consistency (Cronbach's alpha, $\alpha = 0.87$). The factorial analysis identified three factors, representing the cognitive dimension ($\alpha = 0.87$), a general aspect of apathy ($\alpha = 0.84$), and the behavioral–emotional aspects ($\alpha = 0.74$), respectively. The factors were significantly correlated with the total AES score (all $r_{rho} \geq 0.73$, $p < 0.001$). The total AES score showed fair convergent validity ($r_{rho} = 0.38$) and discriminant validity when compared to Expanded Disability Status Scale ($r_{rho} = 0.38$), Mini Mental State Examination ($r_{rho} = -0.17$), and Hamilton Depression Rating Scale ($r_{rho} = 0.37$). Receiver-operating characteristic curve analysis demonstrated that a cutoff > 35.5 can identify clinically significant apathy with good sensitivity (88%) and specificity (72%); such a cutoff identified apathy in 35.7% of our sample of non-demented MS patients. Total AES score was significantly correlated with reduced global cognitive efficiency and more severe frontal executive dysfunctions.
Conclusion: AES-S can be considered as an easy and reliable tool to assess apathy in non-demented MS. The use of AES-S in non-demented MS patients is clinically important since apathy is relatively frequent and is correlated to more severe cognitive dysfunction.

1. Introduction

Apathy is a complex neurobehavioral syndrome characterized by lack of motivation not attributable to emotional distress, intellectual impairment, or diminished level of consciousness [1]. Apathy is associated with poor treatment compliance, cognitive deficits (in particular frontal/executive dysfunctions), low level of functioning, and high caregiver distress in several psychiatric and neurological diseases such as major depression, Alzheimer's disease, and Parkinson's disease [2–7].

In recent years, apathy is receiving growing attention in multiple sclerosis (MS) too. A first indication that apathy is a symptom independent from disability, and disease duration has been reported by Figved et al. [8] in a study on neuropsychiatric manifestations in MS patients. Subsequently, apathy has been found to be significantly associated with cognitive dysfunctions [9], and particularly with executive dysfunctions [10], and with increased caregivers' distress [11]. However, data about prevalence of apathy in MS are rather mixed, with some authors reporting prevalence rates as high as 35% [12].

Uncertainty about prevalence estimates of apathy in MS can be partially ascribed to the fact that in most studies apathy has been evaluated by means of assessment tools not specifically developed to detect apathy, such as the Neuropsychiatric Inventory and the Frontal Systems Behavior Scale [8,12,13].

Availability of a standardized and validated scale to evaluate apathy would allow to increase comprehension of clinical impact of apathy in MS and to improve management strategies. The Apathy Evaluation Scale (AES, [1,14–17]) appears to be a good candidate for clinical evaluation of apathy in MS patients. The AES has been validated in several

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neurological diseases, such as Alzheimer's disease and other dementias, stroke, traumatic brain injury, major depression, and Parkinson's disease, in which it can reliably discriminate apathetic from non-apathetic individuals [15,18–23]. The AES has been validated in three versions: self-report version, devised for use in non-demented patients without severe cognitive impairment, with relatively preserved insight; a clinical-rated version and an informant-rated version (AES-I), suitable to evaluate patients with severe cognitive impairment or dementia, who likely have poor awareness of their emotional blunting and lack of initiative [15].

All versions of AES are brief and easy to complete, provide a quantitative assessment of general loss of motivation, and also include three specific subscores relative to cognitive, behavioral, and emotional aspects of apathy. These characteristics make AES particularly suitable for assessing changes in the manifestation of apathy over time and in response to specific treatment [24,25]. However, applicability of AES in MS has not been tested yet.

The present study aimed at evaluating applicability and clinimetric properties of the self-rated version of AES (AES-S) in a large cohort of patients affected by MS. In particular, we assessed internal consistency, convergent and divergent validity, factorial structure, and the agreement between patients' and caregivers' evaluations of apathy. We also aimed at identifying a cutoff score to detect presence of clinically significant apathetic symptoms and at evaluating cognitive correlates of apathy in non-demented MS patients.

2. Subjects and methods

2.1. Subjects

We screened 103 consecutive outpatients with diagnosis of MS according to established diagnostic criteria [26] referred to the Multiple Sclerosis Center of Moscati Hospital, Avellino (Italy). Patients were excluded from the present study on the basis of the following criteria: diagnosis of clinically evident dementia according to Diagnostic and Statistical Manual of Mental Disorders (DSM) IV-Text Revised [27]; general intellectual decline, as defined by an age- and education-adjusted score lower than 23.8 on the Mini Mental State Examination (MMSE; [28]), according to Italian norms [29]; severe disability as indicated by a score higher than 7 on the Expanded Disability Status Scale (EDSS; [30]); history of alcohol or drug abuse; history of previous psychiatric illness; history of head trauma or other neurologic diseases; illiteracy; non-native Italian-speaking subjects.

2.2. Assessment

In all patients, we collected information about demographic aspects (age, sex, level of education), medical history, and current pharmacological treatment. An interview based on Robert et al.'s [31] criteria was used for clinical diagnosis of apathy. Severity of motor symptoms and disability was assessed by EDSS [30]. Global cognitive status was assessed by MMSE [28], whereas the presence of clinically relevant depressive symptoms was assessed by Hamilton Depression Rating Scale (HDRS; [32]). Moreover, visuospatial and executive functions were assessed by Clock Drawing Test (CDT; [33]) and Frontal Assessment Battery (FAB; [34]), respectively.

After completing the above tests, all patients fulfilled the Italian version of AES-S [15,35], a questionnaire including 18 items concerning behavioral (items 2, 6, 10, 11, 12), cognitive (items 1, 3, 4, 5, 7, 9, 13, 16), emotional (items 8, 14), and other (items 15, 17, 18) aspects of apathy. All items are scored on 4-point Likert scale (to mean “not at all true”, “slightly true”, “somewhat true” or “very true”; scoring is reversed for items 6, 7, 11 because of the way they are written). The total score ranges from 18 to 72 points (higher scores indicate more severe apathy).

Finally, available patients' caregivers were required to complete the Neuropsychiatric Inventory (NPI; [36]) for evaluation of several psychological and behavioral symptoms. According to standard instructions, the frequency of each symptom is rated on a 4-point scale, and its severity on a 3-point scale; then the score for each symptom is obtained by multiplying severity by frequency. For the purpose of the present study, we considered apathy to be present according to caregivers' evaluation if the apathy score was ≥ 1 [37,38].

2.3. Statistical analysis

The following psychometric attributes were explored: acceptability, internal consistency, and construct validity.

Acceptability was considered appropriate if there was <5% of missing values and <15% of the respondents with the lowest and highest possible scores (floor and ceiling effect, [39]). Moreover, skewness of the total AES score (limits: -1 to $+1$) was determined [40].

Internal consistency was evaluated by means of Cronbach's alpha [41]. A value ≥ 0.70 was considered as acceptable [42]. Scaling assumptions referring to the correct grouping of items and the appropriateness of their summed score were checked using corrected item-total correlation (standard ≥ 0.40; [43]).

The principal component analysis was used to extract the factors followed by Promax rotation. Non-parametric correlation analysis (Spearman's r for non-parametric data) was performed to investigate the association of AES-S total score with Factor Scores.

Convergent validity was assessed by correlation analysis between AES-S total score and NPI apathy score. Discriminant validity was assessed by correlation analysis between AES and MMSE, HDRS, and EDSS. The correlation between severity of apathy and cognitive functions was assessed by correlation analysis between AES and two neuropsychological tests: FAB and CDT. Bonferroni's adjustment to the p-value was performed for multiple correlations ($p < 0.008$). Effect size for the correlation coefficient was defined by the following criteria: $r_{rho} < 0.3$ weak; $r_{rho} = 0.3$–0.5 moderate; $r_{rho} > 0.05$ strong [44].

For the purpose of standardization, we employed receiver-operating characteristic (ROC) curve analysis, using diagnostic criteria for apathy [31] as the gold standard to determine the optimal cutoff score for screening of clinically relevant apathy. Finally, we tested diagnostic agreement between patients' self-report evaluation on AES and caregivers' impression on NPI by kappa statistic [45].

All analyses were performed using SPSS version 20, with p value < 0.05 considered statistically significant.

3. Results

On the bases of exclusion criteria, 3 patients were not enrolled in the study because of clinically evident dementia, 8 for a global cognitive decline, 16 because of severe disability, 1 because of illiteracy, 2 for presence of relevant traumatic brain injury, and 3 because they were not native Italian-speakers.

The final sample consisted of 70 patients affected by MS (56 females and 14 males); 62 patients were affected by remitting relapsing MS, 5 by secondary progressive MS, and 3 by primary progressive MS. Forty-five patients were treated with interferon beta 1a, 4 patients with interferon beta 1b, 6 patients with glatiramer, 2 patients with natalizumab, 1 patient with fingolimod and 12 patients received no treatment. The demographic and clinical characteristics of the whole sample are shown in Table 1.

3.1. Validation

AES-S showed very good acceptability as shown by the lack of missing data, and by low floor or ceiling effects (1.42% and 0%, respectively). The difference between the mean and the median in the AES was 0.6 point (skewness $= 0.336$, kurtosis $= -0.270$).