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Apathy evaluation scale-informant version in progressive supranuclear palsy: Psychometric properties and clinical correlates

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1. Introduction

Progressive Supranuclear Palsy (PSP) is a rare neurodegenerative disease characterized by ocular motor dysfunction, akinesia, postural instability and cognitive and behavioral disturbances [1]. PSP can present with different phenotypes as PSP with Richardson's syndrome (PSP-RS) and the other variant syndromes of PSP (vPSP) [1,2].

Irrespective of the phenotype, a number of neuropsychiatric symptoms characterize the disease [3–5]. Up to 91% of PSP patients disclose apathy defined as a lack of motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress [4,6–9].

In neurodegenerative diseases, apathy has a strong correlation with lower patients and caregivers' quality of life [10,11], representing a major barrier to the engagement in rehabilitative activities as well as an important determinant of increased healthcare costs, functional disability and need for care [12]. Furthermore, apathy is a marker of cognitive impairment [9,13,14] representing a risk factor for conversion from Mild Cognitive Impairment to dementia in Parkinson Disease (PD) [9,15].

Available evidence shows heterogeneous data on the prevalence and clinical correlates of apathy in PSP [7,8]. Indeed, this is in part due to the lack of consensus on clinical criteria, scales and tools to evaluate apathy in PSP [16].

The Apathy Evaluation Scale has three versions: self-rated (AES-S), clinician-rated (AES-C) and informant-rated (AES-I) and evaluates and quantifies emotional, behavioral and cognitive aspects of apathy [6,17,18]. As apathetic patients usually have poor insight [19] and a lack of subjective distress [20], a scale filled by an informant, such the AES-I, may be more explanatory [19,21].

This study is part of an ongoing longitudinal project aiming at evaluating disease progression in PSP by collecting extensive demographic, motor, cognitive and behavioral data assessments [22–24]. The specific goals of the present study were (I) to report the psychometric properties of the AES-I in PSP and (II) to describe the clinical correlates of apathy in PSP patients.

2. Methods

2.1. Patients

Between November 2015 and December 2019, consecutive cases of suspected PSP referred to the Center for Neurodegenerative Diseases (CEMAND) of the University of Salerno, Italy, were proposed a dedicated set of assessments including a clinical interview, a motor evaluation, cognitive screening test and behavioral rating scale [2,5,24,25]. Patients were enrolled upon evaluation with the Movement Disorders Society (MDS) criteria for PSP [1] and the PSP phenotype was defined according to a pre-specified algorithm [52 PSP-RS, 7 PSP with predominant parkinsonism (PSP–P), 6 PSP with predominant progressive gait freezing (PSP-PGF) and 1 PSP with predominant frontal presentation (PSP–F) [1,26]. Diagnosis as well as phenotypic attribution was verified for all patients during at least one subsequent visit. As PSP-P, PSP-PGF and PSP-F included a limited number of patients, those

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subtypes were grouped together as the other variant syndromes of PSP (vPSP = 14). Details on inclusion/exclusion criteria are available elsewhere [24]. Specific additional inclusion criteria for the present study were: (1) presence of an Italian-speaking caregiver; (2) absence of severe significant language or speech impairment preventing a minimal communication with the examiner, assessing by qualitative analysis of spontaneous speech and language items of Mini-Mental State Examination (MMSE), such as naming and comprehension of the three verbal commands with arbitrary total sub-score ≥3; (3) MMSE score >13.

The project was performed in accordance with the ethical standards laid-down in the 1964 Declaration of Helsinki and was approved by the local Ethics Committee (Campania Sud) and each subject was included upon signature of the informed consent form.

2.2. Clinical and cognitive-behavioral assessments

Severity of disease was rated with the Progressive Supranuclear Palsy rating scale (PSP-rs) including 28 items divided in six sub-scores (i.e., activities of daily living, behaviour, bulbar, ocular, limb and gait/midline) [27].

Apathetic symptoms were evaluated with the AES-I as well as with the item of the Natural History and Neuroprotection in Parkinson Plus Syndromes- Parkinson Plus Scale (NNIPPS) assessing motivation [28]. Specifically, the AES-I was filled in by the patient's caregiver supported by the neuropsychologist who, when requested, reduced the ambiguity of the questions, emphasizing the difference between reduced motivation and difficulty in movements. The AES-I consists of 18 questions exploring apathetic symptoms in the previous four weeks; all items are scored on a 4-point Likert Scale ranging from 0 to 3. The total score ranges from 0 to 54 (with higher scores indicating more severe apathy).

Furthermore, quality of life was evaluated with the Progressive Supranuclear Palsy Quality of Life Questionnaire (PSP-QoL) [25] and depression was screened with the corresponding item from the NNIPPS [32] and with the Beck Depression Inventory-II (BDI-II) [16].

Global cognitive functioning was evaluated with the Italian version of the Montreal Cognitive Assessment (MOCA) [29] at baseline in all patients and after 15.86 ± 9.52 (mean ± standard deviation) months in subgroup of 22 out of 66 patients.

2.3. Statistical analysis

Demographic, clinical and cognitive variables were explored with parametric tests.

The following psychometric properties were explored for the AES-I total score: acceptability, internal consistency and construct validity. Acceptability was considered appropriate for each AES-I item if there were ≤5% of missing values and for the total score if there were ≤15% of the lowest and highest possible scores (floor and ceiling effect). Moreover, skewness of total score was determined (limits, −1 to + 1). Internal consistency was evaluated by means of Cronbach's alpha. A value ≥ 0.70 was considered acceptable. Scaling assumptions referring to the correct grouping of items and the appropriateness of their summed score were checked using corrected item-total correlation for AES-I (standard ≥0.40). Construct validity was explored with Spearman's correlation between AES-I and the PSP-rs, MOCA, PSP-QoL, NIPPS-apathy item, BDI-II and NIPPS-depression item. Correlations were considered strong with coefficients >0.70 and moderate with coefficients between 0.30 and 0.70.

Previous studies proposed that apathy is a multidimensional construct based on three different and uncorrelated factors, such as emotional, behavioral and cognitive [30,31] and that AES-I can explore such different constructs by its items [6]. Thus, we used principal component analysis, complemented by Varimax (orthogonal) rotation, to extract the three factors with the highest eigenvalues, in conformity with clinical criteria; more specifically, we selected factors with eigenvalues greater than one [32]. Then, with Spearman's correlation we explored the relationship between AES-I total score and factors and among factors; subsequently we also explored the correlations between factors of AES-I and BDI-II.

Moreover, we analyzed the demographic and clinical differences between patients with and without follow-up by Mann-Whitney test.

Based on the median value of the AES-I in our cohort, PSP patients were divided in two groups (More apathetic PSP, MA-PSP and Less Apathetic PSP, LA-PSP). The Mann-Whitney's test or χ^2 were used to compare demographic and clinical features between such groups.

Finally, ANOVA with Bootstrap method was used to investigate the effect of apathy (using MA_PSP and LA_PSP as independent variable) on the change at follow up in the global cognitive status measured with the delta value between MOCA score at T_1 and T_0 (dependent variable).

All analyses were performed with SPSS for Windows, version 23.0. All statistical tests were two-tailed, with significance level set at 0.05.

3. Results

3.1. Psychometric properties of AES-I in PSP

3.1.1. Sample' characteristics

Sixty-six patients with PSP (31M/35F) entered the present study and completed the proposed assessments. The characteristics of the enrolled sample are described in Table 1.

3.1.2. Acceptability

The mean (± standard deviation, SD) AES-I total score was 45.03 ± 9.78.

One-hundred percent of data were totally computable and there were no missing values.

In the entire sample, neither the ceiling nor the floor effects were observed for the AES-I total score (lowest possible score = 24, 3%; highest possible score = 67, 1.5%).

The skewness of AES-I was within the standard limits (AES-I total score = 0.04).

3.1.3. Reliability

Cronbach's alpha was 0.891 and, thus, it was considered acceptable for internal consistency. Item AES-I correlation was ≥0.40 with $p < 0.001$ for all questions except for item 7 "Does the patient worry about his problems less than he should?" (Table 2).

3.1.4. Convergent and divergent construct validity

Spearman's correlation showed no relation between AES-I total score and age, education, disease duration, MOCA and NNIPPS- depression item ($p > 0.05$). A moderate correlation emerged with PSP-rs (rho = 0.39, p = 0.002), PSP-QoL (rho = 0.45, p = 0.002), NNIPPS-apathy item

Table 1
Demographic and clinical variables of the PSP sample.

	Whole sample N = 66
Age, years	69.92 ± 6.53
Education, years	9.41 ± 5.23
Age onset, years	66.22 ± 6.64
Disease duration, years	3.92 ± 2.75
PSP-rs	40.73 ± 16.46
MOCA	16.20 ± 5.54
PSP-QoL	84.45 ± 40.15
BDI-II	16.84 ± 11.41
NNIPPS-depression	1.75 ± 0.89
NNIPPS- apathy	1.68 ± 1.24

Data are shown in mean ± standard deviation.
Abbreviations: MOCA, Montreal Cognitive Assessment; N, number; NNIPPS, Natural History and Neuroprotection in Parkinson Plus Syndromes- Parkinson Plus Scale; PSP-QoL, Progressive Supranuclear Palsy Quality of Life Questionnaire; PSP-rs, Progressive Supranuclear Palsy rating scale; SD, standard deviation.

Table 2
Results from the reliability, principal component analysis and correlations between BDI-II and factors.

Reliability		Principal component analysis			Target of item in AES-I
Correlation between the total score and each item		Factor 1	Factor 2	Factor 3	
AES_1	0.74*	0.70			*Interest/Autonomy*
AES_2	0.81*	0.77			*Interest/Autonomy*
AES_3	0.79*	0.64			*Interest/Autonomy*
AES_4	0.69*		0.84		*Learning/Proactivity*
AES_5	0.54*		0.83		*Learning/Proactivity*
AES_6	0.45*		0.42		*Learning/Proactivity*
AES_7	0.02	0.19			*Interest/Autonomy*
AES_8	0.67*		0.53		*Learning/Proactivity*
AES_9	0.79*	0.80			*Interest/Autonomy*
AES_10	0.69*	0.68			*Interest/Autonomy*
AES_11	0.51*	0.47			*Interest/Autonomy*
AES_12	0.32*			0.62	*Social Activities*
AES_13	0.49*			0.74	*Social Activities*
AES_14	0.51*	0.47			*Motivation*
AES_15	0.51*	0.75			*Interest/Autonomy*
AES_16	0.73*	0.79			*Interest/Autonomy*
AES_17	0.72*	0.67			*Motivation*
AES_18	0.64*	0.55			*Motivation*
BDI-II		0.44*	0.24	0.03	

Abbreviations: p < 0.001*; AES, apathy evaluation scale; BDI-II, Beck depression inventory-II.

(rho = 0.35, p = 0.01) and with BDI-II (rho = 0.54, p < 0.001).

3.1.5. Principal component analysis

All 18 questions from the AES-I were deemed appropriate for factor analysis, since the Kaiser-Meyer-Olkin (KMO) measure was 0.83. In addition, Bartlett's test was 614.96 (p < 0.001), indicating that the data satisfied the conditions for factor analysis.

Principal component analysis revealed that the three factors (such as "Cognitive-Behavioral", "Learning factor" and "Social factor") with the highest eigenvalues accounted for 58.88% of the total variance (Table 2). The factor 1 explained 30.35% of the variance and included the items 1, 2, 3, 9, 10, 11, 14, 15, 16, 17 and 18 (Cronbach's alpha = 0.90). The factor 2 explained 15.81% of the variance and included the items 4, 5, 6 and 8 (Cronbach's alpha = 0.75). The factor 3 explained 12.72% of the variance and included the items 12 and 13 (Cronbach's alpha = 0.69). The above three factors were not correlated between each other (p > 0.05). Item 7 did not belong to any specific factor and its removal increased the Cronbach's alpha value to 0.91. All factors without item 7, were significantly correlated with the AES-I total score (factor 1: rho = 0.78, p < 0.001; factor 2: rho = 0.50, p < 0.001; factor 3: rho = 0.33, p < 0.001).

The factor 1 correlated with BDI-II (rho = 0.44, p = 0.001); there was no relationship between BDI-II and factor 2 (rho = 0.24, p = 0.09) or factor 3 (rho = 0.03, p = 0.83).

3.2. Clinical features of apathetic PSP patients

According to the median value of the AES-I in the enrolled sample (44.5), 33 patients were classified as MA-PSP and 33 as LA-PSP. Demographic and cognitive features were not different between groups (p > 0.05); however, MA-PSP presented a greater BDI-II scores (p = 0.001) and a greater score of NNIPPS motivation item (p = 0.008) than LA-PSP (Table 3).

Twenty-two out of 66 patients (10 MA-PSP and 12 LA-PSP) completed the MOCA at follow up. Using ANOVA with Bootstrap method, MA_PSP presented greater decline in cognitive performances at follow up compared with LA-PSP [MA-PSP vs LA_PSP, −4.5 (7.25) vs 1.5 (3.), F = 6.12, p = 0.02)]. Furthermore, MA-PSP presented a greater increase in BDI-II (F = 6.485, p = 0.027) but not in the PSP rating scale (F = 1.438, p = 0.249) (further details reported in Supplemental Material).

Table 3
Demographic and clinical variables of MA-PSP and LA-PSP samples.

		MA-PSP N° (%)	LA-PSP N° (%)	P
Phenotypes, N (%)	**PSP-RS**	28 (84.8)	24 (72.7)	0.23
	vPSP	5 (15.2)	9 (27.3)	
Sex, N (%)	**M**	15 (45.5)	16 (48.5)	0.81
	F	18 (54.4)	1 (51.5)	
		Median (IQR)	Median (IQR)	
Age, years		66.50 (11)	70 (9)	0.28
Education, years		8.50 (12)	11 (13)	0.63
Disease duration, years		3.50 (5)	2.0 (2)	0.89
PSP-rs		42 (22)	27 (17)	0.05
MOCA		17 (11)	19 (8)	0.47
PSP-QoL		97 (64.50)	58 (71)	0.12
BDI-II		20 (23)	8 (34)	**0.001**
NNIPPS-item depression		1 (2)	2 (1)	0.93
NNIPPS-item apathy		2 (2.25)	1 (2)	**0.008**

Data are shown in mean ± SD.
Significant results are shown in bold.
Abbreviations: F, females; LA_PSP, Less apathetic Progressive Supranuclear Palsy; M, males; MA_PSP, More apathetic Progressive Supranuclear Palsy; MOCA, Montreal Cognitive Assessment; N, number; NNIPPS, Natural History and Neuroprotection in Parkinson Plus Syndromes- Parkinson Plus Scale; PSP-QoL, Progressive Supranuclear Palsy Quality of Life Questionnaire; PSP-rs, Progressive Supranuclear Palsy rating scale; SD, standard deviation.

4. Discussion

Herein we measured the clinimetric properties of the AES-I in assessing apathy in PSP and explored the clinical correlates of apathy severity in PSP. We found that the available version of the AES-I is a reliable tool in PSP with high internal consistency (Cronbach's alpha = 0.891) [6,33].

Specifically, the AES-I total score had a moderate correlation with all items, with the exception of item 7 (concerns about one's problem). Removal of the item 7 further increased internal consistency of the total score. The double negation present in the item 7 may play a role in such finding.

In accordance with the multidimensional construct of apathy, principal component analysis disclosed three different and unrelated factors of the AES-I in PSP [6]. The first factor included items related to cognitive and behavioral apathy, characterized mainly from interest and behavioral autonomy, motivation and initiatives. This factor is named "Cognitive-Behavioral" and represents a cornerstone of the most recent clinical criteria for the diagnosis of apathy [34]. Then, the second factor was composed of elements that stress learning and structuring of activities and is named "Learning factor". Finally, the third is labeled as "Social factor" and describes the patient's interest in social activities. Overall, our results are not entirely comparable to previous studies [6,33]. Borgi et al. [33] and Marin et al. [6] evaluated the multidimensional construct of apathy in heterogeneous groups of subjects including major depressive disorder, dementia, healthy elderly people and stroke. Indeed, discrepancy between previous results and our findings may depend on the different cohort of patients analyzed. Our data also show satisfactory construct validity of the AES-I supported by a moderate correlation with the corresponding screening question about apathy from the NNIPPS. Our data support in part the divergent validity. As such no correlation was shown between the AES-I and the item on depression from the NNIPPS as well as with the global cognitive status as evaluated with the MOCA total score. However, we found a correlation between the AES-I and the BDI-II. Apathy and depression are the most frequent neuropsychiatric disorders and often co-occur in a variety of neurodegenerative diseases [23,35]. Distinguishing apathy from

depression in clinical practice is a major challenge due to a massive overlap in their clinical expression [16]. Notwithstanding, a solid amount of literature suggests apathy and depression are separate entities underlined by the involvement of different neural networks [36–39]. Our data shows that the AES-I can distinguish apathy from depression when the latter is screened with a generic item as the one from the NNIPPS. However, when both apathy and depression are evaluated in depth with specific scales, the overlapping clinical features are not easily distinguishable. However, only factor 1 (cognitive-behavioral) correlated significantly with the BDI-II. This is not surprising as the items from factor 1 score loss of interest and motivation, psychomotor retardation, fatigue, lack of insight and pessimism, all features in common between apathy and depression [40]. This selective relationship between the BDI-II and apathy factor 1 is also in line with studies on other neurodegenerative diseases [41,42]. Starkstein et al. [42] administered the Hamilton Depression Rating Scale to 154 patients with Alzheimer's disease and demonstrated the presence of two factors named sadness/anxiety (sad mood, guilt and suicidal ideation, anxiety and insomnia) and apathy (psychomotor retardation, loss of interest, low energy, agitation and poor appetite). In agreement with our result, they found a significant positive correlation between both factors and apathy. Being aware of the properties of a specific scale before its addition to a study design is of utmost importance, especially when dealing with interconnected constructs as apathy and depression [43].

Confirming previous findings, we showed apathy in PSP is linked with worse quality of life [44].

At baseline, we failed to show significant demographic or clinical differences in patients disclosing greater apathy. Such data may suggest that in the initial stages of the disease apathy is integral to PSP and is not related to any specific demographic or clinical features. In line with this view, imaging studies have shown that the dorsomesial part of the frontal lobes, a hub in the fronto-basal circuit implicated in the generation of apathy, is involved in PSP since the earliest stages of disease [33]. Although the lack of any relationship between apathy and cognitive status at baseline is in contrast with previous findings in other neurodegenerative disorders [9,14], we found that patients with higher apathy scores at baseline present a greater cognitive worsening at mid-term follow up. This is in line with previous evidence reporting apathy as a risk factor for future development of cognitive decline and dementia [9,15]. The significant correlations between AES-I at baseline and PSP-rs and BDI-II at follow up further strengthen the possibility that greater apathy at baseline identifies a subgroup of patients with a more severe form of disease in terms of motor and non motor progression, irrespective of the specific PSP phenotype [45,46].

Limitations of our study include the lack of an extensive neuropsychological battery describing the cognitive profile of PSP patients and of a comparison between AES-I and AES-self report.

5. Conclusion

Standardized measures in PSP are highly needed. Apathetic symptoms are integral to PSP. Our data demonstrate that the AES-I is an accurate and reliable tool to measure apathy in PSP. The present data are also useful to support quantification of apathy in studies evaluating the effectiveness of any interventions. Greater apathy at diagnosis may represent a marker of worse cognitive deterioration at mid-term follow up. The partial overlap between apathetic and depressive components suggests the role of clustering of behavioral, cognitive and motor symptoms in the differential phenotypization of the disease.

Authors' contributions

Sofia Cuoco, PhD (scuoco@unisa.it): Substantial contributions to the conception or design of the work, analysis and interpretation of data for the work, Drafting the work. Arianna Cappiello, Msc (acappiello@unisa.it): the acquisition of data for the work, analysis and interpretation of data for the work, Drafting the work. Immacolata Carotenuto, Msc (carotenutoimma@gmail.com): the acquisition of data for the work; Rossella Bisogno, Msc (dottoressabisogno@gmail.com): the acquisition of data for the work; Filomena Abate, MD (fiabate@unisa.it): the acquisition of data for the work; Maria Francesca Tepedino, MD (tepedinomariafrancesca@gmail.com): the acquisition of data for the work; Maria Teresa Pellecchia, MD, PhD (mpellecchia@unisa.it): revising it critically for important intellectual content; Roberto Erro, MD, PhD (rerro@unisa.it): revising it critically for important intellectual content; Paolo Barone, MD, PhD (pbarone@unisa.it): revising it critically for important intellectual content; Marina Picillo, MD, PhD (mpicillo@unisa.it): Substantial contributions to the conception or design of the work, analysis and interpretation of data for the work, revising it critically for important intellectual content, Final approval of the version to be published.

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Ethics approval

The project was performed by the local Ethics Committee (Campania Sud).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The participants signed informed consent regarding publishing their data.

Declarations

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

The data has not been previously presented orally or by poster at scientific meetings.

Code availability

Not applicable.

Declaration of Competing interest

No specific funding was received for this work.

The authors declare that there are no conflicts of interest relevant to this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2023.105293.

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