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RESEARCH ARTICLE

Plasma Total and Phosphorylated α-Synuclein as Biomarkers in Multiple System Atrophy: A Multicenter Study

Xinrong Yuan[1,#], Linlin Wan[1,3,4,5,10,#], Zhao Chen[1,3,4,7], Chunrong Wang[3,4,6], Zhe Long[9], Daji Chen[1], Linliu Peng[1], Riwei Ouyang[1], Xiaokang Wu[1], Xiao Dong[1], Xiafei Long[1], Kefang Du[1], Rong Qiu[8], Beisha Tang[1,3,4,7] and Hong Jiang[1,2,3,4,7,10,*]

[1]Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, China; [2]Department of Neurology, The Third Xiangya Hospital of Central South University, Changsha, Hunan, 410008, China; [3]Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha, Hunan, 410008, China; [4]National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, China; [5]Department of Radiology, Xiangya Hospital, Central South University, Changsha, Hunan, China; [6]Department of Pathology, Xiangya Hospital, Central South University, Changsha, Hunan, China; [7]Hunan International Scientific and Technological Cooperation Base of Neurodegenerative and Neurogenetic Diseases, Changsha, China; [8]School of Computer Science and Engineering, Central South University, Changsha, Hunan, 410083, China; [9]Department of Neurology, The Second Xiangya Hospital, Central South University, Changsha, Hunan, 410011, China; [10]National International Collaborative Research Center for Medical Metabolomics, Central South University, Changsha, Hunan, China

Abstract: ***Background*:** The diagnostic value and longitudinal dynamics of plasma α-synuclein (α-syn) and phosphorylated α-syn (p-α-syn) in multiple system atrophy (MSA) remain incompletely understood. This study aimed to investigate the potential of plasma α-syn and p-α-syn as biomarkers for clinical diagnosis and progression monitoring in MSA.

***Methods*:** We quantified plasma α-syn and p-α-syn concentrations in a cross-sectional cohort comprising 228 MSA patients, 71 Parkinson's disease (PD) patients, and 218 healthy controls (HCs), as well as in a longitudinal cohort of 101 MSA patients. An independent validation cohort from another center (51 MSA, 52 HCs) was also included.

***Results*:** Plasma levels of both α-syn and p-α-syn were significantly higher in MSA patients compared to HCs (both $q<0.001$), but not compared to PD patients. Both biomarkers excellently distinguished MSA from HCs (AUCs: α-syn=0.932, p-α-syn=0.909), which was validated in the independent cohort. Both proteins were positively correlated with the severity of autonomic dysfunction. Longitudinally, p-α-syn levels increased significantly, and lower baseline α-syn levels were associated with faster motor progression ($p=0.031$).

***Discussion*:** Our study suggests that plasma α-syn and p-α-syn may have potential as supportive indicators for the clinical diagnosis and monitoring of disease progression in MSA. Their correlation with autonomic dysfunction and dynamic changes offers new insights into the pathophysiology and clinical monitoring in MSA

***Conclusion*:** Plasma α-syn and p-α-syn levels might be potential supportive indicators for clinical diagnosis and progression monitoring in MSA.

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*Address correspondence to this author at the Department of Neurology, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, China; Department of Neurology, The Third Xiangya Hospital of Central South University, Changsha, Hunan, 410008, China; Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha, Hunan, 410008, China; National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha, Hunan, 410008, China; Hunan International Scientific and Technological Cooperation Base of Neurodegenerative and Neurogenetic Diseases, Changsha, China; National International Collaborative Research Center for Medical Metabolomics, Central South University, Changsha, Hunan, China; E-mails: jianghong73868@csu.edu.cn, or jianghong73868@126.com

[#]These authors contributed equally to this work.

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1. INTRODUCTION

Multiple system atrophy (MSA) is a sporadic neurodegenerative disorder characterized by autonomic dysfunction, Parkinsonism, cerebellar ataxia, and pyramidal symptoms. Pathologically, MSA is classified as a synucleinopathy due to the misfolded and aggregated α-synuclein (α-syn) in oligodendroglial cytoplasm (GCIs) [1-5]. To date, autopsy confirmation remains the only definitive method for diagnosing MSA. Due to the clinical heterogeneity and overlapping symptoms with other disorders, the antemortem diagnosis of MSA remains challenging [6]. Moreover, the lack of objective biomarkers for assessing disease severity and progression further limits effective clinical management and the conduct of therapeutic trials. Consequently, identifying reliable biomarkers that facilitate accurate diagnosis and monitoring of MSA is urgently needed [7-12].

Although α-syn is the core pathological protein in MSA, measuring total α-syn in blood has yielded inconsistent results in MSA patients [7]. Besides, phosphorylation of α-syn at serine 129 (p-α-syn) represents another important pathological feature, which is more disease-specific and may promote α-syn aggregation [13]. The potential of blood p-α-syn as a biomarker for Parkinson's disease (PD) has been established [14-17]. However, the studies investigating the blood p-α-syn levels in MSA are quite limited.

Here, we compared plasma total α-syn and p-α-syn levels among MSA, PD, and healthy controls (HCs) in a cross-sectional study and examined their correlation with disease severity. Furthermore, we investigated the longitudinal dynamics of plasma total α-syn and p-α-syn in MSA patients. Our aim was to investigate the efficacy of plasma α-syn and p-α-syn as biomarkers for MSA diagnosis, severity, and progression.

2. METHODS

2.1. Patients

A total of 228 MSA patients, 71 PD patients, and 218 HCs were recruited in the cross-sectional study from Xiangya Hospital, Central South University. 101 participants among the 228 MSA patients received follow-up visits with a minimum interval of 6 months for a longitudinal study. Additionally, 51 MSA patients and 52 HCs were recruited as an independent validation cohort from the Third Xiangya Hospital of Central South University. This study was approved by the Ethics Committee of Xiangya Hospital and the Third Xiangya Hospital of Central South University. Written informed consent was obtained from all participants. The detailed information was presented in the Supplementary materials.

2.2. Clinical Evaluation

All patients were evaluated by two experienced neurologists. The detailed evaluations were provided in the Supplementary materials.

2.3. Measurement of α-syn and p-α-syn Levels

The α-syn and p-α-syn levels in plasma were measured using commercially available enzyme-linked immunosorbent assay kits (RF5187/RF5993, RUIFAN BIOTECHNOLOGY, China) according to the manufacturer's protocols. The average recovery rates for the spike recovery test and the linearity-of-dilution assessment are shown in Supplementary Table **1**. All average recovery rates were within 80%-120%, indicating the reliability of these two kits for the detection in plasma.

Quality control procedures were implemented to ensure assay reliability. Each sample was tested in duplicate, and only those with a coefficient of variation (CV) below 15% were included in the analysis. For inter-assay quality control, internal quality control samples with known concentrations were included in each assay run, and inter-assay CVs were maintained below 15%. All assays were performed by trained technicians who were blinded to clinical data, and standardized protocols were strictly followed across all participating centers to ensure consistency. The detailed methods were provided in the Supplementary materials.

2.4. Statistical Analysis

Statistical analyses were performed using R (4.2.2) and IBM SPSS (26.0). Continuous variables were compared using Student's t test, one-way ANOVA, Mann-Whitney U test, and Kruskal-Wallis test. Categorical variables were compared with Pearson's chi-square test. Logistic regression (LR) was used to adjust for age and sex. ROC curves were established to estimate the diagnostic efficiency of α-syn and p-α-syn. Spearman's rank correlation was used for the correlation analysis, with partial Spearman's rank correlation performed to adjust for age and sex. Linear regression and quadratic regression models were performed to explore the relationship between age and plasma α-syn & p-α-syn levels. For the longitudinal data, linear mixed models were used to investigate the trajectories of p-α-syn, α-syn, and clinical scales as the disease progressed. Subjects with follow-up measurements were included as random effects, with random intercepts specified for each subject to account for individual baseline differences. The repeated covariance structure was set to be unstructured. Furthermore, the predictive factors of MSA clinical progression were explored using the same method. Bootstrap resampling was performed to evaluate the robustness and sensitivity of the final multivariate mixed linear models. False discovery rate (FDR) was used for multiple testing correction, including subgroup analyses of variables across the MSA, PD, and HC groups [8, 18].

3. RESULTS

3.1. Cross-sectional Results

In total, 228 MSA patients, 71 PD patients, and 218 HCs were included in the cross-sectional study. Ages (p<0.001) and sex (p<0.001) composition differed significantly among the three groups (Supplementary Table **2**). No significant differences in plasma α-syn and p-α-syn levels were detected between males and females (Supplementary Table **3** and Supplementary Fig. **1**). Besides, there were no significant correlations between these parameters and ages (Supplementary Tables **4**, **5** and Supplementary Fig. **2**). The plasma p-α-syn and α-syn levels in MSA patients were significantly higher than HCs (q<0.001, FDR-corrected), while no significant difference was observed between MSA and PD patients (Fig. **1A** and **B**). The logistic regression adjusting for age

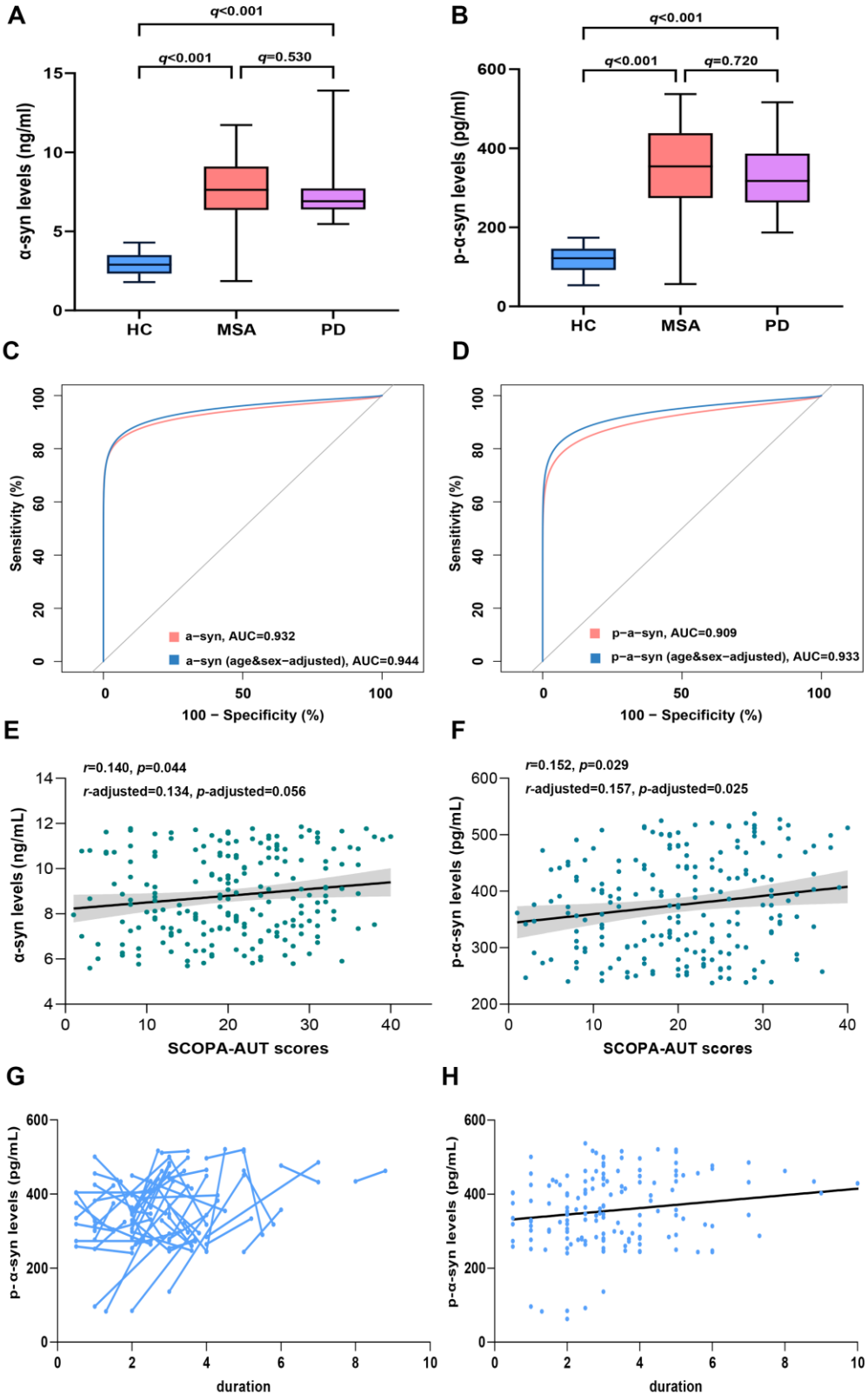

Fig. (1). The biomarker values and dynamics of plasma α-syn and p-α-syn levels in MSA patients. Boxplots illustrate the comparisons of plasma α-syn (**A**) and p-α-syn (**B**) levels among HC, MSA patients and PD patients. ROC curves for α-syn (**C**) and p-α-syn (**D**) in distinguishing MSA patients from HCs are shown, with and without adjustment for age & sex. Scatter plots display the correlations between plasma α-syn (**E**) & p-α-syn (**F**) levels and SCOPA-AUT scores in MSA patients. The actual trajectory (**G**) and linear relationship (**H**) of plasma p-α-syn levels with duration are depicted. P-adjusted represents the p value with adjustment of age and sex, r-adjusted represents the correlation coefficient with adjustment of age and sex. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

and sex yielded similar results (Supplementary Table **6**). No significant difference was found between MSA-C and MSA-P subtypes (Supplementary Table **7**). ROC analysis indicated that both plasma α-syn (AUC=0.932, threshold: 4.944 ng/mL) and p-α-syn (AUC=0.909, threshold: 205.714 pg/mL) levels could effectively distinguish MSA patients from HCs. After adjusting age and sex, both the discriminative efficacy of α-syn (AUC-adjusted=0.944) and p-α-syn (AUC-adjusted=0.933) increased (Fig. **1C** and **D**).

The Spearman's rank correlation analysis revealed that plasma α-syn (r=0.140, *p*=0.044) and p-α-syn (r=0.152, *p*=0.029) levels were significantly positively correlated with SCOPA-AUT scores, but not with other clinical scores. After adjusting age and sex through partial Spearman's rank correlation, the correlation between p-α-syn and SCOPA-AUT scores remained significant (Fig. **1E** and **F**, Supplementary Table **8**).

In the validation cohort, 51 MSA patients and 52 HCs were recruited, with demographic details summarized in Supplementary Table **9**. Both plasma α-syn (p<0.001) and p-α-syn (p<0.001) levels in MSA patients were higher than HCs (Supplementary Table **10**). ROC analysis revealed that plasma α-syn (AUC=0.898) and p-α-syn (AUC=0.809) levels could clearly discriminate MSA from HCs. After adjusting age and sex, both the discriminative efficacy of α-syn (AUC-adjusted=0.908) and p-α-syn (AUC-adjusted=0.826) improved further (Supplementary Fig. **3**).

3.2. Longitudinal Results

For the longitudinal cohort, 101 MSA patients from the cross-sectional study were followed for a mean of 1.337 ± 0.695 years. The demographic details were summarized in Supplementary Table **11**.

Mixed linear model analysis revealed that the plasma p-α-syn levels increased significantly from baseline to follow-up visit, with the mean progression rate of 8.737 pg/(ml*year) (*p*=0.019) (Fig. **1G-H**). In contrast, plasma α-syn levels did not show significant changes over the disease course (Supplementary Fig. **4** and Supplementary Table **12**). Factors associated with disease progression were further explored using UMSARS and SCOPA-AUT scores as primary outcomes in mixed linear models. In univariate anal-

Table 1 The multivariable analysis of factors affecting disease progression of clinical scales.

Fixed Effect Term	Estimate	SE	t	*p*	AIC	BIC
UMSARS-I scores-full model	-	-	-	-	1312.631	1315.884
Interception	14.725	0.986	14.932	<0.001	-	-
Duration	-1.488	0.992	-1.501	0.135	-	-
Duration*AAO	0.056	0.020	2.835	0.0005	-	-
Duration*Subtype (MSA-P)	0.995	0.319	3.116	0.002	-	-
UMSARS-II scores-full model	-	-	-	-	1167.663	1170.694
Interception	12.335	1.558	7.916	<0.001	-	-
Duration	-0.217	1.786	-0.122	0.903	-	-
Duration*AAO	0.084	0.302	2.770	0.006	-	-
Duration*Subtype (MSA-P)	1.816	0.483	3.760	<0.001	-	-
Duration*α-syn level at baseline	-0.227	0.105	-2.176	0.031	-	-
UMSARS total scores-full model	-	-	-	-	1142.635	1145.518
Interception	27.969	2.738	10.214	<0.001	-	-
Duration	-6.343	2.681	-2.366	0.019	-	-
Duration*AAO	0.198	0.0539	3.684	<0.001	-	-
Duration*Subtype (MSA-P)	2.648	0.940	2.816	0.006	-	-
SCOPA-AUT scores-full model	-	-	-	-	1140.449	1143.561
Interception	16.003	1.048	15.267	<0.001	-	-
Duration	0.815	0.271	3.006	0.003	-	-
Duration*Subtype (MSA-P)	2.314	0.324	7.154	<0.001	-	-

Estimates derived from the multivariable model were given as mean and standard error (SE).

These four multivariate mixed linear models were developed for exploring the independent factors influencing the UMSARS-I, UMSARS-II, UMSARS total, and SCOPA-AUT progression. The variables included in these multivariate models were selected using univariate analysis ($p < 0.1$). The random effect of the mixed linear models was the individual patients receiving follow-up. The detailed steps and information in constructing the univariate models were shown in supplementary tables 7-10.

AIC, Akaike's information criterion, BIC, Bayesian information criterion (BIC). MSA, multiple system atrophy. MSA-P, multiple system atrophy-parkinsonian type. OH, orthostatic hypotension. SCOPA-AUT, Scale for Outcomes in Parkinson's Disease-Autonomic. UMSARS, Unified Multiple System Atrophy Rating Scale.

yses, age at onset and subtype could significantly influence the progression rates of UMSARS-I, UMSARS-II, UMSARS total, and SCOPA-AUT scores (Supplementary Tables **13**-**16**). Further multivariate analysis indicated that baseline α-syn level was an important modifier of progression rate of UMSARS-II scores (p=0.031) (Table **1**). Bootstrap resampling confirmed the robustness of these findings (Supplementary Table **17**).

4. DISCUSSION

The present study included a large MSA cohort and investigated the diagnostic and prognostic potential of plasma α-syn and p-α-syn levels in MSA. Both plasma α-syn and p-α-syn concentrations reliably differentiated MSA patients from healthy controls. Moreover, the levels of these biomarkers were significantly correlated with the severity of autonomic dysfunction. Importantly, baseline α-syn levels demonstrated potential prognostic value for disease progression in MSA.

As the core pathological protein of MSA, α-syn in blood has been widely studied, although findings regarding its levels have been inconsistent. Lee *et al*. and Sun *et al*. found higher α-syn levels in the plasma of MSA patients than HCs [19, 20], however, another study detected no significant difference [21]. Comparisons with PD patients also yielded conflicting results, with one study reporting lower α-syn levels in MSA [19], and another finding no significant difference [21]. Here, we observed elevated plasma α-syn levels in MSA patients relative to HCs, but no significant difference compared with PD patients.

Phosphorylation of α-syn at S129 is a major component of glial cytoplasmic inclusions in MSA [3, 22]. This post-translational modification is thought to enhance α-syn toxicity by promoting aggregation [13]. While the biomarker potential of p-α-syn in cerebrospinal fluid has been explored, results have been variable, showing decreased or unchanged levels in MSA patients compared to HCs or PD patients [23-25]. In erythrocytes, Li *et al*. reported significantly increased p-α-syn levels in MSA patients compared to HCs [26]. No studies have explored the plasma p-α-syn levels in MSA patients to date. Consistent with erythrocyte findings, we found plasma p-α-syn levels were significantly elevated in MSA patients compared to HCs but did not differ from PD patients. Similar to previous studies [19, 27], we did not find a significant correlation between plasma α-syn levels and overall disease severity of MSA patients. Interestingly, we found that plasma α-syn and p-α-syn concentrations were both modestly correlated with the severity of autonomic dysfunction for the first time. Prior studies suggested that UMSARS might have limited sensitivity for detecting changes in autonomic dysfunction [28], which may partially explain differences in correlations between plasma α-syn levels and clinical scales. These observations warrant further validation using more objective measures of autonomic function.

Trajectory analysis revealed that only plasma p-α-syn levels increased significantly from baseline to follow-up, highlighting a potential role for p-α-syn in MSA pathogenesis. These longitudinal changes differ from those reported in PD [16], suggesting distinct dynamics of α-syn and p-α-syn in peripheral blood across synucleinopathies. Additionally, baseline α-syn levels emerged as a potential prognostic marker, with lower baseline levels associated with faster disease progression. This aligns with findings in PD, where lower CSF α-syn levels were linked to more rapid progression to disease milestones [29]. We speculate that the lower plasma α-syn levels might reflect greater pathological aggregation in central tissues contributing to disease progression. Besides, it is worth investigating whether disruptions of the blood-brain barrier could facilitate the entry of peripheral α-syn into the brain, as recent studies suggested that pathological α-syn aggregation may originate in peripheral organs and subsequently spread to the central nervous system during the progression of Lewy body diseases [30]. Nonetheless, these hypotheses are preliminary and warrant further experimental studies to validate.

5. STUDY LIMITATIONS

Several limitations should be acknowledged. First, only PD patients were included as disease controls. Differences between MSA and other synucleinopathies, such as dementia with Lewy bodies (DLB), remain to be explored. Second, longer follow-up periods with additional timepoints are needed to better characterize the longitudinal trajectory and predictive value of plasma α-syn and p-α-syn in MSA. Finally, future studies should account for potential confounders, including comorbidities, medication use, and variability across ELISA kit batches.

CONCLUSION

In conclusion, our findings suggest that plasma α-syn and p-α-syn may serve as potential supportive indicators for the clinical diagnosis and monitoring progression in MSA. Future studies with larger cohorts encompassing multiple synucleinopathies and additional follow-up timepoints are necessary to validate the diagnostic and prognostic performance of plasma α-syn and p-α-syn in MSA.

AUTHORS' CONTRIBUTIONS

The authors confirm their contribution to the paper as follows: XRY, LLW, and HJ, designed the study. XRY, LLW, ZC, CRW, ZL, and DJC, recruited subjects and collected data. XRY, LLW, LLP, RWOY, XKW, XD, XFL, and KFD, analyzed the data. XRY, and LLW, drafted the manuscript. ZC, ZL, RQ, BST, and HJ, edited the final version of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

FAB	=	Frontal Assessment Battery
HC	=	Healthy Controls
MMSE	=	Mini Mental State Exam
MSA	=	Multiple System Atrophy
PD	=	Parkinson's Disease
p-α-syn	=	phosphorylated α-syn
SCOPA-AUT	=	Scale for Outcomes in PD for Autonomic Symptoms

UMSARS = Unified Multiple System Atrophy Rating Scale

α-syn = α-synuclein

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of Xiangya Hospital, Central South University in China (Reference number: 202310206), and all participants gave written informed consent in accordance with the Declaration of Helsinki.

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the Declaration of Helsinki.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patients.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author [Hong Jiang], upon reasonable request.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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