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Association of autonomic symptoms with cerebrospinal fluid biomarkers in Parkinson disease and scans without evidence of dopaminergic deficit

Zhenwei Yu, PhD[a,*], Yang Li, PhD[b], and the Parkinson's Progression Markers Initiative

Abstract

Dysautonomia is common in patients with Parkinson disease (PD) since disease early phase. Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT) is a well-designed scale assessing the autonomic dysfunctions of PD patients. Our objectives were to examine the autonomic dysfunction in PD and scan without evidence of dopaminergic deficit (SWEDD) patients and to assess the correlation of autonomic dysfunctions with cerebrospinal fluid (CSF) biomarkers.

An analysis of the Parkinson's Progression Markers Initiative (PPMI) data including 414 PD patients, 60 SWEDD patients, and 170 healthy controls (HCs) with baseline CSF biomarker measurements and SCOPA-AUT assessments was presented. Autonomic symptoms including gastrointestinal, urinary, cardiovascular, pupillomotor, thermoregulatory and sexual dysfunctions were assessed by SCOPA-AUT scales. Spearman correlation test was used to examine the correlations between CSF measurements and each section of SCOPA-AUT scales in HCs and subjects with PD or SWEDD.

More severe autonomic dysfunctions were observed in patients with SWEDD than those with PD ($P < .001$). Specifically, patients with PD have lower scores on the urinary scale [4 (0–17) vs 5 (1–18)], pupillomotor scale [0 (0–3) vs 0 (0–3)], thermoregulatory scale [0 (0–4) vs 1.5 (0–10)] and sexual scale [1 (0–6) vs 2 (0–6)] compared with SWEDD patients. Thermoregulatory dysfunction scores were found correlated with CSF α-syn levels in SWEDD group, and gastrointestinal dysfunction scores were correlated with CSF Abeta1–42 in PD group. Additionally, urinary dysfunction scores were correlated with CSF total tau and tau phosphorylated at threonine 181 (p-tau181) levels in both HCs and PD patients.

Abbreviations: α-syn = α-synuclein, p-tau181 = tau phosphorylated at threonine 181, CNS = central nervous system, CSF = cerebrospinal fluid, HC = healthy control, PD = Parkinson disease, AD = Alzheimer disease, SWEDD = scan without evidence of dopaminergic deficit, MDS-UPDRS III = Movement Disorder Society sponsored Unified Parkinson Disease Rating Scale Part-III, SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic.

Keywords: autonomic symptom, CSF biomarker, Parkinson disease, Scales for Outcomes in Parkinson's disease – Autonomic, scan without evidence of dopaminergic deficit

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The authors have no conflicts of interests to disclose.

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The datasets generated during and/or analyzed during the current study are publicly available.

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1. Introduction

Parkinson's Progression Markers Initiative (PPMI) is an ongoing multicentered study represented a collaboration of Parkinson disease (PD) experts aimed to develop PD progression and diagnostic biomarkers.[1] Dysautonomia is common in patients with PD since disease early phase.[2–4] The symptoms include gastrointestinal, genitourinary, cardiovascular, sudomotor, sleep, and respiratory dysfunctions.[5] Among the clinically diagnosed PD patients, up to 20% patients have normal dopamine transporter (DAT) scans, and these patients are therefore referred as having SWEDDs.[6] Longitudinal study suggested that SWEDD subjects are unlikely to have idiopathic PD at follow-up.[7,8] While others believe that some SWEDD patients are false negative imaging cases.[6] The term "SWEDD" has been widely used in clinical practice, but no disease etiology information was provided, and the true difference between PD and SWEDD remains controversial.

SCOPA-AUT developed by Visser et al is a well-designed scale assessing the autonomic nervous system disorders in PD patients.[4] There is increasing awareness that dysautonomia in PD patients is much more common than in general population, but the frequency of dysautonomia in patients with SWEDD was not well studied. Cerebrospinal fluid (CSF) is an ideal source of biomarkers for neurodegenerative disease because of the proximity of CSF to central nervous system (CNS). Studies have reported CSF α-synuclein (α-syn) species, Abeta1–42, total-tau, and tau phosphorylated at threonine 181 (p-tau181) as diagnostic, prognostic and predictive biomarkers for PD.[9–11] However, the correlations between CSF biomarkers with autonomic dysfunctions in PD and SWEDD patients were not reported before. The objectives of this study were to assess the SCOPA-AUT and its subsection scales' differences between PD and SWEDD patients, and to clarify the correlations of dysautonomia scales with CSF biomarkers.

2. Methods

2.1. Participants and sample size

Four hundred twenty three newly diagnosed, drug-naïve PD patients, 196 HC subjects and 64 SWEDD individuals were recruited from 21 PD centers across Europe, Australia, and the United States according to the PPMI protocols (http://ppmi-info.org/study-design). From the total enrolled individuals, 414 PD patients, 170 HC subjects and 60 SWEDD patients with CSF measurements and clinical assessments at baseline visit were included in the current study. The study was approved by institutional review board of all 21 participating centers (See details at http://ppmi-info.org). Written informed consent was obtained from all participants before inclusion in the study. Subjects underwent clinical (motor, neuropsychiatric, and cognitive) and imaging assessments and donated biologic samples including CSFs. Detailed protocols of clinical assessments and biospecimen analysis were described in the PPMI biologics manual (http://ppmi-info.org). The disease severity was assessed by using Movement Disorder Society sponsored Unified Parkinson Disease Rating Scale Part-III (MDS-UPDRS III, UPDRS III) rating. Autonomic dysfunction was assessed with the SCOPA-AUT questionnaire. Demographic information, clinical characteristics and CSF measurements were downloaded on May 11, 2019 according to the data access guidelines and listed in Table 1.

2.2. CSF assessments

CSF was collected by standardized lumbar puncture procedures, and the shipment and storage were performed as described in the PPMI biologic manual (http://ppmi-info.org).

CSF Abeta1–42, total-tau and p-tau181 were measured using the Elecsys electrochemiluminescence immunoassays on the cobas e 601 platform (Roche Diagnostics, described at http://ppmi-info.org; project ID: 125). CSF α-syn levels were analyzed using appropriate commercially available sandwich type ELISA kits (BioLegend, San Diego, CA; cat. 844101, described at http://ppmi-info.org; project ID: 124) following the manufacturer's instructions.

2.3. Statistical analysis

Statistical analyses were performed using IBMS SPSS version 23 (IBM, Chicago, IL) and GraphPad Prism 6 (GraphPad Software, La Jolla, CA). Normality of clinical characteristics and CSF biomarkers were tested by using the Kolmogorov–Smirnov test. Because most of the SCOPA-AUT sub-section scales did not meet the normality assumption, we used non-parametric Spearman

Table 1

Demographic information, clinical characteristics, and CSF biomarker levels.

				Significance		
	HC	PD	SWEDD	PD vs SWEDD	PD vs HC	SWEDD vs HC
Number of subjects	170	414	60			
Age (mean ± SD)	60.77 ± 11.44	61.75 ± 9.67	60.77 ± 10.05	0.764*	0.536*	>0.999*
Sex (men: women)	111: 59	272: 142	37: 23	0.540†	0.925†	0.614†
UPDRS III (median, range)	1.00 (0–13)	20.00 (4–58)	13.50 (2–42)	**<0.001**‡	**<0.001**‡	**<0.001**‡
SCOPA-AUT (median, range)	5.00 (0–19)	8 (0–39) (N = 341)	13 (3–33) (N = 51)	**<0.001**‡	**<0.001**‡	**0.006**‡
α-syn (pg/ml) (mean ± SD)	1712.53 ± 772.10	1514.70 ± 669.70	1652.76 ± 718.58	0.330*	**0.006***	0.838*
Abeta1–42 (pg/ml) (mean ± SD)	1027.48 ± 512.51	911.91 ± 410.52	947.04 ± 353.19	0.829*	**0.011***	0.436*
Total-tau (pg/ml) (mean ± SD)	191.63 ± 82.26	169.79 ± 57.45	177.46 ± 59.88	0.623*	**<0.001***	0.247*
p-tau181 (pg/ml) (mean ± SD)	16.99 ± 8.67	14.91 ± 5.32	15.69 ± 5.87	0.518*	**<0.001***	0.197*

* Based on one-way ANOVA with Tukey post-hoc test.

† Based on Chi-square test.

‡ Based on Kruskal–Wallis with Dunn multiple comparison test.

All significant *P* values are highlighted by bold characters.

HC = healthy control; PD = Parkinson disease; SWEDD = scan without evidence of dopaminergic deficit; UPDRS III = Movement Disorder Society sponsored Unified Parkinson Disease Rating Scale Part-III; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; α-syn = α-synuclein; p-tau181 = tau phosphorylated at threonine 181.

correlation test to examine the correlations between CSF measurements and each section of SCOPA-AUT scales.

SCOPA-AUT sub-section scales between PD and SWEDD were compared by using the Mann–Whitney *U* test. One-way ANOVA followed by Tukey post-hoc test or Kruskal–Wallis with Dunn multiple comparison test was used for 3-group comparisons depending on the data normality. *P* values <.05 were regarded as significant.

3. Results

3.1. Patient characteristics and CSF measurements

The baseline demographic information, clinical characteristics and CSF biomarker results of HC, PD, and SWEDD are compared and summarized in Table 1. The UPDRS III motor score and SCOPA-AUT total score of patients with PD and SWEDD were significantly higher than those of HC subjects (Fig. 1A-B, $P < .001$, $P < .001$). Patients with SWEDD have better UPDRS III motor performance than those with PD (Fig. 1B, $P < .001$). However, the autonomic dysfunction of SWEDD subjects was even worse than those in PD group (Fig. 1A, $P < .01$).

The levels of CSF α-syn, Abeta1–42, total tau and p-tau181 were significantly lower in PD group compared with HCs (Fig. 1C-F, $P < .01$, $P < .05$, $P < .001$, $P < .001$). However, no statistically significant differences regarding the 4 CSF biomarkers were found between PD and SWEDD groups (Fig. 1C-F).

3.2. SCOPA-AUT subsection scales

Statistically significant differences of autonomic dysfunctions between PD and SWEDD were found in the urinary subsection ($P = .031$, 2 (0–11) vs 2 (0–12)), thermoregulatory sub-section ($P < .001$, 0 (0–4) vs 1.5 (0–10)), pupillomotor subsection ($p = 0.044$, 0 (0–3) vs 0 (0–3)) and sexual sub-section ($P = .033$, 1 (0–6) vs 2 (0–6)). No differences were found in gastrointestinal or

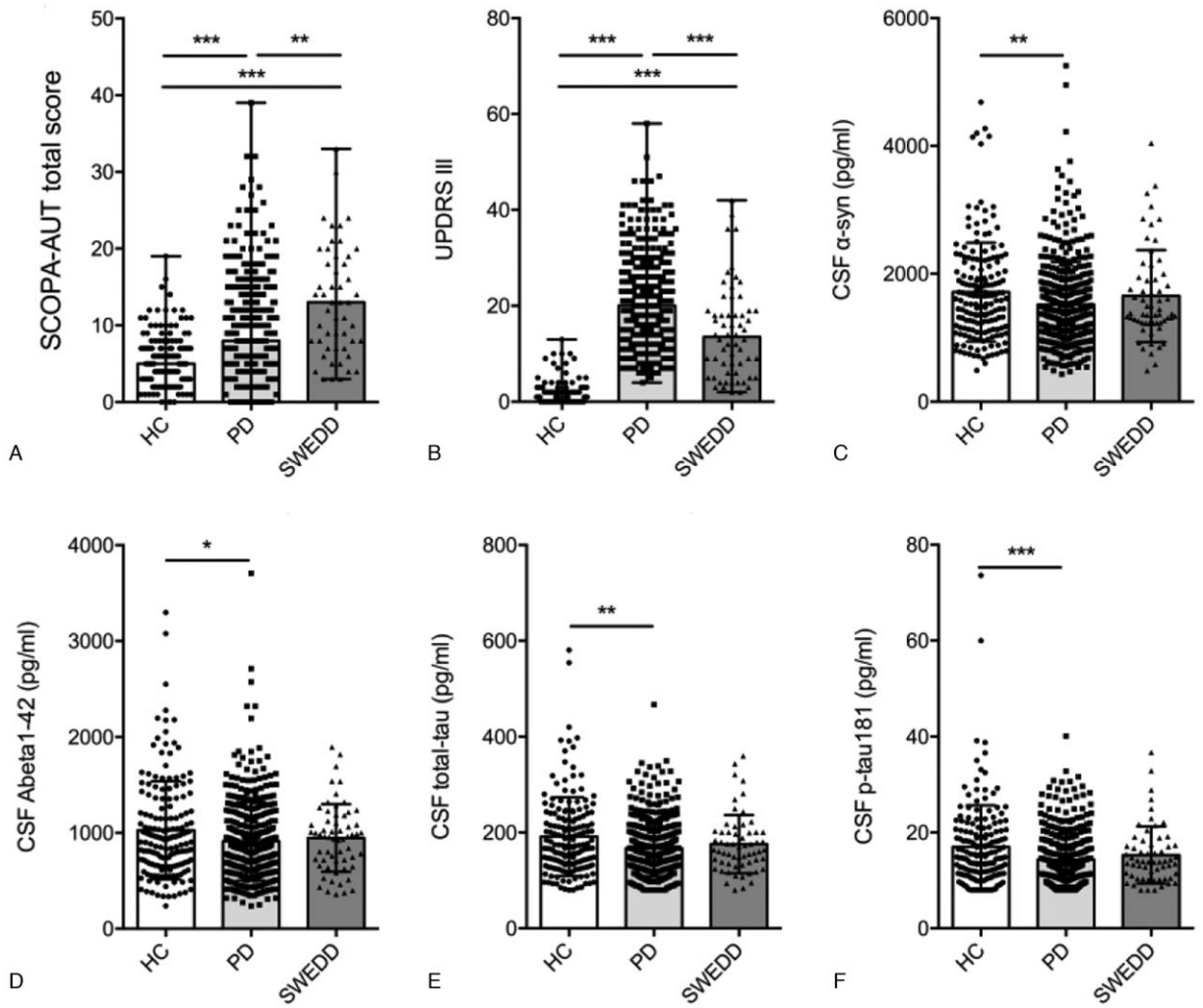

Figure 1. Evaluation of SCOPA-AUT autonomic dysfunction scale, UPDRS III motor score, CSF α-syn, Abeta1-42, total-tau and p-tau181 in PPMI cohort with PD, SWEDD and healthy controls. (A) Autonomic dysfunction scale was assessed by using SCOPA-AUT. (B) Motor dysfunction was assessed by using UPDRS III scale. (C-F) Assessments of CSF α-syn, Abeta1-42, total-tau and p-tau181. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$ (Kruskal–Wallis with Dunn multiple comparison test for SCOPA-AUT and UPDRS III comparisons, data reported as median and range; one-way ANOVA followed by Tukey post-hoc test for CSF biomarker comparisons, data reported as mean and SD). HC = healthy control; PD = Parkinson disease; SWEDD = scan without evidence of dopaminergic deficit; UPDRS III = Movement Disorder Society sponsored Unified Parkinson Disease Rating Scale Part-III; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; α-syn = α-synuclein; p-tau181 = tau phosphorylated at threonine 181.

cardiovascular sub-sections between groups. Data is summarized in Table 2.

3.3. Correlation analysis of SCOPA-AUT and CSF measurements

The correlations between CSF measurements and SCOPA-AUT sub-section scales in HCs and patients with PD and SWEDD are summarized in Supplementary Table 1, http://links.lww.com/MD/F720. Higher CSF α-syn levels within SWEDD group were associated with worsening in SCOPA-AUT thermoregulatory sub-section scales (Fig. 2A, $P < .05$, $r = 0.269$). In addition, CSF Abeta1–42 levels were negatively associated with SCOPA-AUT gastrointestinal sub-section scales within PD group (Fig. 2B, $P < .05$, $r = -0.111$). Higher CSF total-tau and p-tau181 levels within both PD and HC groups were associated with worsening in SCOPA-AUT urinary sub-section scales, respectively (Fig. 2C-D, $P < .05$, $r = 0.099$; $P < .05$, $r = 0.103$; Fig. 2E-F, $P < .05$, $r = 0.177$; $P < .01$, $r = 0.201$). No significant correlations between SCOPA-AUT cardiovascular, pupillomotor and sexual subsection scales, and CSF biomarker measurements were found in HC, PD, or SWEDD groups.

4. Discussion

In the present study, we found that patients with SWEDD have a better motor performance (UPDRS III) than PD, as reported previously.[1] However, the autonomic nervous system functions, especially the urinary function, cardiovascular function, thermoregulatory function and sexual function, were found significantly worse in patients with SWEDD than those with PD. Our results also revealed that CSF α-syn levels were correlated with thermoregulatory function in SWEDD but not PD subjects. CSF Abeta1–42 levels were correlated to gastrointestinal function, which was unique to PD subjects. Additionally, both CSF total-tau and p-tau181 levels were correlated with urinary function in HC and PD but not SWEDD subjects.

The autonomic dysfunction often occurs in patients with PD at an early stage, even precede the typical clinical characteristics and pathological changes.[12–14] Studies have shown that REM behavior disorder (RBD), urinary dysfunction, gastrointestinal dysfunction as well as other autonomic nervous system failures can serve as early sign of PD.[15–18] However, studies on non-motor symptoms in patients with SWEDD were not consistent. Similar to our findings, Fabienne et al reported that SWEDDs scored higher for almost all nonmotor symptoms and autonomic dysfunctions compared to patients with PD.[19] Other studies showed that SWEDDs were more like an early stage of PD and presented less non-motor symptoms.[6] One possible explanation is that only newly diagnosed drug-naïve patients were included in the PPMI study, and we only recruited baseline data in the present study. The autonomic failure may progress over-time in PDs, but remain stable in SWEDDs, resulting in the worsening of autonomic dysfunctions in PDs other than SWEDDs at the late phase of disease.

In practical terms, the diagnosis of PD largely relies on the clinical performance, which results in misdiagnosis especially at disease early phase. Evidence suggested that multiple CSF biomarkers can serve as potential PD diagnostic and predictive models.[20] However, the differences of CSF biomarkers between PD and SWEDD were not well studied. In consistence with previous report, we found that CSF α-syn, Abeta1–42, total-tau and p-tau181 were significantly reduced in PD patients compared with HCs. Although all of the 4 CSF biomarkers showed reducing trends in SWEDD patients compared with HCs, the differences did not reach statistical significances. Notably, no significant differences were found in CSF α-syn, Abeta1–42, total-tau, and p-tau181 between PD and SWEDD patients.

In consistence with our findings, it has been reported that patients with SWEDD bear worse autonomic dysfunctions than those with PD.[19] However, the correlation of autonomic dysfunction scores and CSF biomarkers was never studied. We found a weak correlation of gastrointestinal function score with CSF Abeta1–42 in PD but not SWEDD patients. Both CSF total-tau and p-tau181 were correlated with urinary function score in HCs and patients with PD but not with SWEDD. Although the pathogenesis of SWEDD as an independent clinical entity was not well studied, our results strongly suggest that SWEDD is unlikely to be misdiagnosis or a benign subtype of PD, in consistence with previous imaging assessment study.[7] We also found that CSF α-syn levels were correlated with thermoregulatory function in SWEDD group. Interestingly, no statistically significant correlation coexisted in both PD and SWEDD groups. Notably, all the correlation coefficients in the current study were lower than 0.3, suggesting weak efficiency in predicting clinical autonomic dysfunctions using CSF biomarkers. Further studies of other proteins in CSF may be needed to form an "ideal" panel of dysautonomia biomarkers of PD and SWEDD.

Gastrointestinal manifestations in PD have been observed and studied over the past decades.[21] So far as we know, this is the first study reporting that CSF Abeta1–42 correlates with gastrointestinal function in PD. Researchers have paid most attention to the α-syn deposition throughout enteric nervous system as well as the gut-brain communications.[22,23] In the meantime, CSF Abeta1–42 decreasing usually links to the Abeta1–42 deposition in brain and cognitive impairment.[24] Wang et al found that altering gut bacteria can improve the cognitive function in Alzheimer disease (AD) mice.[25] However, it is still obscure whether the CNS Abeta1–42 deposition leads to the gastrointestinal dysfunction or the gastrointestinal manifestations, possibly induced by gut microbiota imbalance, lead to the CNS symptoms. Furthermore, in comparison with PD, we did not

Table 2

Comparison of SCOPA-AUT subsection scales between groups.

SCOPA-AUT sub-section		Median, range	*P* value
Gastrointestinal	PD (N = 414)	2 (0–11)	.110
	SWEDD (N = 60)	2 (0–12)	
Urinary	PD (N = 412)*	4 (0–17)	**.031**
	SWEDD (N = 60)	5 (1–18)	
Cardiovascular	PD (N = 414)	0 (0–10)	.248
	SWEDD (N = 60)	1 (0–6)	
Thermoregulatory	PD (N = 414)	0 (0–4)	**<.001**
	SWEDD (N = 60)	1.5 (0–10)	
Pupillomotor	PD (N = 414)	0 (0–3)	**.044**
	SWEDD (N = 60)	0 (0–3)	
Sexual	PD (N = 343)*	1 (0–6)	**.033**
	SWEDD (N = 51)*	2 (0–6)	

* Two PD subjects were unavailable to provide urinary subsection scales. Seventy one PD subjects and 9 SWEDD subjects were unavailable to provide sexual subsection scales.

Mann–Whitney *U* test was used for group comparisons.

All significant *P* values are highlighted by bold characters.

PD = Parkinson disease; SWEDD = scan without evidence of dopaminergic deficit; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic.

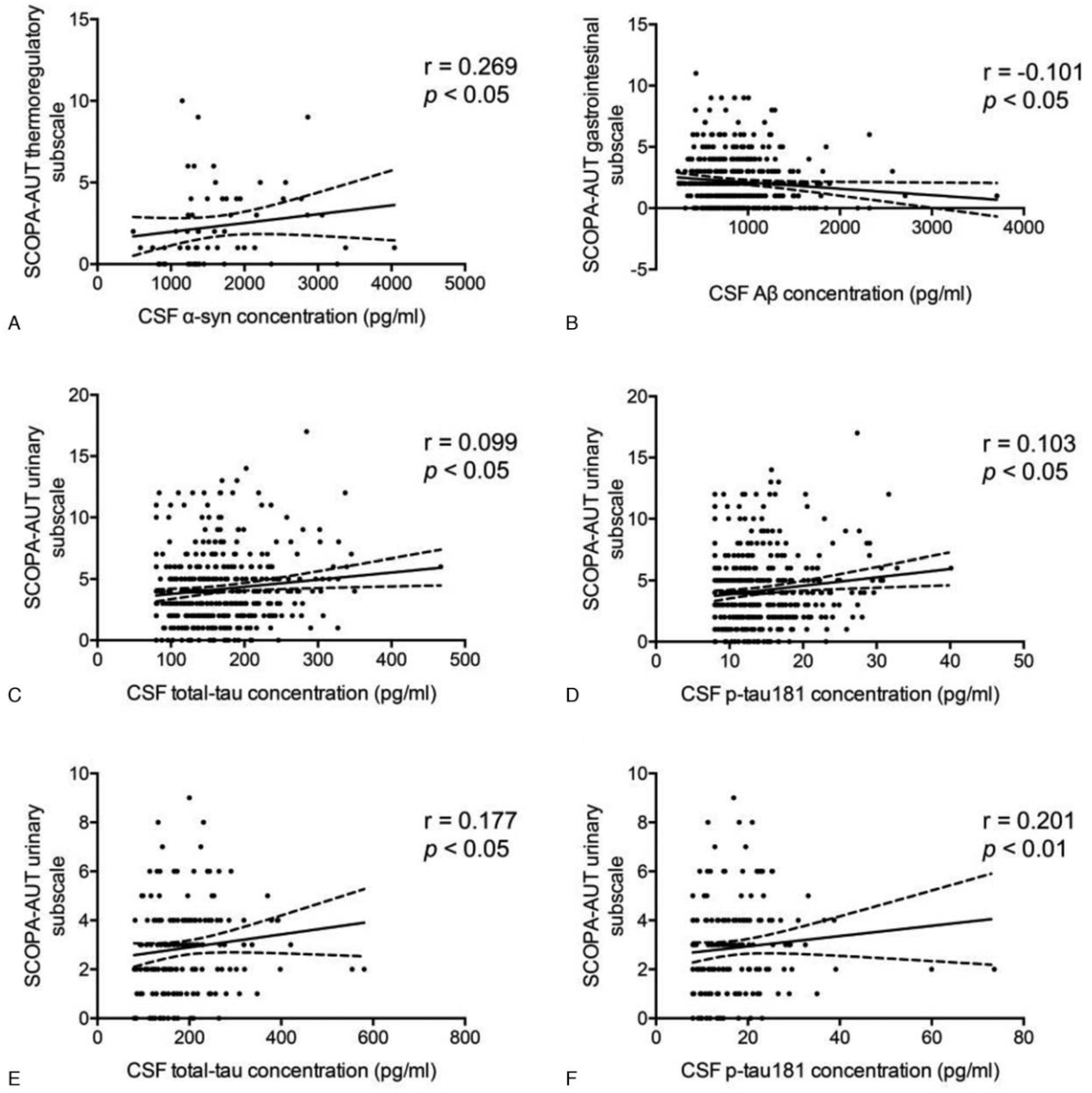

Figure 2. Linear regression analysis of autonomic symptom scales with CSF biomarkers. (A) A significant correlation between CSF α-syn concentration and SCOPA-AUT thermoregulatory sub-section scale was observed in SWEDD patients ($P < .05$, $r = 0.269$, Spearman correlation). (B) CSF Abeta1-42 concentration was correlated with SCOPA-AUT gastrointestinal sub-section scale in PD patients ($P < .05$, $r = -0.101$, Spearman correlation). (C-D) Both CSF total-tau and p-tau181 were correlated with SCOPA-AUT urinary sub-section scale in PD patients ($P < .05$, $r = 0.099$; $P < .05$, $r = 0.103$, Spearman correlation). (E-F) Both CSF total-tau and p-tau181 were correlated with SCOPA-AUT urinary sub-section scale in healthy controls ($P < .05$, $r = 0.177$; $P < .01$, $r = 0.201$, Spearman correlation). Dash lines represent 95% confidence intervals. HC = healthy control; PD = Parkinson disease; SWEDD = scan without evidence of dopaminergic deficit; SCOPA-AUT = Scales for Outcomes in Parkinson's disease – Autonomic; α-syn = α-synuclein; p-tau181 = tau phosphorylated at threonine 181.

find the correlation of CSF Abeta1–42 with gastrointestinal scales in patients with SWEDD. The correlations of urinary scales with both CSF total tau and p-tau181 were found in HCs and PD patients, suggesting a physiologically mechanistic role tau protein played in urinary function, which requires further study. Little was studied about the correlation of α-syn with thermoregulatory function. Though further investigations are needed to yield more insight into the underlying mechanisms, our results clearly provide potential pathological and physiological targets as suggested by the present study and could have good clinical significance.

Author contributions

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Formal analysis: Zhenwei Yu, Yang Li.
Funding acquisition: Zhenwei Yu.
Methodology: Yang Li.
Project administration: Zhenwei Yu.
Software: Yang Li.
Writing – original draft: Zhenwei Yu.
Writing – review & editing: Zhenwei Yu, Yang Li.

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