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Clinical utility of SUDOSCAN in predicting autonomic neuropathy in patients with Parkinson's disease

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ABSTRACT

Introduction: Autonomic neuropathy is common in Parkinson's disease (PD). We evaluated whether SUDOSCAN, a novel electrophysiological device that provides a simple and quantitative assessment of sudomotor function, was able to detect PD-related autonomic neuropathy. We also used the device to examine potential risk factors for PD-related autonomic neuropathy.

Methods: Forty-three hospitalized patients in the later stages of PD underwent assessments including a clinical history, the Unified Parkinson's Disease Rating Scale (UPDRS), the Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT), and measurement of homocysteine (HCY) and vitamin B12 levels. Sudomotor function was assessed by measuring electrochemical skin conductance (ESC) using SUDOSCAN. Forty-two healthy participants served as controls.

Results: ESC of the limbs, and especially the hands, was significantly lower in PD patients than in controls and was significantly correlated with SCOPA-AUT results. ESC was strongly negatively correlated with PD duration. The results also indicated that levodopa exposure and a higher HCY level may be risk factors for PD-related autonomic neuropathy.

Conclusions: SUDOSCAN was able to effectively identify autonomic neuropathy in PD patients. ESC was decreased in PD patients and was correlated with PD-related autonomic symptoms. These findings suggest that SUDOSCAN could be a promising new method for assessing PD-related autonomic neuropathy.

1. Introduction

Although Parkinson's disease (PD) is characterized by motor dysfunction, research is being increasingly focused on the non-motor symptoms of PD, particularly autonomic dysfunction. Up to 70%–80% of PD patients have some form of autonomic dysfunction, and autonomic symptoms can often be traced back to the time of diagnosis [1]. PD-related autonomic neuropathy presents with multiple systemic symptoms, such as orthostatic hypotension, constipation, dysuria, thermoregulatory disorder, and sexual dysfunction [2,3]. Autonomic neuropathy severely affects quality of life and increases mortality in PD patients [4].

Because the autonomic nervous system is dominated by small fibers, damage to these fibers can be difficult to detect. Intraepidermal nerve fiber density (IENFD), sympathetic skin response, and the quantitative sudomotor axonal reflex test are currently the most common methods for measuring small fiber function. However, these methods have their own limitations. For example, IENFD is invasive and time-consuming, the sympathetic skin response has poor reproducibility, and the quantitative sudomotor axonal reflex test requires specialized equipment and skilled operators. The Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms (SCOPA-AUT) is commonly used in clinical practice, but it is subjective [5].

An objective, quantitative, reliable, convenient, and noninvasive methodology is thus urgently needed for the identification of PD-related autonomic dysfunction. Sudomotor dysfunction, which is a manifestation of autonomic neuropathy, can reflect the degree of autonomic neuropathy [6]. SUDOSCAN (Impeto Medical, Paris, France) is a

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recently developed device that accurately and quickly measures sudomotor function using reverse iontophoresis and chronoamperometry [7]. Electrochemical skin conductance (ESC) of the hands and feet, which reflect sudomotor function, can be recorded with SUDOSCAN. In pioneering studies, the SUDOSCAN was used as a tool to detect autonomic damage in PD patients [8,9], however, the application of SUDOSCAN in PD-related autonomic neuropathy was not systematically studied. We therefore assessed sudomotor function in PD patients using SUDOSCAN and analyzed the risk factors for autonomic neuropathy using ESC.

2. Methods

2.1. Study populations

PD patients aged 50–80 years were recruited from the neurological ward of the Third Affiliated Hospital of Sun Yat-Sen University from January to December 2017. PD patients were required to meet the clinical PD diagnostic criteria of the International Parkinson and Movement Disorder Society [10]. Patients were excluded if they had severe cognitive or psychiatric disorders, deep brain stimulation treatment, diabetes, cancer, a former peripheral nerve injury, chronic renal dysfunction, thyroid disease, autoimmune diseases, or poor physical condition preventing them from completing the examination. Of 102 selected patients, 43 met the inclusion criterion. It should be noted that: (1) although having autonomic symptoms was not an inclusion criteria, all enrolled patients had autonomic symptoms (SCOPA-AUT score of $\geq$13); (2) according to the Unified Parkinson's Disease Rating Scale (UPDRS) scores, most included patients were in the later stages of PD; (3) one patient with PD who refused levodopa (LD) treatment because of the drug's adverse effects was excluded from the subgroup analysis because the sample size was too small to analyze. The remaining PD patients were divided into two subgroups as in a previous study [11]: short exposure to LD ($\leq$3 years; SELD group) and long exposure to LD (> 3 years; LELD group). The dose and duration of LD intake was determined using a retrospective chart review. An LD equivalent unit, based on theoretical equivalence to LD, was applied as described elsewhere [12,13]. The LD accumulation dose was then calculated from the date of first prescription until the assessment date. The daily LD dose, which is defined as the average daily LD equivalent dose in the last 3 months, was also obtained. Forty-two age- and sex-matched control participants with no reported history of neurological disease or other illnesses that might predispose them to subclinical peripheral neuropathy were enrolled from our medical examination center. Laboratory examinations were performed to rule out diabetes, tumors, and other diseases that may be associated with peripheral neuropathy. Each subject gave written informed consent of their participation, which had prior ethics approval from the research ethics committee of the Third Affiliated Hospital of Sun Yat-Sen University.

2.2. Laboratory work-up and clinical assessment

Serum homocysteine (HCY) and vitamin B12 levels were measured in all PD patients after overnight fasting. The following examinations were performed to rule out other possible causes of autonomic neuropathy in PD patients: routine blood tests and measurement of electrolytes, creatinine, liver enzymes, fasting glucose, hemoglobin A1C, thyroid function, erythrocyte sedimentation rate, and *C*-reactive protein. All PD patients had their medical history collected and underwent assessments including the UPDRS and SCOPA-AUT scores. The UPDRS and SCOPA-AUT assessments were performed by a trained neurologist during the ON stage in PD patients. All participants also underwent a sweating questionnaire [14].

2.3. Sudomotor function assessment

Assessment of sudomotor function was performed using the SUDOSCAN device following a previously described method [7]. Briefly, the participants placed their hands and feet on stainless steel plates and incremental voltage was applied (< 4 V). ESC (expressed in μS) in the hands and feet was automatically recorded. Low ESC is correlated with a high risk of abnormal sudomotor function. SUDOSCAN assessments were carried out at approximately 7:00 to 9:00 a.m., when PD patients were in the ON stage. The control participants were also assessed in the morning.

2.4. Statistics

After confirming a normal distribution using the Shapiro–Wilk test, all continuous data were analyzed using Student's *t*-test or one-way ANOVA followed by the Student–Newman–Keuls test. Chi-squared analysis and the Mann–Whitney test were used to analyze categorical variables (nominal and ordinal variables, respectively). Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic utility of SUDOSCAN. Pearson analysis (continuous variables) and Spearman correlation analysis (discontinuous variables) were used to evaluate the relationships between variables; if two variables were related, further linear regression analysis was performed. The data are expressed as mean ± SD. Significance was accepted at $p < 0.05$. Statistical analysis was performed using SPSS software v19.0 (IBM corp., Armonk, NY, USA).

3. Results

3.1. Demographics

The demographic characteristics of the participants are shown in Table 1. Sex and age were not significantly different between the PD and control groups. Body mass index was significantly lower in the PD than control group.

3.2. ESC of hands and feet, and average ESC in males and females

The ESC of both the hands and feet was significantly reduced lower in the PD than control group ($p < 0.001$; Fig. 1A). On average, the ESC were 28.0% and 19.1% lower in the hands and feet, respectively, of PD patients. In addition, ESC was significantly lower in the hands than feet in the PD group ($p < 0.01$). Although a similar trend was apparent in the controls, the difference was not significant (Fig. 1A). Average ESC (average of hands and feet ESC values) was significantly lower in the PD than control group ($p < 0.001$). No significant differences were found between males and females in either the PD or control group (Fig. 1B). The PD patients were divided into three groups (hyperhidrosis, hypohidrosis, and normal sweating) according to the sweating questionnaire results. There were no significant differences in ESC among the three groups (Supplemental Table S1).

3.3. ROC curve analysis of ESC

The diagnostic utility of ESC of the hands and feet was evaluated using ROC curve analysis (Fig. 1C and D). When selecting the maximum Youden index (0.70), the ESC cut-off point for the hands was < 58.25 μS, with 74.44% sensitivity and 95.24% specificity. The area under the ROC curve was 0.88 (Fig. 1C). When selecting the maximum Youden index (0.51), the ESC cut-off point for the feet was < 64.75 μS, with 67.44% sensitivity and 83.33% specificity. The area under the ROC curve was 0.82 (Fig. 1D).

Table 1
Demographic characteristics, ESC, scale assessment and possible risk factors in participants.

	control	PD	p (χ^2 or t-test)	PD subgroups		p (χ^2, Mann-Whitney, or ANOVA test)
				SELD	LELD	
N	42	43	–	15	27	–
Sex (male/female)	22/20	20/23	0.59[a]	7/8	13/14	0.91[b]
Age (years)	65.4 ± 8.1	66.0 ± 8.9	0.73[a]	67.4 ± 8.7	65.3 ± 9.0	0.69[b]
Duration of PD (years)	–	6.0 ± 3.9	–	2.4 ± 0.9	7.9 ± 3.5	< 0.001[c]
BMI	23.4 ± 4.4	20.6 ± 3.2	< 0.01[a]	20.7 ± 2.6*	20.6 ± 3.4**	< 0.01[b]
Hands ESC (μS)	69.0 ± 8.2	49.6 ± 14.7	< 0.001[a]	56.7 ± 10.9***	45.8 ± 15.3***##	< 0.001[b]
Feet ESC (μS)	71.9 ± 8.8	58.1 ± 12.0	< 0.001[a]	64.3 ± 8.6*	54.8 ± 12.4***##	< 0.001[b]
Average ESC (μS)	70.4 ± 7.5	53.8 ± 12.5	< 0.001[a]	60.5 ± 8.2**	50.3 ± 13.0***##	< 0.001[b]
UPDRS Score	–	38.5 ± 9.0	–	35.9 ± 8.1	39.9 ± 9.2	0.14[c]
SCOPA-AUT Score	–	32.2 ± 10.8	–	29.9 ± 9.8	33.5 ± 11.2	0.23[c]
LD exposure (years)	–	4.2 ± 2.7	–	1.8 ± 0.8	6.2 ± 2.7	–
LD daily dose (g)	–	0.65 ± 0.33	–	0.43 ± 0.22	0.80 ± 0.23	–
LD accumulation dose (g)	–	1072.4 ± 841.9	–	256.9 ± 177.0	1565.2 ± 667.3	–
HCY (μmol/L)	10.5 ± 2.5	15.6 ± 5.7	< 0.001[a]	15.1 ± 5.3***	15.8 ± 6.0***	< 0.001[b]
Vitamin B12 (pg/mL)	219.5 ± 25.3	209.0 ± 26.4	0.064[a]	211.6 ± 21.0	206.7 ± 29.3	0.16[b]

BMI, body mass index; ESC, electrochemical skin conductance; HCY, homocysteine; LD, levodopa; LELD, long exposure to levodopa > 3 years; PD, Parkinson's disease; SCOPA-AUT, Scale for Outcomes in PD for Autonomic Symptoms; SELD, short exposure to levodopa ≤3 years; UPDRS, Unified Parkinson's Disease Rating Scale.

* indicates a comparison of particular PD subgroups with the control group using ANOVA and the post-hoc Student-Newman-Keuls test.

# indicates a comparison between LELD and SELD subgroup group using ANOVA and the post-hoc Student-Newman-Keuls test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ##$p < 0.01$.

[a] Indicates the χ^2 or t-test between the control and PD group.

[b] Indicates the χ^2 or ANOVA test between the control group and PD subgroups.

[c] Indicates the Mann-Whitney test between the PD two subgroups.

3.4. Correlation between average ESC and clinical scales

Spearman correlation coefficients were calculated to reveal the relationship between average ESC and scale scores (Fig. 2A and B). Average ESC was correlated with the UPDRS scores ($r = -0.67$, $p < 0.001$), with a linear correlation ($r^2 = 0.42$; Fig. 2A). Average ESC was also correlated with the SCOPA-AUT scores ($r = -0.67$, $p < 0.001$), with a linear correlation ($r^2 = 0.46$; Fig. 2B). The score in each domain on the SCOPA-AUT is shown in Table 2, and the correlation coefficients between the SCOPA-AUT domain scores and average ESC are also presented. The severity of gastrointestinal, urinary, cardiovascular, and thermoregulatory symptoms was strongly negatively correlated with the average ESC.

3.5. Correlation of average ESC and PD characteristics

Spearman correlation analysis was performed to reveal the relationship between average ESC and age or PD duration (Fig. 2C and D). There was no significant correlation between average ESC and age ($p = 0.66$; Fig. 2C). However, average ESC was significantly correlated

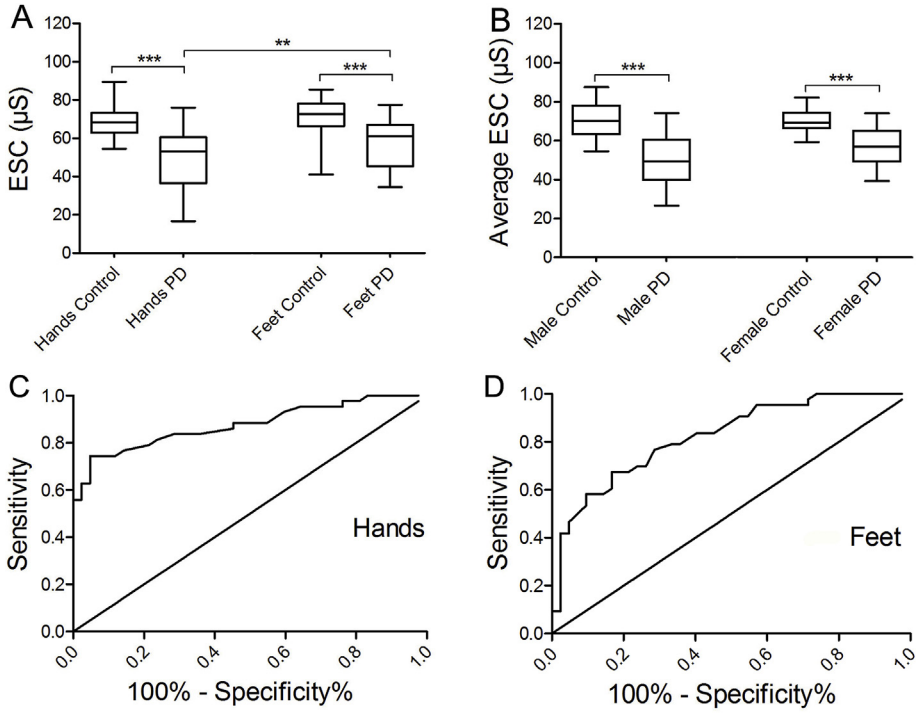

Fig. 1. Electrochemical skin conductance (ESC) in the patients with Parkinson's disease (PD) and control groups and receiver operating characteristic curve analysis. (A) ESC of the hands and feet in the PD and control groups. ESC of the hands and feet were significantly lower in the PD than control group. ESC was significantly lower in the hands than feet in the PD group. (B) Average ESC in males and females in the PD and control groups. The average ESC (average of hands and feet ESC values) was significantly lower in the PD than control group for both males and females, but there was no significant difference between males and females in the PD or control groups. ESC of the (C) hands and (D) feet exhibited high sensitivity and specificity in the diagnosis of autonomic neuropathy. The areas under the curve for ESC of the hands and feet were 0.88 and 0.82, respectively. **$p < 0.01$, ***$p < 0.001$.

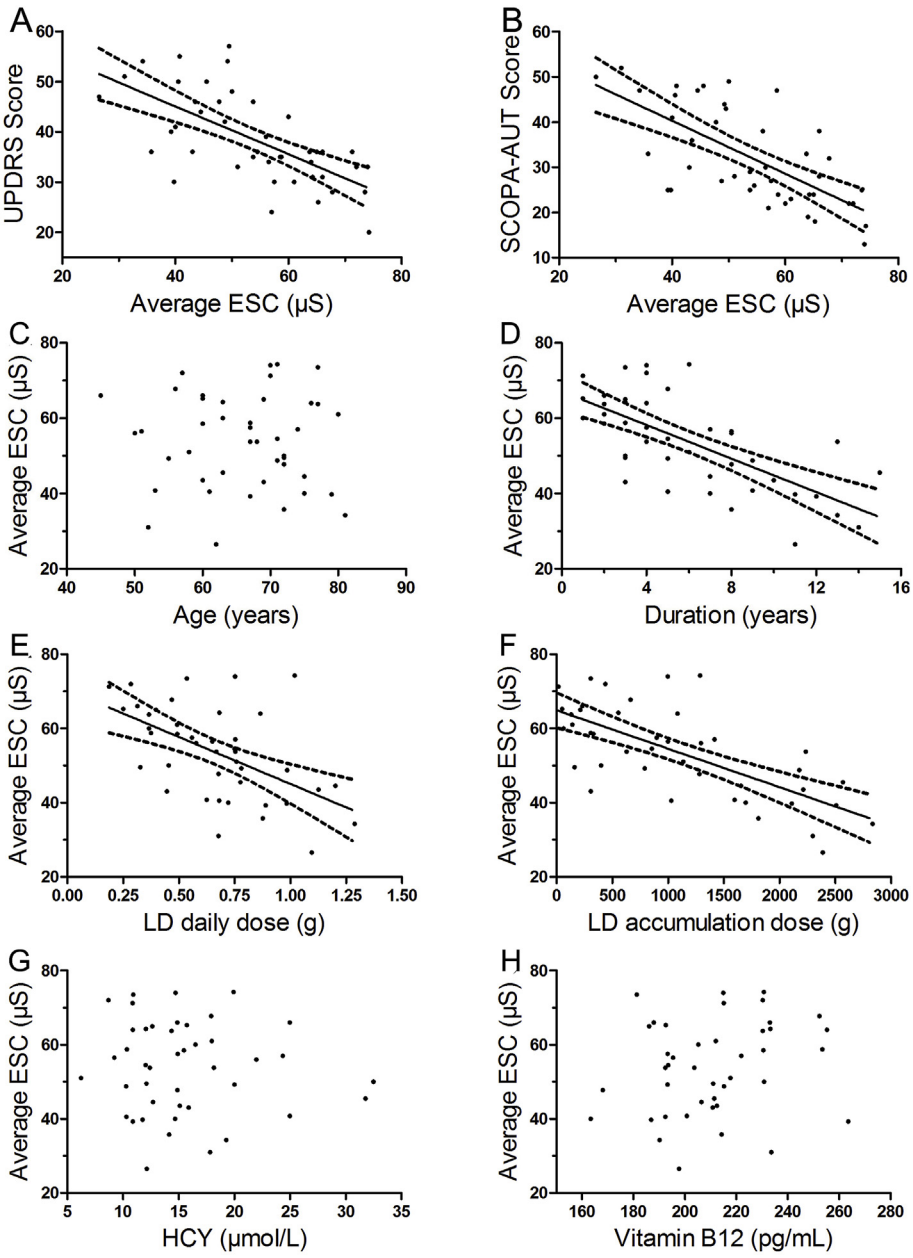

Fig. 2. Relationship between average electrochemical skin conductance (ESC) and clinical scale, age, duration, levodopa (LD) daily dose, LD accumulation dose, homocysteine (HCY) level, and vitamin B12 level in patients with Parkinson's disease (PD). (A) Scatter plot of average ESC and Unified Parkinson's Disease Rating Scale scores. The Spearman correlation coefficient was −0.67 ($p < 0.001$) with a linear correlation ($r^2 = 0.42$). (B) Scatter plot of average ESC and Scale for Outcomes in Parkinson's Disease for Autonomic Symptoms scores. The Spearman correlation coefficient was −0.67 ($p < 0.001$), with a linear correlation ($r^2 = 0.46$). (C) Scatter plot of age and average ESC. Age and average ESC were not correlated in PD patients ($p = 0.66$). (D) Scatter plot of disease duration and average ESC. The Spearman correlation coefficient was −0.69 ($p < 0.001$) with a linear correlation ($r^2 = 0.47$). (E) Scatter plot of LD daily dose and average ESC. The Pearson correlation coefficient was −0.55 ($p < 0.001$) with a linear correlation ($r^2 = 0.30$). (F) Scatter plot of LD accumulation dose and average ESC. The Pearson correlation coefficient was −0.70 ($p < 0.001$) with a linear correlation ($r^2 = 0.48$). (G) Scatter plot of HCY level and average ESC. HCY level and average ESC were not correlated ($p = 0.61$). (H) Scatter plot of vitamin B12 level and average ESC. Vitamin B12 level and average ESC were not correlated ($p = 0.28$).

Table 2
Domain scores of the SCOPA-AUT and the correlation coefficients between SCOPA-AUT domain scores and average ESC (average of hands and feet ESC values).

SCOPA-AUT domains	Mean ± SD	Median (range)	Average ESC
Gastrointestinal	11.4 ± 4.6	11 (3–18)	−0.436**
Urinary	7.5 ± 3.7	8 (1–15)	−0.614***
Cardiovascular	3.7 ± 2.0	3 (1–8)	−0.527***
Thermoregulatory	5.3 ± 2.8	5 (0–12)	−0.467**
Pupillomotor	0.56 ± 0.93	0 (0–3)	−0.155
Sex-male	3.3 ± 2.0	3 (0–6)	0.055
Sex-female	3.9 ± 2.1	5 (0–6)	−0.047
Total score	32.2 ± 10.8	29 (13–52)	−0.667***

ESC, electrochemical skin conductance; SCOPA-AUT, Scale for Outcomes in PD for Autonomic Symptoms. Spearman correlation test **p < 0.01, ***p < 0.001.

with PD duration ($r = -0.69$, $p < 0.001$), with a linear correlation ($r^2 = 0.47$; Fig. 2D).

3.6. Risk factors in subgroups of PD

Table 1 shows the LD exposure duration, LD daily dose, LD accumulation dose, HCY level, vitamin B12 level, and ESC in the PD subgroups and control group. ESC (hands, feet, and average) was significantly lower in the PD subgroups than control group (all $p < 0.05$). ESC (hands, feet, and average) was significantly lower in the LELD than SELD group (all $p < 0.01$). HCY was significantly higher in PD subgroups than control group (all $p < 0.001$), but there was no significant difference in HCY between the SELD and LELD groups. Vitamin B12 showed a downward trend with increasing LD exposure, but there was no significant difference. A Pearson analysis of the correlation between the LD daily dose, LD accumulation dose, HCY level, vitamin B12 level, and average ESC was performed. The LD daily dose was significantly correlated with average ESC ($r = -0.55$, $p < 0.001$), with a linear correlation ($r^2 = 0.30$; Fig. 2E). The LD accumulation dose was also

correlated with average ESC ($r = -0.70$, $p < 0.001$), with a linear correlation ($r^2 = 0.48$; Fig. 2F). There were no significant correlations between the HCY level, vitamin B12 level, and average ESC (Fig. 2G and H).

4. Discussion

Peripheral neuropathy is common in PD patients, although the etiology remains unclear [15]. A previous study showed that both large and small fiber neuropathy exist simultaneously in PD, but with different characteristics: small fiber neuropathy may be more closely related to PD itself, while large fiber neuropathy is more likely to be linked to age, disease severity, and comorbidities [16]. Large fiber neuropathy can be clinically identified and quantified using electrophysiology. However, small fiber neuropathy, especially in the autonomic nervous system, has not been well studied because of the atypical symptoms, lack of specific signs, and no widely available assessment methods. In the present study, we evaluated sudomotor function in PD patients using SUDOSCAN and compared the ESC results with the UPDRS and SCOPA-AUT scores. At the same time, PD patients without known autonomic disease-related comorbidities were selected to explore risk factors for autonomic neuropathy.

The clinical symptoms of sudomotor disorders vary in patients with PD-related autonomic neuropathy. Hyperhidrosis and hypohidrosis are reportedly present in 10%–100% and 0%–40% of PD patients (review [17]). Sweating dysfunction is frequently associated with motor fluctuations in PD, and is usually aggravated at the wearing-off phase [14,18]. Moreover, traditional evaluation methods cannot readily distinguish between mental and peripheral sweating. These conditions have limited the application of traditional sweating examinations in the evaluation of PD autonomic neuropathy. SUDOSCAN, a new sudomotor function detector, is free from these limitations. The examination is unaffected by basic sweating levels or central sweating regulation, and it only reflects changes in the amount of sweat caused by the excitation of autonomic sudomotor fibers under moderate electrical stimulation. In other words, it detects the ability of postganglionic axons of the sweating nerve to respond to electrical stimulation.

Sudomotor dysfunction is widely accepted as an important indicator of autonomic neuropathy [19,20]. Although measurement of the IENFD, considered the gold standard for the diagnosis of small nerve fiber neuropathy, was not performed in the present study, the ESC has been demonstrated to be closely related to nerve fiber density [21]. In addition, SUDOSCAN is widely applied in the assessment of diabetic autonomic neuropathy [7,20]. This previous research laid the foundation for the use of ESC to study PD-related autonomic neuropathy.

Two common clinical scales, the UPDRS and SCOPA-AUT, were used to confirm the correlation between ESC and PD autonomic symptoms. Our results demonstrate that average ESC was strongly negatively correlated with the scores on these two scales. In more detailed analyses of the SCOPA-AUT domains, the severity of gastrointestinal, urinary, cardiovascular, and thermoregulatory symptoms, but not pupillomotor or sexual function symptoms, was strongly negatively correlated with average ESC. Measurement of ESC effectively reflected most of the autonomic nervous symptoms of PD patients.

In the present study, the decrease in ESC was greater in the hands than feet of PD patients. This pattern was markedly different from that in metabolic peripheral neuropathies, such as diabetic neuropathy, which is length-dependent [7]. Previous studies have revealed two types of peripheral neurodegeneration in PD-related peripheral neuropathy: length-dependent and non-length-dependent [22]. The more severe decrease in ESC of the hands (non-length-dependent) appears to be unique to PD patients. Consistent with our findings, a recent study demonstrated a greater loss of intraepidermal nerve fibers in the fingertip than the leg (about 59% vs. 39%) in PD patients [23]. This study also showed a loss of sudomotor nerves, but the underlying mechanisms remain unclear.

Although autonomic neuropathy is widely recognized in PD patients, the causes of this neuropathy are still controversial [24]. LD exposure has been proposed to be a major risk factor for PD-related peripheral neuropathy [11,25]. To further examine the impact of LD exposure and accumulation in autonomic neuropathy, the PD patients were divided into two subgroups: SELD and LELD [11]. Our results revealed a significant difference in ESC between the two groups, with lower ESC in the LELD group. Notably, however, longer LD exposure may indicate a longer PD duration and older age. Thus, we further examined the relationships among age, PD duration, and average ESC. Average ESC exhibited a strong negative correlation with the PD duration, but not with age. However, the present study faced challenges in distinguishing the effects of different risk factors, particularly between the PD duration and LD exposure, because of the lack of patients with no LD exposure. A previous study showed that the risk of PD peripheral neuropathy was not influenced by the disease duration [11]. However, this conclusion is controversial when related to autonomic dysfunction because traditional nerve conduction velocity and clinical sensory symptom scales are less useful for examining the autonomic nervous system [11]. An early pathological study confirmed that alpha-synuclein deposition was present in the autonomic nerves (but not the sensory nerves) of 100% of PD patients, and the degree of alpha-synuclein deposition was positively correlated with greater autonomic dysfunction and higher Hoehn and Yahr scores [26]. The discrepancies between the studies described here highlight the need for an effective and reliable method for detecting autonomic function.

The extent of the association between LD exposure and autonomic neuropathy remains unclear. Conversion of LD to dopamine *in vivo* requires a group of methyl-donates, such as adenosylmethionine, causing an increased HCY level [27,28]. The degeneration of HCY requires methyl to be provided by methylenetetrahydrofolate, with vitamin B12/B6 acting as a coenzyme. Thus, long-term LD exposure combined with a lack of key vitamins may cause the accumulation of HCY. The present study revealed significantly higher serum HCY level, but relatively normal vitamin B12 level, in PD patients than in controls. Increased HCY can lead to peripheral neuropathy [28,29]; therefore, the accumulation of HCY should be carefully considered in the treatment of PD-related autonomic neuropathy. In addition, we found no significant difference in HCY level between the SELD and LELD groups, and there was no correlation between average ESC and HCY level. These results suggest an important role of individual differences in PD-related autonomic neuropathy.

Lower plasma vitamin B12 level have been reported in PD patients who develop peripheral neuropathy, and the level was inversely correlated with the LD exposure dose [25,30]. In the current study, there were no significant differences in the vitamin B12 level among the three groups (control, SELD, and LELD), although a downward trend was observed with an increasing LD exposure duration. However, this discrepancy may be explained by the large dose of vitamin B12 administered to the majority of enrolled patients, who had serious autonomic symptoms, in outpatient and hospital treatments.

The current study had several limitations. The PD patients who were enrolled from the ward commonly had more serious symptoms, a longer disease duration and greater LD accumulation doses than outpatients. Thus, the limited diversity of PD patients in the present study makes it difficult to accurately assess the value of SUDOSCAN in early PD-related autonomic neuropathy. At the same time, all PD patients in the current study were exposed to LD, so the assessment of risk factors was restricted by the lack of a valid control group (no LD exposure). In addition, although our present cross-sectional study samples were relatively large, clinical longitudinal studies are required to evaluate the utility of SUDOSCAN for the stratification of risk factors in PD-related autonomic neuropathy in the future.

5. Conclusions

The present study showed that ESC, measured by the noninvasive electrophysiological device SUDOSCAN, were significantly decreased in patients with later-stage PD. The extent and severity of autonomic symptoms, as well as PD severity, were negatively correlated with ESC. Future cohort studies that focus on using SUDOSCAN in more diverse populations of PD patients should be performed to enhance our understanding of the epidemiology of PD-related autonomic neuropathy and explore possible treatments.

Declarations of interest

All authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.parkreldis.2019.03.007.

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