

# Transcranial sonography in differential diagnosis of Parkinson disease and other movement disorders

Li-Shu Wang<sup>1</sup>, Teng-Fei Yu<sup>1</sup>, Bin Chai<sup>2</sup>, Wen He<sup>1</sup>

<sup>1</sup>Department of Ultrasound, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China;

<sup>2</sup>Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100070, China.

## Abstract

**Background:** Reports evaluating the efficacy of transcranial sonography (TCS) for the differential diagnosis of Parkinson disease (PD) and other movement disorders in China are scarce. Therefore, this study aimed to assess the application of TCS for the differential diagnosis of PD, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), and essential tremor (ET) in Chinese individuals.

**Methods:** From 2017 to 2019, 500 inpatients treated at the Department of Dyskinesia, Beijing Tiantan Hospital, Capital Medical University underwent routine transcranial ultrasound examination. The cross-sections at the midbrain and thalamus levels were scanned, and the incidence rates of substantia nigra (SN) positivity and the incidence rates of lenticular hyperechoic area were recorded. The echo of the SN was manually measured.

**Results:** Of the 500 patients, 125 were excluded due to poor signal in temporal window sound transmission. Among the 375 individuals with good temporal window sound transmission, 200 were diagnosed with PD, 90 with ET, 50 with MSA, and 35 with PSP. The incidence rates of SN positivity differed significantly among the four patient groups ( $\chi^2 = 121.061$ ,  $P < 0.001$ ). Between-group comparisons were performed, and the PD group showed a higher SN positivity rate than the ET ( $\chi^2 = 94.898$ ,  $P < 0.017$ ), MSA ( $\chi^2 = 57.619$ ,  $P < 0.017$ ), and PSP ( $\chi^2 = 37.687$ ,  $P < 0.017$ ) groups. SN positivity showed a good diagnostic value for differentiating PD from the other three movement diseases, collectively or individually. The incidences of lenticular hyperechoic area significantly differed among the four patient groups ( $\chi^2 = 38.904$ ,  $P < 0.001$ ). Next, between-group comparisons were performed. The lenticular hyperechoic area was higher in the PD group than in the ET ( $\chi^2 = 6.714$ ,  $P < 0.017$ ) and MSA ( $\chi^2 = 18.680$ ,  $P < 0.017$ ) groups but lower than that in the PSP group ( $\chi^2 = 0.679$ ,  $P > 0.017$ ).

**Conclusion:** SN positivity could effectively differentiate PD from ET, PSP, and MSA in a Chinese population.

**Keywords:** Transcranial sonography; Movement disorders; Parkinson disease

## Introduction

The clinical diagnosis of Parkinson disease (PD) remains challenging, and approximately 80% of cases of PD were accurately diagnosed.<sup>[1,2]</sup> This is due to the similarities in the early disease stages between PD and other movement disorders, including dementia with Lewy bodies, multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration, essential tremor (ET), drug-induced Parkinsonism, and vascular Parkinsonism.<sup>[2,3]</sup> Meanwhile, it is clear that an accurate diagnosis of PD is an important requirement for its proper therapeutic management.<sup>[4]</sup> Magnetic resonance imaging (MRI) is an important imaging method used in neurological diseases. However, atrophy, signal alterations in the putamen, and several infratentorial regions are considered

to have a very high specificity in differentiating MSA from PD and healthy controls, although the sensitivity of this approach is considered insufficient, particularly in early disease stages.<sup>[5]</sup> Another research has also shown that 3T MRI can have relatively large false-positive results in the diagnosis of PD.<sup>[6]</sup> Functional imaging techniques, such as positron emission tomography (PET) with <sup>11</sup>C-raclopride and single-photon emission computed tomography with <sup>123</sup>I-iodobenzamide, could differentially diagnose PD and some atypical Parkinsonian syndromes (aPS), but it could not accurately diagnose all patients.<sup>[7]</sup> In addition, PET with [<sup>18</sup>F] fluorodeoxyglucose has been applied for assessing regional cerebral glucose metabolism as a marker of neuronal activity and neurodegeneration, with a differential diagnostic accuracy for neurodegenerative Parkinsonism that is similar to that of transcranial B-mode sonography (TCS).<sup>[8]</sup> TCS has many advantages,

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**Correspondence to:** Dr. Wen He, Beijing Tiantan Hospital, Capital Medical University, No. 119, West Nansihuan Road, Beijing 100070, China  
E-Mail: hewen@bjtth.org

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including relatively low cost of equipment, wide availability (is capable of being performed with transducers that echocardiography can be used), short exam time, non-invasive nature, unlimited repeatability, mobility, bedside availability, and not being influenced by patient movements.<sup>[9]</sup> As TCS is based on a different imaging principle from other neuroimaging modalities, it displays intracranial structures with different perspectives. Deep brain tissue imaging can be achieved at a high image resolution using TCS.<sup>[10]</sup> This method can provide high-resolution real-time dynamic imaging. Patient's movement does not adversely affect the results. It can be used in cardiac ultrasound, and it is widely applied in the field of cardiology.<sup>[11]</sup> On the contrary, PET and single photon emission computed tomography (SPECT) are expensive, require radioactivity, and are difficult to popularize.<sup>[12]</sup>

Since Becker *et al*<sup>[13]</sup> first applied TCS in 1995 to detect substantia nigra (SN) hyperechogenicity in patients with PD, its use for the diagnosis of PD and the differential diagnosis of movement disorders has attracted extensive attention from many researchers.<sup>[14-16]</sup> However, most studies on the use of TCS in movement disorders have been conducted in Europe, America, Japan, and Korea.<sup>[17,18]</sup> Reports assessing the application of TCS for the differential diagnosis of PD and other movement disorders in China are scarce. Therefore, the present study aimed to evaluate TCS for the differential diagnosis of PD, ET, MSA, and PSP in Chinese individuals.

## Methods

### Ethical approval

The current study was approved by the Ethics Committee of Beijing Tiantan Hospital (No. KY2019-101-01), Capital Medical University. Informed consent was provided by each patient before enrolment.

### Subjects

From December 2017 to December 2019, 500 inpatients treated in the Department of Dyskinesia of Beijing Tiantan Hospital, Capital Medical University were selected for this study and they underwent routine transcranial ultrasound examination. Inclusion criteria were: (1) older than 18 years of age and (2) hospitalization in the Department of Dyskinesia in our hospital, with data of complete clinical scores (eg, unified PD rating scale part III [UPDRS-III], Hoehn and Yahr [H&Y] scale scores) available. Exclusion criteria were: (1) Parkinson syndrome caused by encephalitis, cerebrovascular disease, craniocerebral tumors, trauma, or drugs; and (2) poor sound transmission through the temporal window (ineligibility to undergo TCS).

### Diagnosis and grouping

The gold standard for diagnosis or differential diagnosis of PD is histopathology. Because this could not be performed in the current patients, clinical diagnostic standards were used to make a diagnosis. Assessment was performed by two neurologists (each having >5 years experience in

handling patients with movement disorders). When a consensus diagnosis could not be reached, a diagnosis was made by asking a third expert (with >10 years of experience in handling patients with movement disorders) for his opinion. Sonographic examinations were carried out by two experienced sonographers (with >5 years of experience in ultrasound and >2 years of experience in TCS examination). Both the neurologists and sonographers were blinded to each other's results.

The neurologists collected the full medical histories of the patients and their families, and performed thorough physical and neurological examinations. To assess disease-associated disability, the patients were examined using UPDRS-III, and graded according to the H&Y stage.

Clinical diagnosis was based on the current clinical diagnostic criteria for PD, ET, MSA, and PSP. For PD, the UK Parkinson Disease Society brain bank clinical diagnostic criteria for PD<sup>[19]</sup> were used. The tremor consensus statement established by the International Movement Disorders Association in 1998 was used to diagnose ET.<sup>[20]</sup> MSA was diagnosed according to the second edition of MSA diagnostic criteria developed by Gilman and collaborators in 2008.<sup>[21]</sup> Patients with PSP were clinically diagnosed according to the Clinical Diagnostic Criteria of the National Institute of Neurological Disease and Stroke and the Society for PSP, as reported previously.<sup>[22]</sup> The diagnosis was made by independent assessors who aimed to use only clinical diagnostic criteria as a standard independent of clinical impressions, which might bias diagnostic certainty, particularly in the early disease stages.

### Data collection

A Philips IU22 color Doppler ultrasound system (Philips Healthcare, Bothell, WA, USA) equipped with a S5-1 broadband sector array transducer (frequency, 1.5–3.0 MHz; dynamic range, 45–55 dB; depth, 14–16 cm) was employed for patient evaluation. Ultrasound gel (Shanghai Shenfeng Medical Care Products, Co., Ltd., China) was used to couple the transducer with the skin.

TCS was performed in a blinded manner; before the TCS examination, the sonographer was blinded to the patient's clinical history and diagnosis. Image analysis was performed independently by two sonographers. When a consensus diagnosis could not be reached, a diagnosis was made when a third expert (with >10 years of experience in ultrasound and >2 years of experience in TCS examination) was asked to give his opinion. Each subject assumed the supine position with the head turned to one side. The same sonographer pressed the probe tightly against the temporal window for axial scanning with harmonic waves. The scanned sections included the cross-sections at the midbrain and thalamus levels. The displays of the midbrain and lenticular nucleus were recorded. After completing the examination on one side, the subject was instructed to turn the head to the other side for contralateral scanning.

In patients with hyperechoic SN, the areas of the butterfly-shaped midbrain and hyperechoic SN were manually measured in the horizontal transverse sections of the midbrain. According to the semiquantitative grading

standard by Koloudk *et al.*,<sup>[23]</sup> the echo of the SN was manually measured above level III using the basal cistern as the control. According to expert consensus,<sup>[24]</sup> the high echo area of the SN was manually measured in the ipsilateral temporal windows. Then, the ratio of the high echo areas of the bilateral SN to the total area of the midbrain (hyper-substantia nigra/midbrain [S/M]), and SN area  $\geq 0.25 \text{ cm}^2$  and/or S/M  $\geq 7\%$  indicated SN to be positive; otherwise, it was deemed negative.<sup>[25,26]</sup>

The lentiform nucleus (LN) and the thalamus therein were evaluated with parenchymal echo around as a contrast. The LN was considered to have a uniform distribution with a low echo; an echo equivalent to that of the surrounding brain parenchyma was defined as LN-, while that with a patchy echo or with an echo above that of the surrounding brain parenchyma was defined as LN+. For patients with LN+, the LN hyperechoic area was manually measured.

### Statistical analysis

SPSS statistical software (SPSS version 20.0, Armonk, NY, USA) was used for data analysis. Measurement data are presented as the mean  $\pm$  standard deviation. Data were assessed by analysis of variance.  $P < 0.05$  was considered statistically significant. Count data were expressed as frequency (percentage) and compared by the  $\chi^2$  test. Pairwise comparisons between groups were adjusted by the Bonferroni method, and  $P < 0.017$  was considered statistically significant.

## Results

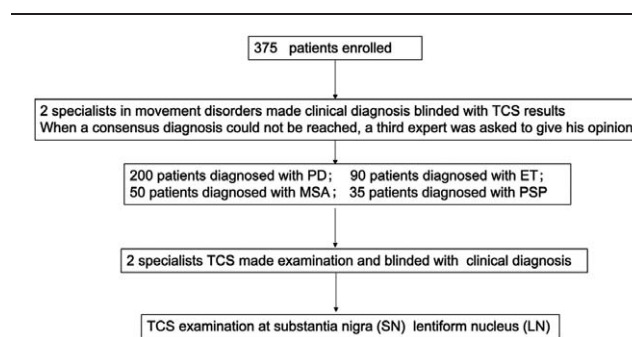
### Patient baseline features

Of the 500 patients, 125 were excluded due to poor signal in temporal window sound transmission. Two sonographers examined each of the 125 patients, and both sonographers made the same diagnosis of poor temporal acoustic bone windows (including bilateral poor temporal acoustic bone window and unilateral poor temporal acoustic bone window). Finally, 375 patients with good temporal window sound transmission were included in this study. Of the 375 patients with good temporal window sound transmission, 200 were diagnosed with PD, 90 with ET, 50 with MSA, and 35 with PSP. Figure 1 depicts the study flowchart.

There were no significant differences in the gender and duration of symptoms among the PD, ET, MSA, and PSP groups. There were no significant differences in the UPDRS-III and H&Y scale scores among the PD, MSA, and PSP groups (all  $P > 0.050$ ) [Table 1]. Meanwhile, results of the *post hoc* analysis revealed significant differences in age between the PD and ET groups alone [Table 1].

### Incidence rates of SN positivity in various groups

The incidence rates of SN positivity significantly differed among the four patient groups (Table 2;  $\chi^2 = 121.061$ ,  $P < 0.001$ ; Figure 2). Next, between-group comparisons were performed. The PD group showed a higher rate of SN



**Figure 1:** Study flowchart. The 375 included patients were diagnosed with PD ( $n = 200$ ), ET ( $n = 90$ ), MSA ( $n = 50$ ), and PSP ( $n = 35$ ), and examined. ET: Essential tremor; MSA: Multiple system atrophy; PD: Parkinson disease; PSP: Progressive supranuclear palsy.

positivity than the ET ( $\chi^2 = 94.898$ ,  $P < 0.017$ ), MSA ( $\chi^2 = 57.619$ ,  $P < 0.017$ ), and PSP ( $\chi^2 = 37.687$ ,  $P < 0.017$ ) groups.

### Value of SN positivity in differentiating between PD and other movement diseases

First, we determined the value of SN positivity in differentiating between PD and the other three movement diseases. SN positivity had a sensitivity of 81.0%, specificity of 75.4%, and positive and negative predictive values of 79.0% and 77.6%, respectively, in the differential diagnosis of PD from ET, PSP, and MSA.

SN positivity had a sensitivity, specificity, positive predictive value, and negative predictive value of 81.0%, 78.9%, 89.5%, and 65.1%, respectively, in the differential diagnosis of PD from ET.

The sensitivity, specificity, positive predictive value, and negative predictive value of SN positivity in the differential diagnosis of PD and MSA were 81.0%, 74.0%, 92.5%, and 49.3%, respectively.

For the differential diagnosis of PD and PSP, the sensitivity, specificity, positive predictive value, and negative predictive value of SN positivity were 81.0%, 68.6%, 93.6%, and 38.7%, respectively.

### Incidence rates of lenticular hyperechoic area in various groups

The incidence rates of lenticular hyperechoic area differed significantly among the four patient groups (Table 3;  $\chi^2 = 38.904$ ,  $P < 0.001$ ; Figure 3). The results of the intergroup comparisons revealed that the lenticular hyperechoic area in the PD group was higher than that in the ET ( $\chi^2 = 6.714$ ,  $P < 0.017$ ) and MSA ( $\chi^2 = 18.680$ ,  $P < 0.017$ ) groups, but lower than that in the PSP group ( $\chi^2 = 0.679$ ,  $P > 0.017$ ).

## Discussion

This study demonstrated that the TCS-derived feature of SN positivity could effectively differentiate PD from ET, PSP, and MSA in a Chinese population. Furthermore, the

**Table 1: Baseline demographic and clinical characteristics of patients with movement disorders.**

Groups, n	Sex (female/male)	Age (years)	Symptom duration (years)	H&Y scale	UPDRS-III score
PD, 200	70/130	62.6 (7.3)	3.5 (1.7)	3.4 (0.8)	28.8 (8.8)
ET, 90	41/49	51.4 (8.2)*	3.8 (2.3)	NA	NA
MSA, 50	18/32	61.9 (8.3) <sup>†</sup>	3.3 (1.7)	3.5 (0.8)	30.1 (6.9)
PSP, 35	15/20	63.6 (5.9) <sup>†</sup>	3.7 (1.2)	3.4 (0.9)	28.6 (6.2)
P	0.342	<0.001	0.348	0.627	0.557

Data represent n/n or mean value (SD). \*ANOVA PD vs. ET ( $P < 0.001$ ),  $P < 0.05$ . <sup>†</sup>ANOVA PD vs. MSA ( $P = 0.673$ ) and PD vs. PSP ( $P = 0.652$ ),  $P > 0.05$ . ET: Essential tremor; H&Y: Hoehn and Yahr; MSA: Multiple system atrophy; NA: Not applicable; PD: Parkinson disease; PSP: Progressive supranuclear palsy; SD: Standard deviation; UPDRS-III: Unified Parkinson disease rating scale motor score.

**Table 2: Comparison of the incidence of SN positive in four groups of patients.**

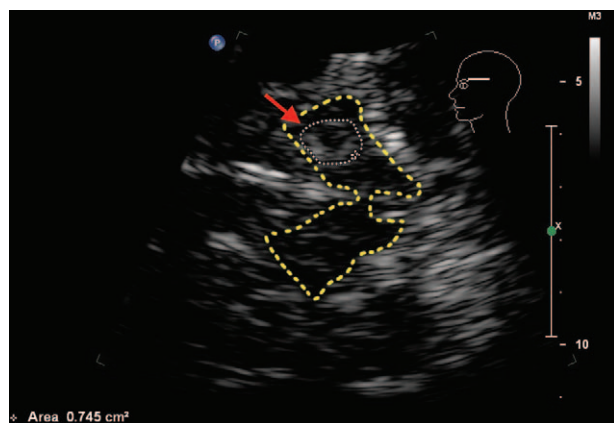
Groups	N	Substantia nigra positive	Substantia nigra negative
PD	200	162 (81%)	38 (19%)
ET	90	19 (21%)	71 (79%)
MSA	50	13 (26%)	37 (74%)
PSP	35	11 (31%)	24 (69%)
$\chi^2$		121.061	
P		<0.001	

Data were expressed as number (N) and percentage, and assessed by the  $\chi^2$  test. ET: Essential tremor; MSA: Multiple system atrophy; PD: Parkinson disease; PSP: Progressive supranuclear palsy; SN: Substantia nigra.

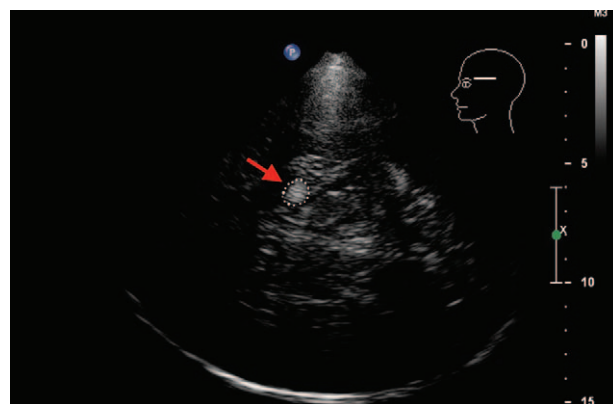
**Table 3: Comparison of the incidence of lenticular hyperechoic area in four groups of patients.**

Groups	N	Lenticular hyperechoic	Normal lenticular echo
PD	157	17 (11%)	140
ET	78	1 (0.01%)	77
MSA	45	3 (0.06%)	42
PSP	31	13 (42%)	18
$\chi^2$		38.904	
P		<0.001	

Data were expressed as number (N) and percentage, and assessed by the  $\chi^2$  test. ET: Essential tremor; MSA: Multiple system atrophy; PD: Parkinson disease; PSP: Progressive supranuclear palsy.



**Figure 2:** TCS axial scan through the brain at midbrain level indicates that there is a hyperechogenicity of the substantia nigra (arrow) (traced by the white dotted line) in the butterfly-shaped midbrain (traced by the yellow dotted line). TCS: Transcranial sonography.



**Figure 3:** TCS axial scan through the brain at thalamus level, the LN hyperechoic area was manually measured (arrow) (traced by the white dotted line). LN: Lenticular nucleus; TCS: Transcranial sonography.

incidence of lenticular hyperechoic areas is relatively low in PD and in other movement disorders in our study.

The human brain structure differs considerably across different ethnic groups,<sup>[27]</sup> which is the reason for studying SN positivity in PD, ET, PSP, and MSA in Chinese populations. The brain structure of Chinese and Caucasian populations is perceptibly different. The Chinese brain structure has a smaller length and height, making it appear rounder.<sup>[27]</sup> Similarly, changes in the brain structure in PD patients are also different across different races.<sup>[28]</sup>

According to previous findings, clear midbrain sonograms cannot be obtained in approximately 5% to 20% of

Caucasians and 12% to 60% of Asians due to poor sound transmission through the temporal window.<sup>[24,29,30]</sup> In addition, studies with large sample size assessing TCS display rates for intracranial structures in Chinese people are lacking, indicating that this imaging technique should be further evaluated for its clinical application in movement disorders.

The present study found no significant differences among the PD, MSA, and PSP groups in terms of UPDRS-III and H&Y scale scores, indicating clinical similarities of movement diseases in the current population. However, a study evaluating Chilean patients found significant differences in these scores among the idiopathic PD, MSA, and PSP groups.<sup>[31]</sup>



The results of the present study found significant differences in age among the PD, ET, MSA, and PSP groups. However, pair-wise comparison between groups found no significant difference in age between the PD and MSA groups and between the PD and PSP groups, suggesting that differences in age did not affect the accuracy of the results. However, there was a significant difference in age between the PD and ET groups; this may be because PD is more common in elderly people and ET is more common in middle-aged people. Therefore, age has an influence on our results between the PD and ET groups, which is one of the limitations of this study.

As shown above, the incidence rates of SN positivity significantly differed among the PD, ET, MSA, and PSP groups, suggesting that it plays an important role in the differential diagnosis of PD and other movement disorders. In our study, SN positivity had a sensitivity of 81% in differentiating PD from the other three movement disorders, collectively, with relatively high specificity and negative and positive predictive values, further demonstrating the usefulness of TCS in PD diagnosis. In addition, SN positivity could distinguish PD from each of these movement disorders. A Japanese study reported SN hyperechogenicity in approximately 83% of accessible SNs in PD patients, which is significantly higher than those of healthy individuals and those of patients with PSP, MSA, and ET.<sup>[32]</sup> A meta-analysis of 39 studies – including 3123 participants with PD – indicated that the sensitivity and specificity of TCS were 0.84 and 0.85 for differentiating PD from normal controls or participants with other Parkinsonian syndromes,<sup>[33]</sup> which partially corroborates our findings. The origin of SN hyperechogenicity is still unclear. Animal studies have shown an association between SN hyperechogenicity and increased iron levels and decreased neuromelanin levels of the SN.<sup>[34]</sup>

The motor features of PD encompass tremor, rigidity, slowness, and balance issues, which are detected relatively late in the disease course when about half of the SN's dopaminergic neurons are lost.<sup>[35,36]</sup> Therefore, using imaging techniques such as TCS for early diagnosis could be beneficial for the proper and timely management of PD. As TCS is based on a different imaging principle from other neuroimaging modalities, it displays intracranial structures with different perspectives. Deep brain tissue imaging can be achieved at a high image resolution using TCS. This method can provide high-resolution real-time dynamic imaging. It has a short investigation time, offers the advantage of low cost, is available for patients at the bedside, is non-invasive, and can be used repeatedly. Patient's movements do not adversely affect the results. Interestingly, DaTSCAN was shown to have comparable diagnostic accuracy with TCS for early stage PD *vs.* ET,<sup>[37]</sup> although other movement diseases were not assessed in the latter study.

In our study, the lenticular hyperechoic area significantly differed among the PD, ET, MSA, and PSP groups, with PD cases showing a higher rate *vs.* the ET and MSA groups, while the PSP group had the highest rate. These findings indicate that lenticular hyperechoic area could be helpful in differentiating PD from the other three movement

disorders. Another research by Smajlovic and Ibrahimagic<sup>[9]</sup> came to the same conclusion. Recent studies have demonstrated that TCS could differentiate non-tremor dominant PD from MSA with predominant Parkinsonism to a certain degree, albeit with low specificity, particularly at the early stage.<sup>[38,39]</sup> Trace metal accumulation and calcification are the most frequent causes of lenticular hyperechogenicity.<sup>[39]</sup> According to a recent study, topographic patterns of widespread iron deposition in deep brain nuclei have been described as differing between patients with MSA and PSP and those with PD.<sup>[10]</sup> This may account for the differences of the lenticular hyperechogenicity between the groups.

The current evidence suggests that TCS is useful in the diagnosis of Parkinsonian syndromes, especially with regard to the differentiation of aPS (class I evidence, Level A).<sup>[40]</sup> In our study, SN positivity had a sensitivity of 81% for distinguishing PD from the other three movement disorders, which is in line with results reported previously.<sup>[40]</sup> SN positivity occurs in approximately 10% of the healthy population.<sup>[41]</sup> Therefore, TCS should be combined with other screening procedures.

The limitations of the present study should be mentioned. This was a single-center study, with potential selection bias. Second, the sample size of this study is very small at 375 patients. Therefore, further confirmation of the present findings requires large multicenter trials with a bigger sample size.

In conclusion, SN positivity could effectively distinguish PD from ET, PSP, and MSA in a Chinese population. These findings indicate that TCS could facilitate the diagnosis of PD.

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### Conflicts of interest

None.

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