


RESEARCH

Open Access



The role of substantia nigra sonography in the differentiation of Parkinson's disease and multiple system atrophy

Hai-Yan Zhou^{1†}, Pei Huang^{1†} , Qian Sun¹, Juan-Juan Du¹, Shi-Shuang Cui¹, Yun-Yun Hu², Wei-Wei Zhan², Ying Wang¹, Qin Xiao¹, Jun Liu¹, Yu-Yan Tan^{1*} and Sheng-Di Chen^{1*}

Abstract

Background: The differential diagnosis of Parkinson's disease (PD) and multiple system atrophy (MSA) remains a challenge, especially in the early stage. Here, we assessed the value of transcranial sonography (TCS) to discriminate non-tremor dominant (non-TD) PD from MSA with predominant parkinsonism (MSA-P).

Methods: Eighty-six MSA-P patients and 147 age and gender-matched non-TD PD patients who had appropriate temporal acoustic bone windows were included in this study. All the patients were followed up for at least 2 years to confirm the initial diagnosis. Patients with at least one substantia nigra (SN) echogenic size ≥ 18 mm² were classified as hyperechogenic, those with at least one SN echogenic size ≥ 25 mm² was defined as markedly hyperechogenic.

Results: The frequency of SN hyperechogenicity in non-TD PD patients was significantly higher than that in MSA-P patients (74.1% vs. 38.4%, $p < 0.001$). SN hyperechogenicity discriminated non-TD PD from MSA-P with sensitivity of 74.1%, specificity of 61.6%, and positive predictive value of 76.8%. If marked SN hyperechogenicity was used as the cutoff value (≥ 25 mm²), the sensitivity decreased to 46.3%, but the specificity and positive predictive value increased to 80.2 and 80.0%. Additionally, in those patients with SN hyperechogenicity, positive correlation between SN hyperechogenicity area and disease duration was found in non-TD PD rather than in MSA-P patients. In this context, among early-stage patients with disease duration ≤ 3 years, the sensitivity, specificity and positive predictive value of SN hyperechogenicity further declined to 69.8%, 52.2%, and 66.7%, respectively.

Conclusions: TCS could help discriminate non-TD PD from MSA-P in a certain extent, but the limitation was also obvious with relatively low specificity, especially in the early stage.

Keywords: Parkinson's disease, Multiple system atrophy, Atypical parkinsonian disorders, Transcranial sonography, Substantia nigra, Disease duration

Background

The diagnosis of Parkinson's disease (PD) mainly depends on the clinical manifestations [1], which results in the accuracy of diagnosis affected by the physicians' experiences in a great extent. Although as high as 90% accurate diagnosis of PD could be reached in the movement disorders clinics [2, 3], it was already the best

scenario. A recent clinical pathology study demonstrated that in the early stage of the disease, only 50% parkinsonian patients received an accurate diagnosis of PD [4]. The most diagnostic confusing diseases are atypical parkinsonian disorders (APD), including progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal ganglionic degeneration (CBD) and dementia with Lewy bodies (DLB). Those APD share some clinical features with PD, but progress aggressively and have much poorer prognosis. The misdiagnosis not only posed psychosocial and economic burden to patients and their families, but also set up obstacles to the

* Correspondence: yuyantan00@126.com; ruijincsd@126.com

[†]Hai-Yan Zhou and Pei Huang contributed equally to this work.

¹Department of Neurology & Institute of Neurology, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, No.197 Ruijin 2nd Road, Shanghai 200025, China

Full list of author information is available at the end of the article



neuroprotective or modified therapies for both PD and APD. Therefore, it is currently eager to find a battery of tools to help diagnosis and differential diagnosis. Transcranial sonography (TCS) is a non-invasive, convenient and economic tool. Recent evidence has shown that it not only helps in the diagnosis of PD, but also helps to differentiate it from APD [5, 6]. However, most of evidence came from Caucasians [6]. Moreover, in most previous differentiation studies not only the number of APD recruited was relatively small, but those distinct entities were pooled into one single APD group for comparison [6]. Among those APD, MSA with predominant parkinsonism (MSA-P), a subtype of MSA, presents most similar clinical features with PD and could be most easily confused with non-tremor dominant (non-TD) PD, especially in the early stage [7, 8]. In our study, we collected 86 clinical probable MSA-P and 147 age and gender matched non-TD PD patients who were clinically diagnosed, and explored if TCS could help the differential diagnosis.

Methods

This cross-sectional study was performed at the Movement Disorder Clinic, Department of Neurology, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine from April 2014 to September 2017.

Subjects

Two hundred and thirty-three Chinese patients with parkinsonism were included, 86 MSA-P and 147 age and gender-matched non-TD PD. All the PD patients met the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease [9]. Among them, 79 (53.7%) patients met clinically established PD and 68 (46.3%) patients met clinically probable PD at the beginning of recruitment. Moreover, they all met the classification criterion of non-TD PD [10]. Briefly, an average global tremor score was calculated as the mean of 9 items. A mean score for the complex of postural instability and gait difficulty (PIGD) was calculated as the mean of 5 items. The non-TD group was defined as patients with a ratio of mean tremor score/mean PIGD score less than 1.5. Also, the established criterion was used for the diagnosis of probable MSA-P [8]. Cases demonstrated identifiable possible causes of other secondary parkinsonism were excluded. All the patients had appropriate temporal acoustic bone windows and were followed for at least 2 years to confirm the initial diagnosis. During the period of follow-up, no clinical diagnosis was changed. At the end of follow-up, 119 (81.0%) patients met clinically established PD and 28 (19.0%) patients met clinically probable PD. We further analyzed a subgroup of early-stage non-TD PD and MSA-P patients, which was defined as the patients with 3 years or

less disease duration. For clinical assessment, disease severity was rated using the Hoehn and Yahr (H-Y) stage.

Transcranial sonography

The sonographic examinations were done as previously described [11]. Briefly, it was performed by one experienced sonographer blinded to the clinical data of all patients. TCS was performed by a 2.5 MHz sonographic device (MyLab90, ESAOTE, Italy) with 16 cm depth and 45 dB dynamic range. Initially, the butterfly shaped hypoechogenic midbrain was identified. Then, the one with the hyperechogenic signal at the anatomical region of SN in its maximum extent was stored. Bilateral SN echogenic areas were then manually encircled and measured. Reproducibility of the SN sonographic measurement had been previously validated by two independent investigators [11]. The larger value of bilateral SN echogenicity was defined as SN_L . Those with SN_L less than 18 mm^2 were identified as normal; the others with at least one SN echogenic size $\geq 18 \text{ mm}^2$ were classified as hyperechogenic as previously described [11]. Besides, to keep consistent with the literatures [5, 12–15], in this study $SN_L \geq 25 \text{ mm}^2$ was defined as markedly hyperechogenic, and sizes between 18 and 25 mm^2 as moderately hyperechogenic. For intergroup comparisons, the SN_L was used.

Statistical analyses

All analyses were performed using SPSS 18.0. Continuous variables were given as means (\pm standard deviation, SD). Categorical variables were summarized by counts of patients and percentages. All variables were tested for normality by Kolmogorov-Smirnov. Two-sample T test or Chi-square test was applied for the comparison of clinical data between non-TD PD and MSA-P. For the comparison of the frequency of different echogenic intensity between groups, Chi-square test was used. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TCS were determined for SN hyperechogenicity as a marker for the differential diagnosis of non-TD PD from MSA-P. Correlation analyses between the variables and SN_L were performed by Spearman correlation coefficients. Adjusted p values were calculated by controlling other confounding factors. The significant level was set at $\alpha = 0.05$.

Results

Demographics

Table 1 presents the demographic data of non-TD PD and MSA-P. Group MSA-P consisted of 57 men and 29 women with clinically probable MSA. Their age was 62.3 ± 7.5 years, onset age 58.7 ± 7.6 years, disease duration 3.6 ± 2.1 years, and H-Y stage 3.5 ± 1.0 . Group non-TD PD consisted of 104 men and 43 women. Their age was 62.2 ± 8.4 years,

Table 1 Demographic data and substantia nigra echogenicity of patients

	non-TD PD (<i>n</i> = 147)	MSA-P (<i>n</i> = 86)	P value
Age (y)	62.2 (8.4)	62.3 (7.5)	0.912
Gender (M/F)	104/43	57/29	0.557
Onset age (y)	56.8 (8.9)	58.7 (7.6)	0.096
Disease duration (y)	5.4 (4.4)	3.6 (2.1)	< 0.001*
H-Y stage	2.0 (0.8)	3.5 (1.0)	< 0.001*
SN _L (mm ²)	24.7 (12.8)	12.2 (13.6)	< 0.001*

Non-TD PD non-tremor dominant Parkinson’s disease, *MSA-P* multiple system atrophy with predominant parkinsonism, *H-Y* Hoehn and Yahr, *SN_L* the larger value of bilateral SN hyperechogenicity. Two-sample T test or Chi-square test was applied for the comparisons. *P values below 0.05 were considered significant

onset age 56.8 ± 8.9 years, disease duration 5.4 ± 4.4 years, and H-Y stage 2.0 ± 0.8. The age and gender were matched between those two groups (*p* = 0.912 and *p* = 0.557, respectively). No difference was found in their onset age (*p* = 0.096). However, MSA-P patients had shorter disease duration (*p* < 0.001) and higher H-Y stage (*p* < 0.001).

SN echogenicity of non-TD PD and MSA-P

The mean SN_L of non-TD PD was 24.7 ± 12.8 mm², larger than that of MSA-P patients, which was 12.2 ± 13.6 mm² (*p* < 0.001). In non-TD PD group, 109 (74.1%) of 147 patients exhibited SN hyperechogenicity. Forty-one (27.9%)

were classified as moderate, and 68 (46.3%) as marked. Thirty-eight (25.9%) of 147 non-TD PD patients had normal SN echogenicity. On the contrary, in the MSA-P group, only 33 (38.4%) of 86 patients exhibited SN hyperechogenicity, and the frequency was lower than that in non-TD PD (*p* < 0.001). Among them, 16 (18.6%) patients were classified as moderate, and 17 (19.8%) as marked. Fifty-three (61.6%) patients exhibited normal SN echogenicity (Fig. 1a).

In the subgroup of patients with disease duration ≤3 years (*n* = 109), the mean SN_L of non-TD PD (*n* = 63) was 23.9 ± 12.0 mm², also larger than that of MSA-P patients (*n* = 46), which was 15.2 ± 14.9 mm² (*p* = 0.002). In non-TD PD group, 44 (69.8%) of 63 patients exhibited SN hyperechogenicity. Eighteen (28.6%) of 63 patients were classified as moderate, and 26 (41.3%) patients as marked. Nineteen (30.2%) of 63 non-TD PD patients had normal SN echogenicity. On the contrary, in the MSA-P group, 24 (52.2%) of 46 patients exhibited normal SN echogenicity and 22 (47.8%) patients exhibited SN hyperechogenicity. Among them, 10 (21.7%) patients were classified as moderate, and 12 (26.1%) patients as marked (Fig. 1b).

SN hyperechogenicity differentiating non-TD PD from MSA-P

Table 2 summarizes SN sonographic findings discriminating non-TD PD from MSA-P. Of all the 233 patients,

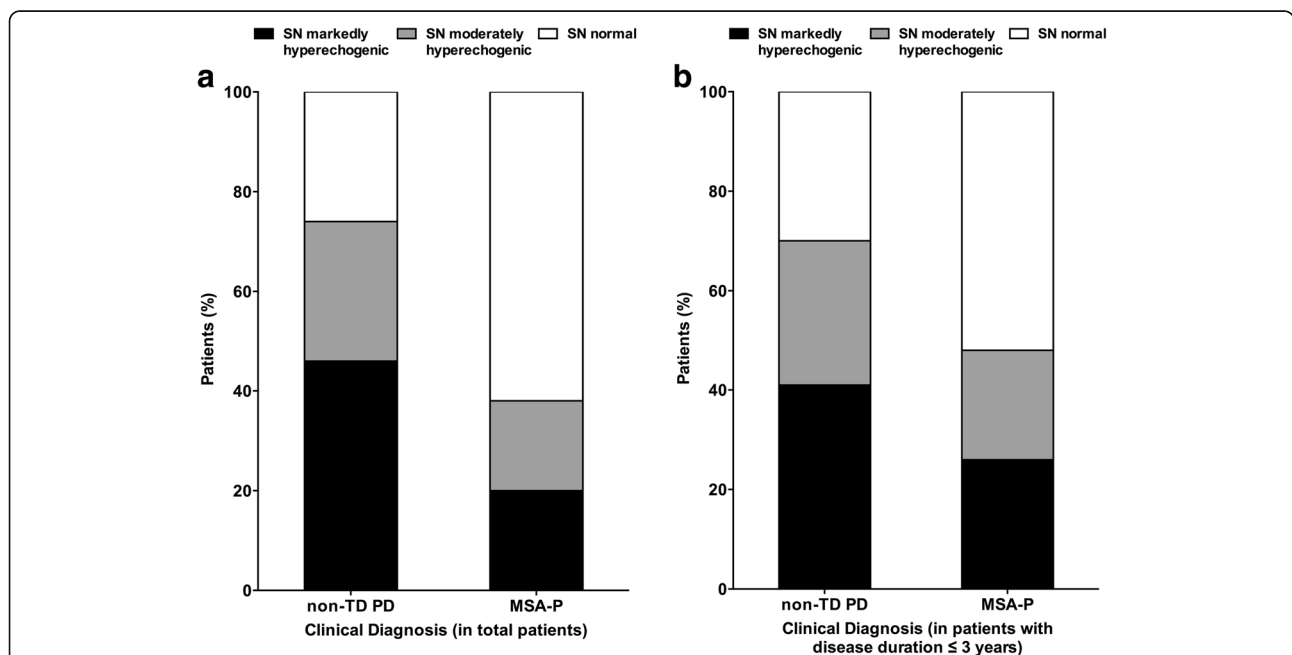


Figure 1 Percentage of patients with different ultrasound findings in the two groups. **a** showed the percentage of cases with different sonographic findings in total patients. **b** showed the percentage of cases with different sonographic findings in the subgroup of patients with disease duration ≤3 years. Black: percentage of patients with a marked substantia nigra (SN) hyperechogenicity; grey: percentage of patients who exhibited a moderate increase in SN echogenicity; and white: percentage of patients with a normal SN echogenicity; non-TD PD, non-tremor dominant Parkinson’s disease; MSA-P, parkinsonian variant of multiple system atrophy.

SN echogenicity correctly diagnosed 162 (69.5%) cases as non-TD PD ($n = 109$) or MSA-P ($n = 53$). For the clinical diagnosis of non-TD PD, sensitivity, specificity and PPV of SN hyperechogenicity were 74.1%, 61.6% and 76.8%; while for being diagnosed as MSA-P, normal SN echogenicity had a NPV of 58.2%. For marked SN hyperechogenicity, sensitivity, specificity and PPV for the diagnosis of non-TD PD were 46.3%, 80.2% and 80.0%, respectively. Conversely, normal SN echogenicity indicated MSA-P with 46.6% NPV.

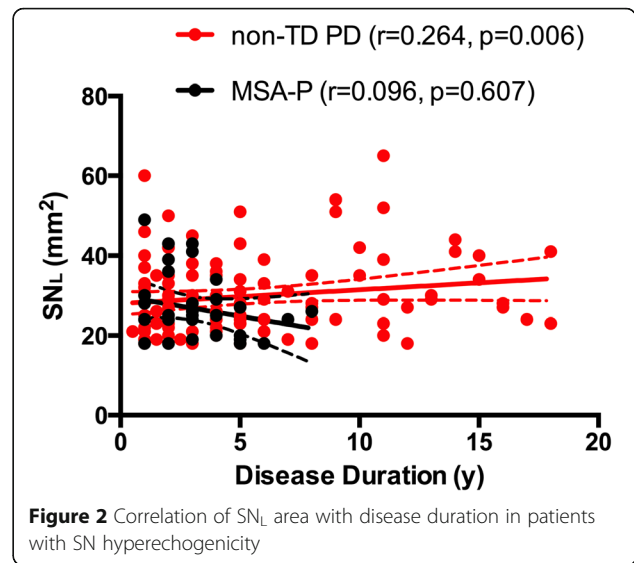
In the subgroup of patients with disease duration ≤ 3 years ($n = 109$), SN echogenicity correctly diagnosed 68 (62.4%) cases as non-TD PD ($n = 44$) or MSA-P ($n = 24$). SN hyperechogenicity had 66.7% PPV for the clinical diagnosis of non-TD PD and normal SN echogenicity had 55.8% NPV for being diagnosed as MSA-P. Sensitivity and specificity of SN hyperechogenicity for detecting non-TD PD patients decreased to 69.8% and 52.2%. For marked SN hyperechogenicity, sensitivity, specificity, and PPV for non-TD PD were 41.3%, 73.9% and 68.4%. Conversely, normal SN echogenicity indicated MSA-P with 47.9% NPV.

Correlation of SN_L with disease duration in the patients with SN hyperechogenicity

Correlation analysis of SN_L with disease duration was performed in patients with SN hyperechogenicity. The results indicated that SN_L did not correlated with disease duration either in MSA-P ($r = -0.114, p = 0.526$) or in non-TD PD patients ($r = 0.137, p = 0.156$). However, after controlling onset age and H-Y stage as confounding factors, significant correlation was found only in non-TD PD patients ($r = 0.264, p = 0.006$) rather than in MSA-P patients ($r = -0.096, p = 0.607$) (Fig. 2).

Discussion

Consistent with previous results [12, 15, 16], our present study demonstrated that more percentage of SN hyperechogenicity was detected in non-TD PD patients than in MSA-P patients. However, the sensitivity for the non-TD PD patients in our cohort was only 74.1%, which was lower than most of previous studies performed by other researchers [5, 6, 12–22]. The majority of earlier studies



were conducted in Caucasians and the sensitivity was almost more than 90%, even reaching up to 100% [5, 6, 12–19]. Only a few studies were performed in the Asian patients, and the sensitivity varied widely (50%~80%) [11, 20–28]. Ethnic differences might not be completely excluded between Caucasians and Asians, but the spectrum bias should be the more reasonable cause. It has been well known that PD is a heterogeneous disorder, and it can be divided into various phenotypes based on the onset age or prominent clinical presentations, such as early or late onset PD, TD PD or non-TD PD [29–31]. Different patterns of SN echogenicity have been shown to be associated with different clinical subtypes [32] and different onset ages [22]. Also, gender and disease duration could affect the SN echogenic pattern [11, 20, 22, 33]. In view of above-mentioned various factors, it was not surprising that varied sensitivity was found in our own studies. Lower sensitivity in our previous studies with a larger number of PD patients could also be due to different patient’s enrollment standard [11]. In the current study, PD patients were limited to the non-TD patients, and their ages and genders were strictly matched with that of MSA-P. Finally, the possibility of misdiagnosis could not be absolutely ruled out

Table 2 Substantia nigra sonography findings indicating non-TD PD rather than MSA-P

	Total patients		Patients with disease duration ≤ 3 years	
	SN _L ≥ 18 mm ²	SN _L ≥ 25 mm ²	SN _L ≥ 18 mm ²	SN _L ≥ 25 mm ²
Sensitivity, %	74.1	46.3	69.8	41.3
Specificity, %	61.6	80.2	52.2	73.9
PPV, %	76.8	80.0	66.7	68.4
NPV, %	58.2	46.6	55.8	47.9

Non-TD PD non-tremor dominant Parkinson’s disease, MSA-P multiple system atrophy with predominant parkinsonism, SN_L the larger value of bilateral SN hyperechogenicity, PPV positive predictive value, NPV negative predictive value

since a fairly part of non-TD PD patients were at their early disease stages. However, similar with a recent study conducted in Japanese patients where the sensitivity of SN hyperechogenicity was around 50% [23], all the patients in our cohort were followed up for at least 2 years to confirm the diagnosis. In supporting for the minimum possibility of misdiagnosis, the differing characteristics of non-TD PD and MSA-P in our study were obvious, that is, MSA-P patients had higher H-Y stages with shorter disease duration, which suggesting more aggressive progression.

In contrast, the sensitivity of SN hyperechogenicity for MSA-P was 38.4%. Even only the marked SN hyperechogenicity was considered, the sensitivity was up to 19.8%, which was still higher than most of previous reports [5, 6, 12, 15, 16, 18, 19, 21, 23]. The majority of sensitivity of SN hyperechogenicity for MSA was reported as about 10%, except for two studies, which were 25 and 50%, respectively [12, 27]. Just as occurred in PD, the most probable reason for the discrepancy between earlier studies and ours could be the spectrum bias. In the previous studies, the number of MSA patients enrolled was relatively small and ranged from 8 to 32 [5, 6]. A small sample size could not only affect statistical power, but also influence the statistical results even with a few cases of misdiagnosis. Moreover, there are two variants of MSA, which are MSA with predominant cerebellar ataxia (MSA-C) and MSA-P. No evidence could make sure that their SN hyperechogenicity pattern should be the same. Therefore, to minimum the bias mentioned above, the MSA patients selected in our study were all MSA-P variants and were followed up for at least two years to confirm the diagnosis in the same movement disorder clinic. In addition, the sample size of MSA-P in the present study reached up to 86, which was the largest one so far.

For overall patients, the sensitivity of SN hyperechogenicity for PD was 74.1%, and the specificity was 61.6%. If SN hyperechogenicity was marked, the specificity increased to 80.2%, but the sensitivity decreased to 46.3%. With either cutoff value, the positive predictive value for the diagnosis of non-TD PD was around 80%. However, among the patients with equal to or less than 3 years disease duration, the sensitivity and specificity further declined to 69.8% and 52.2% respectively, so did PPV decrease to 66.7%. The exact reason was not clear, and the possibility of misdiagnosis could not be definitely excluded since a fairly part of patients were at their early stages. However, it might be explained by the fact that there were different patterns between non-TD PD and MSA-P with regard to the correlation of SN hyperechogenicity with disease duration. In non-TD PD, it seems that with disease course prolonged, the area of SN hyperechogenicity became larger, which was discrepant

with recent studies indicating that SN hyperechogenicity was stable during disease progression [17, 32, 34, 35]. Although the correlation between SN_L and disease duration was weak, several investigations [20, 22, 33] and our previous study [36] did support this positive correlation. In contrast, a tendency of reversed correlation was found in MSA-P patients, although without statistical significance. Therefore, it could be expected that within shorter disease duration, non-TD PD patients had smaller SN echogenicity, which could lead to lower percentage of SN hyperechogenicity, whereas MSA-P patients might have larger SN echogenicity, which could lead to higher percentage of SN hyperechogenicity. Additionally, this different correlation of SN hyperechogenicity with disease duration might also support the hypothesis about the distinct underlying mechanisms in the pattern of SN echogenicity of PD and MSA. So far, the origin of SN hyperechogenicity was not completely elucidated, nonchelated forms of iron, protein bound iron and microglia activation were all supposed to be involved in the reflection of SN hyperechogenicity signals [33, 37, 38]. Tissue iron has been shown to be elevated in both PD and MSA-P [39], but the detailed iron metabolism and gliosis might be different in PD and MSA [33, 37–39].

Limitations of this study need to be mentioned. Indeed, we could not promise absolutely accurate diagnosis of PD and MSA, since no post-mortem verification was achieved. This also was the problem for the differentiation between MSA and other APD, such as CBD and DLB. SN hyperechogenicity has been reported frequent in CBD and DLB [40, 41], therefore misdiagnosis of those disorders could also contribute to higher sensitivity of SN hyperechogenicity in MSA-P. Additionally, although non-TD PD was considered as the phenotype that was most difficult to discriminate from MSA-P, one should note that non-TD and TD PD subtypes do not necessarily represent different subtypes of PD. TD subtype was much more likely to shift to non-TD subtype during the disease progression [42].

Conclusions

In summary, our present study demonstrated that SN hyperechogenicity could help to discriminate non-TD PD from MSA-P; however, both sensitivity and specificity were not satisfactory, particularly in the earlier stage. Combination with other auxiliary tests seemed a necessary way to help differentiation of these two entities.

Abbreviations

APD: Atypical parkinsonian disorders; CBD: Corticobasal ganglionic degeneration; DLB: Dementia with Lewy bodies; H-Y: Hoehn and Yahr; MSA: Multiple system atrophy; MSA-C: MSA with predominant cerebellar ataxia; MSA-P: MSA with predominant parkinsonism; non-TD PD: Non-tremor dominant PD; NPV: Negative predictive value; PD: Parkinson's disease; PIGD: Postural instability and gait difficulty; PPV: Positive predictive value;

PSP: Progressive supranuclear palsy; SN: Substantia nigra; TCS: Transcranial sonography

Funding

This study was supported by Natural Science Fund of China (No. 81430022, 81371407, 81771374), Innovation Program of Shanghai Municipal Education Commission (2017-01-07-00-01-E00046) and Natural Science Foundation of Science and Technology of Shanghai (No. 15ZR1426700).

Availability of data and materials

All the data mentioned in this article are available on published article.

Authors' contributions

H-YZ was responsible for the conception of the project; design, review and critique of statistical analysis, and writing the first draft. PH was responsible for organization and execution of this project, as well as design and execution of statistical analysis. QS, J-JD and S-SC were responsible for collecting parts of patients' data. Y-YH was responsible for performing ultrasound. W-WZ was responsible for supervising ultrasound. YW, QX and JL provided patient data. Y-YT was responsible for review and critique the manuscript. S-DC was responsible for providing most of the patient data, and was involved in the conception of this project and review and critique the manuscript.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Ruijin Hospital and all participants have given written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Neurology & Institute of Neurology, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, No.197 Ruijin 2nd Road, Shanghai 200025, China. ²Department of Ultrasonography, Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China.

Received: 10 February 2018 Accepted: 2 July 2018

Published online: 23 July 2018

References

- Saeed U, Compagnone J, Aviv RI, Strafella AP, Black SE, Lang AE, Masellis M. Imaging biomarkers in Parkinson's disease and parkinsonian syndromes: current and emerging concepts. *Transl Neurodegener.* 2017;6:8.
- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J Neurol Neurosurg Psychiatry.* 1992;55:181-4.
- Rizzo G, Copetti M, Arcuti S, Martino D, Fontana A, Logroscino G. Accuracy of clinical diagnosis of Parkinson disease: a systematic review and meta-analysis. *Neurology.* 2016;86:566-76.
- Adler CH, Beach TG, Hentz JG, Shill HA, Caviness JN, Driver-Dunckley E, Sabbagh MN, Sue LI, Jacobson SA, Belden CM, et al. Low clinical diagnostic accuracy of early vs advanced Parkinson disease: clinicopathologic study. *Neurology.* 2014;83:406-12.
- Bouwman AE, Vlaar AM, Srijles K, Mess WH, Weber WE. Transcranial sonography for the discrimination of idiopathic Parkinson's disease from the atypical parkinsonian syndromes. *Int Rev Neurobiol.* 2010;90:121-46.
- Shafieesabet A, Fereshtehnejad SM, Shafieesabet A, Delbari A, Baradaran HR, Postuma RB, Lökk J. Hyperechogenicity of substantia nigra for differential diagnosis of Parkinson's disease: a meta-analysis. *Parkinsonism Relat Disord.* 2017;42:1-11.
- Geser F, Wenning GK, Seppi K, Stampfer-Kountchev M, Scherfler C, Sawires M, Frick C, Ndayisaba JP, Ulmer H, Pallecchia MT, et al. Progression of multiple system atrophy (MSA): a prospective natural history study by the European MSA study group (EMSA SG). *Mov Disord.* 2006;21:179-86.
- Gilman S, Wenning GK, Low PA, Brooks DJ, Mathias CJ, Trojanowski JQ, Wood NW, Colosimo C, Durr A, Fowler CJ, et al. Second consensus statement on the diagnosis of multiple system atrophy. *Neurology.* 2008;71:670-6.
- Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W, Obeso J, Marek K, Litvan I, Lang AE, et al. MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord.* 2015;30:1591-601.
- Jankovic J, McDermott M, Carter J, Gauthier S, Goetz C, Golbe L, Huber S, Koller W, Olanow C, Shoulson I, et al. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson study group. *Neurology.* 1990;40:1529-34.
- Zhou HY, Sun Q, Tan YY, Hu YY, Zhan WW, Li DH, Wang Y, Xiao Q, Liu J, Chen SD. Substantia nigra echogenicity correlated with clinical features of Parkinson's disease. *Parkinsonism Relat Disord.* 2016;24:28-33.
- Behnke S, Berg D, Naumann M, Becker G. Differentiation of Parkinson's disease and atypical parkinsonian syndromes by transcranial ultrasound. *J Neurol Neurosurg Psychiatry.* 2005;76:423-5.
- Walter U, Wittstock M, Benecke R, Dressler D. Substantia nigra echogenicity is normal in non-extrapyramidal cerebral disorders but increased in Parkinson's disease. *J Neural Transm (Vienna).* 2002;109:191-6.
- Berg D, Siefker C, Ruprecht-Dorfler P, Becker G. Relationship of substantia nigra echogenicity and motor function in elderly subjects. *Neurology.* 2001;56:13-7.
- Walter U, Niehaus L, Probst T, Benecke R, Meyer BU, Dressler D. Brain parenchyma sonography discriminates Parkinson's disease and atypical parkinsonian syndromes. *Neurology.* 2003;60:74-7.
- Gaenslen A, Unmuth B, Godau J, Liepelt I, Di Santo A, Schweitzer KJ, Gasser T, Machulla HJ, Reimold M, Marek K, et al. The specificity and sensitivity of transcranial ultrasound in the differential diagnosis of Parkinson's disease: a prospective blinded study. *Lancet Neurol.* 2008;7:417-24.
- Berg D, Siefker C, Becker G. Echogenicity of the substantia nigra in Parkinson's disease and its relation to clinical findings. *J Neurol.* 2001;248:684-9.
- Walter U, Dressler D, Probst T, Wolters A, Abu-Mugheisib M, Wittstock M, Benecke R. Transcranial brain sonography findings in discriminating between parkinsonism and idiopathic Parkinson disease. *Arch Neurol.* 2007;64:1635-40.
- Busse K, Heilmann R, Kleinschmidt S, Abu-Mugheisib M, Hoppner J, Wunderlich C, Gemende I, Kaulitz L, Wolters A, Benecke R, et al. Value of combined midbrain sonography, olfactory and motor function assessment in the differential diagnosis of early Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 2012;83:441-7.
- Kim JY, Kim ST, Jeon SH, Lee WY. Midbrain transcranial sonography in Korean patients with Parkinson's disease. *Mov Disord.* 2007;22:1922-6.
- Okawa M, Miwa H, Kajimoto Y, Hama K, Morita S, Nakanishi I, Kondo T. Transcranial sonography of the substantia nigra in Japanese patients with Parkinson's disease or atypical parkinsonism: clinical potential and limitations. *Intern Med.* 2007;46:1527-31.
- Huang YW, Jeng JS, Tsai CF, Chen LL, Wu RM. Transcranial imaging of substantia nigra hyperechogenicity in a Taiwanese cohort of Parkinson's disease. *Mov Disord.* 2007;22:550-5.
- Fujita H, Suzuki K, Numao A, Watanabe Y, Uchiyama T, Miyamoto T, Miyamoto M, Hirata K. Usefulness of cardiac MIBG scintigraphy, olfactory testing and substantia nigra hyperechogenicity as additional diagnostic markers for distinguishing between Parkinson's disease and atypical parkinsonian syndromes. *PLoS One.* 2016;11:e0165869.
- Chen W, Tan YY, Hu YY, Zhan WW, Wu L, Lou Y, Wang X, Zhou Y, Huang P, Gao Y, et al. Combination of olfactory test and substantia nigra transcranial sonography in the differential diagnosis of Parkinson's disease: a pilot study from China. *Transl Neurodegener.* 2012;1:25.
- Li DH, Zhang LY, Hu YY, Jiang XF, Zhou HY, Yang Q, Kang WY, Liu J, Chen SD. Transcranial sonography of the substantia nigra and its correlation with DAT-SPECT in the diagnosis of Parkinson's disease. *Parkinsonism Relat Disord.* 2015;21:923-8.
- Liu P, Li X, Li FF, Ou-Yang QH, Zhang HX, Feng T. The predictive value of transcranial sonography in clinically diagnosed patients with early stage Parkinson's disease: comparison with DAT PET scans. *Neurosci Lett.* 2014;582:99-103.
- Bartova P, Skoloudik T, Fadrna P, Ressler P, Kanovsky P, Herzig R. Substantia nigra evaluation in atypical parkinsonian syndromes and Parkinson's disease. *Mov Disord.* 2007;22:S140.
- Luo WF, Zhang YC, Sheng YJ, Fang JC, Liu CF. Transcranial sonography on Parkinson's disease and essential tremor in a Chinese population. *Neurol Sci.* 2012;33:1005-9.

29. Thenganatt MA, Jankovic J. Parkinson disease subtypes. *JAMA Neuro*. 2014; 71:499–504.
30. Schrag A, Schott JM. Epidemiological, clinical, and genetic characteristics of early-onset parkinsonism. *Lancet Neurol*. 2006;5:355–63.
31. van Rooden SM, Heiser WJ, Kok JN, Verbaan D, van Hilten JJ, Marinus J. The identification of Parkinson's disease subtypes using cluster analysis: a systematic review. *Mov Disord*. 2010;25:969–78.
32. Walter U, Dressler D, Wolters A, Wittstock M, Benecke R. Transcranial brain sonography findings in clinical subgroups of idiopathic Parkinson's disease. *Mov Disord*. 2007;22:48–54.
33. Becker G, Seufert J, Bogdahn U, Reichmann H, Reiners K. Degeneration of substantia nigra in chronic Parkinson's disease visualized by transcranial color-coded real-time sonography. *Neurology*. 1995;45:182–4.
34. Behnke S, Runkel A, Kassar HA, Ortmann M, Guidez D, Dillmann U, Fassbender K, Spiegel J. Long-term course of substantia nigra hyperechogenicity in Parkinson's disease. *Mov Disord*. 2013;28:455–9.
35. Berg D, Merz B, Reiners K, Naumann M, Becker G. Five-year follow-up study of hyperechogenicity of the substantia nigra in Parkinson's disease. *Mov Disord*. 2005;20:383–5.
36. Zhou HY, Huang P, Sun Q, Du JJ, Cui SS, Tan YY, Hu YY, Zhan WW, Wang Y, Xiao Q et al. Substantia nigra echogenicity associated with clinical subtypes of Parkinson's disease. *J Parkinson Dis* 2018; doi: <https://doi.org/10.3233/JPD-171264>.
37. Berg D, Godau J, Riederer P, Gerlach M, Arzberger T. Microglia activation is related to substantia nigra echogenicity. *J Neural Transm (Vienna)*. 2010;117: 1287–92.
38. Berg D, Becker G, Zeiler B, Tucha O, Hofmann E, Preier M, Benz P, Jost W, Reiners K, Lange KW. Vulnerability of the nigrostriatal system as detected by transcranial ultrasound. *Neurology*. 1999;53:1026–31.
39. Dexter DT, Jenner P, Schapira AH, Marsden CD. Alterations in levels of iron, ferritin, and other trace metals in neurodegenerative diseases affecting the basal ganglia. The Royal Kings and Queens Parkinson's Disease Research Group. *Ann Neurol*. 1992;32(Suppl):S94–100.
40. Walter U, Dressler D, Wolters A, Probst T, Grossmann A, Benecke R. Sonographic discrimination of corticobasal degeneration vs progressive supranuclear palsy. *Neurology*. 2004;63:504–9.
41. Walter U, Dressler D, Wolters A, Wittstock M, Greim B, Benecke R. Sonographic discrimination of dementia with Lewy bodies and Parkinson's disease with dementia. *J Neurol*. 2006;253:448–54.
42. Nutt JG. Motor subtype in Parkinson's disease: different disorders or different stages of disease? *Mov Disord*. 2016;31:957–61.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

