Parkinsonism and Related Disorders 68 (2019) 40–45

Contents lists available at ScienceDirect

Parkinsonism and Related Disorders

journal homepage: www.elsevier.com/locate/parkreldis

Transcranial sonography in atypical parkinsonism: How reliable is it in real clinical practice? A multicentre comprehensive study

Araceli Alonso-Canovas[a,*], José Ignacio Tembl Ferrairó[b], Irene Martínez-Torres[b], Jose Luis Lopez-Sendon Moreno[a], Isabel Parees-Moreno[a], Enric Monreal-Laguillo[a], Paula Pérez-Torre[a], Rafael Toledano Delgado[a], Guillermo García Ribas[a], Isabel Sastre Bataller[b], Jaime Masjuan[a], Juan Carlos Martinez-Castrillo[a], Uwe Walter[c,d]

[a] Neurology Department. Hospital Universitario Ramón y Cajal, Madrid, Spain
[b] Neurology Department. Hospital Universitari La Fe, Valencia, Spain
[c] Department of Neurology, University of Rostock, Rostock, Germany
[d] German Centre for Neurodegenerative Diseases (DZNE) Rostock/Greifswald, Rostock, Germany

ARTICLE INFO

Keywords:
Atypical parkinsonism
Transcranial sonography
Substantia nigra hyperechogenicity
Lenticular nucleus
Third ventricle
Parkinson's disease

ABSTRACT

Introduction: Substantia nigra hyperechogenicity (SN+) in transcranial sonography (TCS) is frequent in Parkinson's disease (PD), while lenticular nucleus hyperechogenicity (LN+) and 3rd ventricle enlargement (3V+) are typical of Atypical Parkinsonisms (AP). However, there are no studies assessing the diagnostic yield of all TCS biomarkers in the three AP (progressive supranuclear palsy, PSP, multiple system atrophy, MSA, corticobasal degeneration, CBD). Previous references lack homogeneous criteria and data are incomprehensive.
Methods: Analysis of TCS performed in routine clinical practice in AP and PD patients from two tertiary hospitals. Expert recommendations were strictly followed. Previous literature was critically analysed.
Results: 155 AP (98 PSP, 40 MSA, 14 CBD), 254 PD, 145 control subjects were included. We confirmed good sensitivity for SN+ in PD (80%), but specificity was lower than reported (61%). LN+ and 3V + had moderate sensitivity for AP and PSP diagnosis respectively (65%, 63%), but specificity was higher than reported (87%, 91%). We confirmed high specificity and positive predictive value of the combination SN/LN (98%, 93% AP; 83%, 86% PD). The combinations of two or three echofeatures, previously unreported, showed high specificity but lower sensitivity (SN/3V: 75% sensitivity, 87% specificity PD; 42% sensitivity, 98% specificity PSP) (SN + LN+: 79% sensitivity, 86% specificity CBD) (SN/3V/LN: 67% sensitivity, 89% specificity PD; 29% sensitivity, 99% specificity PSP; 41% sensitivity, 95% specificity MSA; 57% sensitivity 91% specificity CBD).
Conclusions: We present a large comprehensive study of TCS, confirming its usefulness and certain limitations in AP diagnosis. Adherence to consensus criteria is critical to implement TCS for clinical and research purposes.

1. Introduction

Atypical Parkinsonisms (AP) are a group of neurodegenerative disorders (progressive supranuclear palsy, PSP, multiple system atrophy, MSA, corticobasal degeneration, CBD), with different underlying pathology and an overall poor prognosis. Upon presentation and in the early period of the disease, specific clinical signs and symptoms may not be clear, and render differential diagnosis with Parkinson's disease (PD) challenging. Ancillary tests are costly and may be frequently unhelpful, especially in the early stages of the disease [1].

Transcranial sonography (TCS) is a non-invasive, inexpensive, reliable, and reproducible technique with proven usefulness for PD diagnosis. The main marker of interest is substantia nigra hyperechogenicity (SN+), more frequent in Parkinson's disease (PD) (80–85%) than in control subjects (10%) and other movement disorders (essential tremor, vascular or drug induced parkinsonism). SN assessment with TCS has proven useful and reliable for PD diagnosis, as recognized by the EFNS/MDS guidelines with level of evidence IA [2]. On the other hand, AP often show distinctive features on TCS scans. Specifically, SN+ is less common in AP (PSP, MSA), while other echofeatures [lenticular nucleus hyperechogenicity (LN+) and 3rd ventricle enlargement (3V+)] are considered typical of AP. Experts in the field stated typical TCS features for each AP (Table A, supplementary material), mainly based on studies published in the early 2000s, which

* Corresponding author. Neurology Department, Hospital Universitario Ramón y Cajal, Carretera de Colmenar km 9.100, 28034, Madrid, Spain.
E-mail address: aracelialonsocanovas@gmail.com (A. Alonso-Canovas).

https://doi.org/10.1016/j.parkreldis.2019.09.032
Received 7 May 2019; Received in revised form 12 July 2019; Accepted 30 September 2019

Table 1
Literature review of studies of TUS in AP [6–23]. Echofeatures analysed in each study (present: +; absent: ; present but not fully disclosed as to allow analysis: ±), and subjects of each diagnostic category available for analysis are disclosed. NA: non assessable, whenever data of the echofeature was given as the addition of 2 or more APs without distinction of diagnostic category (disclosed in "Mixed AP").

	Echofeature			PD			PSP			MSA			CBD			MIXED AP		
	SN	LN	3V	n SN	n LN	n 3V	n SN	n LN	n 3V	n SN	n LN	n 3V	n SN	n LN	n 3V	n SN	n LN	n 3V
Walter 2003	+	+	+	25	22	25	7	7	7	16	15	14	-	-	-	-	-	-
Walter 2004	+	+	+	-	-	-	11	10	11	-	-	-	8	6	8	-	-	-
Behnke 2005	+	+	-	88	88	-	18	18	-	32	32	-	-	-	-	-	-	-
Walter 2007	+	+	+	134	125	134	20	19	20	21	20	21	-	-	-	-	-	-
Okawa 2007	+	-	-	63		-	13	-	-	11	-	-	-	-	-	-	-	-
Gaenslen 2008	+	+	-	43	39	-	4	NA	-	6	NA	-	3	NA	-	-	12	-
Ebenthover 2010	+	-	+	-	-	-	34	-	34	-	-	-	-	-	-	-	-	-
Busse 2012	+	-	-	371	-	-	NA	-	-	NA	-	-	-	-	-	18	-	-
Bouwmans 2013	+	-	-	102	-	-	6	-	-	8	-	-	4	-	-	-	-	-
Kostic 2013	+	+	+	-	-	-	32	32	32	-	-	-	-	-	-	-	-	-
Sastre Bataller 2013	-	-	+	-	-	39	-	-	13	-	-	-	-	-	-	-	-	-
Bartova 2014	+	-	-	29	-	-	5	-	-	2	-	-	-	-	-	-	-	-
Sadowski 2014	+	+	-	-	-	-	20	20	-	-	-	-	12	11	-	-	-	-
Sanzaro 2015	+	±	-	30	-	-	3	3	3	2	2	2	-	-	-	-	-	-
Fujita 2016	+	-	-	64	-	-	9	-	-	15	-	-	-	-	-	-	-	-
Li 2017	+	+	±	22	22	-	-	-	-	21	21	-	-	-	-	-	-	-
Zhou 2018	+	-	-	147	-	-	-	-	-	86	-	-	-	-	-	-	-	-
Monaco 2018	+	+	-	121	121	-	-	-	-	-	-	-	-	-	-	92	92	-
				1239	**417**	**198**	**182**	**109**	**120**	**220**	**90**	**37**	**27**	**17**	**8**	**110**	**104**	**0**

showed consistent results [3]. They considered not only SN assessment, but also LN echogenicity and 3V amplitude measurement [4–7]. SN hyperechogenicity was described as typical of PD and CBD, while LN hyperechogenicity was associated with PSP, CBD and MSA, and III ventricle enlargement only with PSP. The study groups had vast experience with the technique and results were solid despite relatively small sample sizes. A review paper offering guidelines to support the application of this technique in clinical practice and research was subsequently published [3]. However, several studies published thereafter, generally in a research setting, did not strictly follow these recommendations. Most did not assess the three echofeatures, did not include all the diagnostic categories, or did not show full data on frequencies and diagnostic reliability of each echofeature, separately or in combination (Table 1) [8–21]. From a methodological point of view, the selection of the cut-off value for SN hyperechogenicity has not been homogeneous, with certain studies selecting moderate (75th percentile of a control population) instead of marked echogenicity (90th percentile of a control population), disregarding general consensus [9,10,16,18]. In fact, certain studies used qualitative measures of SN echogenicity [8]. As for the third ventricle, the recommended cut-off value of 10 mm for subjects aged over 60 and 7 mm below this age has been also ignored by many authors, while others did not assess this variable in a dichotomic way, but rather continuously [14,17,22]. Moreover, some authors used individually defined sonographic patterns instead of disclosing comprehensively all the sonographic findings, all of this hindering comparison with other references. [21] A recent meta-analysis also failed to include all three echofeatures to assess TCS usefulness in AP vs PD diagnosis. Furthermore, studies including vascular or drug induced parkinsonism were misclassified as AP [23]. All these methodologic flaws probably explain the heterogeneity in the reported frequencies of sonographic variables in each diagnostic category. Until unequivocal reliability of TCS in this setting is not established, its implementation in routine clinical practice and inclusion in AP diagnostic guidelines will be hampered.

In this multicentre study, we aimed to assess diagnostic accuracy of TCS (SN and LN echogenicity and 3V amplitude) for each AP (PSP, MSA, CBD) and PD in real clinical practice. In addition, we aimed to critically analyse previous literature on the subject, perform a systematic review and compare it with our own findings.

2. Material and methods

Two tertiary university hospitals (Hospital Universitario Ramón y Cajal, HURC, Madrid, Hospital Universitario La Fe, HULF Valencia, Spain) participated in the study. TCS is routinely performed for research and clinical purposes in both centres by experienced sonographers (AAC and JTF) from 2013, following consensus criteria and a similar standard methodology [24]. In HURC a TOSHIBA Xsario system was used until 2014 and an EsaoteMyLab25Gold thereafter, while in HULF a TOSHIBA Aplio system was used during all the study period. For each TCS system, previously published cut-off values for marked SN hyperechogenicity (90th percentile of control population) were applied ($\geq 0.21\ cm^2$ in TOSHIBA systems and $\geq 0.25\ cm^2$ in Esaote) [24]. Experience of the sonographers in PD and control subjects TCS assessment, as well as in differential diagnosis with other movement disorders has been published elsewhere. **[References 33–36, supplementary material]** The TCS investigators were aware of the diagnosis of parkinsonism of unclear entity, and were blinded to the final clinical diagnosis. In both centres, patients with parkinsonism of unclear origin (idiopathic, atypical, vascular, drug induced, among others) undergo TCS examination upon treating neurologist request in clinical practice, as a part of the routine work-up.

In 2018, electronic clinical records of the Movement Disorders and Neurosonology Units of each centre were reviewed. Patients with AP diagnosis confirmed by Movement Disorders specialists of each centre, fulfilling MDS criteria for probable PD, probable PSP, probable MSA or CBD, were selected, all of them had undergone TCS during follow-up [25–28]. Patients were included if data on SN echogenicity (bilaterally unless hyperechogenic) as well as 3V amplitude were available. Lenticular nucleus echogenicity was not assessable in a number of subjects in both centres, but was recorded whenever available (bilaterally unless hyperechogenic). Thus, in patients with only unilateral insonability and findings of normal SN or LN the TCS result was regarded as inconclusive for this echofeature, following experts recommendations [11]. A group of patients with PD diagnosis confirmed by a Movement Disorders specialist from both centres, as well as control subjects from HURC, were selected for comparison, using the same TCS criteria.

Demographic variables were registered. Ultrasound echofeatures (SN and LN echogenicity, 3V amplitude) were registered in a dichotomic way (SN+/SN-; LN+/LN-; 3V+/3V-) (Fig. 2, supplementary material). SN hyperechogenicity (90th percentile of echogenic area of a

control sample) and 3V enlargement cut off value (10 mm in subjects over 60 years and over 7 mm below 60 years) were established following previous expert recommendations [22,24]. Diagnostic reliability (sensitivity, specificity, positive predictive values, PPV, with 95% confidence intervals) of each echofeature in isolation and in combination (taken two by two –SN and LN, SN and 3V- and three by three – SN, 3V, LN) was calculated.

A comprehensive review of the literature including studies published before October 2018 analysing diagnostic reliability of TCS in AP diagnosis was performed. Search terms were “atypical parkinsonism” “progressive supranuclear palsy” “multiple system atrophy” “corticobasal syndrome” “corticobasal degeneration” “transcranial sonography” transcranial ultrasound” “substantia nigra echogenicity” “third ventricle” “basal ganglia echogenicity”. Studies including any of the three AP syndromes were included provided diagnostic groups were clearly stated. The methodology was critically analysed, paying attention to cut-off values, types of ultrasound system used, comparison groups selected and potential pitfalls. Number of echo-features available for each subject was registered and results were analysed in order to estimate average diagnostic reliability from previous references. Proportion of each echofeature and average diagnostic reliability for each diagnostic category was calculated separately for comparison with our data. Statistical methods were descriptive statistics; Chi square tests and ROC curve analysis.

3. Results

A total number of 454 patients with clinical diagnosis of PD (283) or AP (174) were screened. MD specialists established clinical diagnoses at the end of recorded follow-up for each patient. Forty-five of them could not be included due to insufficient transtemporal bone window (10%). The remaining 155 subjects with AP, 254 subjects with PD and also 145 control subjects were available for SN and 3V analysis. A large proportion of them (73% AP, 61% PD, 70% control subjects) also had LN echogenicity registered. Fig. 1 shows the flowchart of the study population. Table 2 shows demographic data and mean times from onset to TCS and to final clinical diagnosis, as well as TCS findings in the PD, AP and control subjects. SN + was significantly more frequent in PD group (80%) than in control (11%) or AP subjects, with the exception of CBD (86%). Conversely, lenticular hyperechogenicity was significantly more frequent in all three AP (MSA 57%, PSP 66% and CBD 86%) than in control subjects (8%) or PD patients (13%). The third structure considered, 3rd ventricle enlargement, was significantly more frequent in PSP (63%) than in any other diagnostic category, with the exception of CBD (43%, non significant difference).

Eighteen previous references met inclusion criteria for our analysis (Table 1) [4–21]. Four previous studies (including a range of 8–88 patients) disclosed data regarding diagnostic reliability of the combination of two echofeatures (SN and LN or SN and 3V), but none of the previous references showed concise data of the diagnostic reliability of the combination of three echofeatures [5–7,16].

Table 3 shows the frequency of different combinations of echofeatures and its diagnostic reliability in our study as compared with the analysis of previous references. With single echofeatures, we found similar sensitivity, but lower specificity and positive predictive value of SN + for PD diagnosis, as a result of a higher proportion of SN + in PSP and MSA patients (35%) than previously reported. LN hyperechogenicity had also slightly lower sensitivity (65% vs. 74%) than previously reported for AP diagnosis, but specificity and positive predictive value were as high as in previous studies (87% and 79%). Conversely, 3V + had a better diagnostic yield for PSP diagnosis in our study, with similar sensitivity (63%) but higher specificity and positive predictive value (91% and 70% vs. 75% and 55%). For CBD diagnosis, differences were more remarkable: SN + and LN + were more common than in previous literature (SN + 86% vs 70%; LN + 86% vs. 29%), and 3V + was detected in 43% of our patients, but in none of the 8 CBD patients previously reported.

When echofeatures were taken in pairs (SN and 3V or LN), sensitivity was good only in PD (75% SN + 3V-, SN + LN-) and CBD (79% SN + LN +). Specificity was high for all diagnostic categories: 83% SN + 3V- and 87% SN + LN- for PD group; 98% SN- 3V + and 93% SN- LN + for PSP patients; 81% SN-3V- for MSA patients; 86% SN + LN +

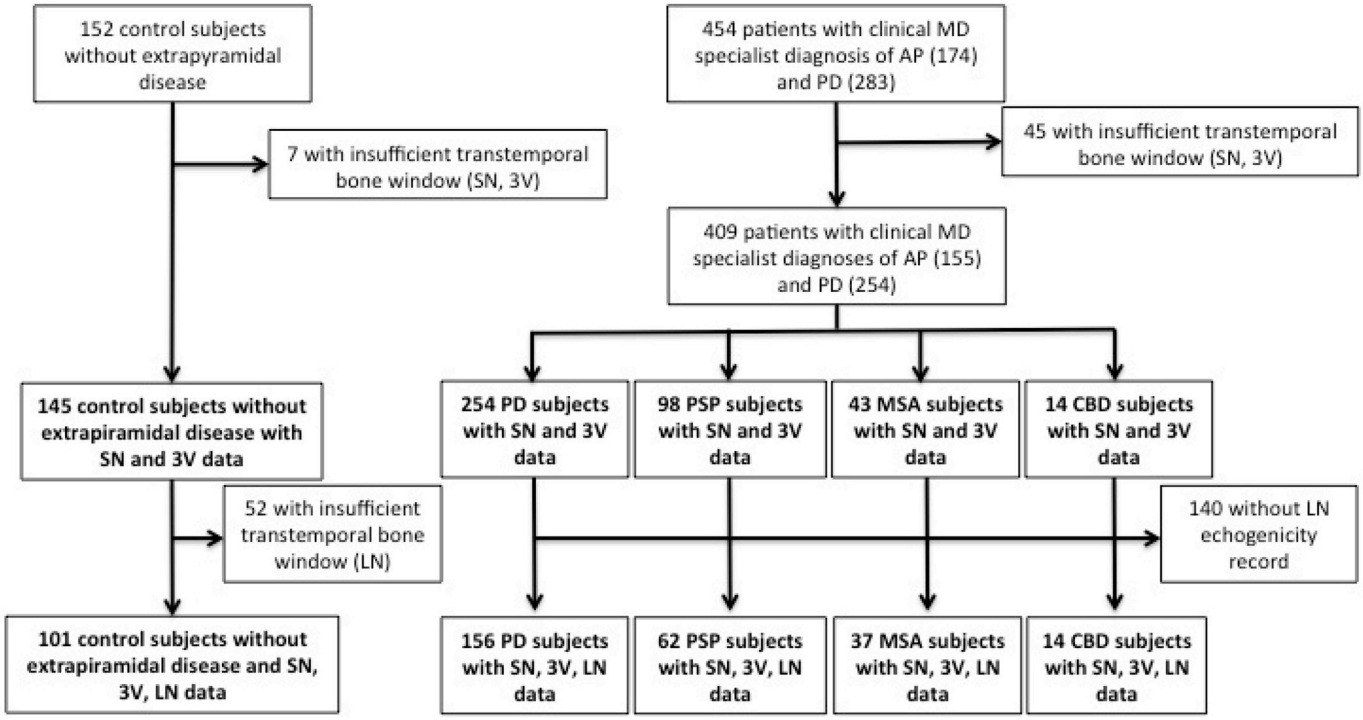

Fig. 1. Study flowchart. AP: atypical parkinsonism. CBD: corticobasal degeneration, 3V: third ventricle, LN: lenticular nucleus, MD: movement disorders, MSA: multiple system atrophy, PD: Parkinson's Disease, PSP: progressive supranuclear palsy, SN: substantia nigra.

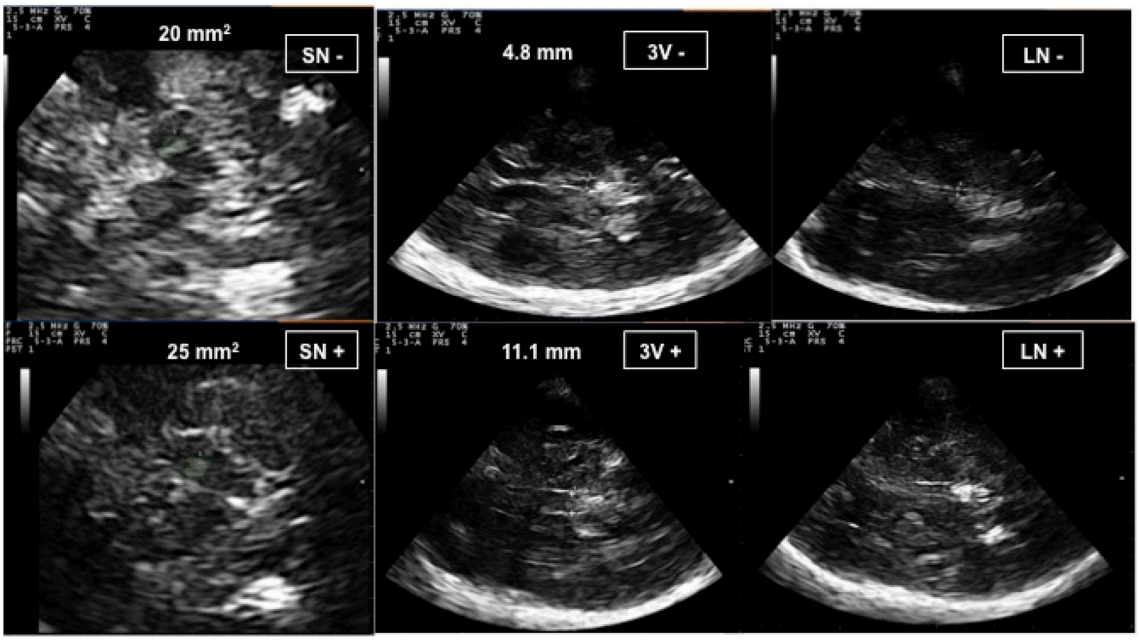

Fig. 2. Ultrasound images showing normal and abnormal scans of substantia nigra echogenicity, third ventricle amplitude and lenticular nucleus echogenicity (Esaote MyLab25Gold). 3V: third ventricle, LN: lenticular nucleus, SN: substantia nigra.

and 87% SN + 3V- for CBD patients; 98% SN-LN + for PSP and MSA as a group. Positive predictive value was maximal for PD (86%, 94%), PSP (89%, 96%) and low in MSA and CBD. Previous references analysis showed generally high PPV for the combinations available (91–100%), but sample sizes were smaller and no confidence intervals were disclosed.

Finally, when the three echofeatures were taken into consideration, sensitivity was low (67% PD, 29% PSP, 41% MSA, 57% CBD), but specificity was maximal in all diagnostic categories (89% PD, 99% PSP, 95% MSA, 91% CBD). Positive predictive value was high for PD and PSP (89% and 90%) but low for the less frequent categories MSA and CBD (58% and 26% respectively). Further data on diagnostic yield of our own study and previous references are disclosed in Supplementary material (Tables B and C).

4. Discussion

We present a large comprehensive series of TCS performed in real clinical practice of Movement Disorders Units, showing its strengths and limitations in AP diagnosis work-up. TCS was performed by skilled sonographers with documented clinical and research experience, with full adherence to consensus recommendations, and blinding to clinical diagnoses. Also, diagnoses of PD, PSP, MSA and CBD were established by Movement Disorders specialists, which, acknowledging the limitations of any clinical diagnosis, especially in the AP setting, supports the value of the gold standard used in this study. We provide data on certain echofeatures that previously had been scarcely reported (3rd ventricle in PD, MSA and CBD; lenticular nucleus in CBD). In addition, for the first time we assess diagnostic reliability of the combinations of three echofeatures for each diagnostic entity.

SN assessment with TCS has proven useful and reliable for PD diagnosis, as recognized by the EFNS/MDS guidelines with level of evidence IA [2]. We further confirm that SN hyperechogenicity is a valuable marker for PD diagnosis, with higher sensitivity than the average of previous studies. Nonetheless, a higher rate of false positives in PSP and MSA patients (35%) needs to be considered. SN hyperechogenicity is suspected to arise from changes in tissue iron deposition, especially regarding the union to different proteins, and individual genetic background is thought to play a critical role. Although strongly associated with PD, it is also found with high frequency in unrelated disorders, as motor neuron disease or melanoma. This background helps explain the lower specificity we observed and is a caveat for clinicians upon interpretation of TCS findings [2].

On the other hand, as for the other echofeatures, sensitivity of LN hyperechogenicity for PSP and MSA was slightly lower than reported. However, we confirmed its high specificity and positive predictive value. Third ventricle enlargement showed a similar profile in PSP diagnosis (63% sensitivity, 91% specificity and 75% PPV), which improves the previous records, probably due to a larger number of subjects assessable for this echofeature in all diagnostic categories.

Another relevant finding in our series is the reliability of the combinations of echofeatures. It is noteworthy that only in PD sensitivity is

Table 2
Clinical, demographic, and ultrasound data of study participants. The frequency of each echofeature in our sample is expressed in percentage, with the number of assessable subjects between brackets (n). CON: control subjects. CBD: corticobasal degeneration, MSA: multiple system atrophy, NA: non applicable, PD: Parkinson's Disease, PSP: progressive supranuclear palsy.

	PD	PSP	MSA	CBD	CON	p
Age in years (TCS)	69 ± 11	73 ± 9	67 ± 11	74 ± 5	64 ± 16	
Sex (% male)	67%	65%	51%	57%	49%	
Disease duration upon clinical diagnosis	7.5 ± 4.1	5.2 ± 2.5	5.2 ± 1.9	3.5 ± 2.2	NA	
Time from onset to TCS	3.38 ± 3.8	3.7 ± 2.4	3.1 ± 1.7	3.1 ± 2.4	NA	
Hyperechogenic substantia nigra (SN+)	80% (254)	35% (98)	35% (43)	86% (14)	11% (145)	**p < 0.001** (PD and CBD vs. MSA, PSP, CON)
Enlarged third ventricle (3V+)	7% (254)	63% (98)	5% (43)	43% (14)	4% (145)	**p < 0.001** (PSP and CBD vs. PD, MSA, CON)
Hyperechogenic lenticular nucleus (LN+)	13% (156)	66% (62)	57% (37)	86% (14)	8% (101)	**p < 0.001** (PSP, MSA and CBD vs. PD, CON)

Table 3
Diagnostic reliability of each echofeature for each diagnostic category. Data are disclosed as sensitivity, specificity and positive predictive value with 95% confidence intervals between brackets. Four specific previous references of relevance are noted between brackets in italics. CBD: corticobasal degeneration, 3V+: enlarged third ventricle, LN+: hyperechogenic lenticular nucleus, MSA: multiple system atrophy, PD: Parkinson's Disease, PSP: progressive supranuclear palsy, SN+: hyperechogenic substantia nigra.

					AC et al. (2019)				Previous literature analysis			
Diagnostic category A vs. B		SN	3V	LN	Sample size	Sensitivity	Specificity	PPV	Sample size	Sensitivity	Specificity	PPV
PD	PSP/MSA/CBD	+			254 vs. 155	0.80 [0.75,0.85]	0.61 [0.52,0.68]	0.77 [0.72, 0.82]	1239 vs. 539	0.77 [0.75,0.80]	0.81 [0.77,0.84]	0.90 [0.88,0.92]
	PSP/MSA/CBD	+		-	156 vs. 113	0.75 [0.67,0.82]	0.83 [0.75,0.90]	0.86 [0.80, 0.92]	88 vs. 50 *[8]*			0.91
	PSP	+	-		254 vs. 98	0.75 [0.69,0.80]	0.87 [0.78,0.93]	0.94 [0.90,0.97]				
	PSP/MSA/CBD	+	-	-	156 vs. 113	0.67 [0.59,0.75]	0.89 [0.81,0.94]	0.89 [0.83,0.95]				
PSP	PD/MSA/CBD		+		98 vs. 311	0.63 [0.53,0.73]	0.91 [0.88,0.94]	0.70 [0.60, 0.79]	113 vs. 229	0.63 [0.53,0.72]	0.75 [0.69,0.80]	0.55 [0.47,0.64]
	PD/MSA/CBD	-	+		98 vs. 311	0.42 [0.32,0.52]	0.98 [0.96,0.99]	0.89 [0.80,0.98]				
	CBD	-		+	62 vs. 14	0.42 [0.30,0.55]	0.93 [0.66,1.00]	0.96 [0.89,1.00]	20 vs. 11 *[18]*	1.00	0.67	1.00
	PD/MSA/CBD	-	+	+	62 vs. 207	0.29 [0.18,0.42]	0.99 [0.97,1.00]	0.90 [0.77,1.00]				
MSA	PD/PSP/CBD	-	-		43 vs. 366	0.63 [0.47,0.77]	0.81 [0.76,0.85]	0.28 [0.19,0.37]				
	PD/PSP/CBD	-	-	+	37 vs. 232	0.41 [0.25,0.58]	0.95 [0.92,0.98]	0.58 [0.39,0.77]				
CBD	PD/PSP/MSA	+		+	14 vs. 255	0.79 [0.49,0.95]	0.86 [0.81,0.90]	0.23 [0.11, 0.35]				
	PD/PSP/MSA	+	-	+	14 vs. 255	0.57 [0.29,0.82]	0.91 [0.87,0.94]	0.26 [0.10,0.41]				
	PSP	+	-		14 vs. 98	0.57 [0.29,0.82]	0.87 [0.78,0.93]	0.38 [0.17,0.59]	8 vs. 10 *[7]*	0.83	1.00	1.00
PD/CBD	PSP/MSA	+			268 vs. 141	0.81 [0.75,0.85]	0.65 [0.57,0.73]	0.82 [0.77, 0.86]	1266 vs. 512	0.77 [0.75,0.80]	0.83 [0.80,0.87]	0.92 [0.90,0.94]
PSP/MSA/CBD	PD			+	113 vs. 156	0.65 [0.56,0.74]	0.87 [0.81,0.92]	0.79 [0.70, 0.87]	320 vs. 417	0.74 [0.69,0.78]	0.84 [0.80,0.87]	0.79 [0.73,0.83]
PSP/MSA	PD	-		+	99 vs. 156	0.42 [0.33,0.53]	0.98 [0.94,1.00]	0.93 [0.86,1.00	39 vs. 125 *[9]* 50 vs. 88 *[8]*	0.59	1.00 0.96	1.00

substantial (75% for SN + LN- and SN+3V-, 67% for SN+3V-LN-), while in PSP and MSA it is much lower (42% and 63% for paired echofeatures, 29% and 41% for the triplets). Conversely, specificity markedly increases in PD, PSP and MSA when more than one echofeatures are analysed, reaching 89% in PD, 99% in PSP, 95% in MSA, and 91% in CBD with three echofeatures.

As for CBD, the least common AP, in which diagnosis is especially difficult and ancillary tests least contributory, we offer the largest TCS sample to date. Sensitivity of SN and LN hyperechogenicity was remarkably better than previously reported, and specificity was high, around 90%, for the combinations of two or three echofeatures, despite the higher than expected 3V enlargement frequency (43%). This later finding might be explained by a clinical overlap of CBD and PSP, as in clinicopathological studies of corticobasal syndrome, a significant proportion turns out to have a post mortem PSP diagnosis. All in all, it is intriguing that this infrequent condition with challenging diagnosis shows such a homogenous sonographic profile. In fact, former studies pointed in the same direction [5,16].

These figures of diagnostic reliability of TCS in AP are not far, or may improve data from other more complex, expensive techniques, as MRI and nuclear medicine studies [2]. Recent reviews on conventional structural MRI usefulness in this setting underscore the lack of sensitivity, especially in early stages, with heterogeneous findings and wide confidence intervals in different studies. Specificity of typical AP findings is high (over 90%), mainly in advanced-stage PSP, while some findings of MSA may be seen in PD and heredo-degenerative ataxias. Although higher field MRI may increase sensitivity, false positive rates are also higher, for example for putaminal changes in MSA. Volumetry, diffusion, iron MRI studies certainly improve diagnostic reliability but are not generally available and interpretation may be challenging [29]. So far, no clearly defined MRI pattern is sufficiently reliable to support CBD diagnosis [2,29].

As for PET/SPECT scans, presynaptic dopaminergic studies do not reliably distinguish PD from AP, and postsynaptic dopaminergic studies yield no neatly different patterns in PSP, MSA and CBD. Likewise, MIBG scintigraphy is generally abnormal in PD, and presumably normal in AP (especially MSA) without distinctions [2]. Finally, neurophysiology studies, such as startle reflex abnormalities (typically absent or reduced in PSP, and enhanced in MSA) or transcranial magnetic stimulation, although promising, have not been properly tested for diagnostic reliability in large studies, and are not universally available [30].

In this field of clinical uncertainty, TCS offers good diagnostic reliability at a low cost beyond the research setting, provided experts' recommendations are strictly followed. Neurologists may acquire the skills and experience to implement this feasible, low time consuming, comfortable and reproducible technique in Movement Disorders clinics. Clearly defined consensus criteria for methodology and interpretation of sonographic findings are warranted.

Several limitations of the present study deserve consideration. First, the retrospective design and also the inclusion of patients with longer disease duration, while strengthening the certainty of clinical diagnosis, might reduce the diagnostic value in early, short duration disease cases. Second, despite following international criteria, some degree of uncertainty remains in AP clinical diagnosis, limiting the validity of our gold standard for comparison with TCS findings. Certainly, clinical-ultrasound-pathologic studies would contribute to truly ascertain the diagnostic value of TCS in AP. In addition, lack of sufficient bone window or registry of certain findings (such as LN) reduced the number of subjects with assessment of all echofeatures available for analysis. Specifically, in PD subgroup LN was not assessable in a significant proportion of patients. Although the large sample size may compensate for this, a potential bias needs to be acknowledged. Finally, the external

validity of our results depends on sonographers' skills and expertise, a critical requirement to implement TCS reliably in clinical practice. Recently, neuroimaging-based computer-aided diagnosis applied to TCS systems offer an opportunity to improve diagnostic classification accuracy of sonographic findings, which may be particularly useful for less trained explorers [31,32].

Author contributorship

All authors have contributed sufficiently, reviewed and approved the final version of the manuscript, and take responsibility for the present work.

Competing interests and funding sources

There are no competing interests or funding sources to disclose.

Ethical comitee approval

Local ethics committee approval was obtained for the present study.

Acknowledgements

We thank our fellow neurologists for the referral of PD and AP patients for TCS in clinical practice: Alicia de Felipe-Mimbrera, Maria Consuelo Matute-Lozano, Nuria García-Barragan, Francisco Javier Buisan-Catevilla, Susana Sainz de la Maza, Lucienne Costa-Frossard, Beatriz Zarza Sanz, Iñigo Corral, Carlos Estevez Fraga, and Iciar Aviles-Olmos.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.parkreldis.2019.09.032.

References

[1] G.U. Höglinger, J. Kassubek, I. Csoti, et al., Differentiation of atypical Parkinson syndromes, J. Neural Transm. 124 (2017) 997–1004.
[2] A. Berardelli, G.K. Wenning, A. Antonini, et al., EFNS/MDS-ES recommendations for the diagnosis of Parkinson's disease, Eur. J. Neurol. 20 (2013) 16–34.
[3] A.E. Bouwmans, A.M. Vlaar, K. Srulijes, W.H. Mess, W.E. Weber, Transcranial sonography for the discrimination of idiopathic Parkinson's disease from the atypical Parkinsonian syndromes, Int. Rev. Neurobiol. 90 (2010) 121–146.
[4] U. Walter, L. Niehaus, T. Probst, R. Benecke, B.U. Meyer, D. Dressler, Brain parenchyma sonography discriminates Parkinson's disease and atypical parkinsonian syndromes, Neurology 60 (2003) 74–77.
[5] U. Walter, D. Dressler, A. Wolters, T. Probst, A. Grossmann, R. Benecke, Sonographic discrimination of corticobasal degeneration vs progressive supranuclear palsy, Neurology 63 (2004) 504–509.
[6] S. Behnke, D. Berg, M. Naumann, G. Becker, Differentiation of Parkinson's disease and atypical parkinsonian syndromes by transcranial sonography, J. Neurol. Neurosurg. Psychiatry 76 (2005) 423–425.
[7] U. Walter, D. Dressler, T. Probst, et al., Transcranial brain sonography findings in discriminating between parkinsonism and idiopathic Parkinson disease, Arch. Neurol. 64 (2007) 1635–1640.
[8] M. Okawa, H. Miwa, Y. Kajimoto, et al., Transcranial sonography of the substantia nigra in Japanese patients with Parkinson's disease or atypical parkinsonism: clinical potential and limitations, Intern. Med. 46 (2007) 1527–1531.
[9] A. Gaenslen, B. Unmuth, J. Godau, et al., The specificity and sensitivity of transcranial sonography in the differential diagnosis of Parkinson's disease: a prospective blinded study, Lancet Neurol. 7 (2008) 417–424.
[10] J. Ebentheuer, M. Canelo, E. Trautmann, C. Trenkwalder, Substantia nigra echogenicity in progressive supranuclear palsy, Mov. Disord. 25 (2010) 773–777.
[11] K. Busse, R. Heilmann, S. Kleinschmidt, 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 83 (2012) 441–447.
[12] A.E. Bouwmans, A.M. Vlaar, W.H. Mess, A. Kessels, W.E. Weber, Specificity and sensitivity of transcranial sonography of the substantia nigra in the diagnosis of Parkinson's disease: prospective cohort study in 196 patients, BMJ Open 3 (2013) 1–8.
[13] V.S. Kostic, M. Mijajlovic, D. Smajlovic, M.J. Lukic, A. Tomic, M. Svetel, Transcranial brain sonography findings in two main variants of progressive supranuclear palsy, Eur. J. Neurol. 20 (2013) 552–557.
[14] I. Sastre-Bataller, J.F. Vázquez, I. Martínez-Torres, et al., Mesencephalic area measured by transcranial sonography in the differential diagnosis of parkinsonism, Park. Relat. Disord. 19 (2013) 732–736.
[15] P. Bártová, O. Kraft, J. Bernátek, et al., Transcranial sonography and123I-FP-CIT single photon emission computed tomography in movement disorders, Ultrasound Med. Biol. 40 (2014) 2365–2371.
[16] K. Sadowski, M. Serafin-Król, K. Szlachta, A. Friedman, Basal ganglia echogenicity in tauopathies, J. Neural Transm. 122 (2015) 863–865.
[17] E. Sanzaro, F. Iemolo, Transcranial sonography in movement disorders: an interesting tool for diagnostic perspectives, Neurol. Sci. 37 (2016) 373–376.
[18] H. Fujita, K. Suzuki, A. Numao, et al., 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 11 (2016) 1–13.
[19] X. Li, S. Xue, S. Jia, et al., Transcranial sonography in idiopathic REM sleep behavior disorder and multiple system atrophy, Psychiatry Clin. Neurosci. 71 (2017) 238–246.
[20] H.Y. Zhou, P. Huang, Q. Sun, et al., The role of substantia nigra sonography in the differentiation of Parkinson's disease and multiple system atrophy, Transl. Neurodegener. 7 (2018) 1–7.
[21] D. Monaco, D. Berg, A. Thomas, et al., The predictive power of transcranial sonography in movement disorders: a longitudinal cohort study, Neurol. Sci. 39 (2018) 1887–1894.
[22] G. Seidel, M. Kaps, T. Gerriets, A. Hutzelmann, Evaluation of the ventricular system in adults by transcranial duplex sonography, J. Neuroimaging 5 (1995) 105–108.
[23] A. Shafieesabet, S.M. Fereshtehnejad, A. Shafieesabet, et al., Hyperechogenicity of substantia nigra for differential diagnosis of Parkinson's disease: a meta-analysis, Park. Relat. Disord. 42 (2017) 1–11.
[24] U. Walter, How to measure substantia nigra hyperechogenicity in Parkinson disease: detailed guide with video, J. Ultrasound Med. 32 (2013) 1837–1843.
[25] R.B. Postuma, D. Berg, M. Stern, et al., MDS clinical diagnostic criteria for Parkinson's disease, Mov. Disord. 30 (2015) 1591–1601.
[26] G.U. Höglinger, G. Respondek, M. Stamelou, et al., Clinical diagnosis of progressive supranuclear palsy: the Movement Disorder Society criteria, Mov. Disord. 32 (2017) 853–864.
[27] S. Gilman, G.K. Wenning, P.A. Low, et al., Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (2008) 670–676.
[28] M.J. Armstrong, I. Litvan, A.E. Lang, et al., Criteria for the diagnosis of corticobasal degeneration, Neurology 80 (2013) 496–503.
[29] B. Heim, F. Krismer, R. De Marzi, K. Seppi, Magnetic resonance imaging for the diagnosis of Parkinson's disease, J. Neural Transm. 124 (2017) 915–964.
[30] M. Bologna, A. Suppa, F. Di Stasio, A. Conte, G. Fabbrini, A. Berardelli, Neurophysiological studies on atypical parkinsonian syndromes, Park. Relat. Disord. 42 (2017) 12–21.
[31] J. Shi, Z. Xue, Y. Dai, et al., Cascaded multi-column RVFL+ classifier for single-modal neuroimaging-based diagnosis of Parkinson's disease, IEEE Trans. Biomed. Eng. (2018 Dec 24), https://doi.org/10.1109/TBME.2018.2889398 ([Epub ahead of print]).
[32] B. Gong, J. Shi, S. Ying, et al., Neuroimaging-based diagnosis of Parkinson's disease with deep neural mapping large margin distribution machine, Neurocomputing (2018), https://doi.org/10.1016/j.neucom.2018.09.025 ([Epub ahead of print]).