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Utility of transcranial sonography in the diagnosis of drug-induced parkinsonism: a prospective study

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Background and purpose: Drug-induced parkinsonism usually resolves after discontinuation of the causative agent. However, it persists in some patients, who actually have subclinical neurodegenerative parkinsonism. Identification of this condition is important because these patients could benefit from therapeutic measures. The objective of this study was to prove whether transcranial sonography, a technique used in the diagnosis of neurodegenerative parkinsonism, can be used for the said identification.

Methods: In this prospective study, patients with drug-induced parkinsonism were followed for at least 6 months after discontinuation of the causative drug and performance of blinded transcranial sonography. Patients were categorized as having iatrogenic parkinsonism if the clinical presentation had resolved or subclinical drug-exacerbated parkinsonism if it persisted. Once the patient was classified into one of the two groups, an expert assessed the transcranial sonography findings and their agreement with the clinical diagnosis.

Results: Twenty patients composed the group for analysis of results. Assessing hyperechogenicity in the substantia nigra >20 mm^2 and/or hyperechogenic lentiform nucleus, differences were detected between the iatrogenic parkinsonism and the subclinical drug-exacerbated parkinsonism groups, although they did not reach statistical significance (Fisher's exact test 0.09). Joint assessment of sonographic alterations in both structures had a negative predictive value of 85.7% for diagnosis of drug-induced parkinsonism, with a negative likelihood ratio of 0.3.

Conclusions: Although in our study statistically significant differences were not found between the transcranial sonography characteristics of subclinical drug-exacerbated parkinsonism and iatrogenic parkinsonism patients, we believe that transcranial sonography is a valid technique for diagnosis of drug-induced parkinsonism.

Introduction

Drug-induced parkinsonism (DIP) is the second leading cause of parkinsonism in the elderly and in the general population [1], after Parkinson's disease (PD), and the most frequent cause of secondary parkinsonism in the western world [2]. DIP occurs secondary to the use of a broad range of substances, among which dopaminergic blockers (neuroleptics and benzamides) and, to a lesser extent, antidepressants and calcium channel blockers stand out [2–4]. DIP symptoms usually disappear within 6 months of discontinuation of the causative drug [4,5]. However, in a subset of patients (10%–48%), symptoms persist [2–4,6]. These subjects are considered to have latent parkinsonism that was simply made manifest by the drug. This clinical entity is known as subclinical drug-exacerbated parkinsonism (SDEP). Some studies have shown that, in this group, aside from discontinuation of the causative drug, treatment with levodopa may also be beneficial [7,8]; hence, early identification of SDEP is important. Unfortunately, the clinical similarity between pure DIP (iatrogenic parkinsonism or IP) and neurodegenerative parkinsonism [7,9,10] makes it difficult to distinguish them on the basis of clinical findings, which is why imaging studies are often required to establish the diagnosis. Currently, single photon emission computed tomography (SPECT) with

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ioflupane (^{123}I), also known as FP/CIT or DaTscan, is the benchmark for the differential diagnosis between DIP and other neurodegenerative parkinsonisms [7,9]. IP occurs as a consequence of dopamine receptor blockade by the pharmaceutical agent, without affecting the nigrostriatal pathway and thus without altering uptake of the radioactive tracer [8,9,11]. Conversely, neurodegenerative parkinsonism will necessarily present with radioactive marker uptake changes [8,9]. Despite its advantages, the SPECT FP/CIT technique is expensive and not without discomfort for the patient; therefore development of a more affordable and less aggressive diagnostic could be a good alternative. Within this context, the detection of hyperechogenicity in the substantia nigra (SN) and the lentiform nucleus (LN) on transcranial sonography (TCS) is a reliable technique in the diagnosis of neurodegenerative parkinsonism and healthy control subjects [12]. Some studies have gone so far as to suggest reliability comparable to that of SPECT FP/CIT [13], although others have shown that the sensitivity (Sn) and specificity (Sp) of SPECT FP/CIT is higher than that of TCS for the diagnosis of PD, using healthy subjects as a control group [14].

Few studies have used TCS in the setting of DIP [12,15–18]. The conclusion drawn from these studies is that increased echogenicity of the SN can be associated with subclinical changes in the nigrostriatal pathway that were made manifest by use of the causative drug and hence behave as a vulnerability trait or risk marker for the development of neurodegenerative parkinsonism. On the basis of these findings, a prospective study was designed with the main objective of verifying whether differences in the sonographic appearance of DIP exist between patients with IP and SDEP, and whether TCS is a valid and safe technique (i.e. provides adequate Sn, Sp and predictive values) for identification of the two subgroups. This study also sought to calculate the Sn, Sp and predictive values of TCS in the diagnosis of PD in our sample.

Methods

A prospective, blinded study design was employed. Two groups were defined.

Cohort A comprised elderly patients who presented with a parkinsonian syndrome of unknown origin and took drugs that were potentially parkinsonism-inducing. These patients were evaluated using the United Parkinson's Disease Rating Scale (UPDRS) Motor Subscale. The parkinsonism-inducing drug was discontinued, a structural neuroimaging study was requested, and patients were referred to a neurosonology laboratory to undergo a TCS study of the cerebral parenchyma. Follow-up appointments were scheduled after a minimum of 6 months for clinical reassessment. Patients in whom the parkinsonian syndrome had resolved were classified as having IP, whereas those in whom parkinsonian symptoms persisted were classified as SDEP. Once the patient was classified into one of the two groups, an expert assessed the TCS findings and their agreement with the clinical reference diagnosis.

Group B was recruited from the database of the Movement Disorders Unit and comprised patients with PD according to the diagnostic criteria of the United Kingdom Parkinson's Disease Society Brain Bank (PDS-UKBB) criteria. The main purpose of this group was to blind the associated investigator.

To this end, patients from the two groups were referred, randomly and without any type of clinical information, to the neurosonology laboratory, where they underwent TCS using a Siemens Acuson ultrasonography system.

The established cutoff was 20 mm^2 for the SN (normal <20 mm^2) [19]. The presence of moderate or severe hyperechogenicity in the LN was considered pathological.

We excluded patients with a medical or clinical history of parkinsonism prior to starting treatment with the potentially parkinsonism-inducing drug, signs of cognitive impairment that began simultaneously with (or within <1 year of) parkinsonian signs and symptoms, structural neuroimaging evidence of basal ganglia calcifications (hyperechogenicity of the LN can be caused by calcium [19]) and lesions that could produce parkinsonism, or physical examination findings highly suggestive of non-pharmacological parkinsonism, as well as those in whom the potentially parkinsonism-inducing drug could not be discontinued.

The study was approved by the Torrecárdenas Hospital research ethics committee. All participants included in the study provided written informed consent.

Statistical analysis

A descriptive analysis of qualitative variables was carried out using absolute and relative frequencies (counts and percentages). Quantitative variables were described using means, standard deviations, medians, confidence intervals, and the range of the groups formed by the *final diagnosis* variable. The size of the echogenic zone was compared in the two groups by means of Student's *t*-test (parametric) or the Mann–Whitney *U* (non-parametric) test, considering a significance level of 0.05.

TCS findings were compared with the clinical diagnosis, which was considered the gold standard for this

study, and a receiver operating characteristic curve was obtained with the different cutoffs formed by hyperechogenic area values. Sn, Sp, positive predictive value (PPV) and negative predictive value (NPV) were then calculated for each cutoff.

Results

Between 2008 and 2011, 55 patients were recruited, 15 of whom (27.2%) were excluded from the study. Most (86.7%) were women, and the most frequent cause of exclusion was the absence of a temporal bone window (46.7%); other causes of exclusion were pathological neuroimaging, desertion and change of residence. The resulting sample for statistical calculations comprised 40 patients, 20 in the DIP group and 20 in the PD group; their demographic and clinical characteristics, as well as the results of different imaging and laboratory studies carried out, are detailed in Tables 1 and 2. Figure 1 shows examples of the sonographic findings for the studied patients.

Sn, Sp, PPV and NPV and likelihood ratios of TCS in the diagnosis of DIP were calculated from the data of the 20 patients in the DIP group. This sample was reduced to 17 patients when SN and LN findings were considered for the sonographic diagnosis, as the LN could not be visualized sonographically in three patients.

For calculation of the Sn of TCS in the diagnosis of PD, 20 patients from group B plus one patient from cohort A (who ultimately received a clinical diagnosis of PD) were used as cases. The 15 patients classified as having IP at the end of the study were considered healthy subjects, i.e. they were included as the control group for calculation of Sp, PPV and NPV.

Mean age in the PD group was 62.8 ± 11.5 years (range 37–79 years; 95% CI). Mean disease duration was 8.8 ± 4.3 years (95% CI). The mean size of the hyperechogenic area in the left SN was 23.5 ± 11.3 mm^2, and in the right SN 21 ± 9.4 mm^2 (95% CI). The mean hyperechogenic area of the entire SN was 43.3 ± 15.6 mm^2 (95% CI). Statistically significant differences were found between this mean area and that of the IP group (30.5 ± 16.3 mm^2) (Mann–Whitney U 0.04). Applying qualitative criteria, i.e. the

Table 1 Clinical-demographic data and results in patients with drug-induced parkinsonism

Age	Gender	Parkinsonism-related drug	Follow-up time (months)	Comorbidity	UPDRS III		Final Dx	Echogenicity in the SN	Echog. area SN (mm^2)		Echogenicity in the LN	Dx –TCS only SN/SN + LN
					INI	END			L	R		
81	M	Clebopride	12	ATD	17	3	IP	+	30	41	+ (bilateral)	FP/FP
79	F	Clebopride	16	MD	41	0	IP	–	15	NA	NA	TN/NA
70	M	Sulpiride	7		20	0	IP	+	27	NA	NA	FP/FP
47	M	Ziprasidone/ Pimozide	7	FTD	15	3	IP	–	10	15	–	TN/TN
74	M	Risperidone	17	MD	18	0	IP	–	16	13	NA	TN/NA
76	F	Flunaricine	7		9	0	IP	–	8	10	–	TN/TN
73	F	Trimetazidine	7	MD	21	2	IP	–	9	8	–	TN/TN
74	F	Cinnarizine	7	MD	11	2	IP	–	12	11	–	TN/TN
70	F	Sulpiride	10		21	4	IP	–	16	15	–	TN/TN
74	F	Clebopride	9	MD	19	2	IP	–	8	19	+	TN/FP
58	M	Valproate +Levomepromazine	6		23	0	IP	–	17	13	–	TN/TN
69[a]	F	Depamide	10	MD	27	3	IP	–	NA	9	NA	TN/NA
75	F	Clebopride	27	MD	43	7	IP/ET	–	14	19	–	TN/TN
75	M	Sulpiride	33	MCD	41	2	IP/ET	+	36	22	–	FP/FP
58	M	Olanzapine	34		26	7	IP/ET	+	14	30	+ (bilateral)	FP/FP
79	M	Flupentixol	14	MD	28	11	SDEP: AP	+	29	17	–	TP/TP
75	F	Clebopride	25	MD	39	52	SDEP: AP	–	16	14	–	FN/FN
56	M	Cinitapride	27	MD	13	25	SDEP: IPD	+	27	24	–	TP/TP
82	F	Cinnarizine	26	MCD	22	22	SDEP: MSA-P	–	10	10	+	FN/TP
79	F	Trimetazidine	15	MD	25	18	SDEP: PSP	–	12	19	+ (left)	FN/TP

UPDRS III, United Parkinson's Disease Rating Scale, part III; Dx, diagnostic; SN, substantia nigra; LN, lentiform nucleus; TCS, transcranial sonography; INI, initial; L, left; R, right; M, male; ATD, Alzheimer-type dementia; IP, iatrogenic parkinsonism; FP, false positive; F, female; MD, mood disorders; NA, non-assessable; TN, true negative; FTD, frontotemporal dementia; ET, essential tremor; TP, true positive; MCD, mild cognitive disorder; SDEP, subclinical drug-exacerbated parkinsonism; AP, atypical parkinsonism; FN, false negative; IPD, idiopathic Parkinson's disease; MSA-P, multisystem atrophy with predominant Parkinson; PSP, progressive supranuclear palsy.

[a]Included because the parkinsonism was of left predominance, which is why echogenicity <20 mm^2 in the right SN is accepted as significant.

Table 2 Clinical-demographic data and results in a group for blinding of the associated investigator, composed of patients with Parkinson's disease

Age	Gender	Years of evolution	SN echogenicity	SN echogenic area (mm^2)		LN echogenicity	TCS/clinical Dx
				L	R		
72	F	8	–	8	11	–	FN
77	F	8	–	12	11	NA	FN
79	F	18	–	12	10	NA	FN
76	F	5	–	14	16	+ (right)	FN
55[a]	M	15	–	7	12	–	FN
52	F	9	+	46	12	–	TP
57	F	7	+	36	22	NA	TP
54	F	9	+	14	29	–	TP
78	F	11	+	32	30	–	TP
74	F	20	+	NA	29	–	TP
46	M	6	+	NA	28	–	TP
56	F	7	+	30	NA	–	TP
67	M	10	+	14	27	NA	TP
59	M	6	+	27	29	+ (left)	TP
37	F	6	+	27	20	–	TP
55	F	9	+	33	27	–	TP
59	M	3	+	35	17	–	TP
66	M	9	+	18	43	–	TP
69	M	4	+	31	8	–	TP
68*	M	6	+	28	18	–	TP

SN, substantia nigra; LN, lentiform nucleus; TCS, transcranial sonography; Dx, diagnostic; L, left; R, right; F, female; FN, false negative; NA, non-assessable; M, male; TP, true positive.
[a]Hereditary Parkinson's disease. PARK2 mutation.

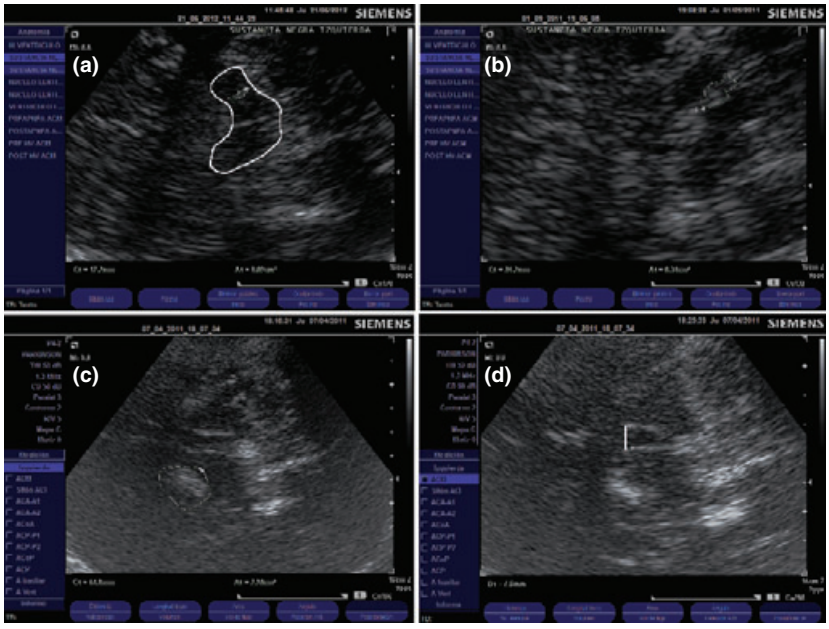

Figure 1 Transcranial sonography in patients with drug-induced parkinsonism. (A) Midbrain (delimited by a thick line) and substantia nigra (delimited by a fine line) of a patient with iatrogenic parkinsonism. (B) Hyperechogenic substantia nigra (delimited by a continuous line) in a patient with idiopathic Parkinson's disease. (C) Hyperechogenic contralateral lentiform nucleus (delimited by a continuous line) in a patient with subclinical drug-exacerbated parkinsonism. (D) Dilated third ventricle in a patient with iatrogenic parkinsonism.

presence of a hyperechogenic area of <20 or >20 mm^2 in the SN, statistical significance was also reached between the PD group and the IP (control) group (chi-squared test with Yates's correction, 0.01).

Mean age in the DIP group was 71.2 ± 9.3 years (range 47–82 years; 95% CI). The most frequently implicated parkinsonism-inducing drug was clebopride (25%), although neuroleptics (particularly sulpiride) were the most commonly implicated group (40%), above prokinetics (30%). We found no clinical differences between patients taking calcium antagonists and those taking dopamine receptor blockers, although they have different dopaminergic pathway action mechanisms. The mean duration of clinical follow-up was 15.8 ± 9.4 months (range 6–34 months). Twenty-five per cent of patients had a final clinical diagnosis of SDEP, and the remaining 75% were diagnosed as having IP. In two of the patients with a diagnosis of SDEP the final UPDRS III score was higher than the initial score, in another it did not change and in the other two it decreased, although it continued to show a clear bradykinetic syndrome. Some patients with IP scored above 0 on the final UPDRS III because they showed signs such as essential tremor, dyspraxia in alternating manoeuvres, hypokinesia due to anhedonia or lack of agility due to joint problems (Table 1). In all, 80% of SDEP cases exhibited hyperechogenicity in the SN >20 mm^2 and/or hyperechogenic LN, whereas this TCS finding was pathological in 33.3% of subjects in the IP group. Analysis did not reveal any statistically significant differences between the SDEP and IP groups, although the result approached significance (Fisher's exact test 0.09). Furthermore, there were no significant between-group differences in size of the hyperechogenic area in the SN or of presence or absence of isolated hyperechogenicity in the LN (Table 3).

Sn, Sp, predictive values and likelihood ratios for the diagnosis of DIP with TCS are shown in Table 4.

The Sn value obtained for diagnosis of PD with TCS in our sample was 76.2% (55.6%–96.8%). Sp was 73.3% (47.6%–99%), the PPV was 80% (60%–100%) and the NPV was 68.7% (42.9%–94.6%).

Discussion

Analysis of findings regarding the primary objective of this study must take into account the fact that joint assessment of hyperechogenicity in the SN and LN is required to distinguish IP from SDEP sonographically. The reason for this imposition is that patients included in the SDEP subgroup may have had PD or atypical parkinsonisms, such as progressive supranuclear palsy or multisystem atrophy (MSA-P). Isolated

Table 3 Level of statistical significance between subgroups of the drug-induced parkinsonism group, considering sonographic findings

	SDEP subgroup (N = 5)	IP subgroup (N = 15)	Significance ($P < 0.05$)
L SN (mm^2)	18.8 (SD 8.7)	(N = 14)[a] 16.6 (SD 8.5)	0.6*
R SN (mm^2)	16.8 (SD 5.3)	(N = 13)[b] 17.3 (SD 9.3)	0.7*
SN total (mm^2)	36 (SD 12.6)	(N = 12)[c] 30.5 (SD 16.3)	0.3*
SN > 20 mm^2	n = 2 (40%)	n = 4 (26.6%)	0.5**
Hyperechogenic LN	n = 2 (40%)	(N = 11)[d] n = 3 (27.3%)	0.5**
SN > 20 mm^2 and/or hyperechogenic LN	n = 4 (80%)	n = 5 (33.3%)	0.09**

SDEP, subclinical drug-exacerbated parkinsonism; N, sample size; IP, iatrogenic parkinsonism; L SN, left substantia nigra; SD, standard deviation; *Mann–Whitney test; R SN, right substantia nigra; n, number of patients in each subgroup that have that feature; **Fisher test; LN, lentiform nucleus.

[a]For one patient it was not possible to determine the L SN, which is why N is reduced to 14.

[b]For two patients it was not possible to determine the R SN, which is why N is reduced to 13.

[c]For three patients it was not possible to determine the SN total, which is why N is reduced to 12.

[d]For four patients it was not possible to determine the LN, which is why N is reduced to 11.

Table 4 Data on reliability and safety (95% confidence interval) of transcranial sonography in the diagnosis of drug-induced parkinsonism

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Positive likelihood ratio	Negative likelihood ratio
TCS: Hyperechogenicity SN > 20 mm^2	40% (0–92.9)	73.3% (47.6–99)	33.3% (0–79.4)	78.6% (53.5–100)	1.5 (0.4–5.9)	0.8 (0.4–1.8)
TCS: SN Hyperechogenicity > 20 mm^2 + LN hyperechogenicity	80% (35–100)	58.3% (26.3–90.4)	44.4% (6.4–82.5)	87.5% (58.3–100)	1.9 (0–4.3)	0.3 (0–2.1)

TCS, transcranial sonography; SN, substantia nigra; LN, lentiform nucleus.

assessment of the SN is only useful when trying to discriminate between PD and MSA-P (specifically, the finding of normal echogenicity in the SN is characteristic of MSA-P but not of PD [20]); however, it does not suffice for the patient group in question, as, according to this criterion, TCS findings in the case of IP can be the similar to those of MSA-P (i.e. normal). Taking these considerations into account, relevant differences were detected between the IP and the SDEP groups, although they did not reach statistical significance (Table 3). However, the results of a recent study [21] confirm that the presence of hyperechogenicity in the SN can be interpreted as a trait of vulnerability of the striatonigral system and therefore as a risk marker for the development of PD; this is a finding of such clinical magnitude that, regardless of statistical analysis, it immediately makes the differences found in our study of clinical interest, and supports the impression that the presence of hyperechogenicity in the SN and/or in the LN in patients with DIP is also a trait of vulnerability of the striatonigral system. Furthermore, these differences were so close to statistical significance that we believe a larger sample size would ultimately confirm it. This finding has major prognostic and therapeutic implications, as its identification would determine the specialist's later course of action, both with respect to the ethical need of informing the patient that he or she may have a neurodegenerative disease and to the possibility of starting antiparkinsonian therapy.

When hyperechogenicity was assessed in both the SN and LN, the Sn and NPV obtained in our study for diagnosis of DIP by means of TCS were 80% and 87.5% respectively. Other studies [18] have obtained similar values for these same statistics (Sn, 88.2%; NPV, 77.8%), although only the SN was assessed and DIP was compared with PD. One must take into account, however, that the results may be associated with the low prevalence of the condition of interest (around 2%–3%) [2]. Therefore, the correct approach would be to interpret the results in terms of odds ratios, which are statistical calculations that are not affected by prevalence. The negative likelihood ratio of TCS when hyperechogenicity is assessed in both the SN and the LN is 0.3, which means that the test is three times more likely to be negative in a healthy subject than in a patient with the condition.

The Sp and PPV obtained in this study were low due to the high rate of false positives in the sample (33%); comparatively, this figure is approximately 12% in the healthy population [12]. We believe that the presence of associated comorbidities, mainly essential tremor and mood disorders, may have been a determinant of this high rate, as SN hyperechogenicity is more common in subjects with essential tremor [22] and in those with depression [23] than in the healthy population.

In our study the hyperechogenic SN area size is significantly higher in PD group than in IP group. Then we could conclude that TCS can distinguish both entities, but this assertion should be interpreted with caution because this study was not designed for that purpose. The results of S obtained for the diagnosis of PD by means of TCS (76.2%) are close to those published in other studies [22,24–26].

A small subgroup of three patients exhibited hereditary PD with mutations in the *parkina* gene (PARK2). The total number of mutated alleles was greatest in the patient who showed a more extensive hyperechogenic area (complete deletion in homozygosis of exons 3 and 4). This matches the findings of a previous study [27] which concluded that, the greater the number of mutated alleles, the greater the area of SN echogenicity.

One of the main limitations of this study is its small sample size, which is a consequence of the difficulty of recruiting patients to the DIP cohort. The exclusion criteria were very restrictive but were absolutely necessary for adequate conduct of the study. The most limiting factor was the impossibility of discontinuing the drug, because in our usual clinical practice, as in prior publications on the topic [4,28], the therapeutic class most often implicated in the onset of parkinsonism was neuroleptics. In a considerable number of patients that would otherwise have met the inclusion criteria, the neuroleptic drug could not be discontinued, either due to a specialist's opinion or because of the fear that the subject themselves – and their families – had of the possibility that psychiatric symptoms might return or worsen. Nevertheless, over the 3-year study period, we were able to recruit the minimum number of patients necessary to obtain results with sufficient statistical power. Unfortunately, the percentage of excluded subjects was 27.2%, slightly above that estimated for calculation of sample size (20%). Most probably this excess was mainly due to two causes: the first is that the main reason for exclusion was the absence of a temporal bone window, and the second, directly associated with the first, is that elderly women predominated in the group. The literature shows that age and female gender, as well as ethnicity [19,29,30], are the main factors that limit attainment of a good sonographic window.

Another major limitation of this study is that duration of clinical follow-up (minimum of 6 months) could be considered insufficient, as publications have reported that up to 7% of patients who were apparently cured may exhibit new parkinsonian symptoms within 1 year [6]. Only nine of the 20 patients

included were followed for <12 months: three were completely asymptomatic (UPDRS III score 0) and the other six showed no parkinsonian symptoms at the time of assessment (Table 1). Parkinsonian syndrome did not recur in any of the six patients with IP followed for 12 or more months.

The final limitation is that the reference diagnosis was established by clinical assessment by the principal investigator. For cases of DIP, follow-up of clinical progression can be regarded as the gold standard as there are no established diagnostic criteria; however, in cases of SDEP, only anatomopathological diagnosis could be considered definitive.

The main conclusion of this study is that no statistically significant differences were found between the TCS characteristics of SDEP and IP patients. However, these differences approached statistical significance, and we believe that a larger sample would ultimately allow significant findings. We also believe this finding is a marker of vulnerability for the development of neurodegenerative parkinsonism. Finally, and although this must be tested on a greater number of patients, we consider combined assessment of SN and LN echogenicity by means of TCS to be a useful technique for the diagnosis of DIP.

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Conflicts of interest

The authors declare no financial or other conflict of interests.

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