Ultrasonographic and clinical findings in overlapping phenotype of essential tremor and Parkinson's disease

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Abstract

Background
Essential tremor (ET) and Parkinson’s disease (PD) are considered distinct disorders. The aim of the study was to look for a link or any distinguishing features by transcranial sonography (TCS), together with the clinical examination findings in a group of patients with overlapping phenotype of ET and PD (ET-PD).

Methods
A prospective observational case-control study was carried out from the 3rd January 2011 until 30th January 2013 at the Hospital of Lithuanian University of Health Sciences. The final study group consisted of 15 patients with ET-PD, 116 patients with ET-only and 141 patients with PD-only. The control group included 101 subjects. Clinical diagnosis was of a diagnostic standard.

Results
The main ultrasonographic findings in the ET-PD group were similar to those of the PD-only: hyperechogenicity of the substantia nigra (66.7%, p<0.001) and nuclei raphe interruptions/absence (38.5%, p<0.001). The single distinguishing TCS finding in ET-PD group was a lentiform nucleus hyperechogenicity (26.7%), however this was only significant when compared to controls (p=0.006). An asymmetrical onset of symptoms (73.3%) in ET-PD group was characteristic to PD-only. The ET-PD patients had the longest disease duration (median 6 years, p<0.001), the most frequent rate of positive family history (53.3%, p=0.005), rather low prevalence of cogwheel rigidity (26.7%, p<0.001), and higher mean Hoehn & Yahr scores compared to PD-only (2.6±0.8 vs. 1.8±0.8, p=0.012).
Conclusions
The main TCS findings of the present study in patients with overlapping ET-PD phenotype were similar to PD-only group. The clinical findings supported the evidence that longstanding asymmetrical isolated postural tremor may evolve to PD. The highest positive family history rate among ET-PD patients indicates strong hereditary predisposition and needs genetic underpinnings. Imaging with TCS helped to highlight a few clinical diagnoses of ET-PD phenotype with a possible atypical parkinsonian syndrome.

Keywords
Essential tremor, Parkinson’s disease, co-morbidity, phenotype, transcranial sonography

Background
Essential tremor (ET) is one of the most common movement disorders, followed by Parkinson’s disease (PD) [1, 2]. ET affects up to 14% and PD up to 1% of the population aged 65 years and over [3, 4]. ET and PD are considered distinct disorders. However, an overlap of some clinical features in individual patients may appear [5]. Since the diagnosis of both ET and PD remains based only on the clinical criteria, many questions regarding a nosological association remain unanswered: 1) does PD in ET patients develop over the time along an ‘‘ET-PD’’ syndrome [5]; 2) which factors could influence the conversion from ET to PD [6]; 3) has the same patient co-occurrence of the two disorders already started from the onset, as the chances of the diseases of high prevalence having co-morbidity is inevitable, and any link could be only coincidental [7, 8]; 4) if ET can occur in conjunction with familial PD [9] and 5) is it simply incorrectly classified diagnosis [10, 11]?
Another debated controversy is whether ET should be viewed as a mono-symptomatic (“benign”) disorder, or whether it is a syndrome of several diseases including neurodegenerative [6]. Based on the new findings, our attitude is also changing towards PD as a complex disorder with a long latency period, classified to proposed four hierarchical stages [12]. PD can be sometimes viewed as “benign” in some tremor-dominant (TD) patients, as it progresses very slowly [9].

Some attempts were made to find specific biomarkers, which could help to differentiate or to link ET-PD patients to ET-only, or PD-only. All the studies dealing with this issue, published until 2011, were summarized in a thorough review of Fekete and Jankovic [13]. A few studies were published later, which add valuable information, and questions. Patients with ET–PD obtained significantly lower scores compared to ET-only on several cognitive tests, and showed more frequent familial history, and lower levodopa responsiveness [14]. Although the results of a follow-up radionuclide imaging study with $^{123}$I-Ioflupane (DaTscan) in ET patients did not support the hypothesis of a link between ET and PD, but in ET patients striatal binding was significantly reduced compared to healthy controls [15]. The most recent post-mortem study of 89 ET patients reported that 11 (12.4%) had pathological findings of progressive supranuclear palsy (PSP) [16]. This raised other questions, whether ET patients are at an increased risk of developing PSP, and what proportion of ET patients who develop presumed PD or Alzheimer’s disease, actually have PSP [16].

A hyperechogenicity of the substantia nigra (SN+) without any abnormalities in other brain structures is a common finding in transcranial ultrasound (TCS) of PD patients [17]. Recently, imaging by TCS has been recommended (European guidelines): 1) for the differential diagnosis of PD from atypical or secondary parkinsonian syndromes...
(PS); 2) for early PD diagnosis, and 3) for the detection of subjects at risk for PD [18]. However, TCS shows the SN+ in a percentage of non-PD patients. This echo feature is found in up to 26% of ET patients, compared to approximately 10% of healthy controls [17, 19, 20]. The aim of the study was to look for a link or any distinguishing features by TCS, together with the clinical examination findings in a group of patients with overlapping phenotype of ET-PD.

**Methods**

**Design and subjects**
A prospective observational case-control study was performed during a period from the 3rd of January 2011, until the 30th of January 2013, at the Hospital of Lithuanian University of Health Sciences (HLUHS, Kaunas, Lithuania). Initially, 433 subjects (332 patients and 101 controls) were referred for examinations from both Out-patient and In-patient units of the Neurology Department. Control subjects were recruited from the patients who were referred for carotid ultrasound and who had other neurological diseases, but not including movement disorders.

After one year all medical records of the patients were reviewed to see if the treating neurologists made any changes to the final clinical diagnoses. Only the ET-PD patients were invited for a re-consultation after a year, they were all contacted by phone. After the study, if a patient of any other group did not come for a re-consultation, the diagnosis was classified as recorded at the time of the last visit.

Of 332 patients directed for TCS, 46 patients (13.9 %) were excluded from the study because of bilateral temporal acoustic bone insufficiency. In addition, 14 (4.9 %) patients were excluded because their diagnoses changed or remained uncertain (N/A) after a follow-up: for 11 (2.5 %) diagnosis remained N/A, for 1 (0.2 %) diagnosis
converted to atypical PS, and for 2 (0.5 %) patients diagnosis changed to secondary PS.

Thus, 373 subjects were eligible for the final analysis: 272 patients and 101 controls. The patient group consisted of ET-PD (n=15), PD-only (n=141), and ET-only (n=116). The higher percentage of all patients (68.3 %) was referred for a de novo diagnosis. The majority of PD-only patients were at an early stage of the disease (80.1%). TD PD-only accounted for 48 (34%), non-TD – for 90 (63.8%), while 3 cases (2.1%) were N/A.

**Ethics**
Before the study was initiated, permission was obtained from Kaunas Regional Research Ethics Committee (No BE-2-70). All subjects recruited gave a written informed consent. Additionally, a written agreement from the patients was obtained to reproduce the images and video material anonymously.

**Clinical approach**
During a visit of every subject, a neurological examination and a structured interview were performed (DŠ, BV, GD). The case history data included: duration of symptoms, topography, (a)symmetry, relation to voluntary movements, posture and task, heredity. The subjects were also asked about possible contact with toxic agents and history of head traumas. The most effective pharmacotherapy was recorded.

The diagnostic standard in our study was a clinical diagnosis, made by a treating neurologist, which was based on widely accepted criteria: for PD - the United Kingdom Brain Bank criteria, for ET- the consensus statement of the Movement Disorder Society [21, 22]. When clinically the diagnosis was debated, for those patients DaTscan (General Electrics Healthcare, the United Kingdom) imaging was performed at the HLUHS, Department of Nuclear Medicine. For the atypical cases,
brain computed tomography (CT) and/or magnetic resonance imaging (MRI, Siemens Magnetom Avanto Syngo, 1.5 T) scans were made (RG). See an illustrative case (Figure 1, the case No. 9 in Table 1) with ET-PD plus restless legs syndrome (ET-PD-RLS) co-morbidity, where different imaging methods were applied and the findings were described.

For a thorough assessment, both objective and subjective questionnaires were applied. The clinician-rated scales that we used included the Unified Parkinson’s Disease Rating Scale (UPDRS), modified Hoehn and Yahr (H&Y) Stages Scale, and the Hospital Anxiety and Depression (HAD) Scale that was self-rated [23-25].

**Ultrasonographic approach**
TCS imaging was performed by one neurosonographer (KL). The sonographer was blinded to the clinical data, but still could see the examined subjects. We used a 2–5 MHz phased array transducer on a commercially available ultrasound system, Voluson 730 Expert (General Electrics Healthcare, Austria). With the subjects laid in a supine position, the transducer was placed over the pre-auricular temporal acoustic window bilaterally. The ultrasound beam was focused at a depth of 16.8/55Hz, manually adapting gain and degree of compression, to allow optimal image quality at the mesencephalic, diencephalic and sella media planes. The SN+ we classified by a plot of an area in cm$^2$. The normative threshold values of the SN calculated in our laboratory were <0.20 cm$^2$ (mean+1 standard deviation, SD) and <0.26 cm$^2$ (mean+2 SD) [26]. The SN+ was treated when it was enlarged at least on one side. For the ventricular system, the normative values were as follows: the third ventricle (V3) diameter <1.0 cm (mean+2 SD); the lateral ventricles (LV) <2.1 cm (mean+2 SD).
Statistical analyses
An analysis was performed with a statistical package SPSS version 19.0 (IBM, USA). Descriptive statistics were given as absolute numbers, percentages, mean ± SD, median and interquartile range. Normality of the variables was explored by the Shapiro-Wilk test. For the comparisons of non-parametric data, the Kruskal-Wallis test was used. For parametric data, the means between three or four groups were compared by analysis of variance (ANOVA), and between two groups, the Student t test was used. For categorical data $\chi^2$ criterion was used. Correlation analysis of non-parametrical data was performed by Spearman's correlation, and of parametric, Pearson’s. A $p$ value of less than 0.05 was used as the criterion for statistical significance.

Results
Clinical findings
The sample of the ET-PD patients accounted for 5.5% of all patients (15/272). The demographic and clinical characteristics of each patient of the ET-PD group are presented in Table 1. The mean age of ET-PD patients was $69 \pm 9.6$ years (yrs), 46.7% were male, median symptom duration was 6 yrs. In the ET-PD group, 11 of 15 (73.3%) patients had asymmetrical distribution of tremor at onset. The disease for the majority of patients in the PD-only group (n=122, 86.5%) started asymmetrically, whereas for the majority (n=81, 73%) in ET-only, it was bilateral ($\chi^2$ test, $p<0.001$). Out of 15 ET-PD patients, 8 (53.3%) had the onset of tremor after 50 yrs of age, and in 10 (66.7%) of them the ET-type tremor was present $\geq 5$ yrs before the onset of PD-related symptoms. The types of tremor in all ET-PD patients were a mixture of an action and/or posture plus of a rest. The topography of tremor in ET-PD patients on examination was as follows: arm(s) - in 15 (100%), head – in 9 (60%), leg(s) - in 3
(20%), voice – in 2 (13.3%). In PD-only patients tremor involved arm(s) in 133 (94.3%), leg(s) in 78 (55.3%), and head in 11 (7.8%) of cases (χ² test, p<0.001). A positive cogwheel sign was present in only 4 (26.7%) of ET-PD patients. More than a half (n=8, 53.3%) of ET-PD patients denoted positive family history of tremor. Levodopa (n=6, 40%), dopamine agonists (DA, n=6, 40%), benzodiazepines (n=6, 40%) and propranolol (n=5, 33.3%) were prescribed separately or in combinations for the patients with ET-PD.

When comparing the ET-PD patient group to other groups of patients and controls (summarized in Table 2), statistically significant differences were found: between genders, there was a male (53.2%) predominance in PD-only, and a female (66.4%) in ET-only group (χ² test, p=0.007); within symptom duration, which was the longest (median 6 yrs) in the ET-PD group (Kruskal-Wallis test, p=0.003); between the rate of positive family history, which was the most frequent (53.3%) in the ET-PD group (χ² test, p=0.005); in cogwheel sign, which was the most frequently detected (91.5%) in PD-only group (χ² test, p<0.001); in pyramidal signs, which were the most frequent (13%) both in ET-PD and PD-only groups (χ² test, p=0.009); also there were differences in the mean H&Y scores with the higher (2.6 ± 0.8) in ET-PD group (t test, p=0.021). When comparing TD to non-TD PD-only groups, they did not differ in any clinical or demographic aspects, except for H&Y scores, which were higher in non-TD (1.96 ± 0.74 vs. 1.6 ± 0.70, t test, p=0.009). We did not detect any significant differences in the other clinimetric scales (the UPDRS and HAD), between patient groups and controls.

A correlative analysis, taking into account all the groups, revealed significant correlations between: an age and HAD-Depression (r=0.22, p=0.034); the duration of
symptoms and HAD-Anxiety (r=0.26, p=0.009), H&Y scale (r=0.4, p<0.001),
UPDRS part I (Mentation, Behavior and Mood) scores (r=-0.33, p=0.043).

**Ultrasonographic findings**
The TCS findings in the patient groups and controls are given in Table 3. When
comparing TD to non-TD PD-only patients, they differed in the mean largest SN
\( \text{SN}_{\text{Max}} \) plots, which were higher for non-TD group (0.35 ± 0.17 vs. 0.28 ± 0.25 cm\(^2\), t
\text{test}, p=0.015). Significant differences were detected: between the frequency of
disrupted/absent nuclei raphe \( \chi^2 \text{ test}, p<0.001 \), which were the most affected in ET-
PD (38.5%) and PD-only (38.6%) groups; in hyperechogenic lentiform nucleus (LN+)
rate, which was the most frequently (26.7%) observed in ET-PD group \( \chi^2 \text{ test}, p=0.006 \); within red nucleus hyperechogenicity rate \( \chi^2 \text{ test}, p=0.005 \), the most
frequently visible in ET-only (17.2%) and the control (18.8%) groups (probably
because the SN+ did not overtook its area). Specifically in the subgroup of ET-PD
patients, to whom ET-type tremor presented ≥5 yrs before the onset of PD-related
symptoms (n=10), the LN+ was detected in only 2/10 (20%) of them \( \chi^2 \text{ test}, p=0.088 \).

A correlative analysis, taking into account all the groups together, revealed a
significant relationship between: the age and V3 diameter \( r=0.23, p<0.001 \), the right
\( r=0.18, p=0.004 \) and also the left LV diameters \( r=0.25, p<0.001 \); the \( \text{SN}_{\text{Max}} \) plot
and V3 diameter \( r=0.15, p=0.04 \).

**Discussion**
The main echo findings of the present study in the patients with overlapping ET-PD
phenotype, were similar to PD-only group, as more than two thirds (66.7%) of ET-PD
patients had the SN+ at a threshold value ≥0.20 cm\(^2\), and nuclei raphe interruptions or
absence were detected in 38.5%. From the ultrasonographic comparative point, the
closest idea to our study was the recent investigation by Kim et al., focusing on TCS in 47 PD-only and 64 ET-only patients, in relation with putative pre-motor symptoms of PD [20]. The authors detected a significant association between SN+ and each pre-motor symptom in the ET-only group, linking the results that SN+ in patients with ET is influenced by the putative pre-motor symptoms of PD [20].

The single distinguishing TCS feature, was an increased frequency (26.7%) of detected LN+ in the group of patients with ET-PD (Figure 1), however significant when compared to controls only ($\chi^2$ test, p=0.006). Usually such ultrasonographic findings are characteristic to PS [17, 18]. In the study of Behnke et al., unilateral or bilateral LN+ was found in 13/18 (72.2%) patients with PSP, in 23/32 (71.9%) patients with parkinsonian variant of multisystem atrophy (MSA-P), and in only 10 of 88 (11.4%) patients with idiopathic PD [27]. Taking into account the SN echogenicity and V3 diameter, the normal SN indicated MSA-P rather than PD, whereas V3 dilatation of >1.0 cm in combination with LN+ indicated PSP rather than PD [28]. In the present study, when analyzing the subgroup of ET-PD patients, to whom ET-type tremor presented $\geq 5$ yrs before the onset of PD-related symptoms, TCS helped to reveal the LN+ in only 2/10 (20%) of them, this was indistinguishable even from the control group (p=0.088). This is probably because a few patients with PS were misclassified as having ET-PD. These echo findings in ET-PD group have similarities to the results of the recent post-mortem study, where in 12.4% (11/89) of the ET patients PSP pathological findings were detected (ET-PSP) [16].

By comparing clinical results, the significant differences between the patient groups were detected. In the ET-PD group male rate was similar to PD-only (46.7% and 53.2% respectively). There were similarities in the duration of symptoms between the ET-PD and ET-only groups (median 6 yrs and 5 yrs respectively). Chaudhuri et al.
showed that longstanding isolated asymmetrical postural tremor may evolve to PD, and this was supported in 5 of the 13 reported cases (38%) by abnormal radionuclide imaging [29]. Whereas in 5 out of 24 cases, uncertain parkinsonian signs and normal imaging led to a change of the diagnosis to ET [29].

A positive family history rate was highest in the ET-PD group. This feature was similar to ET-only group (53.3% and 31.3% respectively). Even though ET is one of the most common genetic disorders, it is yet to be identified as being a specific gene mutation. Puschmann et al. extensively investigated large kindred whose family members had PD, ET, RLS and depression, an overlap (mainly ET-PD or PD-RLS) was detected in 64% (7/11) of these individuals [30]. The fact that the risk of ET is significantly increased in relatives of patients with PD, suggests the possibility that both conditions are genetically related and probably share common hereditary predisposition [6]. In the recent study of Barut et al., the patients with ET–PD displayed a higher frequency of familial tremor history, as was recorded in our study [14]. The same authors also found significantly lower scores compared to the ET-only group on several cognitive tests, and lower levodopa responsiveness [9, 14]. Our sample of the ET-PD patients, which accounted for only 5.5% of all patients, was small, but quite heterogeneous itself. Less than a half (40%) of the ET-PD patients responded well to levodopa, and the majority (66.7%) required additional medications traditionally used for ET.

We noticed a dissociation between the presence of a positive cogwheel rigidity in 26.7% of the ET-PD patients vs. 91.5% in the PD-only group, but a much higher mean of H&Y scores (2.6 ± 0.8 vs. 1.8 ± 0.8 respectively). Moreover, in the majority of the ET-PD group, 11/15 (73.3%) of patients had asymmetrical distribution of tremor, and 8/15 (53.3%) had an onset of tremor after 50 yrs. The results of the
radionuclide imaging study by Coria et al. suggested that current the diagnostic
criteria for ET should be revised to include asymmetry and late-onset tremor as
predictors of nigrostriatal denervation [10]. This is because often found isolated action
tremor is a frequent presenting symptom in a subset of individuals with PD, who are
often misdiagnosed as having ET [10].
The main limitations of our study were that there was no pathological or functional
imaging confirmation for all ET-PD patients. Also there was a limited time for a
follow-up.

**Conclusions**
The clinical features linking ET-PD to PD-only group were an asymmetrical and late-
onset tremor, presence of a rest tremor on examination, and male gender. But the
linking to ET-only group features were long symptom duration, high positive family
history rate, was rarely cogwheel rigidity present, which dissociated from H&Y
scores. The ultrasonographic findings linking ET-PD to PD-only group were the rate
of the SN+ and of the red nucleus, and nuclei raphe disruptions or absence. The LN+
was the most frequent finding among the ET-PD patients, this is characteristic to the
TCS findings detectable in PS, which raised awareness about correct clinical
diagnosis in a few cases the study covered.
Further research questions: the highest positive family history rate among ET-PD
patients indicates strong hereditary predisposition and needs genetic underpinnings of
this PD-spectrum disorder; an addition of longitudinal follow-up studies is
substantially needed to increase diagnostic certainty; the confirmatory
neuropathological studies of ET-PD clinical phenotype are required to describe and
quantify the pathological changes.
Authors' contributions
KL made ultrasound evaluation, conceived of the study, performed the statistical analysis, drafted the manuscript. BV, GD and DŠ performed clinical evaluation of the patients and controls, applied the scales and interviews. RG performed brain MRI and CT imaging. AS helped with preparing the draft of the manuscript. AV participated in the design of the study. DR participated in its design and coordination, also revised the manuscript critically. All authors read and approved the final manuscript.

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References


**Figures**

**Figure 1** - The images of TCS, cranial CT and MRI of one patient with ET-PD plus restless legs syndrome co-morbidity.

A- cranial MRI, T2W, B- cranial CT, markedly hyperintensive signals bilaterally in the lentiform nucleus (white arrows), C- TCS, mesencephalic plane, moderate SN and red nucleus hyperechogenicity (white arrow), D- TCS, diencephalic plane, bilaterally markedly hyperechogenic lentiform nuclei (white arrows).
Tables

Table 1 - The detailed demographic and clinical characteristics of every ET-PD patient.
Abbreviations: F- female, M- male, FH- family history, H- head, A- arm, V- voice, L- leg, D- right, S- left, B- bilateral, Symp. durat.- symptom duration, Lat.- lateralization, Extr.- extrapyramidal, SN- substantia nigra, L-Dopa- levodopa, DA- dopamine receptor agonists.

Table 2 - Demographic and clinical characteristics of ET-PD patients in comparison to both ET-only and PD-only patients, and to controls.
Values are presented as mean ± standard deviation or median with interquartile range, and numbers (percentages). *- p values were counted comparing 3 groups of patients, #- p values were counted comparing 4 groups of subjects where available.
Abbreviations: UPDRS- Unified Parkinson’s Disease Rating Scale, HAD- Hospital Anxiety and Depression Scale, N/A- not applicable, NS- not significant.

Table 3 - Ultrasonographic findings in the groups of patients and control subjects.
Values are presented as mean ±SD or numbers (percentages). *- p values were counted comparing 3 groups, #- p values were counted comparing 4 groups.
Abbreviations: SN- substantia nigra, R- right, L-left, Max- biggest, V3- third ventricle, LV- lateral ventricles, + hyperechogenic, - or +/- absent or disrupted, NS- not significant.
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<td>Yes</td>
<td>Paroxetine, clonazepam 0.25 mg, vit. E, coenzyme Q10</td>
</tr>
<tr>
<td>15.</td>
<td>M</td>
<td>83</td>
<td>10</td>
<td>No</td>
<td>A</td>
<td>B</td>
<td>No</td>
<td>No</td>
<td>Gabapentine 100 mg, vinpocetine 20 mg, piracetam 400 mg, vit. E</td>
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Table 2

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Patients (n=272)</th>
<th>Controls (n=101)</th>
<th>P value*</th>
<th>P value#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ET-PD (n=15)</td>
<td>ET-only (n=116)</td>
<td>PD-only (n=141)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69±9.6</td>
<td>63.9±14.4</td>
<td>64.4±11.2 NS</td>
<td>61.7±12.4 NS</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>7 (46.7)</td>
<td>39 (33.6)</td>
<td>75 (53.2) 0.007</td>
<td>56 (55.4) 0.004</td>
</tr>
<tr>
<td>Symptom duration, y</td>
<td>6 (3-15)</td>
<td>5 (1-10)</td>
<td>3 (1-6) 0.003</td>
<td>N/A N/A</td>
</tr>
<tr>
<td>Family history +</td>
<td>8 (53.3)</td>
<td>35 (31.3)</td>
<td>23 (17) 0.005</td>
<td>4 (4.3) &lt;0.001</td>
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<tr>
<td>Toxic exposure</td>
<td>3 (20)</td>
<td>19 (16.4)</td>
<td>23 (16.3) NS</td>
<td>16 (15.8) NS</td>
</tr>
<tr>
<td>Living in rural area</td>
<td>4 (26.7)</td>
<td>19 (16.4)</td>
<td>29 (20.6) NS</td>
<td>16 (15.8) NS</td>
</tr>
<tr>
<td>Cogwheel sign</td>
<td>4 (26.7)</td>
<td>3 (2.6)</td>
<td>129 (91.5) &lt;0.001</td>
<td>0 (0) &lt;0.001</td>
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<tr>
<td>Pyramidal signs</td>
<td>2 (13.3)</td>
<td>3 (2.6)</td>
<td>19 (13.5) 0.009</td>
<td>10 (9.9) 0.025</td>
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<td>H&amp;Y stage</td>
<td>2.6±0.8</td>
<td>N/A</td>
<td>1.8±0.8 0.012</td>
<td>N/A N/A</td>
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<tr>
<td>UPDRS part I</td>
<td>1 (0-1)</td>
<td>1 (0-3)</td>
<td>3 (1-4) NS</td>
<td>N/A N/A</td>
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<tr>
<td>UPDRS part II</td>
<td>5 (4-6)</td>
<td>13 (12-13)</td>
<td>11 (7-16) NS</td>
<td>N/A N/A</td>
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<tr>
<td>UPDRS part III</td>
<td>5 (3-6)</td>
<td>N/A</td>
<td>14 (9-20) NS</td>
<td>N/A N/A</td>
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<tr>
<td>HAD-Anxiety</td>
<td>1 (1-8)</td>
<td>6 (2-10)</td>
<td>8 (5-11) NS</td>
<td>5 (3-8) NS</td>
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<tr>
<td>HAD-Depression</td>
<td>4 (4-7)</td>
<td>4 (2-6)</td>
<td>6 (4-9) NS</td>
<td>3 (1-7) NS</td>
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Table 3

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<tr>
<th>Ultrasonographic parameters</th>
<th>Patients (n=272)</th>
<th>Controls (n=101)</th>
<th>P value*</th>
<th>P value#</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ET-PD (n=15)</td>
<td>ET-only (n=116)</td>
<td>PD-only (n=141)</td>
<td></td>
</tr>
<tr>
<td>SN&lt;sub&gt;R&lt;/sub&gt; cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.22±0.12</td>
<td>0.20±0.11</td>
<td>0.27±0.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SN&lt;sub&gt;L&lt;/sub&gt; cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.27±0.15</td>
<td>0.23±0.14</td>
<td>0.31±0.16</td>
<td>0.001</td>
</tr>
<tr>
<td>SN&lt;sub&gt;Max&lt;/sub&gt; cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.30±0.16</td>
<td>0.24±0.14</td>
<td>0.34±0.16</td>
<td>&lt;0.001</td>
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<tr>
<td>SN&lt;sub&gt;Max&lt;/sub&gt; ≥0.20 cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10 (66.7)</td>
<td>49 (42.2)</td>
<td>106 (75.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SN&lt;sub&gt;Max&lt;/sub&gt; ≥0.26 cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>8 (53.3)</td>
<td>38 (32.8)</td>
<td>89 (63.1)</td>
<td>0.001</td>
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<tr>
<td>V&lt;sub&gt;3&lt;/sub&gt; cm</td>
<td>0.69±0.31</td>
<td>0.58±0.28</td>
<td>0.58±0.27</td>
<td>NS</td>
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<tr>
<td>LV&lt;sub&gt;R&lt;/sub&gt; cm</td>
<td>1.81±0.3</td>
<td>1.82±0.26</td>
<td>1.78±0.24</td>
<td>NS</td>
</tr>
<tr>
<td>LV&lt;sub&gt;L&lt;/sub&gt; cm</td>
<td>1.78±0.26</td>
<td>1.81±0.3</td>
<td>1.75±0.24</td>
<td>NS</td>
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<tr>
<td>N. raphe – or +/–</td>
<td>5 (38.5)</td>
<td>22 (20)</td>
<td>51 (38.6)</td>
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<tr>
<td>N. caudatus +</td>
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<td>2 (1.4)</td>
<td>NS</td>
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<tr>
<td>N. lentiformis +</td>
<td>4 (26.7)</td>
<td>20 (17.2)</td>
<td>12 (8.5)</td>
<td>NS</td>
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<tr>
<td>Thalamus +</td>
<td>2 (13.3)</td>
<td>10 (8.6)</td>
<td>10 (7.1)</td>
<td>NS</td>
</tr>
<tr>
<td>N. ruber +</td>
<td>1 (6.7)</td>
<td>20 (17.2)</td>
<td>9 (6.4)</td>
<td>0.008</td>
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</table>
Figure 1