# TRANSCRANIAL SONOGRAPHY IN MOVEMENT DISORDERS

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SUMMARY – Neuroimaging techniques are nonspecific for basal ganglia impairment in the majority of movement disorders, therefore the diagnosis is still based on clinical examination. Recent reports show the substantia nigra (SN) hyperechogenicity detected by transcranial sonography (TCS) to be a specific finding in Parkinson's disease (PD). The aim of the study was to assess the possibility of TCS to help differentiate PD from essential tremor (ET) by measuring SN echogenicity. The study included 50 PD patients, 20 ET patients, and 50 healthy control subjects. The recordings were done in axial plane by a standardized protocol; SN was displayed, encircled, measured two times, and mean value was calculated and presented in $cm^2$. In the control, PD and ET groups, bilateral combined mean SN size was 0.17 $cm^2$ ($\pm0.06$), 0.26 $cm^2$ ($\pm0.06$) and 0.16 $cm^2$ ($\pm0.04$), respectively. Our data showed a significant difference in SN echogenic size between PD and control group as well as between ET and PD group ($p<0.001$) but not between control and ET group ($p=0.240$). The measurement of SN by use of TCS was found to be a valuable tool in differentiating PD from other movement disorders. Due to the portability, noninvasiveness and easy reproducibility, TCS might help in diagnosing PD, or in the differential diagnosis of vague clinical cases.

Key words: *Parkinson disease – diagnosis; Parkinson disease – ultrasonography; Substantia nigra – ultrasonography; Ultrasonography, Doppler – transcranial*

## Introduction

Neuroimaging techniques are quite nonspecific for basal ganglia impairment in the majority of movement disorders, therefore the diagnosis is still based on clinical examination[1-3]. Maximal accuracy in such a differential diagnostic procedure for Parkinson's disease (PD) as the most common movement disorder is 90%, while the average misdiagnosis rate for PD in early stages is as high as 20%-30%[4].

Recent reports show that substantia nigra (SN) hyperechogenicity detected by transcranial sonography (TCS) is a specific finding of PD[5-8]. Based on ultrasound wave reflection and velocity, quantified in echogenicity,

TCS allows brain imaging in two-dimensional black and white slices. Although its spatial resolution is lower than in other imaging modalities, it enables visualization of some basal ganglia as hyperechogenic structures. Lately, TCS B-mode has also been used as a functional marker in the detection of disrupted midline brainstem raphe in patients with unipolar depression and for evaluation of basal ganglia in some movement disorders. Also, TCS proved to be reliable in the evaluation of the ventricular system of the brain and vascular status of the patient[9-12]. We initiated this study to assess the possibility of TCS to help differentiate PD from essential tremor (ET) by measuring echogenicity of the SN.

## Patients and Methods

### Patients

The study included 50 PD patients, 20 ET patients, and 50 healthy control subjects. PD diagnosis and se-

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verity were based on the Parkinson's Disease Society Brain Research Centre clinical criteria, Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr rating scale (H&Y)[13,14]. Inclusion criteria for control group were no prediagnosed PD or any form of extrapyramidal disorders. ET diagnosis was established according to the Consensus Statement of the Movement Disorder Society on Tremor[15]. All patients were treated at University Department of Neurology, Sestre milosrdnice University Hospital, Zagreb, Croatia, and received optimal medical anti-PD treatment. Each patient underwent complete neurological and sonographic examination performed by two independent physicians blinded for the results of the other one and of clinical examination. We also correlated TCS findings with clinical characteristics of PD.

## Methods

We used Aloka ProSound SSD-5500 equipped with 2 MHz transducer to perform TCS. Insonation was done through both temporal "bone windows" on intact skull. Penetration depth was 12 cm and image gain was adopted individually. Recordings were done in axial plane by standardized protocol; SN was displayed, encircled, measured two times, and mean value was calculated and presented in $cm^2$. Special attention was paid to the lateral part, locus of SN within[5]. Tilting the probe by 10 degrees up, the ventricular system is shown as anechoic area, surrounded by a thin hyperechogenic margin. The distance between two hyperechogenic margins was calculated as a diameter of the $3^{rd}$ ventricle. As a cut-off margin for detection of hyperechogenicity 0.20 $cm^2$ was used because it represents the upper $75^{th}$ percentile of the median value in healthy subjects[5-7].

## Statistics

Descriptive statistics included median with lower ($25^{th}$ percentile) and upper ($75^{th}$ percentile) quartile. Mann Whitney U-test and Kruskal Wallis test were used on between-group comparison.

## Results

Median age of our PD and ET patients was 63.3 and 61.5 years, respectively. Control group included 25 female and 25 male subjects, median age of 60.5 years. We excluded ten (12%) individuals due to impossible recording or incomplete insonation. Clinical examination of PD patients revealed an average H&Y score of 2 (1-5) and UPDRS-III score of 18.3 ($\pm6.4$). The average duration of PD was 5 (1-19) years. Patient clinical and demographic data are shown in Table 1.

In the control group, bilateral combined mean SN size was 0.17 $cm^2$ ($\pm0.06$); 0.18 $cm^2$ ($\pm0.04$) on the right and 0.17 $cm^2$($\pm0.04$) on the left side. All but seven (14%) healthy subjects had SN size below the hyperechogenic 0.20 $cm^2$ margin. The mean bilateral SN size in PD group was 0.26 $cm^2$ ($\pm0.06$); 0.26 $cm^2$ ($\pm0.05$) on the left and 0.27 $cm^2$ ($\pm0.06$) on the right side, which was statistically highly significantly different from the control group (p<0.001). Six PD patients had SN extent (12%) within the normal range, whereas 44 (88%)

*Table 1. Patient demographic and epidemiological data*

|  | Parkinson's disease patients | Essential tremor patients | Control subjects |
|---|---|---|---|
| n | 50 | 20 | 50 |
| Age (yrs) | 63.3±11 | 61.5±10 | 60.5±19 |
| Duration (yrs) | 5 (1-19) | | |
| Side affected | Left 63% Right 37% | | |
| Dominant symptom | Tremor 45% Rigor 55% | | |
| Hoehn and Yahr rating scale | 2 (1-5) | | |
| UPDRS III | 18.3 (±6.4) | | |

UPDRS=Unified Parkinson's Disease Rating Scale motor part III

*Table 2. Transcranial sonography findings*

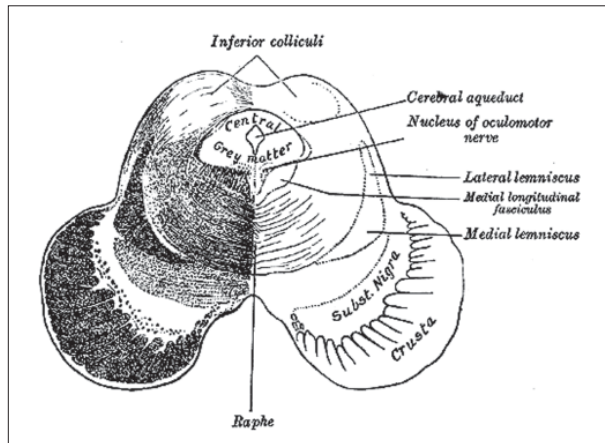|  | Parkinson's disease patients | Essential tremor patients | Control subjects |
|---|---|---|---|
| Substantia nigra median size ($cm^2$) | 0.26 $cm^2$ (±0.06) | 0.16$cm^2$ (±0.04) | 0.17$cm^2$ (±0.06) |
| Substantia nigra size <0.20 $cm^2$ | n=6 (12%) | n=16 (80%) | n=43 (86%) |
| Substantia nigra size >0.20 $cm^2$ | n=44 (88%) | n=4 (20%) | n=7 (14%) |
| Third ventricle | 8.0 mm (7.5-9.1)* | 8.3 mm (6.9-9.6)* | 7.8 mm (7.2-7.9)* |

\* $25^{th}$ – $75^{th}$ percentile

*Fig. 1. Midbrain transsection at the level of mesencephalon.*

patients had marked bilateral SN hyperechogenicity. Patients with ET had a mean SN size of 0.16 cm² (±0.04); 0.16 cm² (±0.04) on the right and 0.15 cm² (±0.05) on the left side, which was significantly different from PD group (p<0.001) but not from control group (p=0.240). Hyperechogenicity was found in four (20%) ET group patients. The mean 3rd ventricle diameter in PD, control and ET group was 8.0 mm (7.5-9.1, 25th – 75th percentile), 7.8 mm (7.2-7.9) and 8.3 mm (6.9-9.6), respectively, yielding no statistically significant difference (Table 2). There was no significant correlation of PD clinical characteristics (UPDRS, H&Y, predominant symptom and disease duration) with TCS findings.

## Discussion

Our study showed the increased SN echogenicity on TCS to be a characteristic feature of PD. Assuming appropriate temporal bone windows, this finding could be used to distinguish patients with PD from ET or healthy controls from PD. However, TCS failed to make such a differentiation between ET patients and healthy controls, indicating that the pathological substrate of ET might not involve SN impairment. All but 14% of healthy subjects had SN echogenicity within the normal range. Such findings are consistent with the results of recent studies that showed 90% of patients with Parkinson's disease to exhibit SN hyperechogenicity, while the prevalence of this pattern in healthy individuals is around 10%[5-7]. In those cases, it might present a functional marker for the subclinical phase of the disease. It is also noteworthy that the prevalence rate of SN hyperechogenicity in healthy individuals matches the rate of incidental Lewy body disease, which is considered as a preclinical form of PD[6].

Since the diagnosis of PD is still based on clinical examination, there is a high rate of misdiagnosed cases largely due to the failure to distinguish PD from similar disorders the symptoms of which are often overlapping, including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal degeneration, dementia with Lewy bodies and ET[4]. The rate of misdiagnosis is particularly high at the early stage of the disease, when motor signs have not yet fully developed.
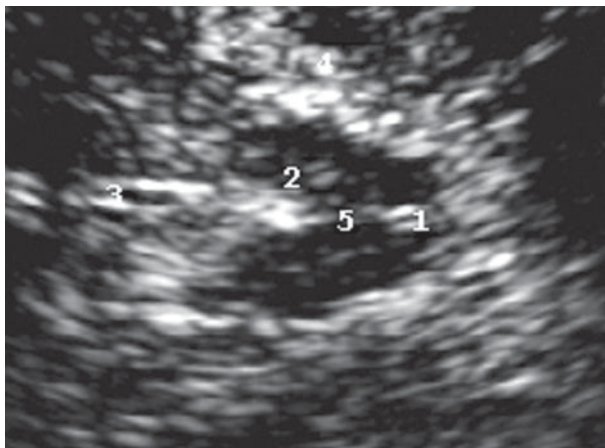


*Fig. 2. TCS image at the same level. Normal TCS findings in a healthy adult. Butterfly-shaped mesencephalon of low echogenicity surrounded by hyperechogenic basal cisterns (4). In medial line NN raphe (5) and (1) aqueducts are shown. Nucleus ruber (2). Third ventricle (3).*
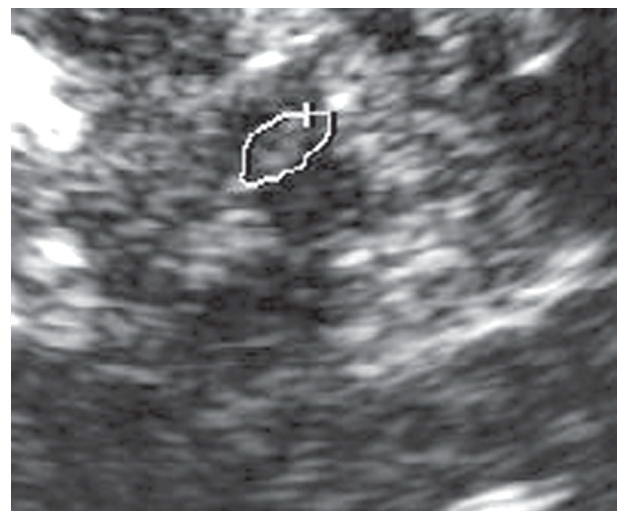


*Fig. 3. TCS pattern of hyperechogenic substantia nigra in a Parkinson's disease patient. The substantia nigra area is encircled and measured.*

Even at that point, 60%-80% of the dopamine-producing neurons have died-off and therapy initiation appears to be crucial[16]. TCS proved to be able to record even these subtle changes before the symptoms have occurred[7,17]. The cause of such an increased echogenic feature in PD is still unknown[18,19]. Since every ultrasonographic examination registers changes in tissue impedance and SN is shown as low echogenic or anechogenic in the majority of healthy individuals, it is possible that changes in the cytoarchitecture or mineral deposits might be the cause of this specific SN finding[20,21]. Recent reports have revealed that the increase in SN signal might be evoked by elevated brain tissue iron levels. Iron is a potent catalyst of reactions forming oxygen radicals, which can induce a cascade of cell damages, mitochondrial or membrane lipid peroxidation[22-24]. Results of such neurodegenerations can be seen on TCS but there is the need of an appropriate temporal "bone-window". The prevalence of inappropriate temporal bone windows for TCS is around 10%-15% and it increases with age. Also, axial resolution is limited by the length of the transmitted ultrasound pulse, and lateral resolution depends on the width of the ultrasonic beam. On the other hand, the image quality depends on the system parameters set by each investigator, resulting in certain subjectivity that can be overridden by semiquantitative assessment.

In conclusion, the measurement of SN by TCS is a valuable tool in differentiating PD from other movement disorders. Due to portability, noninvasiveness and easy reproducibility, TCS might help in diagnosing PD, or in differential diagnosis in vague clinical cases.

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Sažetak

## TRANSKRANIJSKI ULTRAZVUK KOD POREMEĆAJA KRETANJA

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Metode slikovnog prikaza mozga su kod većine poremećaja kretanja nespecifične te se dijagnosticiranje takvih poremećaja većinom temelji na kliničkom pregledu. Dok u 90% zdravih pojedinaca supstancija nigra (SN) prikazuje urednu ehogenost ($<0,20$ cm$^2$), u većine bolesnika s Parkinsonovom bolešću (PB) transkranijskom sonografijom (TCS) se bilježi povećanje njene ehogenosti. Cilj studije bio je ispitati mogućnosti razlikovanja bolesnika s PB i bolesnika s esencijalnim tremorom (ET) pomoću transkranijskog mjerenja SN. Pregled je učinjen standardiziranom metodom; SN je prikazana, obilježena te dva puta izmjerena. Izračunata je srednja vrijednost. Primijenjen je Mann-Whitney U-test i Kruskal Wallis test za usporedbu između skupina. Istraživanje je provedeno u 50 bolesnika s PB, 20 bolesnika s ET te 50 zdravih kontrolnih osoba. Kao granica vrijednosti prema hiperehogenom prikazu primijenjena je vrijednost od 0,20 cm$^2$. Bilateralna hiperehogenost nađena je kod 88% bolesnika s PB, 20% bolesnika s ET i 14% kontrolnih osoba. Rezultati su pokazali statistički značajnu razliku u veličini ehogenosti SN između bolesnika s PB i ET ($p<0,001$), kao i razliku između bolesnika s PB i kontrolne skupine ($p<0,001$), ali ne i značajnu razliku između kontrolne skupine i skupine bolesnika s ET ($p=0,240$). Zaključeno kako je povećana ehogenost SN na TCS specifičan nalaz Parkinsonove bolesti. Mjerenje veličine SN pomoću TCS omogućuje razlikovanje bolesnika s Parkinsonovom bolešću od bolesnika s esencijalnim tremorom.

Ključne riječi: *Parkinsonova bolest – dijagnostika; Parkinsonova bolest – ultrazvuk; Supstancija nigra – ultrazvuk; Ultrazvuk, Dopplerov – transkranijski*