

## TRANSCRANIAL SONOGRAPHY CAN DISCRIMINATE PARKINSON'S DISEASE FROM OTHER MOVEMENT DISORDERS

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**SUMMARY** – While nigral substance (NS) is either barely detectable or undetectable in healthy individuals, the majority of patients with Parkinson's disease (PD) display its increased echogenicity on transcranial sonography (TCS). The aim of the study was to assess the possibility of TCS to differentiate PD from other movement disorders by the measurement of NS. TCS was performed in 28 PD patients, 10 patients with movement disorders different from PD (4 with essential tremor, 2 with neuroleptic parkinsonism, 4 with cervical dystonia) and 18 age-matched healthy controls. Fifteen patients were excluded due to inappropriate temporal acoustic bone window. TCS was applied by standardized protocol; NS was displayed, encircled, and measured twice, and mean area was calculated. Mann Whitney U-test was used for between-group comparison. TCS was possible to perform in 56 of 71 (79%) subjects. NS was undetectable or barely detectable in 9 (50%) healthy controls and 2 (20%) patients with movement disorders. Median NS size in controls was 0.17 (0.16-0.21) cm<sup>2</sup>. A 0.21 cm<sup>2</sup> cut-off margin was used for detection of hyperechogenicity. Combined hyperechogenic NS was detected in 25 (89%) PD patients, 2 (20%) patients with movement disorders, and 3 (16%) healthy individuals. Study results showed a statistically significant difference in NS echogenic size between PD patients and control group (Mann Whitney  $u=42$ ;  $p<0.001$ ) as well as between patients with movement disorder and PD group (Mann Whitney  $u=23.5$ ;  $p<0.001$ ) but no significant difference between controls and patients with movement disorders (Mann Whitney  $u=83.0$ ;  $p=0.737$ ). Thus, assuming appropriate temporal "bone-window", the measurement of NS by use of TCS is a valuable tool in differentiating PD from other movement disorders.

**Key words:** *Parkinson disease – diagnosis; Parkinson disease – ultrasonography; Ultrasonography, Doppler, transcranial; Neurologic examination*

### Introduction

Until recent reports on structural neuroimaging in Parkinson's disease (PD), brain imaging in PD patients was only used to differentiate idiopathic Parkinson's disease from similar disorders<sup>1-4</sup>. Structural neuroimaging

modalities like brain computer tomography or magnetic resonance imaging are not specific and do not correlate with disease duration or clinical severity. Positron emission tomography (PET) and single photon emission computer tomography (SPECT) are able to measure biochemical changes in the striatum, expressing the loss of dopamine cells in the substantia nigra, thus confirming clinical PD diagnosis<sup>5-7</sup>. By means of PET or SPECT, PD can be differentiated from similar movement disorders. However, the cost is high and such techniques are not available in all centers for daily practice. Transcranial sonography (TCS) is an easy bedside method, allow-

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ing for brain imaging in two-dimensional black and white slices<sup>8,9</sup>. In combination with power based transcranial sonography (p-TCS), it generates intravascular color signals from the amplitude of the echo signal and provides useful information on cerebrovascular state of the patient as well<sup>8,10,12,13</sup>. Although spatial resolution is lower than other imaging modalities, it enables visualization of the mesencephalic nuclei as hyperechogenic structures<sup>1-3,14</sup>. Since differentiation between these nuclei is not always possible, measurement of hyperechogenic area is performed. In recent TCS studies<sup>1-3</sup>, in the majority of PD patients elevated echogenicity of NS was observed as the result of NS impairment, probably due to oxidative stress<sup>15</sup>.

Due to the lack of evidence for a similar echo pattern in other movement disorders, this study was performed to differentiate idiopathic PD from similar movement disorders by use of TCS.

## Patients and Methods

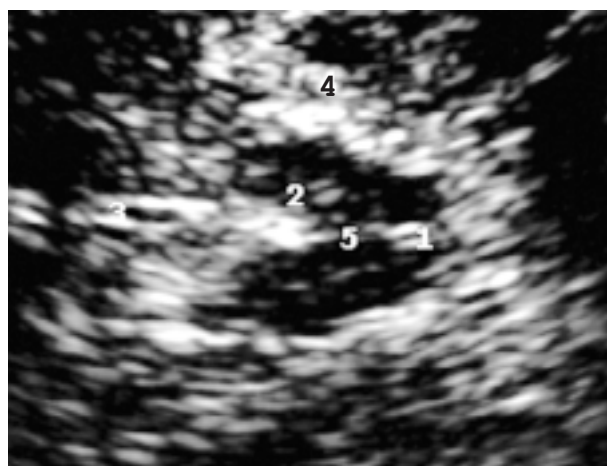
The study included 71 subjects in total. Analysis was possible in 56 of them, whereas 15 subjects were excluded due to inappropriate temporal acoustic bone window. There were 28 PD patients (19 male and nine female), ten patients with non-Parkinson's disease movement disorder (NPMD; four with essential tremor, two with drug-induced parkinsonism, and four with cervical dystonia), and 18 healthy controls (12 male and six female). An informed consent was obtained before entering the study.

All PD patients underwent complete neurological examination performed by two independent physicians blinded for results of the other and for clinical findings. The diagnosis and severity of PD were based on the Unified Parkinson's Disease Rating Scale (UPDRS) and Hoehn & Yahr rating scale (H&Y)<sup>16</sup>. The possible exposure to toxins during lifetime was also noted.

Four patients with NPMD had only tremor, two patients had neuroleptic drug induced iatrogenic parkinsonism, and four patients suffered from focal cervical dystonia. Control group consisted of 18 healthy age- and sex-matched subjects. Inclusion criteria for control group were no previous diagnosis of PD or any form of extrapyramidal disorder.

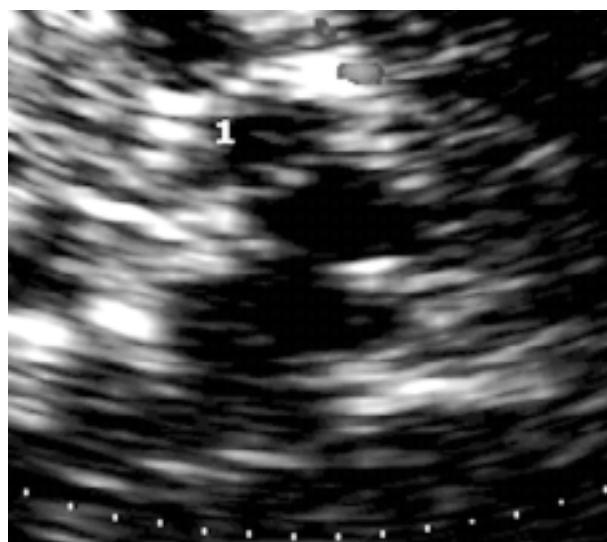
## Methods

TCS was performed on an Aloka ProSound SSD-550. Insonation was done through both temporal "bone win-



*Fig. 1. Normal TCS findings in 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).*

dows" on intact skull with a 2 MHz transducer. Penetration depth was 12 cm. Two imaging planes were performed. Brain parenchyma was visualized first as a homogeneously hypoechogenic matrix with some hyperechogenic areas like falx cerebri, choroid plexus or mesencephalic brainstem. After identification of a butterfly-shaped structure of mesencephalic brainstem, special attention was paid to the lateral part, the locus of NS within it (Fig. 1). Firstly, quantitative measurement of NS area was performed in each subject, calculating the hyperechogenic area in cm<sup>2</sup>. Then, median NS size



*Fig. 2. (A) TCS pattern of hyperechogenic SN in a PD patient;*

for each group was calculated and between-group comparison was done (Fig. 2). Since NS echogenicity data have not yet been standardized, we used upper 75<sup>th</sup> percentile of median as a cut-off margin for confirmation of PD diagnosis. Tilting the probe by 10 degrees up, the ventricular system was shown as anechoic, surrounded by a thin hyperechogenic margin. The distance between two hyperechogenic margins was calculated as diameter of the 3<sup>rd</sup> ventricle.

### Statistics

Descriptive statistics is shown as median with lower (25<sup>th</sup> percentile) and upper (75<sup>th</sup> percentile) quartile. Between-group comparison was performed by Mann Whitney U-test.

### Results

TCS insonation was possible in 56 of 71 (79%) subjects, including 14 male and 42 female subjects, median age 65.1. Patient demographic and epidemiological data are shown in Table 1. TCS findings are presented in Table 2. Nigral substance was undetectable or barely detectable in nine (50%) healthy controls and two (20%) patients with movement disorders. In control group, bilateral combined median NS size was 0.17 (0.16-0.21) cm<sup>2</sup>; 0.17 (0.15-0.21) cm<sup>2</sup> on the right side and 0.18 (0.16-0.22) cm<sup>2</sup> on the left side. Upper 75<sup>th</sup> percentile of median, 0.21 cm<sup>2</sup>, was used as a cut-off margin for PD diagnosis confirmation. The mean bilateral NS size in PD group was 0.32 (0.27-0.36) cm<sup>2</sup>; 0.31 (0.27-0.39) cm<sup>2</sup> on the left side and 0.33 (0.27-0.38) cm<sup>2</sup> on the right



Fig. 2. (B) SN area is encircled and measured.

Table 1. Patient demographic and epidemiological data

	Parkinson's disease patients	Control subjects	Non-Parkinson's disease movement disorder
n	28	18	10
Age (yrs)	65.3±11	67.6±10	62.3±19
Gender (M/F)	19 M / 9 F	12 M / 6 F	6 M / 4 F
Toxin exposure	15 (54%)	6 (33%)	4 (40%)
Hoehn and Yahr rating scale	3 (2;3)		
UPDRS	18 (14;22)		

UPDRS=unified Parkinson's disease rating scale motor part

side, yielding a statistically highly significant difference from the control group (Mann Whitney  $u=42$ ;  $p<0.001$ ). In 25 of 28 (89%) PD patients, the NS area size was well above the 75<sup>th</sup> percentile of the control group size, while only three (11%) patients had bilateral NS area within the normal size. A marked bilateral hyperechogenic NS value (over 90<sup>th</sup> percentile of the control group) was also found in three of 18 (16%) healthy subjects. Patients with NPMD showed a median NS size of 0.18 (0.16-0.21) cm<sup>2</sup>, which was not statistically significantly different from the control group (Mann Whitney  $u=83.0$ ;  $p=0.737$ ), however, significant difference was present on comparison with the group of PD patients (Mann Whitney  $u=23.5$ ;  $p<0.001$ ). Within the same group, patients with essential tremor had a median NS

Table 2. Transcranial sonography findings

	Parkinson's disease patients (n=28)	Control subjects (n=18)	Non-Parkinson's disease movement disorder (n=10)
NS median size	0.32 cm <sup>2</sup> (0.27-0.36)	0.17 cm <sup>2</sup> (0.16-0.21)	0.18 cm <sup>2</sup> (0.16-0.21)
NS size <0.21 cm <sup>2</sup>	n=3 (11%)	n=15 (84%)	n=8 (80%)
NS size >0.21 cm <sup>2</sup>	n=25 (89%)	n=3 (16%)	n=2 (20%)
Third ventricle	8.2 mm (7.3-9.1)	8 mm (6.9-9.2)	7.8 mm (7.3-7.9)

size of 0.19 cm<sup>2</sup> and two of them exhibited bilateral NS hyperechogenicity. Two patients with neuroleptic-induced parkinsonian syndrome had bilateral NS size of 0.21 cm<sup>2</sup> and 0.15 cm<sup>2</sup>, and four patients with cervical dystonia had a median of 0.19 cm<sup>2</sup>.

Clinical examination of PD patients revealed a mean H&Y score of 3 (2-3) and UPDRS-III score of 18 (14-22). The mean 3<sup>rd</sup> ventricle diameter in PD and control groups was 8.2 (7.3-9.1) mm and 8.0 (6.9-9.2) mm, respectively; the difference did not reach statistical significance. Epidemiological data showed 25 (45%) study subjects to have been exposed to one or more exotoxins (herbicides, pesticides, insecticides, heavy metals, solvents, glues and paints) during life, however, there was no statistically significant difference in TCS results between the toxin exposed and toxin non-exposed groups.

## Discussion

Our study showed NS hyperechogenicity in TCS to be a finding highly specific for PD. We found median NS size in PD patients of 0.32 cm<sup>2</sup> compared with 0.17 cm<sup>2</sup> in controls and 0.18 cm<sup>2</sup> in NPDM group. A NS size overlapping the margin of 0.21 cm<sup>2</sup> was present in 89% of PD patients and in only 16% and 20% of controls and NPDM patients, respectively. These findings are consistent with those reported by Berg *et al.*<sup>3</sup> and Becker *et al.*<sup>1</sup> on 90% of PD patients exhibiting NS hyperechogenicity, with a ~10% prevalence of this pattern in healthy individuals. TCS is becoming a valuable tool in diagnosing PD and differentiating it from similar disorders. The possibility of detecting small NS impairment, which is still undetectable by CT or MR, might put TCS in the first line of PD diagnostic algorithm. Epidemiological studies suggest that up to 40% of PD patients are unidentified or misdiagnosed, whereas approximately 8% are waiting for two years of symptom onset for an accurate diagnosis. Since there is no widely accepted test to help us confirm PD, clinical examination for well-established parkinsonian symptoms is still the most accurate way of PD diagnosis. However, in that stage of disease over 80% of dopamine-producing neurons have died-off and the possibility of treatment is reduced. The cause of this neural degeneration and resulting hyperechogenicity is still unknown. Some reports suggest that toxic exposure is a crucial mechanism of nigral injury<sup>11,17</sup>. It has been reported that exposure to various exo- and endochemicals as well as genetic factors might have a

leading role in the initiation of the degenerative process<sup>18</sup>. Significantly elevated odds ratio for pesticide, herbicide, heavy metals, solvents and carbon monoxide have been reported<sup>17</sup>. Once initiated by oxidative stress including free radicals and lipid peroxidation, the process of neurodegeneration inevitably leads over years to microstructural changes of the cytoarchitecture, gliosis and/or mineral deposits of NS<sup>15</sup>. Some post mortem studies reported an increased content of iron deposits in NS, which might explain the source of increased echogenicity<sup>19</sup>. Whether hyperechogenic healthy individuals are at a higher risk of developing PD later in life or are in a preclinical stage of PD, is still a matter of speculation. The fact that the prevalence rate of NS hyperechogenicity in healthy individuals matches the rate of incidental Lewy body disease, which is regarded to be a preclinical form of PD, appears to support the hypothesis that TCS might detect preclinical NS impairment. All three healthy hyperechogenic subjects from this study have been included in the prospective follow-up, since they might be at a greater risk of developing PD later in life.

In conclusion, TCS examination classified correctly 25 of 28 prediagnosed PD patients. In three subjects TCS findings were similar to the control group or NPDM group. Distinguishing between the control group and NPDM group, or within NPDM group by use of TCS examination alone was impossible because of the close correlation of their sonographic findings.

This study showed that enhanced NS echogenicity could be recorded by TCS examination in the majority of PD patients, which might help in confirming PD diagnosis in vague clinical cases or in early stages of the disease. Comparing NPDM group and PD group TCS findings will definitely help discriminate the two conditions, the symptoms of which are often overlapping. TCS did not help in differentiating NPDM and control group by comparing either NS size or median 3<sup>rd</sup> ventricle width.

Due to fine resolution, portability, noninvasiveness and low cost, and assuming appropriate temporal bone window, TCS may be a useful tool in diagnosing PD and discriminating it from similar disorders.

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## Sažetak

## TRANSKRANIJSKA SONOGRAFIJA RAZLIKUJE PARKINSONOVU BOLEST OD DRUGIH POREMEĆAJA KRETANJA

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Za razliku od bolesnika s Parkinsonovom bolesti (PB), prikazivanje substancije nigre (SN) pomoću transkranijске sonografije (TCS) u zdrave populacije je često nepotpuno. Većina PB bolesnika na TCS prikazu pokazuje SN povećane ehogenosti. Cilj studije bio je ispitati mogućnosti razlikovanja PB bolesnika i bolesnika sa sličnim poremećajima kretanja putem otkrivanja substancije nigre. Istraživanje je provedeno u 28 bolesnika s PB, 10 bolesnika s poremećajima kretanja različitim od PB (4 s esencijalnim tremorom, 2 s parkinsonizmom izazvanim upotrebom neuroleptičnih lijekova, 4 s cervikalnom distonijom) te 18 zdravih kontrolnih osoba iste dobi. Zbog nemoguće ili nepotpune insonacije 15 bolesnika je naknadno isključeno iz studije. Otkrivanje je provedeno standardiziranom metodom; prikazom SN, zatim ručnim obilježavanjem te dvostrukim mjerenjem. Izračunata je srednja vrijednost, a statistika je obrađena Mann-Whitney U-testom. Pretraga je bila izvediva u 56 od 71 osobe (79%). U 50% osoba kontrolne skupine i 20% bolesnika iz skupine s poremećajima kretanja različitim od PB prikazivanje je bilo nemoguće ili nepotpuno. Srednja vrijednost veličine SN u kontrolnoj skupini bila je 0,17 cm<sup>2</sup> (0,16-0,21). Kao granica vrijednosti prema hiperehogenom prikazu primijenjena je vrijednost od 0,21cm<sup>2</sup>. Obostrana hiperehogenost nađena je u 25 bolesnika s PD (89%), 2 (20%) u skupini s poremećajima kretanja različitim od PB i u 3 (16%) kontrolne osobe. Rezultati su pokazali statistički značajnu razliku u veličini ehogenosti SN između PB bolesnika i kontrolne skupine (Mann Whitney u=42; p<0,001), kao i razliku između PB i skupine s poremećajima kretanja različitim od PB (Mann Whitney u=23,5; p<0,001), ali ne i značajnu razliku između kontrolne skupine i bolesnika s poremećajima kretanja različitim od PB (Mann Whitney u=83,0; p=0,737). Zaključeno je kako otkrivanje i mjerenje ehogenosti SN putem TCS omogućuje razlikovanje Parkinsonove bolesti od sličnih motoričkih poremećaja.

Ključne riječi: *Parkinsonova bolest – dijagnostika; Parkinsonova bolest – ultrasonografija; Ultrasonografija, Doppler, transkranijски; Neurološki pregled*