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# Transcranial Brain Sonography in Parkinson's Disease and Other Parkinsonian Disorders: a Hospital Study from Tuzla, Bosnia and Herzegovina

Dzevdet Smajlovic<sup>1,2</sup>, Omer C. Ibrahimagic<sup>1,2</sup>

<sup>1</sup>Department of Neurology, University Clinical Center Tuzla, Tuzla, Bosnia and Herzegovina

<sup>2</sup>Medical Faculty, University of Tuzla, Bosnia and Herzegovina, Tuzla, Bosnia and Herzegovina

**Corresponding author:** Dzevdet Smajlovic.  
Department of Neurology, University Clinical Center Tuzla, Medical Faculty, University of Tuzla, Bosnia and Herzegovina. Tel. + 387 61 179 373. E-mail: dzsmajlovic@hotmail.com

## ABSTRACT

**Introduction.** Transcranial sonography (TCS) is a relatively new ultrasound modality which could display echogenicity of human brain tissue through the intact skull. TCS may be useful in differentiation of idiopathic Parkinson's disease (PD) from other parkinsonian disorders. Therefore, we studied different ultrasound markers by TCS in individuals with Parkinson's disease. **Patients and Methods.** We performed TCS in 44 patients with PD and 22 patients with other parkinsonian disorders. Echogenic sizes of the substantia nigra (SN) and the lentiform nuclei (LN), as well as the width of the third ventricle and the frontal horns of the lateral ventricle, were measured. We also analyzed the echogenicity of the brainstem raphe (BR). **Results.** An unilateral hyperechogenic SN was observed in 31 (70%) patients with PD and only in 2 patients (9%) with other parkinsonian disorders ( $P < 0.0001$ ). Hyperechogenicity of the LN was not observed in patients with PD; however, it was present in 7 (32%) patients with other parkinsonian disorders ( $P = 0.0002$ ). Diameter of third ventricle ( $8.6 \pm 2.2$  mm vs.  $6.9 \pm 1.7$  mm,  $P = 0.001$ ), right ( $18.5 \pm 2.6$  mm vs.  $16.5 \pm 2.3$  mm,  $P = 0.003$ ) and left frontal horn of lateral ventricle ( $19.0 \pm 3.7$  mm vs.  $16.2 \pm 2.6$  mm,  $P = 0.0006$ ) was significantly wider in patients with other parkinsonian disorders compared with patients with PD. There was no difference in presence of hypoechogenic or interrupted BR in patients with PD and patients with other parkinsonian disorders (39% vs. 27%,  $P = 0.4$ ). **Conclusion.** TCS is a promising diagnostic technique and can be very helpful in differentiating between idiopathic Parkinson's disease and other parkinsonian disorders.

**Keywords:** Transcranial Brain Sonography, Basal ganglia echogenicity, Parkinson's disease, Parkinsonian syndromes, Differential diagnosis.

## 1. INTRODUCTION

Transcranial sonography (TCS) of brain parenchyma is a relatively new ultrasound modality which could display echogenicity of human brain tissue through the intact skull. Becker and colleagues (1995) first observed hyperechogenicity of the substantia nigra in patients with Parkinson's disease (PD) using TCS (1). Since then, TCS of brain parenchyma in patients with movement and other neurodegenerative disorders has developed with increasing dynamics during the past two decades. The specific advantages of TCS are different visualization of brain structures compared to other neuroimaging methods due to different physical imaging principle, high-resolution imaging of echogenic deep brain structures, on-time dynamic imaging with high resolution in

time, relatively low costs of technical equipment, wide availability, short investigation time, noninvasivity and unlimited repeatability, mobility and bedside availability, and little corruptions by patients' movements. The main limitations of TCS are insufficient temporal bone window (5-20% of patients) and its dependency on the experience and skills of the investigator (2).

The aim of this study was to analyze different ultrasound markers by TCS in individuals with Parkinson's disease and other parkinsonian disorders.

## 2. PATIENTS AND METHODS

In the study we included 47 consecutive patients with idiopathic PD and 22 patients with other parkinsonian disorders. All patients were hospitalized at the Department of Neurology

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Tuzla, Bosnia and Herzegovina, in the period between January 1<sup>st</sup> and December 31<sup>st</sup> 2015. Experienced, certified neurologists made the clinical diagnoses. Diagnosis of PD was made on the basis of the Queen Square Brain Bank criteria (3). Other parkinsonian disorder included progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD) and vascular parkinsonism, and diagnoses were established according to relevant clinical criteria (4-6). Exclusion criteria were drug-induced parkinsonism and neurodegenerative disorders such as neurodegeneration with brain iron accumulation, Wilson's disease, Huntington's disease. Furthermore, patients with an insufficient temporal bone window were not included in the calculation and statistical analysis.

TCS examination was performed in 44 patients with PD (3 patients had insufficient temporal bone window) and in 22 patients with other parkinsonian disorders with a phased array ultrasound system, equipped with a 2.5 MHz transducer (EnVisor C HD, Philips, Netherlands).

All participants underwent TCS in a standard manner (7) and the TCS examination was performed by a trained examiner blinded to clinical data. Measurements of echogenic size of substantia nigra (SN) were carried out on axial TCS scans automatically, after manually encircling the outer circumference of the SN echogenic area. SN echogenic size  $\geq 0.20$  cm<sup>2</sup> was classified hyperechogenic. The echogenicity of the brainstem raphe (BR) was scanned at the mesencephalic plane and assessed qualitatively: grade 1–BR appear as continuous hyperechogenic line (normal finding); and grade 0–BR appear interrupted, hypoechogenic or invisible on both scanning sides (pathological finding). Echogenicity of the lentiform nuclei, the head of the caudate nuclei and the thalami were graded qualitatively as well, and if hyperechogenic structures with more intense signal than the surrounding white matter were detected in these regions, they were regarded as pathological finding. The width of the third ventricle and the frontal horns of the lateral ventricles were measured in a standardized diencephalic axial scanning plane, and was determined by the minimum transverse diameter on axial TCS scan. The diameter of the ventricular system was expressed in millimeters.

Statistical analysis was performed with the Student's t-test for two independent samples (for continuous variables), while for comparisons of categorical variables the Fisher exact test was applied. Results were considered statistically significant if  $p < 0.05$ .

### 3. RESULTS

The study comprised 44 patients classified as having PD and 22 patients as having other parkinsonian disorders. There were no differences in sex distribution, age of the patients and mean age at onset between analyzed groups (Table 1).

Among the patients with PD 39 (89%) had a hyperechogenic SN vs. only 8 (36%) patients with other parkinsonian disorders ( $p < 0.001$ ); while hyperechogenic

	PD	OPD	p
Number of patients	44	22	-
Males	26	14	0.8
Age (years)	64.9 +/- 7.8	61.7 +/- 13.0	0.2
Age at onset (years)	60.5 +/- 7.8	58.4 +/- 13.3	0.4

**Table 1. Demographic characteristics of patients with Parkinson's disease and other parkinsonian disorders. PD- Parkinson's disease; OPD- other parkinsonian disorder**

lentiform nucleus had 7 (32%) patients with other parkinsonian disorders vs. no patients with PD ( $p = 0.002$ ) (Table 2). Out of 39 PD patients with hyperechogenic SN, 31 had unilateral and 8 bilateral marked hyperechogenicity. At the other hand, in the group with other parkinsonian disorders, 2 patients had unilateral and 6 bilateral marked SN hyperechogenicity. Third ventricle and the frontal horns of the lateral ventricles were significantly wider in patients with other parkinsonian disorders when compared with patients with PD (Table 2). There were no differences in the prevalence of pathological brainstem raphe findings (grade 0) between two analyzed groups.

	PD	OPD	p
Hyperechogenic SN	39 (89%)	8 (36%)	<0.001
Hyperechogenic LN	0 (0%)	7 (32%)	=0.002
Third ventricle (mm)	6.9 +/- 1.7	8.6 +/- 2.2	=0.001
LV- right frontal horn	16.5 +/- 2.3	18.5 +/- 2.6	=0.003
LV- left frontal horn	16.2 +/- 2.6	19.0 +/- 3.7	=0.0006
BR- grade 0	17 (39%)	6 (27%)	=0.4

**Table 2. Comparison of TCS findings between patients with Parkinson's disease and other parkinsonian disorders PD- Parkinson's disease; OPD- other parkinsonian disorders; SN- substantia nigra; LN- lentiform nucleus; LV- lateral ventricle; BR- brainstem raphe**

### 4. DISCUSSION

The ultrasound technique has progressed towards being well established diagnostic method in general practice for more than five decades. However, in the fields of neurology, ultrasound has relatively recently being introduced into clinical practice. For the last 15 years, TCS of brain parenchyma is being increasingly used as a diagnostic tool in movement disorders, particularly idiopathic PD. The diagnosis of idiopathic PD and other movement disorders such as atypical parkinsonian syndromes and secondary parkinsonian syndromes, is based on clinical criteria (8, 9), and the differentiation between idiopathic PD and other parkinsonian syndromes can be difficult especially at the beginning of the disease.

TCS through the preauricular bone window allows the depiction of characteristic abnormalities in the echogenicity of SN and basal ganglia. Increased echogenicity ("hyperechogenicity" is the most common used phrase) of the SN is detected in up to 90% of PD patients and does not remarkably change in the disease course and is unrelated to PD severity (2, 10). Substantia nigra hyperechogenicity could be found unilaterally or asymmetrically bilaterally (Figure 1a, 1b). However, SN hyperechogenicity has also been detected in 8% to 10% of healthy people. In our study, we also found very high prevalence

(89%) of uni- or bilateral hyperechogenicity in patients with PD (Table 2), which is correlated with the results of other studies. In the recent meta-analysis, which included 1,926 PD patients and 2,460 healthy controls from 13 countries, results demonstrated a high clinical utility of TCS in the diagnosis of PD, with a pooled sensitivity (83%), specificity (87%), and an excellent overall accuracy (11).

The typical finding of substantia nigra hyperechogenicity in patients with idiopathic PD is not frequent in atypical (multiple-system atrophy-MSA, and progressive supranuclear palsy-PSP), posttraumatic, or vascular parkinsonism. MSA and PSP can be distinguished from idiopathic PD by the absence of hyperechogenic SN. Contrarily, basal ganglia hyperechogenicity (primarily LN) could be specifically seen in these atypical parkinsonian syndromes. Previous studies reported that normal echogenic SN combined with LN hyperechogenicity indicated MSA or PSP (sensitivity 59%, specificity 100%); normal echogenic SN indicated MSA rather than IPD (sensitivity 90%, specificity 98%); third-ventricle dilatation of more than 10 mm in combination with LN hyperechogenicity indicated PSP rather than IPD (sensitivity 84%, specificity 98%) (7, 12, 13). In the study Kostic et al. authors concluded that TCS can be very helpful in differentiation of two main variants of PSP, PSP Richardson's syndrome and PSP parkinsonism (14). Patients with vascular parkinsonism in most cases do not have pathologic hyperechogenic signals in the substantia nigra and other basal ganglia structures, but usually have pathologic findings on vascular examinations of intracranial vessels (15). In our study, we found no hyperechogenic LN in patients with PD, but hyperechogenic LN was found in one third of patients with other parkinsonian disorders. Patients with other parkinsonian disorders also had significantly wider third ventricle and the frontal horns of the lateral ventricles (Table 2) (Figure 2a, 2b). The European Federation of Neurological Societies and the European Section of the Movement Disorder Society for the diagnosis of PD state that TCS is recommended (Level A) for: (I) the differential diagnosis of PD from atypical Parkinsonian syndromes and secondary Parkinsonian syndromes, (II) the early diagnosis of PD and (III) the detection of subjects at risk for PD (16).

Our study has two main limitations. The first one, the relatively small number of patients and the second one, patients with other forms of parkinsonism are not divided into subgroups (e.g. PSP, MSA, etc.). TCS is a method used at the Department of Neurology Tuzla since 2013. and these are probably the first published results of TCS from Bosnia and Herzegovina. In the coming years we will expand the database, and we expect this method to be initiated in other Departments of Neurology in Bosnia and Herzegovina, which will lead to new TCS studies and publications.

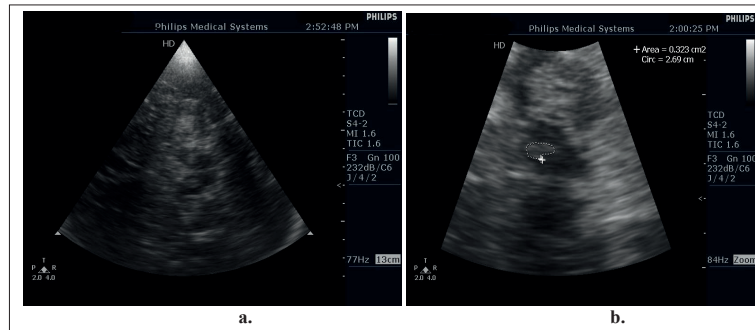


Figure 1. Marked hyperechogenicity of the substantia nigra in patients with idiopathic Parkinson's disease (a-bilateral; b- unilateral)

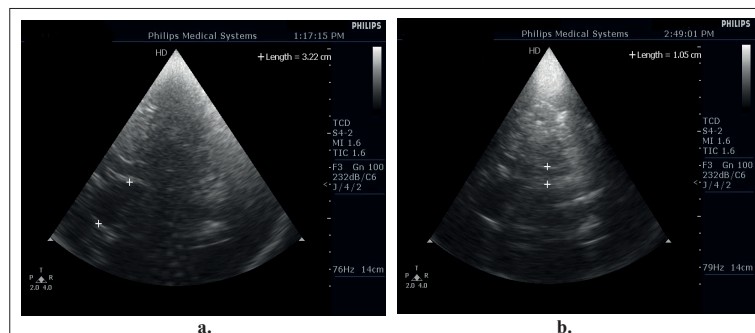


Figure 2. Enlarged ventricular system of the brain in patients with atypical parkinsonian syndromes (a- frontal horn of the lateral ventricle; b- third ventricle)

## 5. CONCLUSION

Patients with PD have significantly high prevalence of hyperechogenic SN detected by TCS in comparison with patients with other parkinsonian disorders. At the other hand, patients with other parkinsonian disorders have more often hyperechogenic LN and wider ventricular system of the brain. TCS is a promising diagnostic technique and can be very helpful in differentiating between idiopathic Parkinson's disease and other parkinsonian disorders.

- Statement: Authors were included in preparing of this article, including final proof reading. Some of the results of this study were presented at the Second National Congress of the Bulgarian Society of Neurosonology and Cerebral Hemodynamics in Sofia, Bulgaria, October 2016.
- Conflict of interest: none declared.
- Author's contributions: Dz. Smajlovic: wrote the manuscript, performed the TCS for all patients in the study, conducted a statistical analysis and responded to the reviewers. O.Ć Ibrahimagic: wrote the manuscript, recruited all the patients for the study.

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