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Research Article

The contribution of transcranial sonographic examination to the diagnosis of Parkinson's disease

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Abstract. The data from multiple recent studies support the utility of transcranial ultrasound in positive and differential diagnosis of PD. The hyperechogenicity of substantia nigra (SN) is used as an accurate indicator of idiopathic PD. The aim of this study was to evaluate by transcranial ultrasound a group of patients with mild or moderate PD and a group of control subjects. Material and method: We conducted a study on patients with diagnosis of early PD, in whom we performed transcranial ultrasound examination of the brainstem through the temporal window. In this study the anatomical structures have been evaluated by bilateral measuring of the ultrasound parameters: diameter of the lateral ventricles (VL), the degree of echogenicity and size of SN, raphe appearance, the diameter of third ventricle. These data sets were compared with those of a control group who have not had a diagnosis of PD. Results: The prevalence of changes in the dopaminergic structures in PD was high: bilateral hyperechogenicity of SN over limit values of 0.20 cm^2 was detected in 100% of patients with PD and in no subject from the control group. The degree of SN hyperechogenicity was important, quantified as moderate in 60% of patients and severe in the remaining 40%. Conclusions: From early PD stages, important sonographic changes can be identified, being a marker for premotor PD.

Key Words: transcranial ultrasound, dopaminergic structure, substantia nigra, hyperechogenicity.

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Introduction

Parkinson's Disease (PD) is a neurodegenerative disease extensively studied, with multiple therapies developed. In recent years, there has been a great emphasis on PD's diagnosis as early as possible, due to the possibility of introducing neuroprotective medications.

Diagnosis in early stages involves maximizing the use of anamnesis focusing on nonmotor complaints and implementation of objective noninvasive exams, easy and fast to perform and with important contribution to positive diagnosis. One of these exams, promising for the future, is transcranial sonography of the brainstem, that shows specific changes in PD.

Transcranial ultrasound is a neuroimaging technique that measures the echogenicity of some brain structures through cranial bone (Berg 2011). In most subjects the midbrain can be identified, looking like a butterfly, through the preauricular acoustic temporal window; in patients with idiopathic PD, the typical ultrasound feature is increasing echogenicity of the lateral sides of the midbrain, which correspond to SN (Berg 2006, Pavese &Brooks 2009).

Multiple studies have established that increased echogenicity of SN can be considered a valuable additional diagnostic marker for PD, in the last decade (Berg 2011).

In specialized centers, transcranial sonographic examination (TCS) is widely used to observe SN hyperechogenicity, which occurs in approximately 90% of patients with PD (Berg 2011, Berg 2006, Berg et al 1999). It was also found that patients with symptomatic or atypical Parkinsonian syndromes rarely have hyperechogenicity of the SN, and thus, the examination can be useful in the differential diagnosis with other entities that evolve with Parkinsonism at the onset (Berg 2006, Walter et al 2007, Tohanean et al 2009, Pilotto et al 2015) .

The importance of examination lies in the fact that sonographic changes occur before the onset of motor symptoms and it can be used as a screening tool in subjects at high risk of developing PD (Berg 2011, Walter et al 2007, Walter 2011). Ultrasound modifications do not change during disease progression both in duration and clinical severity (do not change in duration and clinical severity during disease progression). The method can provide complementary data to evaluate the pathophysiological processes and to identify different subgroups of PD (Walter et al 2007).

The limits of this examination are the same as those of an usual echography, mainly dependence on the examiner's skills, device performance and temporal acoustic bone window that in 10-20% of patients is not penetrable or partially accessible (Berg 2011, Walter et al 2007).

Advantages of the method are telling us that it is noninvasive, repeatable, requiring a short time for investigation, it comes available at the patient's bedside and less dependent on patient compliance (Walter et al 2007, Berg & Riederer 2006). Also, the low cost and the fact that it offers new and complementary diagnostic information to other imaging methods (Berg 2011, Walter et al 2007, Berg & Riederer 2006) creates the premises for the development of this method in the near future as an extremely useful tool in the diagnosis of patients with PD or Parkinsonian syndromes.

We set the following objectives for this study:

1. transcranial ultrasound evaluation of a group of patients with mild or moderate PD submitted at the Neurology Clinic of Cluj-Napoca along with a group of control subjects;
2. statistical analysis of ultrasound parameters (SN size, the diameter of the lateral ventricles, raphe appearance), correlations between the values collected from ultrasound scans and certain clinical characteristics or features of PD.

Material and method

We conducted a study consisting of twelve patients with a diagnosis of PD, in which we performed TCS examination of the brainstem through the temporal window and we identified the anatomical structures of interest, measuring the designated parameters. These patients were diagnosed with early PD (duration of up to three years after diagnosis, H & Y PD stages of disease 1, 1.5 and 2).
In two of our patients, visualization of the anatomical structures, namely the identification of midbrain in the two sections was not possible, probably due to a calcified window.
For the other ten patients bilateral ultrasound parameters were determined: lateral ventricle diameter, grade and size of SN ecogenicity, raphe appearance, diameter of the third ventricle. Data was compared to those belonging to a control group of ten subjects without PD diagnosis.
Patient data and ultrasound parameters have been recorded over a three months range: 10-12.2010.
All patients expressed their consent to inclusion in the study and it should be mentioned that the agreement of the university ethics committee was required in order to conduct the study.
Thus, it was an experimental, case-control study, to set a diagnostic procedure.
The program used for statistical analysis of the study: SPSS (Statistical Package for the Social Science 13.0) and Microsoft Excel(Analyse-it Tool Pack). In order to compare mean values between two groups of subjects we used independent samples t test with statistically significant p value under 0.05. Unifactorial analysis of variance ANOVA was used for size comparison of SN, in stage and disease type, with a significant p value under 0.05. To analyse correlations between measured values of SN and patient age as well as the disease duration we should use parametric Pearson correlation (r): r ranges between -1 and 1 and a value of r near 0 indicates absence of correlations between variables.
Transcranial ultrasound examination - examination technique
Using the transcranial acoustic window located at the preauricular level, TCS accurately evaluates the brain structures so as to visualize the contralateral bone (Walter et al 2007). Table 1 describes the usual technical parameters for TCS examinations.

Table 1. Technical examination (Berg et al 2008, Walter et al 2014)

Transducer frequency: about 1,6-2,5 MHz
Parameters of ultrasonography: penetration depth: 14-16 cm, dynamic range-DR: 45-55dB
The transducer placed firmly on the the preauricular site of the temporal bone window
Supine position of the patient (head up to 60 degree).

B-mode two-dimensional images are obtained, and so depending on the transducer's angulation, four main sections of examination are being described (Walter et al 2007, Berg et al 2008). Hence, in evaluating movement disorders, the following typical planes can be used: midbrain level, cella-media level, cerebellum level, thalamus level (Walter et al 2007, Berg et al 2008, Walter et al 2014).
To view SN, axial plane is aimed, centered to the midbrain. In this plane, the midbrain structure is normally detected as a butterfly-like hypoechogenic area with a slightly hyperechogenic midline (Berg&Riederer 2006, Berg et al 2008).
Taking a closer look to our PD subjects, a marked area of hyperechogenicity corresponding to the SN anatomical area is seen, which is highly suggestive of idiopathic PD (Berg et al 2008). The area of hypersignal on the same side can be measured by encircling it.
The dimension of hyperechogenicity differs depending on the device used, but as convention shows an echogenic area of less than 0.20 cm^2 is considered normal (Berg et al 2008, Walter et al 2014); a SN area of 0.20 - 0.25 cm^2 is considered to be a borderline value (moderate hyperechogenicity) and a size of more than 0.25 cm^2 represents marked hyperechogenicity (Berg et al 2008, Walter et al 2014).
As far as the group of patients and the control group, ultrasound examination was performed in the two main evaluation sections:
- the mesencephalic section (Images 1, 2) is captured when scanning the brain parallel to the orbitomeatal line. The mesencephalic brainstem can be identified as a butterfly-shaped hypoechogenic area in the midline, with the basal cisterns next to it. In this plane, the echogenicity and the size of the ipsilateral SN, ipsilateral red nucleus and median midbrain raphe can be assessed (Walter et al 2007, Berg et al 2008).
- the section used in evaluating the basal ganglia, lateral ventricles, third ventricle (Images 3) is captured by tilting the ultrasound beam about 10-20° upwards. In this locality, the diameter of the frontal horn of the contralateral VL and the diameter of the third ventricle may be measured (Walter et al 2007, Berg et al 2008).
SN echogenicity was quantified by measurement of echogenic area, corresponding to the anatomical area of SN, after encircling it (to be specified that the limit taken into consideration is 0.20 cm^2).
The device used: Fukuda Denshi UF-850XTD.

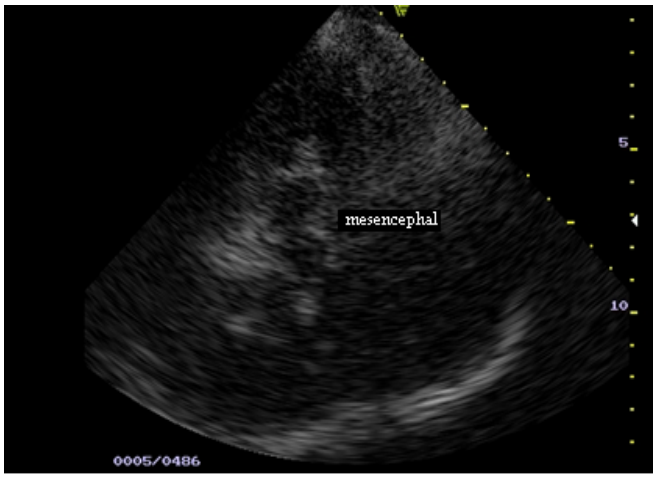

Image 1. The Mesencephalic Section

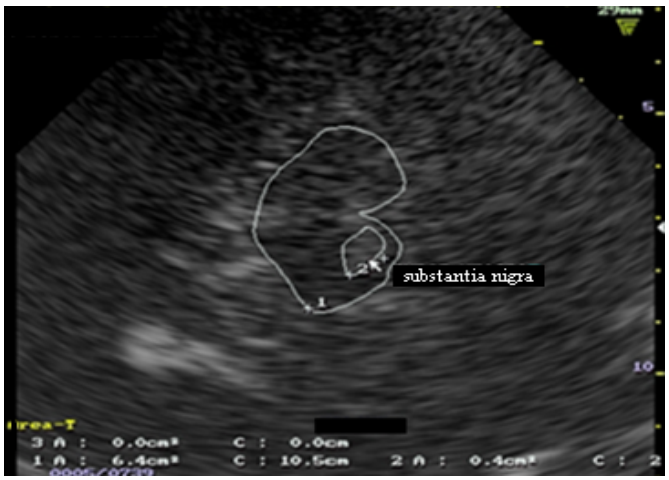

Image 2. The Mesencephalic Section, measurement by encircling of the SN

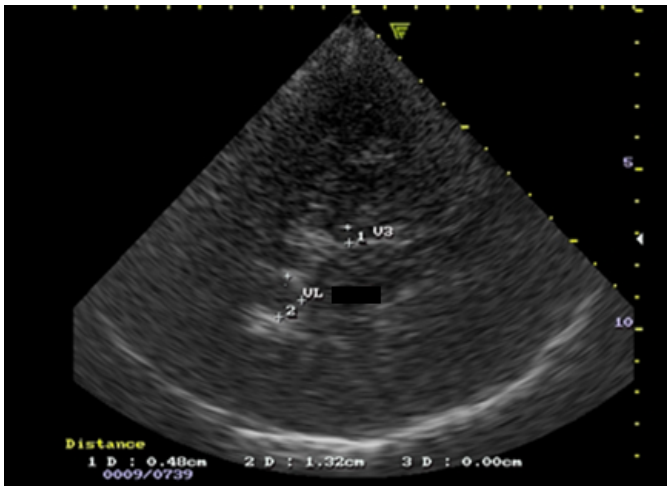

Image 3. The Section For Evaluation Of Basal Ganglia and Ventricles (V 3 - 3rd ventricle, VL- lateral ventricle)

Results

The PD group is comprised of ten patients, more specifically six females and four males, with an average age of 56.3 years (std. dev= 6.39). The Control group consists of ten subjects, six females and four males, with an average age of 58.7 years (std. dev.=7.33). There were no significant age differences between the two groups.

From the point of view of severity of the disease by H & Y stage, we found six patients in stage 1, 3 - in stage 1.5 and one patient was included in stage 2 of motor impaiment. The average age of the disease in the study group was 20.4 months (std. dev.=3.49).

As for the clinical type of disease, six patients had tremorigen form of the disease, three subjects had akinetic-rigidity form and one remaining patient had a mixed mixt form of PD.

Using transcranial ultrasound anatomical elements have been identified and parameters were measured in ten of twelve patients with PD and all ten control subjects.

All subjects demonstrate elevated values of bilateral SN size (the normal value in literature -< 0.20 cm^2): four of them are showing values denoting marked hyperechogenicity (≥ 0.25 cm^2) and while six have moderate hyperechogenicity (0.20 – 0.24 cm^2) . The diameter of the lateral ventricle (VL) is also increased bilaterally to all patients, based on literature data values for corresponding age groups. Under close scrutiny, a pathological appearance of the raphe is seen in eight cases: hypoechogen for five patients and undiscovered in three of our patients. The control group informs us that in nine of our subjects, the raphe is hyperechogen. We find a discontinuous appearance concerning one patient.

In all ten of our patients in whom we managed to study the sections and measure the ultrasound parameters, we reached the conclusion that ultrasound examination revealed a moderate or marked hyperechogenicity of SN and increased diameter of lateral ventricles (table 2).

Table 2. Mean values and variances of ultrasound parameters in the two groups under observation

Variable	Group	Mean±Std. Dev	P
Left SN	Parkinson	0.24±0.02	0.001
	Control	0.18±0.01	
Right SN	Parkinson	0.24±0.01	0.001
	Control	0.18±0.01	
Left VL	Parkinson	23±1.60	0.001
	Control	18.30±1.16	
Right VL	Parkinson	23.50±1.76	0.001
	Control	18.00±1.49	

There were significant differences ($p<0.01$) between the two groups considering all variables analyzed (table 2).

In order to be able to analyze the correlations shown below we must take into account the average SN size in patients studied bilaterally, using independent samples t-test.

Statistically speaking, there aren't any differences between genders, concerning the SN size in the study group ($p=0.07$).

We detect an elevated average size of the SN to our group, which is not significantly correlated with patient's age ($r = -0.53$). We succeed in identifying an elevated average size of SN, on our group, no patient age related ($r +0.53$).

Also, there is no statistically significant correlation between the SN size and duration of the disease ($r = -0,068$).

Subclinical stages of disease don't not affect the outcome of the ultrasound values expressed by SN size, so there is no significant correlation of SN echogenicity, and none among the three types of PD ($p = 0.127$).

No statistically significant differences were detected concerning the SN size between different stages of disease ($p = 0.22$).

More to the point, no significant correlations are to be noticed between SN hiperechogenicity, expressed by SN size and any of the clinical characteristics (gender, age, duration of disease, type or stage of disease), in our PD group.

Discussions

Transcranial sonography is a more and more widely used method in positive and differential diagnosis of PD (Pilotto et al 2015, Walter et al 2014).

The study is case-control and the two study groups do not differ significantly in age or gender. The patient group incorporates subjects with PD in the early stages, respectively stage 1, 1.5 and 2 after H & Y scale, with all three clinical forms of illness.

Ultrasound examination is performed on two sections, in which dimensions of SN and frontal horn of VL are measured bilaterally and the appearance of the brainstem is coherently described. Anatomical elements are identified in 83.33% of subjects of the PD group, and also in 100% of the subjects of the control group. Temporal bone window is calcified in 10-20% of white subjects, not allowing visualization of midbrain structures (Berg et al 2008).

The findings of this study are consistent with literature data, reporting that in most patients with PD there is an increase in echogenicity of SN, significantly higher than in normal subjects (Berg et al 2008). Studies show that a highly echogenic area in the midbrain, anatomically corresponding to SN, is seen in more than 90% of patients with PD; the results varying depending on the device that is being used and the examiner's skills (Prestel et al 2006). We may say that hyperechogenicity of SN is almost universally present in PD from an early stage; we appreciate that all patients in the PD group had hyperechogenic area of more than 0.20 cm^2. 40% of patients had moderate hyperechgenicity (0.20 to 0.24 cm^2) and the remaining 60% were ranked with marked hyperechogenicity ($\geq$ 0.25 cm^2). Mean hyperechogenicity area was 0.24 cm^2, significantly higher than in control subjects who had an average of 0.18 cm^2 ($p = 0.001$). Also, the other anatomical elements had changed values: in all patients we detected values above the limit for the lateral ventricle diameter and in 80% we discovered a pathological appearance of the raphe. We detected values above the limit for the lateral ventricle diameter in all of our patients, while for the rest of the 80% we discovered a pathological appearance of the raphe. Literature data show that hyperechogenicity of SN is seen in about 10% of healthy adults, revealing a subclinical dysfunction of the dopaminergic system and it is considered a risk factor for PD (Berg et al 2005, Berg 2009). In the control group, SN area values were within normal limits in all patients.

No significant correlations are observed between SN hyperecogenicity and clinical characteristics (gender, age, duration of disease, type and stage of disease).

Previous studies are proving there are no statistically significant correlations between the severity of PD and SN size (Berg et al 2001). Also, SN hyperecogenity is stable during disease progression and does not change in time with duration of disease; these data are supported by a study over a period of five consecutive years in PD patients (Berg et al 2005). The fact that SN echogenicity does not change depending on the stage or duration of the disease led to the hypothesis that the sonographic change in PD is not the consequence of neurodegeneration itself but is a marker of risk for injury of the dopaminergic system, reflecting the metabolism disturbance of Fe (Berg et al 1999, Berg et al 2006).

PD clinical type doesn't significantly affect the size of SN hyperechogenicity.

The study was conducted on patients in early stages of disease and all subjects had elevated size of SN hyperechogenicity. Thus, ultrasound changes precede by several years clinical diagnosis. These data are supported by the literature (Berg 2009), and TCS of SN may be used in the preclinical identification of the population at risk of developing PD (Lerche et al 2015).

The medical world dubbed SN transcranial ultrasound one of the most important methods in neuroimaging investigation of extrapyramidal pathology.

One of the limitations of the study that we identified is the small number of subjects; the public results are experimental; nevertheless its importance is due to its novelty factor and gate opener. We considered it necessary to be presented due to the novelty of the theme and the fresh perspective it offers. Differences between mean values from different groups or correlations between variables should be interpreted with caution, as they may be in the context of decreased variability, given by randomization on small numbers of patients.

Conclusions

SN transcranial sonographic examination is found to be a useful tool in the positive diagnosis of BP.

Experience and data accumulated are limited, but we thought it is appropriate to present it as it is indeed a modern technique of PD diagnosis, with great futuristic potential. So far, Romania has a timid approach and it's integral practice requires ultrasound device and knowledge.

Closely examining other structural neuroimaging methods, TCS does differentiate itself by the fact that it is a method that provides additional information, it is non-invasive, reiterative, easily made available and cost effective. Also, this method has a high degree of sensitivity and specificity, which depends on the investigator's performance and the type of apparratus usage. Due to the fact that sonographic changes precede the onset of the non-motor symptoms, the examination does have the potential to be used in the early premotor diagnosis of the disease. Therefore, this examination should be recommended without limitations as an additional diagnostic tool, which should be used in routine testing for patients who are exhibiting Parkinsonian signs. The sonographic changes should be included into the protocol kit for early diagnosis of PD in order to detect the disease as early as possible.

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