Article

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Transcranial sonography as a diagnostic tool for Parkinson's disease

A pilot study in the city of Rio de Janeiro, Brazil

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ABSTRACT

In Brazil there is no systematic study on Transcranial Sonography (TCS), a neuroimaging method that depicts echogenic deep brain structures using ultrasound. **Objective:** To establish the percentage of subjects with permissive temporal windows and to address the ability of TCS of the substantia nigra (SN) to distinguish parkinsonian patients in a Brazilian sample. **Method:** We performed TCS using the Acuson X300 (Siemens, Germany) in 37 individuals: 23 with Parkinson's disease (PD) and 14 healthy controls. **Results:** 10.8% of subjects had insufficient temporal acoustic bone windows. SN echogenic areas were larger in patients (mean±SD, 0.31±0.08cm^2) compared to controls (mean±SD, 0.17±0.02cm^2). TCS accurately identified 88.2% of PD patients. **Conclusion:** A large proportion of Brazilians seem to be eligible for TCS. An expressive number of PD patients could be diagnosed by TCS based on an expanded SN echogenic area. However, the current data is preliminary and must be corroborated by larger studies.

Key words: diagnostic imaging, ultrasonography, Parkinson's disease.

A Ultrassonografia transcraniana como método diagnóstico para a doença de Parkinson: um estudo piloto na cidade do Rio de Janeiro, Brasil

RESUMO

No Brasil não há estudos sistemáticos sobre a Ultrassonografia Transcraniana (USTC), modalidade de neuroimagem que visualiza estruturas ecogênicas profundas do parênquima cerebral utilizando ultrassom. **Objetivo:** Determinar a porcentagem de indivíduos com janelas ósseas adequadas e a capacidade da USTC da substância negra (SN) de discernir pacientes parkinsonianos em amostra brasileira. **Método:** USTC realizada com equipamento AcusonX300 (Siemens, Germany) em 37 indivíduos: 23 com doença de Parkinson (DP) e 14 controles saudáveis. **Resultados:** 10,8% dos participantes apresentaram janelas acústicas temporais inadequadas. As áreas de ecogenicidade da SN foram maiores nos pacientes (média±desvio padrão, 0,31±0,08 cm^2) do que nos controles (média±desvio padrão, 0,17±0,02 cm^2). A USTC identificou 88,2% dos pacientes com DP. **Conclusão:** Grande proporção de brasileiros parece ser elegível para a realização de USTC. Um número expressivo dos pacientes com DP poderia ser diagnosticado com base no aumento da área ecogênica da SN. Contudo, esses dados preliminares devem ser corroborados com amostra mais numerosa.

Palavras-Chave: diagnóstico por imagem, ultrassonografia, doença de Parkinson.

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Transcranial sonography (TCS) is a promising neuroimaging technique for investigating movement disorders[1]. It is based on reflection and scattering of ultrasound waves at interfaces with diverse acoustic impedance and depicts the brain structures near the midline in most detail such as the mesencephalon and the basal ganglia[2]. Displaying the echo pattern (echogenicity) of brain tissue TCS may provide new and complementary information to other neuroimaging methods[3]. Over the past 16 years, various independent studies have documented a substantial echogenic area detected by TCS at the mesencephalic substantia nigra (SN) of patients with Parkinson's disease (PD)[1,4]. The alteration in SN signal, seen as an area of increased signal intensity and extent (termed hyperechogenicity) is observed in up to 90% of patients with PD and is suggested to be clinically useful in diagnosing this disorder[1-8]. Nevertheless, SN hyperechogenicity can also be observed in a proportion of individuals without parkinsonian signs[4,5,7].

The exam is non-invasive, inexpensive, widely available, and quick to perform in moving patients. Its limitations include an inadequate bone window in some patients and its dependency on qualified personnel. Reference values must also be generated for each ultrasound system[1,6]. So far, there exists primarily data of PD patients from Europe, North America and Asia. In Brazil there has been no systematic study addressing TCS for diagnostic testing of PD. Hence, it needs to be shown how the bone window and echogenicity of the SN is distributed in Brazilian population.

The objectives of this research were: [a] to establish the percentage of eligible subjects (those with permissible temporal windows), and [b] to assess the capability of TCS to distinguish Parkinsonian patients from healthy controls in a sampling of the Brazilian population.

METHOD

For this pilot cross-sectional study on TCS of the SN, 37 participants were divided in two groups: patients diagnosed with PD (n=23) for at least two years based on the UK Brain Bank criteria[9], which was confirmed by a movement disorder specialist (ALZR), and control subjects (n=14), who were either caregivers, staff members, or medical students from the Neurological Unit of the Federal University of Rio de Janeiro. The study was approved by the ethical committee from Hospital Universitário Clementino Fraga Filho. All individuals provided informed consent.

TCS was performed bilaterally through the acoustic temporal windows by a qualified neurologist (RCLF) using the Acuson X300 (Siemens, Germany). Equipment was set according to standards reached at a consensus conference of the European Society of Neurosonology and Cerebral Hemodynamics, including a 1.6-2.5 MHz phased-array transducer, penetration depth of 14.0-16.0 cm, dynamic range of 45-55 dB, and moderate suppression of low echo signals[1].

For the examination, the patient was posed in a supine position and the transducer held preauricularly in the individual optimal acoustic window. The butterfly-shaped mesencephalic area (of low echogenicity) and surrounding hyperechogenic basal cisterns were examined in the axial plane paralleling the orbitomeatal line (Fig 1). After freezing and zooming two or three times, the slim, dotted, or, in some cases, broader area of echogenicity at the anatomical site of the SN ipsilateral to the insonating probe, was planimetrically measured. Of both sides measured, the larger SN of each participant was used for between-group comparisons. According to international data[4,6], extreme superior values (i.e. values above 0.5 cm^2) were considered outliers and excluded.

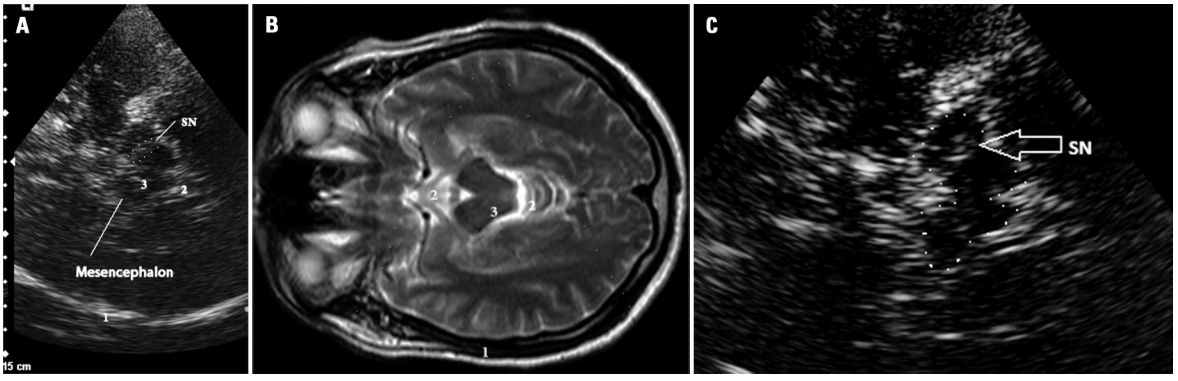

Fig 1. Mesencephalic images on Transcranial Sonography (TCS) and Magnetic Ressonance (MR). [A] TCS performed in the mesencephalic scanning plane using the Acuson X300 (Siemens, Germany). TCS is performed through the temporal window, parallel to the orbitomeatal line. The hypoechoic butterfly-shaped mesencephalon is clearly depicted surrounded by the mesencephalic cisterns. Dotted line: ipsilateral normoechoic substantia nigra (SN). [B] MR image (T2 FAST), similar axial plane (not the same person). [C] Hyperechogenic enlarged SN of a patient with Parkinson's disease. Dotted line: mesencephalon (zoomed image). (1) contralateral temporal bone, (2) basal cisterns, (3) mesencephalon.

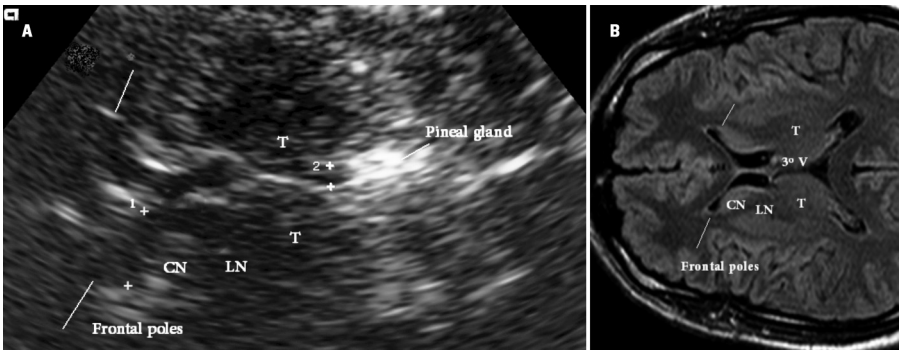

Fig 2. Ventricular and basal ganglia plane images on Transcranial Sonography (TCS) and Magnetic Ressonance (RM). [A] TCS axial plane 10º-20º above the orbitomeatal line (zoomed image) (1) transverse frontal horn diameter, (2) transverse 3rd ventricle diameter; [B] MR image (FLAIR FAST), similar axial plane (not the same person) (T) thalamus, (LN) lenticular nucleus, (CN) caudate nucleus.

By tilting the probe upwards, the basal ganglia, thalamus, 3rd ventricle, and frontal horns of lateral ventricles were evaluated (Fig 2).

SPSS 17.0 software for windows (Chicago, USA) was used for data analysis, computed as the mean± standard deviation or median with lower and upper quartiles. The Mann-Whitney test was employed for group comparisons.

To answer aim [a] the frequency of accessibility of the SN through the temporal bone window was assessed. To answer aim [b] medium values of SN area were compared between PD patients and controls; according to data derived from previous studies[2,6] SN dimensions >0.20 cm^2 (SN+) were considered pathologic, and its frequency of occurrence was compared between the groups. The sensitivity and specificity were determined for SN+ as a diagnostic marker of PD. The level of statistical significance was set at 5.0%.

RESULTS

Aim [a] – Four Caucasians (10.8%): a man and three women, with inadequate temporal bone windows, didn't qualify for sonographic analysis (Table 1). However, all subjects of African descent (n=11) had sufficient acoustic bone windows to perform measurement of the SN.

Aim [b] – Outliers SN areas above 0.5 cm^2 were found in five patients of the PD group that were excluded. There was no outlier in the control group. In the remaining 11 controls and 17 PD patients, SN echogenic zones were significantly larger in patients with PD (Table 2). Fifteen of 17 Parkinsonian patients (88.2%) were accurately identified by TCS on the basis of a SN+ (true positives), while two control subjects (18.2%) displayed this particular echofeature as well (false positives). TCS thus proved 88.2% sensitive (95% CI: 66.3-98.0) and 81.8% specific (95% CI: 47.7-96.7) for the detection of PD by visualizing the SN.

Table 1. Sample characteristics of the pilot study on Transcranial Sonography.

	Total	No window	Window adequate	
			Parkinsonians	Controls
Men	19	1	15	3
Women	18	3	7	8
Caucasians	26	4	15	7
Afrodescendents	11	0	7	4
Asians	0	0	0	0
Age X(SD) years		61.2 (12.55)	66.9 (10.4)	49.5 (11.3)

X: means; SD: standard deviation.

Table 2. Substantia Nigra (SN) echogenic area of patients with Parkinson's disease and healthy controls examined by Transcranial Sonography.

SN area (cm^2)	Controls	Parkinsonians	p
Means	0.17	0.31	0.000
Standard deviation	0.02	0.08	
Medians	0.16	0.31	
1º quartile	0.13	0.23	
3º quartile	0.18	0.43	

DISCUSSION

This is the first study to investigate PD by TCS in Brazil's population including subjects of African descent. Previous efforts have reported a 10%-20% rate of inadequate acoustic bone windows, especially in women and the elderly, in up to 59% of Asian old women[10], and, perhaps, in patients with osteoporosis[1,8]. Although conclusions can only be drawn with caution, as the number

of participants was rather small in this pilot study, only 10.8% of our participants lacked adequate bone windows. Among them, females were more prevalent, but none were of African descent. Our findings, if corroborated, therefore suggest that a large proportion of Brazilians would be eligible for TCS and that the frequency of an insufficient bone window is similar to, for example, the European population.

Since the discovery, in 1995, of a characteristic abnormal hyperechogenic appearance of the SN on TCS of parkinsonian patients[11], the currently most widely used clinical application of TCS in movement disorders is the early and differential diagnosis of PD[8]. There is a progressively growing pool of published studies worldwide demonstrating the characteristic finding of SN enlarged areas (above 0.20 cm^3) in 80-90% of patients with PD[4]. Still, the diagnostic assessment of SN echogenicity needs well-trained investigators, but the intra-rater and inter-rater reliability of the ultrasound measures of SN is very good when conducted by experienced sonographers[2]. In addition, SN areas depicted by TCS have been shown to correlate well with MRI T2-hypointensity and T2-relaxation times in the same brainstem region[3,12]. Therefore, the discrimination between normal echogenic and abnormal hyperechogenic (enlarged) SN can nowadays be regarded as reliable provided adequate performance of TCS[3].

Similar to prior publications[1,4], an expressive number of our subjects (88%) with clinically confirmed PD could be diagnosed by TCS, based on an expanded SN echogenic area. Only two individuals (18%) of the control group displayed this echofeature as well. Other studies have shown that hyperechogenic SN can be found in 8% to 14% of the general population, suggesting a large number of false-positive findings[4]. However, there is some evidence that the SN hyperechogenicity in healthy controls is related to a slight motor impairment[12,13] and that SPECT scans are also abnormal in up to 60% of the asymptomatic individuals with an abnormal TCS[14,15]. These findings raised the question whether the TCS finding of SN hyperechogenicity alone in a healthy individual might be a predictor for subsequent occurrence of PD[15]. The results of ongoing longitudinal studies will give further insight into this question[16].

Although data to date suggest that this simple and inexpensive imaging modality may be useful in improving diagnosis of movement disorders, the present knowledge about the mechanism leading to the changes in SN echomorphology is limited[7]. It has been speculated that SN hyperechogenicity reflects histopathological changes or displays an alteration in tissue impedance due to an abnormal iron accumulation, a process associated with neurodegeneration in PD[17].

Difference in age and gender between the groups need to be named as limitations of this pilot study. However, although distributed unevenly between the groups, these differences are not of importance to evaluate the prevalence of an adequate acoustic bone window in the whole cohort of subjects investigated. Still, it needs to be considered that female sex and higher age are associated with a higher prevalence of insufficient bone windows. Future studies, therefore, need to include even older subjects, especially women.

Results of this pilot study indicate that TCS enables the depiction of the substantia nigra in the Caucasian and African Brazilian population to the same percentage as the European Caucasian population. The prevalence of SN hyperechogenicity among PD patients in Brazil is similar to the prevalence reported in other populations. The current data, however, is preliminary and must be confirmed in larger studies with less participant heterogeneity.

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