ORIGINAL ARTICLE

Transcranial sonography on Parkinson's disease and essential tremor

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Background: The study on transcranial sonocraphy (TCS) as a diagnostic test for Parkinson's disease (PD) has been neglected in some hospitals. The current study was conducted as the first study to investigate the utility of TCS for diagnosis of PD and its ability to distinguish PD from essential tremor (ET) in an Iranian population. **Materials and Methods:** TCS of substantia nigra (SN) was performed on 50 PD, 48 ET, and 50 healthy controls by two blinded investigators. **Results:** Bilateral SN margin over 0.20 cm^2 was found in 39 (90%) and 7 (15%) in PD and ET patients, respectively. Furthermore, 4 (8%) of healthy control displayed this particular echo feature as well (false positives). SN hyperechogenicity ≥0.20 cm^2 was considered as a cut-off point to detected PD. Accordingly, TCS proved 90% (95% confidence interval [CI]: 77.85-97.35) sensitive and 92% (95% CI: 80.75-97.73) specific for the detection of PD by visualizing the SN. **Conclusion:** SN hyperechogenicity ≥20 cm^2 is a specific feature of PD. Since, the symptoms of PD and ET might be overlapping; this method seems to be reliable to confirm PD diagnosis in doubtful clinical cases. Further studies in years to come are warranted to shed light on standardized data for Iranian to enhance the validity of TCS.

Key words: Essential tremor, Parkinson, transcranial sonography

INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegen erative disease. Because there is no definite test for the diagnosis of PD, the disease must be diagnosed according to clinical criteria.[1] The misdiagnosis rates for PD in the early stages are as high as 20-30%.[2,3] In this regard, imaging studies such as cranial computed tomography (CT) and magnetic resonance imaging may have applications to differentiate idiopathic PD from atypical or secondary PD.[4] However, the sensitivity of these methods is low.[5-7] In addition, single photon emission CT and positron emission tomography (PET) are useful to distinguish PD tremor from essential tremor (ET).[4] However, these are expensive methods with technical limitations.[8] Notwithstanding such findings, to date, there is no reliable test for distinguishing PD from ET.

In 1995, for the first time Becker *et al*.[9] has reported that a hyperechogenisity of substantia nigra (SN) in patients with PD was observed by transcranial sonography (TCS) method. Since then, numerous studies conducted to evaluate the efficacy of TCS for diagnosis PD and wide range of movement disorders in European and American. However, the study on TCS as a diagnostic test for PD has been neglected in Iranian population. The racial variations in the temporal skull thickness and the size of brain between European and Asian may result in the difference of findings by using TCS. Considering this, the current study was conducted as the first study to investigate the utility of TCS for diagnosis of PD and its ability to distinguish PD from ET in an Iranian population.

MATERIALS AND METHODS

Patients

This study was conducted from August 2011 to September 2012 in the Department of Neurology at Al-Zahra University Hospital (Isfahan University of Medical Sciences), Isfahan, Iran. Participants were divided into three groups: (1) 50 Patients with definite PD according to unified PD rating scale, which was confirmed by neurologist;[10] (2) 48 subjects with ET met the criteria of movement disorder society on tremor;[11] (3) 50 healthy control subjects who were not pre-diagnosed any form of extrapyramidal disorders. Patients with intention-tremor excluded from the study. The study was implemented in accordance with the tenets of the declaration of Helsinki. The study protocol was approved by the Isfahan University of Medical Science, Isfahan, Iran ethics board and all participants signed informed consent for research.

Transcranial sonography methods

TCS was performed on a SSD-550 (Aloka, Tokyo, Japan). Insonation was done through preauricular acoustic

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bone window using 2-4 MHz probe with 12 cm penetration depth.[9] All examinations were performed independently by two investigators blinded to the results of TCS and clinical diagnosis of patients. The butterfly-shaped of midbrain area and surrounding hyper echogenic basal cisterns were examined on axial plane [Figure 1]. Afterward, the probe was tilted for 10° upward to evaluate the basal ganglia, thalamus, third ventricular, and frontal horns of lateral ventricular. Mesancephalic echogenicity in the area of SN measured two times and mean value was calculated and presented in cm^2. The SN echogenicity was divided into the three following groups: (1) Normal SN echogenicity (<0.20 cm^2); (2) moderate SN hyper echogenicity (between 0.20 cm^2 and 0.25 cm^2); (3) marked SN hyper echogenicity (≥0.25 cm^2). In this respect, the greater value of bilateral measurements was considered for classification of subjects[12,13] [Figure 2].

Statistical measures

The statistical analyses were performed using SPSS version 20.0 software (SPSS, Inc., Chicago, IL, USA). Descriptive analyses were adopted for demographic and clinical characteristics reporting the variables as means ± 1 standard deviation (SD). Kolmogrov-Smirnov test was used to test for normal distribution of quantitative data. One-way analysis of variance (ANOVA) and Kruskal-Wallis were employed for distribution of demographic variables. The differences among groups were assessed using Chi-square test. All statistical tests were two tailed and a $P < 0.05$ was considered the significance threshold.

RESULTS

Study sample

Among 148 individuals who were enrolled, 12 (8.1%, 7 PD and 5 ET) were excluded from the final analysis due to poor temporal window. In the remaining 136 subjects, the mean ± SD age of PD and ET patients group was 63.39 ± 11.49 and 59.44 ± 10.03 years, respectively. There was no significant difference compare to normal controls (58.9 ± 11.09, $P = 0.11$) based on one-way ANOVA. The median [inter-quartile range] time from the diagnosis to study onset was 5.5[3-7] and 5.1[2-8] years in PD and ET group, respectively. Kruskal-Wallis test showed no statistical difference between two groups for duration of disease ($P = 0.85$). The baseline demographic and epidemiologic data of the study samples are summarized in Table 1.

Transcranial sonography findings

The sonographic results are given in Table 2. In the control group, bilateral combined mean ± SD SN size was 0.16 ± 0.03 cm^2, for the right side 0.15 ± 0.03 cm^2 and 0.16 ± 0.03 cm^2 for the left side. In the PD patients, we observed mean ± SD SN bilateral size of 0.32 ± 0.09 cm^2, for the right side 0.32 ± 0.09 cm^2 and 031 ± 0.09 cm^2 for the left, which was significantly different from the control group ($P < 0.0001$). In the ET patients, mean ± SD SN size was 0.17 ± 0.04, 0.16 ± 0.03 for right side and 0.17 ± 0.03 for the left. It was significantly different from PD group ($P < 0.0001$) but not from control group ($P = 0.17$). Bilateral SN margin over 0.20 cm^2 was found in 39 (90%) and 7 (15%) in PD and ET patients, respectively. Furthermore, 4 (8%) of healthy control displayed this particular echo feature as well (false positives).

SN hyperechogenicity ≥0.20 cm^2 was considered as a cut-off point to detected PD. Accordingly, TCS proved 90% (95% CI: 77.85-97.35) sensitive and 92% (95% CI: 80.75-97.73) specific for the detection of PD by visualizing the SN.

DISCUSSION

To the best of our knowledge, this is the first study to investigate PD by TCS and determine the efficacy of TCS for differentiating PD from ET in the Iranian population. Our findings coincide with previous studies that SN

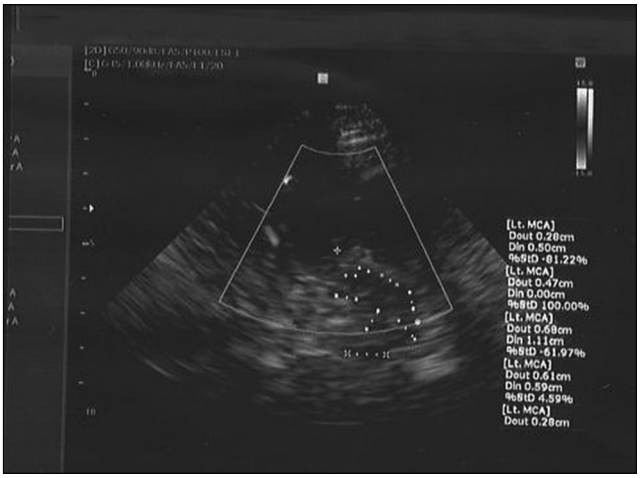

Figure 1: Normal transcranial sonography in healthy adult. Butterfly-shaped mesencephalon of low-echogenicity has been shown

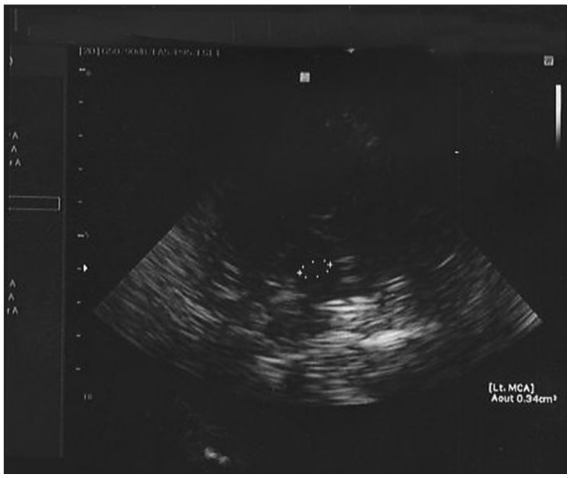

Figure 2: Transcranial sonography findings in patient with Parkinson's disease showing bilateral hyperechogenecity of substantia nigra area

Table 1: Patients demographic and epidemiologic data

Group	Parkinson's disease patients	Essential tremor	Controls
Number of patients	50	48	50
Age (mean±SD; years)	63.39±11.49	59.44±10.03	58.9±11.09
Sex			
Male	32	18	28
Female	11	25	22
Duration of disease in years [IQR]	5.5 [3-7]	5.1 [2-8]	

Median [IQR]=Median [inter-quartile range]; SD=Standard deviation

Table 2: Transcranial sonography results in 136 subjects with adequate bone window

Group	PD (*n*=43) (%)	ET (*n*=43) (%)	Control (*n*=50) (%)
SN mean size*	0.32±0.09	0.17±0.04	0.16±0.03
Normal SN echogenicity	4 (9.3)	36 (83.7)	46 (92)
Moderate SN hyperechogenicity	5 (11.6)	6 (13.9)	4 (8)
Marked SN hyperechogenecity	34 (79.1)	1 (2.3)	0

PD=Parkinson's disease; ET=Essential tremor; SN=Substantia nigra; Normal SN echogenicity: <0.20 cm^2; Moderate SN hyperechogenicity: Between 0.20 cm^2 and 0.25 cm^2; Marked SN hyperechogenecity: ≥0.25 cm^2. *Significant between PD and ET and PD and controls (P<0.0001)

hyperechogenicity ≥20 cm^2 is a specific feature of PD. Since the symptoms of PD and ET might be overlapping, this method seems to be reliable to confirm PD diagnosis in doubtful clinical cases. As the previous studies published,[2,3] the misdiagnosis rates for PD in clinicopathological tests have been as high as 24%. In this regard, TCS with 90% sensitivity and 92% specificity can be considered as an appropriate method for PD detection in the Iranian population. Moreover, detection of initial SN impairment before symptoms presentation, which undetectable by CT and MR, bring the large benefit for TCS.

In our study, seven (16%) patients with ET had the SN hyperechogenicity ≥20 cm^2. It was almost higher percentage than the previous report;[14-17] and may be originated from the variation in sample size. Furthermore, PET studies in ET patients indicated that the impairment of red nucleus, where located near the SN region and the inability of the TCS to differentiate it from the hyper echogenic SN area is the rational explanation for such hyper echogenic feature in ET patients.[16,18] Hence, the linkage between ET and PD is still elusive; and the ET patients might have higher risk to develop PD in the future, though, further longitudinal follow-up studies in ET patients with hyper echogenicity are needed.[19,20]

Our findings are in agreement with those from the study conducted by Luo *et al*.,[17] in which no significant difference was found between the area of SN hyper echogenicity in ET and normal control. A study by Stockner *et al*.[21] in 244 subjects (100 PD, 40 ET, 100 control) reported that the area of SN hyper echogenicity in ET were more than that in control group ($P < 0.05$). Further studies are warranted to clarify this disputed issue.

We found 8% of healthy control with SN hyper echogenicity. The systematic review by Vlaar *et al*.[22] has shown that SN hyper echogenicity can be observed in 8% to 14% of general population. The increased risk of developing PD in this group is still a matter of debate and could be indicated the preclinical form of PD.[12] However, long duration follow-up in healthy individuals with SN hyper echogenicity are required.

Although, reason of SN hyper echogenicity remains unknown, several studies adhered to the notion than "iron concentration in the SN play an important role in the reflection of ultrasound waves."

The major limitation of this study is inadequate temporal bone window. In our study, 8.1% of the subjects were not eligible for exam, which was similar to that (8.08%) reported by Luo *et al*.[17] in Chinese population.

CONCLUSIONS

In summary, TCS is an easy invasiveness approach with good and spatial resolution; wide availability; low-cost; and the ability to display echogenic changes in brain parenchyma and basal ganglia and also, provides sensitive and specific indexes for the diagnosis of PD in an Iranian population. Further studies in the years to come are warranted to shed light on standardized data for Iranian to enhance the validity of TCS.

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