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Midbrain area for differentiating Parkinson's disease from progressive supranuclear palsy

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ABSTRACT

Objectives: We aimed to investigate the values of midbrain area in diagnosing Parkinson's Disease (PD) and progressive supranuclear palsy (PSP) by using transcranial sonography (TCS). Disease duration effect on brain sonographic findings could decrease the accuracy of TCS in PD and PSP patients. We reduced the disease duration effect on sonographic differences found between PD and PSP patients by using multivariate analysis.

Patients and Methods: Patients with clinical diagnosis of PSP and PD were recruited. We used SonoSite Edge II Ultrasound system to measure midbrain area, diameter of third ventricle and substantia nigra echogenicity. Diagnostic value of each measured area in sonography was estimated regarding its power for diagnosing PD or PSP. Independent sample *t*-test, Regression analysis and receiver operating characteristic (ROC) curve were performed using SPSS software.

Results: Of 35 patients, 18 were PD and 17 PSP cases. The mean midbrain area was 4.86 ± 0.71cm^2 in PD patients and 3.61 ± 0.85cm^2 in those with PSP ($P < 0.005$). Regression for reducing the effect of disease duration on midbrain area variances between patients with PD and PSP revealed a significant P value ($P < 0.005$, Adjusted $R^2 = 0.36$). The sensitivity and specificity of midbrain area in diagnosing PD were 83.3% and 70.6% respectively. The sensitivity of the third ventricle size in diagnosing PSP was 82% although its specificity was 62%.

Conclusion: Midbrain area in patients with PD was wider than those with PSP that was not affected by disease duration. Midbrain area was the most accurate index for diagnosing PD by TCS although third ventricle size was the most sensitive one for diagnosing PSP.

1. Introduction

Differentiating atypical Parkinsonian syndromes (APS) such as Progressive supranuclear palsy (PSP) and multiple system atrophy (MSA) from Parkinson's disease (PD) in early stages has been remained challenging even by all progresses in imaging techniques [1]. Considering the prevalence of Parkinsonian syndromes (PS), PSP is the second commonest one after PD. Differentiating these diseases is imperative regarding poor response to Levodopa and rapid progression of the disease in PSP [2].

Although MRI findings like structural indexes and ratios were considered as an important diagnostic tool to differentiate APS from PD [3], it would not seem as an accurate definite technique in this field.

Transcranial sonography (TCS) is a patient- friendly, inexpensive, noninvasive and quick method used safely in patients who cannot undergo brain MRI like those with claustrophobia, implanted metal instruments and cardiac pace-makers [4]. Formerly, TCS investigations on patients with PS revealed hyperechogenicity of substantia nigra (SN) in PD more common than those with MSA or PSP. Also predictive values of SN echogenicity were defined to distinguish PD from other PS [5,6]. Those values might have been accredited by further imaging surveys. All obtained values from previous studies were reconciled on a review article in 2017 that revealed suboptimal predictive values of ultrasound hyperechogenicity of SN for distinguishing PD from APS [7]. On the other hand, SN echogenicity can be affected by other conditions such as history of migraine headaches and psychological disorders [8,9]. Although considering all medical and constitutional conditions in one study is not conceivable, providing more diagnosing techniques

Abbreviations: PD, Parkinson's disease; PSP, progressive supranuclear palsy; TCS, transcranial sonography; SN, sunbstantia nigra; DTV, diameter of third ventricle

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improves the accuracy of differentiating PD from other PSs.

In the present study, we aimed mainly to investigate the predictive values of midbrain area in diagnosing PD and PSP. Diagnosing one of these two facilitates ruling out the other one and it is the main point in our article.

2. Materials and methods

2.1. Ethics

The protocol of the study was conducted in Iran University of Medical Sciences and financial supports were provided by the related community.

Patients were all informed about the aim of the study and the written consent was signed. Helsinki declaration was respected in all steps of the investigation.

2.2. Subjects

In this study, 20 patients were recruited as clinically probable PSP. The patients were selected according to NINDS-Society of PSP Consensus Clinical Research Diagnostic Criteria [10]. Three of them were excluded due to the lack of appropriate temporal bone window in two and history of posterior cerebral artery infarction in the third one. Also 21 patients were enrolled as PD cases. The patients fulfilled UK PD society brain bank clinical criteria for diagnosis of PD [11]. Three of them were excluded because of the poor temporal bone windows. Patients with head trauma, vascular injuries or drug consumers that may mimic parkinisonian symptoms, were all excluded. Because age was a confounding factor in assessing midbrain changes, the age contribution was compared between groups by evaluating normal probability plot. Thus any outlayers were excluded and patients were matched by age during regression analysis [12].

2.3. Design

This cross sectional study was directed from February 2017 to September 2017 on 41 patients referred to the neurology department of Rasoul-Akram hospital. Since our center is one of the biggest referral centers for movement disorders in a country with a population of 80 million, recruiting these patients in this period was not difficult.

Sampling method was non-probability, convenience one. All patients underwent brain MRI to exclude infarction or posterior cerebral circulation damages that might cause brain stem changes. A trained neurologist who performed TCS, authors and analyzer of the study were all blinded to the data setting and the diagnosis of each patient. To reduce the potential research or observational bias, the clinical and radiologic assessments were both performed by the same neurologist.

All data including age, sex, duration of the disease, drug and medical history, dosage of the drugs, psychological symptoms, sleeping history, sonographic and MRI findings were entered to a check list.

2.4. TCS

We used SonoSite Edge II Ultrasound system (Fujifilm SonoSite Inc., Bothell, WA, U.S.A.) with a 2–2.5 MHz sector transducer (S3 probe). We assessed the patients through trans temporal window with a penetration depth of 13–16 cm. The brightness was adjusted manually. The echo signal of substantia nigra reflected as a patchy, oval or band like shape in the midbrain level and its area is being measured in TCS. If this area is more than 0.25 cm^2 it was considered hyperechogenic.

2.5. Statistical analysis

SPSS version 18 was used to analyze the data. Frequency (percentage) was used to present prevalence of basic qualitative variables. Also the mean ± SD was representative for measureable and numerical factors. The prevalence of qualitative variations such as sex was compared by using chi-square test. The mean ages between groups were compared using independent sample *t*-test if the parametric situations were previously found by Shapiro-Wilk test. Pearson correlation test (or non-parametric equivalent) was used to check any correlations that might affect the differences between the ultrasound sizes among the two groups. Multivariate analysis (linear model) was used to reduce the effect of confounding on significant differences. Significance level was set at $P < 0.05$ (two-sided). Receiver operating characteristic (ROC) plots and calculation of the area under the curve (AUC) were used to display the values of ultrasound findings for detection of PSP and PD. Also all predictive values needed for introducing a diagnostic method were calculated.

3. Results

3.1. Frequencies and means

Of 35 patients entered for analysis, 26 (74.3%) were male. Eighteen patients were diagnosed with PD and 17 as PSP. The mean age of patients was 67.23 ± 6.24 years. The mean duration of the disease was 4.89 ± 2.21.

Mean midbrain area was 3.616 cm^2 in PSP and 4.86 cm^2in PD group ($P < 0.001$). Diameter of third ventricle (DTV) was 8.18 ± 2.8 mm in PSP and 4.53 ± 1.72 mm in PD patients ($P < 0.001$) SN echogenicity was 0.348 ± 0.09 cm^2 in PD and 0.25 ± 0.2 cm^2 in PSP group ($p < 0.05$)) Fig. 1).

Demographics and sonographic findings among two groups of patients are shown in Table 1.

3.2. Bivariate analyses

The results of Shapiro-Wilk test showed that all variables were normally distributed except SN echogenicity ($P < 0.05$). Statistical differences between demographic and ultrasound findings among two groups of patients are shown in Table 1. Correlation tests between age and different obtained ultrasound sizes, revealed no significant results. Spearman non parametric correlation test on SN hyperechogenicity and other numeric, revealed significant correlations for duration of the disease ($P = 0.04$, coefficient = -0.34) and third ventricle diameter ($P = 0.02$, coefficient = 0.37). The results of correlation between duration of the disease and ultrasound parameters were significant for both midbrain area and third ventricle diameter ($P < 0.005$) and the coefficients were 0.61 and -0.52 respectively.

3.3. Multivariate analysis

Regression model evaluated the effects of duration of the disease and age on significant differences of ultrasound parameters between patients with PD and PSP. Although “age” was not statistically different between the groups, the five-year difference of ages between groups could cause some clinical concerns. Thus, age was considered as one of the possible confounding factors in our model. Regression for reducing the effects of disease duration and age on SN hyperechogenicity in patients with PD and PSP (PD and PSP were defined 1 and 2, respectively) revealed a significant P value ($P = 0.03$, Adjusted $R^2 = 0.09$, Beta coefficient = -0.35, Confidence interval = -0.22 to -0.007). Regression for reducing the effect of those factors on third ventricle size variances in patients with PD and PSP revealed a significant P value ($P < 0.005$, Adjusted $R^2 = 0.38$, Beta coefficient = 0.63, Confidence interval = 0.2 to 0.52). The model also showed a significant difference between midbrain area in two groups of patients ($P < 0.005$, Adjusted $R^2 = 0.38$, Beta coefficient = -0.632, Confidence interval = -1.7 to -0.7) (Table 2).

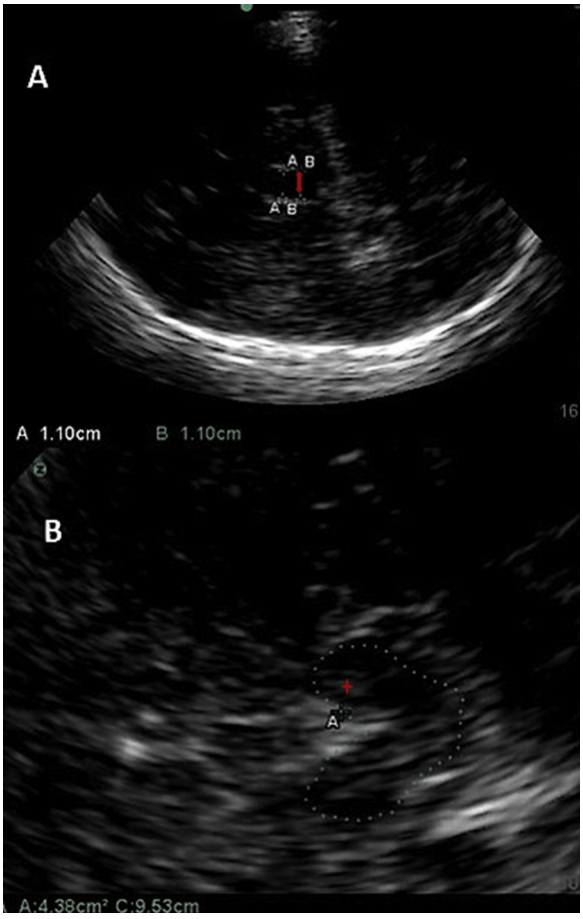

Fig. 1. Increased diameter of third ventricle in a PSP patient (red up-down arrow) (A) and midbrain outlines in a PD patient (white dotted line) with increased substantia nigra echogenicity (red 4 points star) (B) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

3.4. Roc curve analysis

Defining midbrain area and clinical suspicious of PD as testing variable and state variable, respectively (although it is not the gold standard of diagnosis), the accuracy of midbrain area was 86% (95% CI: 74–98%), P < 0.005 (Fig. 2A). The accuracy of third ventricle diameter for diagnosing PD was 12% that was in accordance with high accuracy in diagnosing PSP (Fig. 2B) and the accuracy of SN hyperechogenicity was 75% (95% CI: 56–93%), P = 0.01. The coordinate points for midbrain area and SN echogenicity were considered 4.22 and 0.27, respectively. By defining "PSP clinical diagnosis" as the testing variable, third ventricle was accurate to diagnose the disease by an accuracy of 87% (95% CI: 75–99%), P < 0.005, although the accuracy of PSP diagnosis was less than 50% by midbrain area or SN echogenicity (Fig. 2B). The ROC curve diagrams are shown in two separate figures as it makes it easier to interpret the curves and the related areas. By comparing both curves, it is found that the direction of numeric variables in patients clinically diagnosed as PD (Fig. 2A) are in opposite direction (inversed) to the same measure in the other group (Fig. 2B). It reveals that measures with low accuracy in diagnosing one disease, have high accuracy in diagnosing the opposite diagnosis.

Predictive values of different ultrasound findings are shown in Table 3.

4. Discussion

To increase the skill for distinguishing PSP from PD, which can be challenging at the beginning of the disease, lots of studies have been performed.

The recent meta-analysis by Shafieesabet et al. assessed the value of SN hyperechogenicity for differentiating PD and APS entering 71 articles from PUBMED and EMBASE databases. Their evaluations revealed suboptimal sensitivity and specificity of the index to differentiate PD from APS [7].

Beyond the mentioned article [7], the hyperechogenicity of SN was not related to midbrain area (Table 3). Thus the midbrain area can be used independently regardless of SN echogenicity for diagnosing PD or PSP.

Some studies assumed that hyperechogenicity of SN could delineate PD from MSA and PSP [13]. In patients with Lewy Body dementia (LBD) and Corticobasal degeneration (CBD) with increased echogenicity of SN comparable to PD patients, increased echogenicity of lentiform nuclei can be used as a clue to diagnosis. Also symmetrical SN hyperechogenicity is in favor of LBD [14]. Depression and migraine can also affect SN echogenicity [15,16]. Previous studies comparing SN echogenicity in patients with PD and APS did not consider depression as a confounding factor in PS patients which could affect SN echogenicity. Therefore, the echogenicity of SN cannot be considered as an accurate index for differentiating PS and need to be assessed by more diagnostic tests.

In 2004, Righini et al assessed whether the silhouette of midbrain in MRI could be used as a diagnostic index for discriminating PSP and PD. They found smaller diameters of midbrain in PSP patients but discrepancy between assessing radiologists was an issue [17].

In 2007, MRI findings depicted third ventricle enlargement, smaller diameters of midbrain and thinner quadrigeminal plate in PSP patients in comparison with those suffered from PD [18]. Also midbrain atrophy and smaller midbrain to pons ratio were previously suggested by Cosottini et al [19].

Essential midbrain changes in MRI and enhanced T2 star weighted angiography among patients with PD was previously studied [20].

Our study was conducted to evaluate the predictive value of midbrain area in differentiating PSP and PD. By designing ROC Curve

Table 1
Clinical data of two subgroups of patients.

	PD(18)	PSP(17)	P value
Sex	14 male(77.8%	12 (70.6%) male	NS
Age(years)	65.44 ± 5.84	69.12 ± 6.25	NS(0.08)
Duration of disease(years)	6.33 ± 1.74	3.35 ± 1.5	< 0.005
Mean MA (cm^2)	4.86 ± 0.71	3.61 ± 0.85	< 0.005
MA. %	15(83.3%) > 4.22	5 (29.4%) > 4.22	0.002
Mean DTV (mm)	0.45 ± 0.17	0.81 ± 0.28	< 0.005
DTV %	7(38.9%) > 0.5mm	14(82.4%) > 0.5mm	0.01
SN hyperechogenicity (mm^2)	0.36 ± 0.08	0.25 ± 0.2	0.04
SN hyperechogenicity%	16(88.9%) > 0.27	5(29.4%) > 0.27	< 0.005

MA: midbrain area, DTV: diameter of third ventricle, SN: substantia nigra.

Table 2
Regression model for midbrain area (as dependent variable).

Model parameters	Midbrain area and SN hyperechogenicity	Midbrain area and third ventricle diameter	Midbrain area and disease length and subtype of the disease
P value	0.2	0.01	< 0.005
Adjusted R2	0.007	0.15	0.43
Constant	–	5.16	4.63
Coefficient	–	−1.44	−0.77* for subtype of disease, 0.15 for disease length

* PD was defined as 1 and PSP as 2.

diagram, the accuracy of midbrain area was acceptable (86%) for diagnosing PD although it was not helpful in diagnosing PSP. On the other hand, third ventricular diameter was efficiently useful for diagnosing PSP (87%) but not PD (Fig. 1). According to our findings, the accuracy of the diagnosis may improve remarkably by combining the three investigated sonographic markers. Midbrain area and SN echogenicity were both sensitive and specific markers to diagnose PD in comparison to PSP (Table 3). However, third ventricle diameter showed relatively acceptable predictive values to diagnose PSP in comparison to PD (Table 3). It seems that considering both parameters in TCS improves the accuracy of diagnosis.

By present study, midbrain area in patients with PD was significantly wider than those with PSP. Also third ventricular diameter in PSP patients was significantly wider than PD patients. SN hyperechogenicity was another TCS finding that was higher in patients with PD. Although the three ultrasound findings were significantly different among groups (Table 1), the P value for the differences of midbrain area was much less than the others, revealing its greater importance.

Since the duration of the disease was significantly different between two subtypes of studied diseases, and the duration was also correlated with midbrain and third ventricle diameters, multivariate analysis was applied. The higher midbrain area in patients with PD existed even by reducing the effect of the disease duration on midbrain area. Also, different SN hyperechogenicity and third ventricle diameter between two groups existed regardless of disease duration.

To our knowledge, one other study investigated the predictive values of mesencephalic area in differentiating PD and PSP. Sastre-Bataller et al. in 2013, showed bigger mesencephalic area in 45 PD patients in comparison with 15 PSP patients. According to this study the area larger than 4.27 cm^2 could discriminate PSP from PD with a positive predictive value (PPV) of 100% [21].

A study in 2007 found that the third ventricle dilatation in combined with lenticular nucleus hyperechogenicity supported PSP diagnosis rather than PD (sensitivity, 84%; specificity, 98%) [13]. In our survey, third ventricular diameter did not show an acceptable accuracy in diagnosing PD although it was applicable for PSP (Table 2).

In the present study, the differences of SN hyperechogenicity, midbrain area and third ventricle diameters between PD and PSP were confirmed by reducing the effect of the disease duration on the ultrasound parameters, which was not considered by most of the previous studies.

Our study was subject to some limitations. Postmortem pathological studies, as the gold standard of diagnosis. were not possible. MRI changes in PSP patients could be compared between different subtypes of the disease that was far from our aim in this project.

5. Conclusion

Midbrain area in patients with PD was wider than those with PSP that was not affected by disease duration. In comparison with SN hyperechogenoicity and third ventricle size, midbrain area was the most accurate index for differentiating PD and PSP by TCS.

Conflict of Interest

None.

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Contribution of the authors

Shadi Ghourchian: Primary drafting and statistical analysis. Alireza Mousavi: Executing the project.
Babak Zamani: Study design.
Gholamali Shahidi: Critical revision of the manuscript for important intellectual content.
Mohammad Rohani: Study design, execution and writing the manuscript.

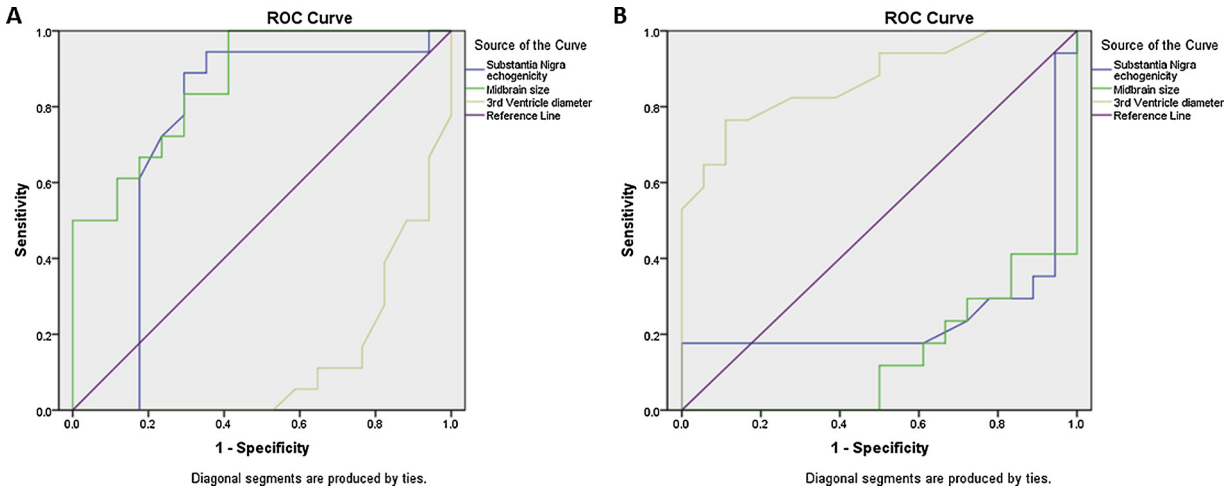

Fig. 2. Roc curve, defining PD as the value of the state variable (A) and defining PSP as the value of the state variable (B).

Table 3
Predictive values of ultrasound findings.

	Coordinate point	Sensitivity%		Specificity%		Positive predictive value %		Negative predictive value %	
		For PSP DX*	For PD DX**	For PSP DX *	For PD DX**	For PSP DX*	For PD DX**	For PSP DX*	For PD DX**
Midbrain Area	4.22 cm^2	29	83.3	17	70.6	25.89	74.11	19.32	81.40
Third Ventricular diameter	0.5 cm^2	82	38.9	62	18	68.33	32.23	77.5	22.78
SN	0.27 cm^2	29	88	12	71	24.79	75.21	14.46	85.54

* PSP DX: progressive supranuclear palsy diagnosis.
** PD DX: Parkinson's Disease diagnosis.

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