European Review for Medical and Pharmacological Sciences 2015; 19: 4621-4626

The ultra early diagnosis of Parkinson's disease by the enhanced substantia nigra echo

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Abstract. – OBJECTIVE: Our objective is to determine the value of enhanced substantia nigra echo in the diagnosis of Parkinson's disease by analyzing the intensity and area of substantia nigra echo by transcranial Doppler sonography (TCS).

PATIENTS AND METHODS: 36 patients diagnosed as ultra early stage Parkinson's disease between 2013 November and 2014 August were selected as the disease group, and 32 healthy people with the similar representation of age and gender were selected as the control group. TCS was used to detect the echo intensity and the echo intensity of the same location of bilateral hemicerebrum was used to evaluate the bilateral substantia nigra echo. The age and gender were also used for correlation analysis with the results of substantia nigra echo.

RESULTS: In the control group, there were 17 patients of substantia nigra echo grade I (53.1%), 13 cases of substantia nigra echo grade II (40.6%), 2 cases of substantia nigra echo grade III (6.3%). While in the disease group, there were 4 cases of substantia nigra echo grade II (11.1%), 13 cases of substantia nigra echo grade III (36.1%), 12 cases of substantia nigra echo grade IV (33.3%) and 7 cases of substantia nigra echo grade V (19.4%). The ratio of enhanced substantia nigra echo in Parkinson's disease patients was significantly higher than the control group. The analysis of the factors related to motor symptoms in Parkinson's disease patients revealed that the area of bilateral substantia nigra echo was negatively correlated with gender, but positively correlated with age, S/M ratio and UPDRS Ⅱ score. However, there was no correlation with H-Y stage. The sensitivity of substantia nigra echo in diagnosing Parkinson's disease was 32/36 = 88.89% and the specificity was 30/32 = 93.75%.

CONCLUSIONS: Analysis of substantia nigra echo is practically useful for the diagnosis of the ultra early stage Parkinson's disease, which can potentially improve the accuracy of clinical diagnosis to significantly enhance the early clinical prevention and reduce later disability.

Key Words:
Substantia nigra echo, Ultra early stage, Parkinson's disease, Diagnosis.

Introduction

Parkinson's disease is also called paralysis agitans, which is a degenerative disease of nervous system in aged people. The inflicted patients manifest the degeneration of dopaminergic neurons in substantia nigra and substantia nigra-striatum pathway[1-4]. As a chronic common disease, Parkinson's disease has been devastating the health of aged population in China, especially in those over 60 years old[5-8]. The motor symptoms mainly include muscular rigidity, bradykinesia, posture abnormality and static tremor, etc. People with advanced stage disease become disable to take care of themselves and even paralyzed[9-11]. In the recent years, the incidence of Parkinson's disease in younger patients is on the rise. Thus, the early diagnosis and treatment are becoming urgently important. At present, the mechanisms of Parkinson's disease remain elusive. However, it's generally considered that it is not caused by a single factor. Contributing environment and genetic factors, such as oxidative stress, dysfunction of mitochondria, unbalance of calcium homeostasis, inflammatory response and etc., can induce the loss or degeneration of dopaminergic neurons in substantia nigra, which leads to Parkinson's disease[12-14]. Transcranial Doppler sonography (TCS) is increasingly applied clinically to detect the specific physiological and pathological process of substantia nigra in Parkinson's disease patients[15]. In this study, we used TCS to detect the echo intensity and area of substantia nigra, to analyze the change of substantia nigra echo in patients with Parkinson's disease, which could potentially provide the ba-

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sis for the ultra early diagnosis of Parkinson's disease.

Patients and Methods

Clinical Materials

36 patients diagnosed with ultra early stage Parkinson's disease between 2013 November and 2014 August were selected as the disease group, including 21 males and 15 females. The age range was 51-72 and the average age was 62.63±7.57. Meanwhile, 32 healthy volunteers with similar representation of age and gender were selected as the control group, including 20 males and 12 females. The age range was 53-77 and the average age was 55.57±6.86. There was no statistical difference of age and gender between two groups (p >0.05), which were comparable.

Inclusion Criteria

The inclusion criteria of ultra early stage Parkinson's disease are as follows[16]: (1) All patients were conformed to the diagnostic criteria made by the Movement Disorder and Parkinson's Disease Group of the Chinese Medical Association Branch of Neurology, with hypokinesia and at least one of the following characteristics, including muscular rigidity, posture instability (caused by non-primary vision, vestibule, cerebellum or sensory dysfunction) or static tremor; (2) the patients were at grade I-V according to the Hoehn-Yahr staging criteria.

Exclusion Criteria

The exclusion criteria were as follows[16]: (1) patients previously received antidepressant drugs, dopamine depletion medicine or patients who were confirmed to contact neurotoxin; (2) patients with the following physical signs: cerebellar signs, dysphonia, postural hypotension, amyotrophy and pyramidal system damage.

Instruments and methods

TDS machine was GE vivid 7. The patients were examined according to the standard Doppler ultrasound diagnosis specification of neurodegenerative diseases made by European Nerve Ultrasonic Conference.

The intensity of substantia nigra echo was divided into 5 grades as previously reported[17], grade I: substantia nigra echo intensity was the same to brainstem; grade II: substantia nigra echo was clear, and the echo intensity was slightly higher than brainstem; grade III: the echo intensity was medium, which was slightly lower than midbrain; grade IV: echo intensity was the same to the midbrain; grade V: echo intensity was higher than the midbrain. Substantia nigra echo intensity of grade I and II was defined as normal. If the substantia nigra echo intensity was ≥ grade III, then the area of strong echo was measured. If the strong echo area was ≥ 0.20 cm^2 the patient was considered to suffer from Parkinson's disease.

Statistical Analysis

All data were analyzed by SPSS 17.0 (SPSS Inc., Chicago, IL, USA). Measurement data were presented as x±s and analyzed by t-test. The independent sample test was used to analyze the difference between two groups. Chi-squared test was used to compare the correlation and difference between echo area and intensity of subsatnia nigra. Spearman correlation analysis was used to analyze the correlation between various factors and bilateral substanti nigra echo area. p <0.05 was considered as statistically significant.

Results

Comparison of Substantia Nigra Echo Between two Groups

TCS was used to detect the substantia nigra echo of 36 patients with ultra early stage Parkinson's disease and 32 healthy volunteers. The results showed that in the control group, there were 17 patients of substantia nigra echo grade I (53.1%), 13 cases of substantia nigra echo grade II (40.6%), 2 cases of substantia nigra echo grade III (6.3%); In the disease group, there were 4 cases of substantia nigra echo grade II (11.1%), 13 cases of substantia nigra echo grade III (36.1%), 12 cases of substantia nigra echo grade IV (33.3%) and 7 cases of substantia nigra echo grade V (19.4%). The ratio of enhanced substantia nigra echo in Parkinson's disease patients was significantly higher than that in the control group (p <0.05), which was statistically significant, as shown in Table I and Figure 1.

The Spearman Correlation Analysis Between Bilateral Substantia Nigra Echo Area and Related Factors

The analysis of the factors related to motor symptoms in Pakinson's disease patients revealed that the area of bilateral substantia nigra

Table I. Comparison of substantia nigra echo between two groups.

Echo intensity	The control group (n=32)		The disease group (n=36)		F	p
	Number of cases	Percent (%)	Number of cases	Percent (%)		
Grade I	17	53.1	0	0.0	7.53	<0.05
Grade II	13	40.6	4	11.1	5.92	<0.05
Grade III	2	6.3	13	36.1	5.31	<0.05
Grade IV	0	0.0	12	33.3	6.48	<0.05
Grade V	0	0.0	7	19.4	4.26	<0.05

echo was negatively correlated with gender, but positively correlated with age, S/M ratio and UPDRS II score. However, there was no relation with H-Y stage, as shown in Table II.

The Sensitivity and the Specificity of Substantia Nigra echo in Diagnosing Pakinson's Disease

There were 32 Pakinson's disease positive patients in the disease group and there were 30 Pakinson's disease negative patients in the control group. The sensitivity was 32/36=88.89% and the specificity was 30/32=93.75%, as shown in Table III.

Discussion

Parkinson's disease has been a common degenerative disease of the nervous system inflicting millions of aged people. With increased age, the mortality is also increased, and the mortality in males is higher than in females[18-20]. Recently, the Parkinson's disease in younger patients is on the rise. It is reported that the severity of dopaminergic neuron loss in compact part of substantia nigra is closely related to the reduction of dopamine in substantia nigra. When dopaminergic neuron loss in compact part of substantia nigra reaches 50% and the dopamine in substantia nigra is reduced to 75%, symptoms of Parkinson's disease are clinically evident, the severity of which is also closely related to the severity of dopaminergic neuron loss in compact part of substantia nigra[21-24]. Thus, determination and monitoring of the pathological change of substantia nigra or basal ganglia at the ultra early stage is important in treating Parkinson's disease and improving their life quality.

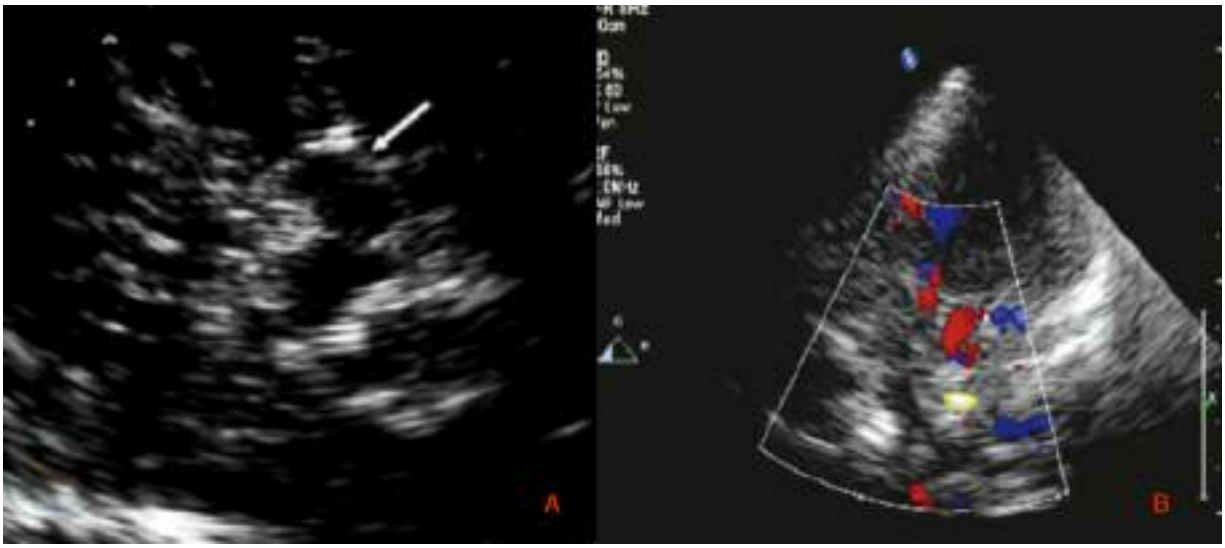

Figure 1. The substantia nigra echo enhanced area. ***A***, The control group (grade I); ***B***, The disease group (grade III).

Table II. The Spearman correlation analysis between bilateral substantia nigra echo area and other related factors.

Factor	Bilateral substantia nigra echo area	
	R value	p-value
Age	0.314**	0.001
Gender	-0.241*	0.017
S/M	0.886**	0.000
UPDRS I score	0.321	0.084
UPDRS II score	0.284*	0.032
UPDRS III score	0.075	0.214
UPDRS IV score	-0.082	0.875
UPDRS 21 items	-0.143	0.427
H-Y stage	0.006	0.973

Note: R represents Spearman coefficient of rank correlation, *means $p < 0.05$; **means $p < 0.01$.

TCS is a noninvasive ultrasonic imaging technology, which can detect the brain structure of patients. Its advantages include convenience, tandetny, no radiation, no invasion and less dependence on patient compliance, which are helpful for the diagnosis of Parkinson's disease. However, there are also some limitations and disadvantages[25,26]. It is reported that[27] there was enhanced echo in bilateral midbrain in most patients who were confirmed with Parkinson's disease. However, the type of enhanced echo by TCS in bilateral substantia nigra of Parkinson's disease patients is not related with the severity of movement restriction in Parkinson's disease. The enhanced echo in midbrain is just one feature of Parkinson's disease, but not the main sensitivity index. TCS itself is still unable to perfectly diagnose Parkinson's disease.

Becker et al[28] for the first time found that there was high level echo in substantia nigra of Parkinson's disease patients, and the following studies verified this phenomenon. Substantia nigra echo detected by TCS is of high sensitivity and specificity[29,30]. In the current study, the rate of enhanced substantia nigra echo in 36 Parkinson's disease patients was 88.8%, which was consistent with the past reports. Also, we did not only use intensity grade to evaluate the intensity of substantia nigra, but used Berg's evaluation method of enhanced substantia nigra area, in which enhanced substantia nigra ≥ 0.20 cm^2 was used to define Parkinson's disease. It is found that the higher the intensity of substantia nigra echo was, the bigger the area of enhanced substantia nigra and S/M value were. The intensity grade of substantia nigra echo, the area of enhanced substantia nigra echo and S/M value can all reflect the condition of enhanced substantia nigra echo. Besides, TCS showed that there was enhanced substantia nigra echo in 3%-9% healthy population. Consistently, we found that there was enhanced substantis nigra echo in 6.3% healthy volunteers in the control group, which fell into the range. Among the patients with ultra early stage Parkinson's disease there were 4 cases of substantia nigra echo grade II (11.1%), 13 cases of substantia nigra echo grade III (36.1%), 12 cases of substantia nigra echo grade IV (33.3%) and 7 cases of substantia nigra echo grade V (19.4%), which were significantly higher than the control group. The analysis of the factors related to motor symptoms in Pakinson's disease patients revealed that the area of bilateral substantia nigra echo was negatively correlated with gender, which may be due to the larger number of male patients in the disease group. The area of bilateral substantia nigra echo was positively correlated with age, S/M ratio and UPDRS II score. However, there was no correlation with H-Y stage.

Conclusions

Analysis of substantia nigra echo is practically useful in diagnosing the ultra early stage Parkinson's disease. It can potentially improve the ac-

Table III. The sensitivity and the specificity of substantia nigra echo in diagnosing Pakinson's disease.

Diagnostic results of substantia nigra echo	Patients with Pakinson's disease	Patients with no Pakinson's disease	In total
+	32	2	34
-	4	30	34
In total	36	32	68

Note: R represents Spearman coefficient of rank correlation, *means $p < 0.05$; **means $p < 0.01$.

curacy of clinical diagnosis, which will sure impact on the early clinical prevention and reduction of later disability.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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