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Plasma ApoA-1 and endothelin-1 levels changes in early Parkinson disease and its relationship with cognitive function and cerebral white matter structure change

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Abstract: The study aimed to investigate the plasma apolipoprotein A-1 (ApoA-1) and endothelin -1 (ET-1) changes in early Parkinson disease (PD), and analyze their relationship with cognitive function and cerebral white matter structure (WMS) change. 76 early PD patients were selected as group PD, and 30 cases of healthy persons were selected as control group. They all scanned with magnetic resonance imaging (MRI) diffusion tensor. The ApoA-1, ET-1, WMS changes, and Montreal Cognitive Assessment (MoCA) scores were recorded in the two groups of subjects. The results revealed that ApoA-1 level and Mo CA score in PD group decreased, FA value in bilateral temporal lobe, left anterior cingulate tract, corpus callosum, and other cerebral WMS area in PD group were also decreased, and ET-1 level in PD group increased (P<0.05). Compared with those of PD group patients with Mo CA≥26, plasma ApoA-1 levels and cerebral WMS FA values of the patients with Mo CA＜26 were decreased, (P<0.05); the MoCA score of PD group was positively correlated with the cerebral WMS FA values (P<0.05). In short, the ApoA-1 level in patients with early PD decreased, while the ET-1 level increased, and both were related to cognitive function and WMS.

Keywords: Parkinson disease, apolipoprotein A-1, endothelin-1, cognitive function, cerebral white matter structure.

INTRODUCTION

PD is a common clinical neurodegenerative disease, patients may develop dyskinesia that interferes with normal activity, neurological abnormalities and cognitive impairment may occur when the condition is serious, it then causes the corresponding dysfunction, which affects the health and quality of life of the patients (Malak *et al*., 2017). Therefore, it is of great significance to treat PD timely and effectively and reduce the occurrence of cognitive impairment. Previous studies have confirmed that PD patients may have structural changes in cerebral WMS of brain, which may be related to cognitive impairment (Rektor *et al*., 2018). Moreover, the occurrence of cognitive impairment involves multiple mechanisms and factors (Winer *et al*., 2018). Therefore, the changes of cerebral WMS and the occurrence of cognitive functions in PD patients were observed, and the correlation between the two was analyzed. The relationship between plasma apolipoprotein A-1 (ApoA-1) and endothelin-1 (ET-1) levels and changes in cerebral WMS and cognitive function were analyzed, so as to provide guidance for early assessment interventions for cognitive impairment in PD and reduce the occurrence of cognitive dysfunction and its related adverse effects in patients.

MATERIALS AND METHODS

Research object information

76 patients with early PD admitted to our hospital from January 2014 to December 2017 were selected as the PD group. Inclusion criteria: they were conformed to the relevant diagnostic criteria established by the movement disorders and PD group of the Chinese neurologic society in 2006 (Ten Harmsen *et al*., BL2018); they were clearly conscious and voluntarily agreed to be enrolled and signed the informed consent after questioning; there was no gender limitation; their ages were between 18 and 80 years old. Exclusion criteria: patients with combined brain disease or history of brain disease; patients with cognitive impairment before PD diagnosis; patients with other disorders that may affect cognitive function and cerebral WMSs; patients with other serious medical diseases; patients were mentally abnormal and unable to communicate normally, etc. No patients were excluded from the PD group, and 76 patients were finally included in the PD group, all of whom were in the early stage of PD (PD included grade 1 to grade 2). Their course of disease ranged from 8 months to 11 years, with an average of 5.66±2.15 years and their length of education ranged from 7 to 20 years, with an average of 9.78±2.11 years. In addition, 30 healthy people who underwent physical examination with our hospital during the same period were selected as the control group. People in the control group all voluntarily entered the group and they were with no obvious abnormalities in physical examination, no history of serious internal and surgical diseases, no gender limitation, no communication barrier, the age range was the same as that of the PD group, and their educational years ranged from 7 to 20 years, with an average of 9.78±2.11 years. This study met the ethical standards reference No.4 and both groups signed the

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informed consent. There was no significant difference in basic information such as gender, age, body mass index (BMI), smoking rate, and drinking rate between the two groups (P>0.05), which was comparable, as shown in table 1.

Treatment methods

After the diagnosis of PD group, the attending doctor would select the appropriate drugs for disease control according to the specific condition, while the control group was a healthy group and no treatment intervention was needed.

Observation indicators and detection method

Fasting venous blood (3mL) was collected from the two groups in the early morning of the second day of enrollment to detect the plasma levels of ApoA-1 and ET-1. The obtained blood samples were placed in ethylene diamine tetra acetic acid (EDTA) anticoagulant tubes, centrifugation was performed at 5000r/min speed, 3cm radius and 4°C for 10min. After stratification, the lower plasma was separated for the detection of relevant indicators. The plasma ApoA-1 level was detected by one-way immunodiffusion method. The plasma ET-1 level was detected by radioimmunoassay. All the related kits were purchased from Beijing Puerweiye Biology Technology CO, LTD. AU5811 automatic biochemical analyser from BECKMAN COULTER (USA), the specific test operation was carried out strictly according to the requirements of the kit and the instructions of the test instrument. After the blood sample was taken, the magnetic resonance diffusion tensor imaging (DTI) was used to examine the microstructure changes of cerebral WMS in the two groups. GE Signa HDxt America 3.0 T nuclear magnetic resonance scanner was used for routine and DTI examination of the skull, and the scanning parameters were as follows. T1WI spatial resolution 1.0mm×1.0mm×1.0mm, TRI 1794ms, TE27.3ms, TI 1100ms, matrix 288×244; FOV 240mm, layer thickness 1.0mm, spacing 0.5mm; a total of 800 layers were collected from 20 directions of DTI, TR 2s, TE 87.9ms, matrix 130×128, FOV 240mm, voxel 3.4×3.4×3mm^3, b value 1000s/mm^2. The scanned image was post processed, AW4.4 workstation was used to detect and analyze fractional anisotropy (FA) values in cerebral WMS such as the temporal lobe, parietal lobe, frontal lobe, occipital lobe, anterior cingulate cortex, posterior cingulate cortex, the splenium of the corpus callosum, the genu of the corpus callosum, midbrain vertebral tract, internal capsule vertebral tract, superior longitudinal fasciculus. The blood samples were taken and the cognitive function of the two groups was evaluated by the Montreal cognitive assessment scale (Mo CA) by the trained and qualified personnel on the same day.

Evaluation method

PD classification (Costa-Mallen *et al*., 2017) was conducted by Hoehn-Yahr classification method. Level 0 meant the patient had no obvious symptoms or signs; level 1 meant that one side of the patient's limb was affected; level 1.5 meant that one side of the patient's limb was involved with somatic muscle involvement; level 2 meant the patient's limbs were involved on both sides but there was no disturbance of balance; level 2.5 meant the patient had mild bilateral limb involvement and mild balance impairment; level 3 meant that the patient's bilateral limbs were moderately affected with postural instability, slow turning and multiple functional limitations, but was able to take care of himself; level 4 meant that the patient had bilateral limb inflammation but was able to walk and stand; level 5 meant the patient had to stay in bed or live in a wheelchair. Level 1~2 was the early stage, level 2.5~3 was the middle stage and level 4~5 was the advanced stage. Mo CA included seven dimensions such as space and executive function, naming ability, attention, and so on (Wang *et al*., 2019; Yau *et al*., 2018; Bledsoe *et al*., 2018). For those who had been educated for 12 years or less, 1 point was added to the test result as the final value. The highest score was 30 points and no less than 26 indicated normal.

STATISTICAL ANALYSIS

Data in this study was processed with SPSS 22.0. The measurement data were expressed in the form of ratio or rate and the chi-square test was used for comparison between groups. All measurement data were in normal distribution and were expressed as mean ± standard deviation. The t-test was used to compare the mean values of two independent samples and Pearson linear correlation method was used for correlation analysis. According to the test standard α=0.05, P < 0.05 indicated there was a statistical significance.

RESULTS

Comparison of plasma ApoA-1 and ET-1 levels, Mo CA scores and FA values in cerebral white matter structure areas between two groups

Compared with the control group, PD group plasma ApoA-1 level and Mo CA score were decreased, FA values in cerebral WMS areas such as bilateral temporal lobe, left anterior cingulate tract and the splenium of corpus callosum were also decreased, and plasma ET-1 level was increased, the differences were statistically significant (P<0.05), as shown in table 2.

Comparison of plasma ApoA-1 and ET-1 levels and cerebral white matter structure changes in patients with Mo CA no less than 26 and Mo CA less than 26 in PD group

Compared with patients with Mo CA no less than 26 in the PD group, patients with Mo CA less than 26 had decreased plasma ApoA-1 and FA values in cerebral white matter areas, and increased plasma ET-1 levels,

Table 1: Basic information comparison of the two groups.

Groups	Patients number	Gender (male/female)	Age (years old)	BMI (kg/m^2)	Smoking rate (number (%)	Drinking rate (number (%)
PD group	76	35/41	63.22 ± 8.56	22.16 ± 3.48	45(59.21)	56(73.68)
Control group	30	17/13	63.18 ± 7.92	22.05 ± 2.96	20(66.67)	23(76.67)
X^2/t group		0.970	0.022	0.153	0.504	0.101
P group		0.325	0.982	0.879	0.478	0.751

Table 2: Comparison of plasma ApoA-1 and ET-1 levels, Mo CA scores, and FA values in cerebral white matter areas between two groups.

Indexes	PD group (n=76)	Control group (n=30)	*t*	*P*
ApoA-1 (g/L)	1.03 ± 0.11	1.26 ± 0.16	8.469	0.011
ET-1 (pg/L)	87.65 ± 9.68	53.22 ± 7.42	17.535	0.000
Mo CA score (score)	26.36 ± 2.28	28.44 ± 1.25	4.716	0.037
Left temporal lobe FA value	0.46 ± 0.03	0.50 ± 0.03	6.184	0.032
Right temporal lobe FA value	0.47 ± 0.02	0.51 ± 0.02	9.276	0.007
Left parietal lobe FA value	0.45 ± 0.03	0.47 ± 0.04	2.803	0.049
Right parietal lobe FA value	0.43 ± 0.02	0.46 ± 0.02	6.957	0.030
Left frontal lobe FA value	0.47 ± 0.03	0.52 ± 0.03	7.730	0.026
Right frontal lobe FA value	0.46 ± 0.02	0.48 ± 0.02	4.638	0.039
Left occipital lobe FA value	0.43 ± 0.04	0.47 ± 0.04	4.638	0.039
Right occipital lobe FA value	0.46 ± 0.02	0.48 ± 0.02	4.638	0.039
Left anterior cingulate cortex FA value	0.45 ± 0.02	0.53 ± 0.04	13.689	0.000
Right anterior cingulate cortex FA value	0.40 ± 0.03	0.44 ± 0.02	6.727	0.031
Left posterior cingulate cortex FA value	0.42 ± 0.02	0.44 ± 0.03	3.994	0.042
Right posterior cingulate cortex FA value	0.40 ± 0.03	0.49 ± 0.02	15.135	0.000
Splenium of the corpus callosum FA value	0.75 ± 0.05	0.79 ± 0.03	4.094	0.041
Genu of the corpus callosum FA value	0.68 ± 0.04	0.72 ± 0.02	5.216	0.035
Left midbrain vertebral tract FA value	0.70 ± 0.02	0.72 ± 0.02	4.638	0.039
Right midbrain vertebral tract FA value	0.70 ± 0.04	0.73 ± 0.03	3.712	0.044
Left internal capsule vertebral tract FA value	0.62 ± 0.03	0.64 ± 0.02	3.363	0.048
Right internal capsule vertebral tract FA value	0.36 ± 0.04	0.63 ± 0.03	33.410	0.000
Left superior longitudinal fasciculus FA value	0.61 ± 0.02	0.63 ± 0.04	3.422	0.046
Right superior longitudinal fasciculus FA value	0.62 ± 0.03	0.65 ± 0.03	4.638	0.039

with statistically significant differences (P<0.05), as shown in table 3.

Relationship between plasma ApoA-1 and ET-1 levels, Mo CA score and white matter structure changes and relationship between its Mo CA score and FA values in white matter areas in PD group

Pearson linear correlation analysis results showed that PD group plasma ApoA-1 level had positive correlation with its Mo CA score and FA values in cerebral WMS such as the left temporal lobe, right temporal lobe, left parietal lobe, right parietal lobe, left frontal lobe, right frontal lobe, left occipital lobe, right occipital lobe, left anterior cingulate cortex, right anterior cingulate cortex, left posterior cingulate cortex, right posterior cingulate cortex, the splenium of the corpus callosum, the genu of the corpus callosum, left midbrain vertebral tract, right midbrain vertebral tract, left internal capsule vertebral tract, right internal capsule vertebral tract, left superior longitudinal fasciculus, and right superior longitudinal fasciculus (Mo CA scores r = 0.722, 0.785, 0.855, 0.878, 0.765, 0.726, 0.773, 0.735, 0.728, 0.715, 0.732, 0.805, 0.798, 0.886, 0.843, 0.892, 0.838, 0.808, 0.769, 0.805; FA values in cerebral white matter areas: r = 0.811, 0.834, 0.795, 0.738, 0.722, 0.785, 0.872, 0.854, 0.886, 0.846, 0.878, 0.815, 0.796, 0.754, 0.778, 0.766, 0.815, 0.789, 0.811, 0.875, P<0.05). PD group plasma ET-1 level had negative correlation with its Mo CA score and FA values in cerebral white matter such as the left temporal lobe, right temporal lobe, left parietal lobe, right parietal lobe, left frontal lobe, right frontal lobe, left occipital lobe, right occipital lobe, left anterior cingulate cortex, right anterior cingulate cortex, left posterior cingulate cortex, right posterior cingulate cortex, the splenium of the corpus callosum, the genu of the corpus callosum, left midbrain vertebral tract, right midbrain vertebral tract, left internal

Table 3: Comparison of plasma ApoA-1 and ET-1 levels and cerebral WMS changes in patients with Mo CA≥26 and Mo CA<26 in PD group.

Indexes	Mo CA≥26 (n=48)	Mo CA<26 (n=28)	*t*	*P*
ApoA-1 (g/L)	1.12 ± 0.08	0.88 ± 0.12	10.455	0.010
ET-1 (pg/L)	83.46 ± 9.22	96.55 ± 8.85	6.058	0.037
Left temporal lobe FA value	0.44 ± 0.02	0.49 ± 0.03	8.712	0.019
Right temporal lobe FA value	0.45 ± 0.03	0.50 ± 0.04	6.186	0.034
Left parietal lobe FA value	0.43 ± 0.04	0.48 ± 0.02	6.168	0.034
Right parietal lobe FA value	0.41 ± 0.03	0.46 ± 0.02	7.849	0.026
Left frontal lobe FA value	0.44 ± 0.02	0.51 ± 0.03	12.197	0.000
Right frontal lobe FA value	0.44 ± 0.03	0.49 ± 0.02	7.849	0.026
Left occipital lobe FA value	0.41 ± 0.02	0.46 ± 0.02	10.513	0.009
Right occipital lobe FA value	0.45 ± 0.05	0.48 ± 0.03	2.882	0.005
Left anterior cingulate cortex FA value	0.42 ± 0.03	0.49 ± 0.02	10.989	0.007
Right anterior cingulate cortex FA value	0.38 ± 0.04	0.44 ± 0.04	6.308	0.030
Left posterior cingulate cortex FA value	0.40 ± 0.03	0.45 ± 0.02	7.849	0.026
Right posterior cingulate cortex FA value	0.38 ± 0.02	0.43 ± 0.03	8.712	0.019
Splenium of the corpus callosum FA value	0.73 ± 0.04	0.78 ± 0.02	6.168	0.034
Genu of the corpus callosum FA value	0.65 ± 0.03	0.71 ± 0.04	7.423	0.027
Left midbrain vertebral tract FA value	0.67 ± 0.04	0.75 ± 0.02	9.869	0.015
Right midbrain vertebral tract FA value	0.68 ± 0.02	0.73 ± 0.03	8.712	0.019
Left internal capsule vertebral tract FA value	0.59 ± 0.04	0.66 ± 0.02	8.635	0.021
Right internal capsule vertebral tract FA value	0.31 ± 0.03	0.43 ± 0.04	14.846	0.000
Left superior longitudinal fasciculus FA value	0.57 ± 0.03	0.67 ± 0.02	15.699	0.000
Right superior longitudinal fasciculus FA value	0.59 ± 0.02	0.66 ± 0.03	12.197	0.000

capsule vertebral tract, right internal capsule vertebral tract, left superior longitudinal fasciculus and right superior longitudinal fasciculus (Mo CA scores r = -0.738, -0.625, -0.722, -0.736, -0.805, -0.778, -0.762, -0.786, -0.811, -0.874, -0.828, -0.875, -0.835, -0.765, -0.812, -0.873, -0.844, -0.785, -0.792, -0.778; FA values in cerebral white matter areas: r = -0.832, -0.844, -0.865, -0.818, -0.796, -0.825, -0.773, -0.768, -0.722, -0.718, -0.831, -0.855, -0.776, -0.739, -0.711, -0.782, -0.745, -0.811, -0.842, -0.877, P<0.05). PD group Mo CA values had positive correlation with the FA values in cerebral white matter such as the left temporal lobe, right temporal lobe, left parietal lobe, right parietal lobe, left frontal lobe, right frontal lobe, left occipital lobe, right occipital lobe, left anterior cingulate cortex, right anterior cingulate cortex, left posterior cingulate cortex, right posterior cingulate cortex, the splenium of the corpus callosum, the genu of the corpus callosum, left midbrain vertebral tract, right midbrain vertebral tract, left internal capsule vertebral tract, right internal capsule vertebral tract, left superior longitudinal fasciculus, and right superior longitudinal fasciculus (r = 0.822, 0.873, 0.811, 0.865, 0.782, 0.846, 0.781, 0.721, 0.844, 0.836, 0.818, 0.793, 0.846, 0.825, 0.887, 0.808, 0.842, 0.866, 0.835, 0.886, P<0.05).

DISCUSSION

In recent years, with the improvement of living standards, the aging population has been developing. PD and other age-related diseases have risen, which has become an important factor seriously affecting the health of the elderly population and restricting the improvement of living standards. PD could cause movement disorders that could significantly affect a person's ability to move around on a daily basis. Besides, non-motor symptoms such as neurological and cognitive impairment could seriously affect the quality of life [7,8]. The cognitive function of PD patients was also paid attention in this study. The results of this study showed that more than 30% of Parkinson's disease patients had Mo CA less than 26 points, that was, they were with cognitive function abnormalities, which could lead to mild cognitive impairment or even dementia. Therefore, timely assessment of the cognitive function of PD patients, timely and effective intervention, and reducing the occurrence of cognitive dysfunction and its related adverse consequences are urgently required.

Study results of Ly *et al*. (2017) showed that cerebral white matter lesions played an important role in cognitive impairment in PD patients (Ly *et al*., 2017). When leukodystrophy occurs, the loop fibers associated with intelligent activity in the cerebral white matter of the brain were disrupted, the external manifestation was cognitive dysfunction. Magnetic resonance was an important adjunct in the long-term observation of PD. Diffusion tensor imaging in magnetic resonance imaging could accurately reflect the loss of cerebral white matter volume and microstructure (Arrigo *et al*., 2017). In the

research of Sterling *et al*. (2017), FA value could be decreased in multiple cerebral white matter areas of the brain of PD patients by means of diffusion tensor imaging, and their cerebral white matter microstructures were damaged. In this study, diffusion tensor imaging was also used to evaluate the micro structural changes in the cerebral white matter of PD patients. The results showed that compared with the normal healthy people, the FA values of the temporal lobe, parietal lobe, frontal lobe, occipital lobe, anterior cingulate cortex, posterior cingulate cortex, the splenium of the corpus callosum, the genu of the corpus callosum, midbrain vertebral tract, internal capsule vertebral tract and superior longitudinal fasciculus in PD patients were all decreased, indicating the occurrence of cerebral white matter micro structural damage. In addition, the FA values of the cerebral white matter region of PD patients with Mo CA less than 26 were lower than those of patients with Mo CA no less than 26 in this study, which suggested that FA value of the cerebral white matter area was correlated with Mo CA score. Further Pearson linear correlation analysis results showed that the Mo CA score of PD patients was positively correlated with FA values of all cerebral white matter areas, which further confirmed the important role of abnormal cerebral white matter microstructure in the cognitive impairment of PD patients.

Early evaluation of cerebral white matter microstructural abnormalities and cognitive impairment in PD patients was helpful for timely intervention and improvement of efficacy and prognosis. In recent years, studies have shown that the occurrence and development of PD was related to abnormal lipid levels, and PD patients may have decreased lipid levels such as ApoA-1 (Dadar *et al*., 2018). ET-1 was a vasoactive substance secreted by endothelial cells, and its concentration in the blood of PD patients could be significantly increased, the increase of its level could strengthen the vasoconstriction, leading to the disturbance of microcirculation and the damage caused by ischemia and hypoxia of the cerebral white matter structure. The hypoxia and ischemia with microcirculation disorder could further enhance the synthesis and secretion of ET-1, thus forming a vicious cycle (Ji *et al*., 2019). In this study, the plasma levels of ApoA-1 and ET-1 were also detected in PD patients. The results showed that PD patients had lower plasma ApoA-1 levels and higher plasma ET-1 levels than normal healthy people, indicating that abnormal plasma ApoA-1 and ET-1 levels were associated with PD. In addition, compared with PD patients with Mo CA no less than 26, PD patients with Mo CA less than 26 had lower plasma ApoA-1 levels, lower FA values in various cerebral white matter areas, and higher plasma ET-1 levels, indicating that the plasma levels of ApoA-1 and ET-1 might be correlated with the impairment of cognitive function. Further Pearson linear correlation analysis results showed that the plasma ApoA-1 level in PD patients was positively correlated with Mo CA score and FA values in all cerebral white matter areas. The level of plasma ET-1 was negatively correlated with Mo CA score and FA values in various cerebral white matter areas. In the control group, ApoA-1 and ET-1 levels were not significantly correlated with Mo CA scores and FA values and the data were not shown in the text. Detection of plasma ApoA-1 and ET-1 levels may be helpful in early detection of damage to cerebral white matter microstructure and risk of cognitive function, indicating to screen the cerebral white matter micro structural damage and cognitive dysfunction as early as possible. Timely intervention for patients with abnormalities could reduce the occurrence of cognitive impairment, so as to reduce the adverse effects of cognitive impairment on patients and improve the health status and quality of life of PD patients.

CONCLUSION

In summary, plasma ApoA-1 and ET-1 levels in patients with early PD were closely related to changes in cerebral white matter microstructure and cognitive function. The detection of plasma ApoA-1 and ET-1 levels may be applied in the early assessment of the risk of cognitive impairment in PD patients to guide the prevention and treatment of cognitive impairment and improve the treatment level of PD.

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