

Serum levels of p-tau181 in patients with Parkinson's disease

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Abstract: Background: Parkinson's disease (PD) is the second most common neurodegenerative disease. Evidence has shown that phosphorylated tau-181 (p-tau181) is involved in the pathological process of PD. The goal of this study was to investigate the changes of serum phosphorylated Microtubule-associated protein tau at threonine-181 in patients with Parkinson's disease and its correlation with disease severity, cognitive impairment and prognosis. Methods: A total of 40 patients with primary Parkinson's disease who were hospitalized or outpatient in the First Affiliated Hospital of Chongqing Medical University from July 2021 to February 2022 were selected as the study subjects. Patients with secondary Parkinson's disease, Parkinson's syndrome, stroke, Alzheimer's disease, craniocerebral surgery or trauma, severe systemic or infectious diseases, local or systemic infectious diseases, motor neurone disease or other central nervous system diseases were excluded. In addition, 35 healthy subjects with similar age and gender matching were selected as the healthy control group. Age, gender, course of disease, Hoehn-Yahr (H-Y) scale, Unified Parkinson's Disease Scale (UPDRS), and MoCA score were recorded in the Parkinson's disease group. According to the H-Y scale, PD group was divided into PD patients in the advanced stage (H-Y \leq 2.5, n=16) and PD patients in the advanced stage (H-Y>2.5, n=24). Six months after blood sample collection, we assessed the H-Y rating and UPDRS score in the Parkinson's group again by telephone follow-up. Those with decreased or unchanged H-Y rating or total UPDRS score were divided into good prognosis group (n=25), and those with increased H-Y rating or total UPDRS score were divided into poor prognosis group (n=14). The serum p-tau181 concentration of all subjects was detected and compared by double-antibody sandwich enzyme-linked immunosorbent assay (ELISA), and the correlation between serum p-tau181 level and UPDRS score, MoCA score and prognosis of Parkinson's disease patients was analyzed. Results: Compared with HC, serum p-tau181 concentration in PD patients were higher, but not statistically significant (1.01[0.28-2.63]vs 0.53[0.04-3.72] μ g/mL, P=0.55, P>0.05). There was no significant difference in p-tau181 concentration between PD patients in early stage and PD patients in advanced stage (P=0.80 P>0.05), and no significant difference in p-tau181 level between PD patients with cognitive impairment, PD patients with normal cognition and HC patients (P=0.63, p>0.05). P-tau181 was not significantly correlated with disease duration (r=-0.14, P=0.37, P>0.05), UPDRS score (r=0.02, P=0.89, P>0.05), and MoCA score (r= 0.16, P=0.32, P > 0.05). There was no significant difference in serum P-tau181 expression between good prognosis group and poor prognosis group (P=0.74, P > 0.05). Conclusions: Serum expression of p-tau181 increased in PD patients, but no statistical difference was observed, and no clear correlation was found between p-tau181 and disease severity and cognitive impairment. Serum p-tau181 level in PD patients has no significant prognostic significance.

Keywords: Parkinson's Disease; P-tau181; Cognitive impairment; Disease severity; Functional prognosis.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease. The main clinical manifestations are motor symptoms such as static tremor, myotonia and kinesia, as well as non-motor symptoms such as olfaction disorder, sleep disorder, cardiovascular dysfunction and refractory constipation [1-3]. PD is the second most common neurodegenerative disease after Alzheimer's disease (AD), and its incidence is increasing year by year. It is estimated that by 2030, the number of PD patients in China will reach 4.94 million, bringing a heavy burden to families and society. The pathogenesis and etiology of Parkinson's disease have not been clarified yet, and its main pathological characteristics are the selective death of dopaminergic neurons in the substantia nigra and the formation of Lewy bodies (LBs), which are mainly composed of α -synaptic nucleoprotein, ubiquitin and neurofilament protein [5,6]. It has been widely recognized that various pathological mechanisms jointly lead to the occurrence and development of Parkinson's disease. Recent studies have also shown that oxidative stress,

mitochondrial dysfunction, protein folding abnormalities caused by endoplasmic reticulum stress, neuroinflammation, microbial-enteric-brain axis and related gene changes are closely related to the occurrence and development of PD [7-11]. At present, the diagnosis of Parkinson's disease is mainly based on typical clinical symptoms, and there is no specific clinical feature in the early stage. When the disease progresses to the middle or late stage, most dopaminergic neurons are damaged, the content of dopamine transmitter is reduced, the treatment effect is poor or ineffective, and many complications occur, which is often difficult to distinguish from other neurodegenerative diseases or movement disorders. The quality of life of patients has seriously deteriorated, bringing a heavy burden to individuals, families and society. Therefore, it is necessary to search for biochemical indicators with high specificity to assist the early diagnosis of Parkinson's disease.

Tau protein is produced from a single human gene named microtubule-associated protein tau (MAPT), which is located on chromosome 17 and encodes a cytoskeletal protein that stabilizes Microtubules. Tau proteins play a role in stabilizing

microtubules, binding to membrane, and regulating axonal transport [13, 14]. However, the abnormally phosphorylated tau protein lost the ability to induce microtubule assembly and maintain microtubule stability, and p-tau competed with tubulin to bind to normal tau protein and other macromolecular microtubule-associated proteins, resulting in microtubule depolymerization, impaired material transport between neuron bodies and nerve endings, and finally caused a series of neuropathological changes. In an autopsy study, co-accumulation of tau protein and α -syn was observed in Lewy bodies. In numerous PD models, α -syn has been shown to cause focal tau pathology and facilitate the phosphorylation of tau; furthermore, increased p-tau aggregations have been found in the striatum of PD patients [17, 18]. Ren, J et al. found that patients with de novo PD had higher plasma levels of α -syn and p-tau181 than healthy controls, and higher plasma p-tau181 concentrations were linked to worse H-Y stages. In a recent longitudinal study from the ADNI and Bio FINDER cohorts, plasma p-tau181 concentrations predicted clinical progression to dementia from MCI.

In our study, we aimed to assess serum levels of p-tau181 in PD patients compared with HC and to explore its relationship with cognitive function, as measured by the Montreal Cognitive Assessment (MoCA).

2. Methods and materials

2.1. Participants

We recruited consecutive PD patients from the Neurology Department of the First Affiliated Hospital of Chongqing Medical University from June 2020 to July 2020. They fulfilled the United Kingdom Parkinson's Disease Society (UKPDS) Brain Bank clinical diagnostic criteria. Controls with no history of PD in the Department of Physical Examination were enrolled at the same time. The following exclusion criteria were applied to both patients and controls: (1) essential tremor, secondary parkinsonism or parkinsonism-plus syndrome; (2) accompanying with tumor, severe infectious diseases, and severe hepatic or renal dysfunction; (3) history of neurological disease: stroke, brain trauma, neurodegenerative diseases, etc.

2.2. Scale assessment

Patients were evaluated using the unified Parkinson's disease rating scale (UPDRS), the modified Parkinson's Disease Rating Scale (Hoehn-Yahr), and the Montreal Cognitive Assessment Scale (MoCA). The total UPDRS score was used to assess the severity of Parkinson's disease. The modified Hoehn-Yahr scale was used to divide Parkinson's patients into early stage ($H-Y \leq 2.5$) and middle stage ($H-Y > 2.5$). MoCA was used to assess the cognitive function of the patients, and according to the results, the patients were divided into PD patients with cognitive impairment (PCI) group ($MoCA < 26$ points) and PD patients with normal cognition of PD (PDN) group ($MoCA \geq 26$ points). Six months after blood sample collection, the H-Y scale and UPDRS score of PD patients were evaluated again by telephone follow-up. Those with increased H-Y scale or UPDRS total score were divided into poor prognosis group, and those with decreased or unchanged H-Y scale or UPDRS total score were divided into good prognosis group. All Parkinson's disease scales were assessed and recorded by two observers, and differences were resolved through discussion.

2.3. Measurement of serum p-tau181 levels

Fasting blood samples of Parkinson's disease group and healthy control group were drawn 4ml blood from the median cubical vein on an empty stomach at 7 a.m., stored and transferred at 4°C. Centrifuge was centrifuged at 2000rpm speed for 20 min in time, supernatant was taken to obtain rapid serum samples, and then frozen at -80°C. We detected serum p-tau181 levels using the commercially available p-tau181 enzyme-linked immunosorbent assay (ELISA) kit (Wuhan, China).

2.4. Statistical analysis

SPSS 26.0 software (IBM, USA) and GraphPad Prism 8.0 (GraphPad Prism software, Inc, USA) were used for data analysis and mapping. The measurement data of normal distribution were expressed as mean \pm standard deviation ($\bar{x} \pm s$), and the independent sample t test was used for comparison between groups. The measurement data of non-normal distribution were expressed as median (interquartile spacing), and the rank sum test was used for comparison between groups. The count data were expressed as constituent ratio (%). The rank sum test was used for the ordered classification variables, and the Chi-square test (χ^2 test) was used for the disordered classification variables. Spearman correlation analysis was used, with correlation coefficient (r value) between 0.5 and 1.0 indicating good correlation. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

We finally recruited 75 patients, including 40 PD patients and 35 HC. Their baseline characteristics were summarized in Table 1. No significant differences in age and sex were found between the two groups ($P = 0.13$, $P = 0.17$, respectively). Serum levels of p-tau181 were not significantly increased in PD patients compared with HC ($1.01 [0.28$ to $2.63]$ vs $0.53 [-0.04$ to $3.72]$ ug/mL, $P = 0.55$, Fig. 1A).

3.2. Association between p-tau181 levels and disease severity

Table 2 displays the baseline characteristics of patients at early and advanced stage of PD. We observed no differences in age and sex within the two groups ($P = 0.42$, $P = 0.90$, respectively), nor in p-tau181 levels ($1.06 [0.14$ to $2.16]$ vs $0.83 [0.31$ to $3.47]$ ug/mL, $P = 0.80$). Furthermore, p-tau181 did not correlate with disease duration ($r = -0.14$, $P = 0.37$, Fig. 1B) and UPDRS III score ($r = -0.02$, $P = 0.89$, Fig. 1C).

3.3. Association between p-tau181 levels and MoCA score

Baseline characteristics of PDN and PCI were concluded in Table 1. There was no significant difference in serum p-tau181 levels between PCI, PDN, and HC ($P = 0.63$, Fig. 1A). Spearman correlation analysis revealed no correlation between serum p-tau181 concentrations and MoCA score ($r = 0.16$, $P = 0.32$, Fig. 1D).

PD, Parkinson's disease; HC, healthy controls; PDN, PD patients with normal cognition; PCI, cognitively impaired PD patients; UPDRS, Unified Parkinson's Disease Rating Scale; H&Y, Hoehn and Yahr Staging Scale; MoCA, Montreal Cognitive Assessment; p-tau181, phosphorylated tau 181; NA, not applicable; P' value for comparison between PDN and

PCI; P^{''} value for comparison between PD and HC Data were presented as mean ± standard deviation, median (interquartile range), or frequency (percentage) as appropriate.

PD, Parkinson's disease; PDE, PD patients in the early stage (Hoehn & Yahr Staging Scale < 2.5); PDA, PD patients

in the advanced stage (Hoehn & Yahr Staging Scale ≥ 2.5); UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment; p-tau181, phosphorylated tau 181; P value for comparison between PDE and PDA.

Table 1. Clinical characteristics of PD patients and healthy controls

| | PD | | | | HC(n=35) | P ^{''} |
|--------------------------|------------------|------------------|------------------|----------------|------------------|-----------------|
| | PD(n=40) | PDN(n=14) | PCI(n=26) | P ['] | | |
| Age (years) | 65.8±8.03 | 60.2±8.3 | 70.7 ± 6.7 | 0.00 | 63.6 ± 10.3 | 0.13 |
| Gender, Male | 22.0(55.0%) | 5.0(35.7%) | 17.0(65.4%) | 0.07 | 13 (37.1%) | 0.17 |
| Disease duration (years) | 3.0(1.0-5.0) | 0.5 (1.0–1.5) | 3.5 (2.0–8.0) | 0.01 | NA | NA |
| UPDRS III | 14.0 (7.3–25.5) | 10.5 (8.5–19.8) | 15.5 (7.0–28.3) | 0.55 | NA | NA |
| H&Y | 2.5(1.5-3.0) | 2.25(1.5-3.0) | 2.5 (1.9–3.3) | 0.47 | NA | NA |
| MoCA | 23.0 (16.5–26.0) | 27.0 (26.0–29.0) | 20.5 (10.8–23.0) | 0.00 | 27.0 (25.0–29.0) | 0.00 |
| p-tau181 (pg/ml) | 1.01(0.28-2.63) | 1.12(0.08-2.11) | 0.87(0.29-7.03) | 0.66 | 0.53(-0.04-3.72) | 0.55 |

Table 2. Clinical characteristics of early and advanced stage PD patients

| | PDE (n = 16) | PDA (n = 24) | P | |
|--------------------------|--------------|-----------------|------------------|------|
| Age (years) | | 65.6 ± 8.0 | 68.0 ± 9.3 | 0.42 |
| Gender, Male | | 9.0 (56.3%) | 13 .0(54.2%) | 0.90 |
| Disease duration (years) | | 2.0 (0.9–5.0) | 3.0 (1.0–5.8) | 0.80 |
| UPDRS III | | 7.0 (5.0–10.8) | 22.5 (15.0–32.0) | 0.00 |
| MoCA | | 24 (19.5–26.0) | 22.5 (13.8–26.8) | 0.61 |
| p-tau181 (pg/ml) | | 1.06(0.14-2.16) | 0.83(0.31-3.47) | 0.80 |

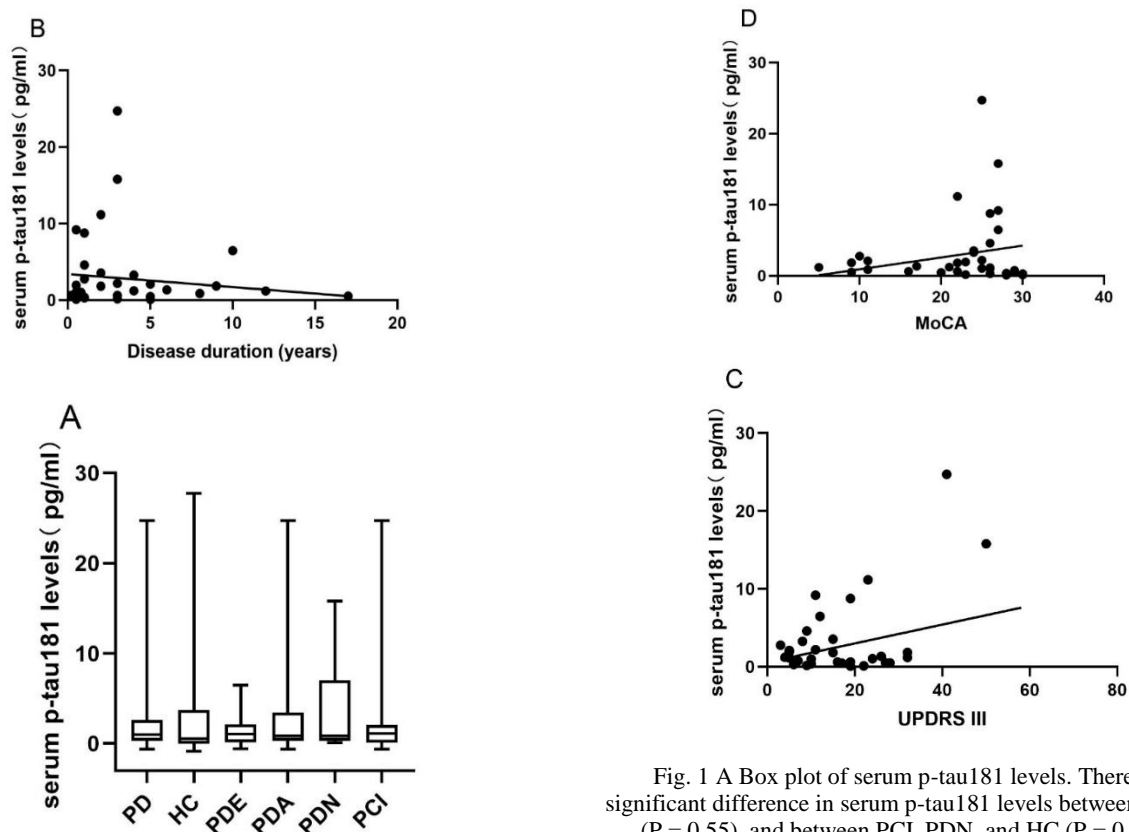


Fig. 1 A Box plot of serum p-tau181 levels. There was no significant difference in serum p-tau181 levels between PD and HC (P = 0.55), and between PCI, PDN, and HC (P = 0.63). B–D Spearman correlation between serum P-tau181 levels and disease duration, UPDRS III score, and MoCA score. Serum p-tau181 levels were not correlated with disease duration (r = -0.14, P = 0.37), UPDRS III score (r = -0.02, P = 0.89), and MoCA score (r = 0.16, P = 0.32). PD, Parkinson's disease; HC, healthy controls; PDE, PD patients in the early stage; PDA, PD patients in the advanced stage; PDN, patients with normal cognition; PCI, cognitively impaired PD patients; UPDRS, Unified Parkinson's Disease Rating Scale; MoCA, Montreal Cognitive Assessment.

3.4. Association between p-tau181 levels and functional prognosis

Six months after blood samples were collected, the UPDRS score and H-Y staging of Parkinson's patients were evaluated again. A total of 39 patients were followed up (one of them dropped out of the follow-up group due to accidental death),

including 25 patients in the good prognosis group and 14 patients in the poor prognosis group. The age ($P=0.81$), gender ($P=0.76$) and course of disease ($P=0.55$) of the good prognosis group and the poor prognosis group were not statistically significant. There was no significant difference in serum P-TAU181 expression between the good prognosis group and the poor prognosis group ($P=0.74$, Table 3).

Table 3. Clinical characteristics of the good and poor prognosis groups

| | good prognosis group (n =25) | poor prognosis group (n = 14) | P |
|--------------------------|------------------------------|-------------------------------|------|
| Age(year) | 65.6 ± 9.0 | 66.2 ± 9.7 | 0.81 |
| Gender, Male | 13(52.0%) | 8(57.1%) | 0.76 |
| Disease duration (years) | 3.0(1.0–4.5) | 3.5(1.0–8.3) | 0.55 |
| p-tau181 (pg/ml) | 0.62(0.13-3.01) | 1.01(0.44-2.45) | 0.74 |

4. Discussion

The main pathological features of Parkinson's disease are dopaminergic neuron necrosis and lewy body formation. Neuroinflammation plays an important role in Parkinson's disease and is also the main trigger of dopaminergic neuron degeneration. α -syn, as the main component of lewy bodies, plays an important role in neuroinflammation of Parkinson's disease. The important progression of its neuroinflammation is to activate microglia cells, which can produce IL-1 β , activate neuron p38 MAPK, and cause tau protein hyperphosphorylation. P38 MAPK phosphorylates tau at Thr181 in vivo. REN et al. found that serum p-tau181 expression in PD patients increased. Therefore, p-tau181 may play a role in the pathogenesis of Parkinson's disease through a specific pathway, and ultimately lead to the death of dopaminergic neurons.

Surprisingly, our study showed that serum concentrations of p-tau181 were elevated in PD patients compared with HC, but not statistically significant. Since Parkinson's disease itself is a progressive disease, the serum p-tau181 concentration may change differently with the progression of the disease due to some mechanism. Therefore, we further studied the serum p-tau181 concentration in the early and middle and advanced groups, and the results showed that there was no significant difference between the early and middle and advanced PD patients. Spearman correlation analysis also showed no correlation between p-tau181 level and disease duration, UPDRS score, and disease severity. In addition, our results were inconsistent with those of Lin et al., who found a significant increase in serum p-tau181 concentration in the PD group compared to the HC group. There are several possible reasons for the inconsistent results from the two studies. Firstly, a large number of studies have shown that oxidative stress and neuroinflammation play an important role in the occurrence and development of PD, and some studies have shown that oxidative stress promotes tau protein phosphorylation [23,24]. However, some studies have shown that oxidative stress can inhibit tau phosphorylation under certain conditions [25,26]. Therefore, the change characteristics of serum p-tau181 in the whole course of Parkinson's disease are unclear, and more studies are needed to study the multi-aspect and long-term trend of p-tau181 in PD. Second, the conflicting results could be attributed to the small number of patients in both cohorts. Finally, Lin and his colleagues used the Immunomagnetic reduction (IMR) method to detect plasma p-tau181 level. However, in our

study, they were detected by ELISA, and the influence of different determination methods on the results should be considered.

Our study also showed that serum p-tau181 level had no statistical difference between cognitively normal PD patients, cognitively impaired PD patients and HC, and was not related to MoCA score. Some previous studies have shown the potential relationship between p-tau181 and cognition [27-29], indicating that the higher the level of p-tau181, the worse the cognitive state. However, other studies have shown that serum p-tau181 has no significant relationship with cognitive function decline [30,31]. More studies are needed to confirm the relationship between serum p-tau181 and cognitive dysfunction in patients with Parkinson's disease.

Our study had several limitations. First, the number of cases in this study is relatively small, and further comparative studies on more PD patients are needed to find the statistical correlation between the level of circulating p-tau181 and PD. Second, this was a cross-sectional study that did not dynamically measure serum p-tau181 concentration in patients, and more longitudinal studies are needed to further clarify this. Third, medication histories and laboratory tests (e.g., complete blood count, blood glucose, coagulation, liver and kidney function, etc.) were incomplete and therefore did not consider their potential impact on p-tau181 levels. In conclusion, this study failed to confirm the relationship between p-tau181 and its distribution characteristics in the blood of patients with Parkinson's disease, and its relationship with cognitive impairment and functional prognosis in Parkinson's disease.

5. Conclusion

We investigated the correlation between serum p-tau181 level and Parkinson's disease. Although serum p-tau181 level was elevated in patients with Parkinson's disease, it was not statistically significant. In addition, we found no significant correlation between serum p-tau181 level and disease severity or cognitive impairment in patients. Serum p-tau181 level had no special significance for the prognosis of the disease. Therefore, it is necessary to conduct multi-center and large sample trials to further explore the correlation between p-tau181 and Parkinson's disease, as well as the specific mechanism of action in the occurrence and development of Parkinson's disease.

Declarations

Ethical approval

Our research was approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

Informed consent

Written informed consent of all participants was obtained.

Conflict of interest

The authors declare no competing interests.

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