**ABSTRACT**

A common acute phase protein, is generated mainly by the physiological homeostasis in nerves. Severe neuropathy that may correlate with the increases in the levels of hs-CRP, IL-1β and IL-6, and early intervention may mitigate the development and progression of peripheral neuropathy.

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**Correlation between the peripheral neuropathy and levels of hs-CRP, IL-1β and IL-6 in senile Parkinson’s disease patients**

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This study was carried out to investigate the correlation between the onset of peripheral neuropathy and levels of hypersensitive C-reactive protein (hs-CRP), interleukin 1β (IL-1β) and IL-6 in senile Parkinson’s disease (PD) patients. For this purpose, a total of 60 PD patients and 60 age-matched healthy subjects were enrolled in this study and received the assessment for peripheral nerves by using the quantified method. Besides, levels of hs-CRP, IL-1β and IL-6 in serum were determined to analyze the correlation between the clinical features, including the severity of PD and cognitive decline, and the levels of hs-CRP, IL-1β and IL-6. Results showed that PD patients had more cases of peripheral neuropathy than those in the healthy control group. Levels of hs-CRP, IL-1β and IL-6 in the serum of PD patients were much higher than those in the healthy control (P<0.05). Besides, PD patients had lower scores of MMSE and MoCA but higher CNPI scores when compared to the healthy control group. As a result, we found that the severity of peripheral neuropathy was in a positive correlation with the levels of hs-CRP, IL-1β and IL-6. It was concluded that PD patients generally have peripheral neuropathy that may correlate with the increases in the levels of hs-CRP, IL-1β and IL-6, and early intervention may mitigate the development and progression of peripheral neuropathy.

**Introduction**

Parkinson’s disease (PD), as a kind of neurodegenerative disease, have the hallmarks of abnormal accumulation of α-synuclein and loss of dopaminergic neurons, leading to a variety of clinical symptoms, including the myotonia, bradykinesia, tremor and postural instability (1-3). Pathogens of PD include autonomous antibodies in the nerve, a reduction in the number of lymphocytes in peripheral blood, a decline in the secretion of immunoglobulin and variations in the cytokines secreted by cells in the brain and peripheral blood (4).

Neuroinflammation is a key process of PD. IL-1β can induce the inflammatory cascade by glutamate excitotoxicity to result in the death of neurons, and the level of IL-1β fluctuates dynamically in the progression of PD (5-7). In addition, IL-1β is involved in levodopa-induced dyskinesia (8,9), leading to the decline in cognitive function and the inhibition of hippocampus-dependent learning ability (10). Interleukin 6 (IL-6) plays a pivotal role in the pathogenesis of inflammatory diseases and in sustaining the physiological homeostasis in nerves. Severe neuropathological changes, including multiple sclerosis (MS), PD and Alzheimer’s disease, are related to the changes in the levels of IL-6 in the brain (11,12). C-reactive protein, as a common acute phase protein, is generated mainly by the liver in inflammation and IL-6-induced responses. Recently, hs-CRP performs much better in determining subclinical inflammation than CRP (13). An increase in the level of hs-CRP is also noted in a variety of neurodegenerative diseases and neurovascular diseases, including PD and age-related macular degeneration (14,15). Though people have gained a sufficient understanding of the role of inflammation in neurodegenerative changes, potential inflammatory pathogenesis and the correlation with PD-specific symptoms remain unknown. Currently, there remains no evidence suggesting that inflammation is commonly shared by all neurodegenerative diseases. In this study, we aimed to investigate the correlation between PD-specific inflammatory markers and clinical symptoms, providing valuable information for elucidating the pathogenesis of PD to improve the diagnosis and prognosis of PD.

**Materials and Methods**

**PD group and control group**

PD group: 60 PD patients who were treated in The First Hospital of Hebei Medical University between March 2021 and September 2022 were enrolled into the PD group as per the following criteria: Patients with the symptoms conforming to diagnostic criteria of PD stipulated by Motor Dysfunction and Parkinson’s disease Group, Neuro-
logy Society of Chinese Medical Academy (16); Patients that were proficient in language and expression and could cooperate with the arrangement of staff; Patients who or whose family were informed of the study and signed the written informed consent.

Control group: 60 healthy subjects were selected randomly from the people who visited the physical examination center of The First Hospital of Hebei Medical University during the same period and enrolled into the control group.

A comparison of the baseline data between the two groups showed no evident difference ($P>0.05$), suggesting that the data were comparable.

Assessment of peripheral nerve injury

At room temperature (25°C), all 120 subjects fulfilled the determination of sensory and motor nerve conduction velocity (SCV, MCV). For those with abnormal measurements, the determination was repeated and the measurement that could reflect better neurological function would be taken. Criteria for assessment of peripheral nerve injury: With a critical value (Critical value = Average of nerve conduction velocity in normal adults – 2.5 × standard deviation), subjects with measurement lower than critical value would be considered as significant asymmetry around the nerve (> 10% of conduction velocity), or latency of F wave > 130% of the upper bound of normal range and extraction rate < 70%, were considered as an anomaly.

Measurement of hs-CRP, IL-1β and IL-6 in serum

In the morning, 3 mL of fasting venous blood was drawn from subjects in two groups and placed in a 100 μL tube supplemented with 2% ethylene diamine tetraacetic acid (EDTA). Tubes were then centrifuged at 3000 r/min for 10 min to obtain the supernatant which was then stored at -80°C for the following determination. Enzyme-linked immunosorbent assay was performed to determine the levels of IL-1β and IL-6, while hs-CRP was measured by turbidimetry.

Evaluation of cognitive function

Cognitive function was evaluated by using the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Chinese version of the neuropsychiatric inventory (CNPI). Patients with higher scores of MMSE and MoCA would be considered to have a better cognitive function, while the cognitive function of those with higher CNPI scores would be poor.

Statistical analysis

SPSS 19.0 software was utilized to perform the statistical analysis. Measurement data were expressed in form of mean ± standard deviation (SD), and t-test would be carried out to determine the difference between two independent samples. Enumeration data were compared by chi-square test, while correlation would be validated by Spearman correlation analysis.

Results

Prevalence of peripheral neurology of patients in two groups

There were 25 patients (41.7%) with peripheral neuropathy in the PD group, significantly more than 13 (21.7%) in the healthy control group ($P<0.05$).

Comparison of the UA, hs-CRP, IL-1β and IL-6 between two groups

UA level of patients in the PD group was much lower than that in the healthy control group ($P<0.01$), while levels of hs-CRP, IL-1β and IL-6 in the serum of patients in PD group were much higher than those in the healthy control group ($P<0.01$, Table 1 and Figure 1).

Comparison of the cognitive function between two groups

In comparison with the healthy control group, patients in the PD group had lower MMSE and MoCA scores but higher CNPI scores ($P<0.05$, Table 2 and Figure 2).

| Table 1. Comparison of the UA, hs-CRP, IL-1β and IL-6 between two groups (mean ± SD). |
|-----------------|---------------|---------------|---------------|---------------|
| Group           | UA (μmol/L)   | IL-1β (pg/ml) | IL-6 (pg/ml)  | hs-CRP (mg/L) |
| PD              | 285.35±82.64  | 7.96±2.82     | 8.16±3.72     | 0.93±0.64     |
| Healthy control | 353.82±76.05  | 6.24±1.85     | 1.20±4.06     | 0.50±0.30     |
| t               | 5.390         | 2.725         | 11.862        | 3.305         |
| P               | 0.000         | 0.031         | 0.000         | 0.006         |

| Table 2. Comparison of the cognitive function between two groups (mean ± SD). |
|-----------------|---------------|---------------|---------------|
| Group           | n             | MMSE score    | MoCA score    | CNPI score    |
| PD              | 60            | 18.35±2.45    | 23.85±3.07    | 19.36±2.46    |
| Healthy control | 60            | 23.56±3.28    | 29.65±2.85    | 15.20±1.85    |
| t               | 6.465         | 6.364         | 7.268         |               |
| P               | 0.000         | 0.000         | 0.000         |               |
Analysis of correlation between peripheral nerve injury and levels of hs-CRP, IL-1β and IL-6 in serum

According to the analysis of the Pearson correlation coefficient, we found that levels of hs-CRP, IL-1β and IL-6 were in negative correlation with the sensory and motor nerve conduction velocity, but in positive correlation with the latency of sensory and motor nerve conduction (all P<0.05; Table 4).

Discussion

Generally, PD patients usually suffer the evident injury of peripheral neurological function, and as the disease progresses, they will be afflicted by sensory or motor dysfunction, including static tremor and postural instability — the more severe the peripheral nerve injury is, the poorer the patients behave in balance. Thus, understanding the correlation between the pathogenesis of peripheral neuropathy and disease-related factors is critical to the prevention and treatment of PD.

IL-1β, as an effective pro-inflammatory cytokine, can target a variety of cells by interacting with the IL-1 receptor, including neurons and microglial cells (17). IL-1 can maintain the lipopolysaccharide-induced inflammatory cycle by upregulating the NF-κB-mediated pro-inflammatory cytokines. Besides, IL-1β is up-regulated in the cerebrospinal fluid (CSF) (18), corpus striatum (19) and SN (20) in PD patients. Genetic studies have shown that the T allele in the regulation area of \(\text{IL-1β}\) in PD patients is up-regulated, increasing IL-1β (21,22). In our study, we infer that the overexpression of IL-1β in patients may result in the increase of susceptibility of dopaminergic neurons to the exogenous toxins, with an increase in the risk of PD development. The data above suggested that IL-1β may have a key role in the development of PD, which, however, has been reported in published studies (23-25). Similarly, we also found that the level of IL-1β in the serum of PD patients elevated significantly as compared to the healthy control group.

IL-6, as an effective factor inducing the acute response...
of the liver (26), is involved in the differentiation of lymphocytes and monocytes and targets the B lymphocyte, T lymphocyte, hepatocyte and hemopoietic progenitor cell (27). In addition, IL-6 is pivotal to the dynamic balance of neurons, and the lack of IL-6 can induce a reduction in the activation of glial cells and alterations in cognitive function in traumatic brain injury (28,29). Other, excessive generation of IL-6 in the brain can also induce nerve degenerative changes (30,31). Likewise, our studies have shown that in the PD group, the IL-6 level in patients was much higher than that of the healthy control group, and, PD patients performed poorly in MMSE and MoCA scores, with a higher score of CNPI.

Hs-CRP is a non-specific marker of low-grade inflammation. Though hs-CRP may have a role in the acute phase of infection or organic injury, hs-CRP level in circulation can reflect ongoing low-grade inflammation (32). Neuroinflammation or stimuli can trigger the generation of peripheral inflammatory proteins and increase cell permeability, and the increased inflammatory proteins in CNS can further augment the level of peripheral inflammatory proteins by passing through the blood-brain barrier (33). In this case, the peripheral concentration of inflammatory protein can display the changes in the neuroinflammation of CNS. Previous literatures have shown that hs-CRP is increased in PD patients (34-36). Consistent with these studies, we also noted the increases in hs-CRP in PD patients when compared to the healthy control group.

This study, however, is limited in the following aspects: small sample size, cross-sectional design, and lack of evaluation for other inflammatory markers (like cytokines). These problems will be addressed in future studies.

Overall, levels of hs-CRP, IL-1β and IL-6 are associated with the development of PD. PD patients usually have higher levels of hs-CRP, IL-1β and IL-6 than the healthy subjects, which may be a cause for the neuroinflammation and neurodegenerative changes in PD. Early intervention can prevent the development and progression of peripheral nerve injuries.

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