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Relationship between levels of inflammatory cytokines in the peripheral blood and the severity of depression and anxiety in patients with Parkinson's disease

X.-M. WANG[1], Y.-G. ZHANG[1], A.-L. LI[2], Z.-H. LONG[3], D. WANG[1], X.-X. LI[1], J.-H. XIA[3], S.-Y. LUO[1], Y.-H. SHAN[1]

[1]Department of Intensive Care Unit, Zhumadian Central Hospital, Zhumadian, Henan Province, China
[2]Department of Neurology, The Second Hospital of Jilin University, Nanguan, Jilin Province, China
[3]Department of Neurology, Zhumadian Central Hospital, Zhumadian, Henan Province, China

Xi-Mei Wang, Yong-Gang Zhang, should be regarded as co-first Authors

Abstract. – OBJECTIVE: The present study aims to investigate the relationship between expression of inflammatory cytokines in the peripheral blood and the severity of depression and anxiety in patients with Parkinson's disease (PD).

PATIENTS AND METHODS: Between January 2012 and December 2015, 62 PD patients admitted to our institution were included in the PD group, and 62 healthy subjects seeking health check-up at our institution during the same period of time were enrolled in the control group. Levels of inflammatory cytokines, including IL-1β, IL-6, interferon-γ (INF-γ), hypersensitive C-reactive protein (hsCRP) and soluble IL-2 receptor (sIL-2R), were measured by using Enzyme-linked immunosorbent assay (ELISA). Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) were used to assess the severity of depression and anxiety, respectively.

RESULTS: A total of 124 subjects were included into PD group and control group, 62 for each. No significant differences were observed in the gender, age, body mass index (BMI), smoking history and alcohol history between two groups ($p > 0.05$). Levels of IL-1β, IL-6, TNF-α, hsCRP and sIL-2R were significantly higher in patients of PD group than those in the control group ($p < 0.05$). HAMD and HAMA scores in PD group were significantly higher than those in the control group [(22.74 ± 6.34), (20.90 ± 5.86) vs. (2.17±3.46), (3.79 ± 3.55), $p < 0.05$]. HAMD and HAMA scores were positively correlated with the levels of TNF-α, hsCRP and sIL-2R in the peripheral blood of PD patients ($p < 0.05$).

CONCLUSIONS: Expression of inflammatory cytokines are elevated in the peripheral blood of PD patients, and the severity of depression and anxiety is correlated with levels of TNF-α, hsCRP and sIL-2R in the peripheral blood of these patients.

Key Words:
Parkinson's disease, Inflammatory cytokines, Depression, Anxiety.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases caused by degeneration of dopaminergic neurons in substantia nigra[1], featured by some major motor symptoms including resting tremor, rigidity, bradykinesia and postural instability[2]. Neuropsychiatric symptoms including depression, anxiety and apathy are common in PD, and other symptoms such as cognitive impairment, dementia and psychosis are frequently seen at a late stage of the disease[3]. The incidence of PD increases with age with an incidence of 0.04% in patients with an age range of 41-49 years and an incidence up to 1.90% in patients of age > 80 years[4]. Dorsey et al[5] reported that the projected number of PD patients over age 50 in Western Europe's five most and the world's ten most populous nations would double by 2030. Although the pathogenesis of PD is still elusive, authors have shown that neuroinflammation and microglia play important roles in PD pathogenesis[6]. Microglia is the first line of defense in the central nervous system (CNS); however, excessive activation of microglia causes over-production of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-2 and interleukin (IL)-4, directly affecting CNS[7]. Some study[8] found that levels of inflammatory cytokines are associated with depression. In addition, an increasing body

Corresponding Author: Shan Yan-Hua, MD; e-mail: kehli342@sina.com

of evidence proved that inflammatory cytokines are involved in the pathophysiology of depression[9]. The present study investigated the relationship between levels of inflammatory cytokines in the peripheral blood of PD patients and the severity of depression and anxiety in these patients, in an effort to provide insight into the clinical management of PD.

Patients and Methods

Patients

Between January 2012 and December 2015, PD patients admitted to our institution were included in the PD group. Patients who were confirmed with idiopathic PD[10] according to the Diagnostic criteria of PD published in 2005 were included in the present study. The exclusion criteria are as follows: (1) Complicated with other neurological diseases. (2) Accompanied by autoimmune diseases. (3) Severe dementia that affects emotional expression. (4) Comorbidities of malignant tumor or severe dysfunction of the liver and the kidney. (5) Patients who were receiving non-steroidal anti-inflammatory drugs or glucocorticoids. In addition, healthy subjects seeking health check-up at our institution during the same period were enrolled in the control group.

Methods

Measurement of inflammatory Cytokines in the Peripheral Blood

Peripheral blood samples were collected from all patients in the morning, centrifuged at 300 rpm for 5 min and stored at 4°C. Enzyme-linked immunosorbent assay (ELISA) was used to measure the levels of inflammatory cytokines, including IL-1β, IL-6, interferon-γ (INF-γ), hypersensitive C-reactive protein (hsCRP) and soluble IL-2 receptor (sIL-2R).

Assessment of Depression and Anxiety

Hamilton Depression Scale (HAMD) and Hamilton Anxiety Scale (HAMA) were used to assess the severity of depression and anxiety, respectively. HAMD contains 17 items yielding a maximum score of 52, with higher scores indicating greater depressive symptom severity. HAMA consists of 14 items. Each item is scored on a scale of 0-4 (0 = not present, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe), with a total score range of 0-56 and higher scores suggesting a greater severity of anxiety.

Statistical Analysis

All data were input into a database with Epidata3.1 software. The statistical analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Qualitative data were expressed as number of cases as well as proportions and analyzed using the χ^2 test. Quantitative data were expressed as mean ± SD. Differences between groups were analyzed using independent sample *t*-test. $p < 0.05$ was considered statistically significant.

Results

Characteristics of subjects

A total of 124 subjects were included into PD group and control group, 62 for each. Thirty-eight male patients were included in the PD group and 36 in the control group. No significant differences were observed in the gender, age, body mass index (BMI), smoking history and alcohol history between two groups ($p > 0.05$) (Table I).

Levels of Inflammatory Cytokines in the Peripheral Blood

As presented in Table II, levels of IL-1β, IL-6, TNF-α, hsCRP and sIL-2R were significantly higher in patients of the PD group than those in the control group ($p < 0.05$). However, no significant difference was observed in the level of INF-γ between groups ($p > 0.05$).

HAMD and HAMA Scores

HAMD and HAMA scores in PD group were significantly higher than those in control group [(22.74 ± 6.34), (20.90 ± 5.86) *vs.* (2.17 ± 3.46), (3.79 ± 3.55), $t = 22.425$ $p = 0.000$; $t = 19.664$ $p = 0.000$].

Relationship of Inflammatory Cytokines Levels with HAMD and HAMA Scores

In PD group, HAMD and HAMA scores were positively correlated with the levels of TNF-α, hsCRP and sIL-2R in the peripheral blood of PD patients ($p < 0.05$) (Table III). With the increase in the levels of TNF-α, hsCRP and sIL-2R, HAMD and HAMA scores rose, indicating the aggravation of depression and anxiety. However, HAMD and HAMA scores were not associated

Table I. Characteristics of patients and controls.

Group	Gender (M/F)	Age (years)	BMI (kg/m^2)	Smoking history (yes)	Alcohol history (yes)
PD group (n=62)	38/24	65.02±7.21	21.92±2.01	33	22
Control group (n=62)	36/26	64.61±7.51	22.04±1.98	35	26
t/χ^2	0.134	0.310	-0.335	0.130	0.544
p	0.714	0.757	0.738	0.718	0.461

Table II. Levels of inflammatory cytokines in the peripheral blood.

Group	IL-1 (pg /ml)	IL-6 (pg /ml)	TNF- (pg /ml)	INF- (pg /ml)	hsCRP (mg /L)	sIL-2R (pg /ml)
PD group (n=62)	220.3±68.2	20.2±7.2	342.6±100.3	32.2±14.2	4.5±1.3	280.3±129.2
Control group (n=62)	24.3±15.2	2.2±1.8	180.4±80.8	30.4±16.7	1.8±0.9	150.2±98.2
t/χ^2	22.087	19.097	9.916	0.647	13.446	6.312
p	0.000	0.000	0.000	0.519	0.000	0.000

with levels of IL-1β, IL-6 and INF-γ ($p > 0.05$) (Table III).

Discussion

Inflammatory cytokines play important roles in the neurodegenerative diseases[11]. The present study showed that levels of IL-1β, IL-6, TNF-α, hsCRP and sIL-2R in PD patients were higher than those in healthy controls, indicating aberrant expression of inflammatory cytokines in the peripheral blood of PD patients. In agreement with these results, Cai et al[12] reported that levels of TNF-α, IL-1β, IL-2 and IL-10 were higher in PD patients (n=230) than those in controls (n=93). Moreover, some authors[13] found that levels of IL-1β and TNF-α are increased in a rat model of PD, and they can enhance the neuronal toxicity of dopaminergic neurotoxin. Inflammatory cytokines can influence neuronal apoptosis through various pathways, and the injury is achieved through a negative feedback regulation. For example, inflammatory cytokines can enhance the toxic effect on neurons by activating microglia, and neuronal injury can, in turn, promote the release of inflammatory cytokines, thereby enhancing damage to the nervous system[14]. It has been reported that inflammatory cytokines induced in a different part of the brain can migrate to the peripheral blood through the blood-brain-barrier, thereby leading to elevated levels of these cytokines in the peripheral blood of PD patients[15]. Fewer studies have been reported on the impact of sIL-2R in PD. sIL-2R, mainly derived from proteolytic cleavage of membrane bound IL-2R in T cell membrane, is a major inflammatory factor playing a key role in the regulation of immune response. sIL-2R, by binging cell membrane, can participate in mitosis through either paracrine or autocrine pathway[16].

Table III. Correlation of inflammatory cytokines levels with HAMD and HAMA scores.

Cytokines	HAMD r	HAMD p	HAMA r	HAMA p
IL-1β	0.151	0.241	0.112	0.386
IL-6	0.223	0.081	0.194	0.131
TNF-α	0.345	0.006	0.386	0.002
INF-γ	0.028	0.829	-0.032	0.805
hsCRP	0.393	0.002	0.423	0.001
sIL-2R	0.452	0.000	0.364	0.004

Depression and anxiety are two most common psychiatric symptoms in PD patients[17]. The present study revealed that severity of depression and anxiety was positively correlated with levels of TNF-α, hsCRP and sIL-2R in the peripheral blood of PD patients. Lindqvist et al[18] showed that CRP level is associated with severity of depression in PD patients ($p = 0.010$), which is consistent with the finding of the present study. In addition, some other study[19] suggested that high expression of sIL-2R and TNF-α is correlated with the severity of depression and anxiety, and sIL-2 level can predict Hospital Anxiety and Depression (HAD) scores after the effects of age,

gender, anti-PD medications and severity of motor symptoms are controlled for. Menza et al[20] demonstrated that TNF-α is correlated with cognition, disability and depression, being consistent with the results of the present study as well. However, underlying mechanisms were not mentioned in the above studies.

Conclusions

Therefore, by far, the mechanisms by which inflammatory cytokines affect depression or anxiety are not clear. We demonstrated correlations between levels of TNF-α, hsCRP as well as sIL-2R in the peripheral blood and the severity of anxiety and depression in PD patients, but the underlying mechanism needs to be further studied.

In brief, levels of inflammatory cytokines are increased in the peripheral blood of PD patients, and the severity of depression and anxiety is correlated with levels of TNF-α, hsCRP as well as sIL-2R in the peripheral blood.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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