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Increased serum levels of TNF-α and decreased serum levels of IL-27 in patients with Parkinson disease and their correlation with disease severity

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ABSTRACT

Objectives: : Immunological basis of neurodegenerative diseases including Alzheimer and Parkinson disease (PD) has some important roles in their pathogenesis. There are conflicting studies to serum level of TNF-α in PD. Also, according to our finding there is no report evaluating serum level of IL-27 in PD. This study correlates the serum level of those factors with severity of PD.

Patients and methods: : In this case-control study, 83 patients with PD and 83 healthy volunteers were enrolled. The diagnosis was fulfilled in accordance with clinical diagnostic criteria of the UK Parkinson's Disease Society Brain Bank by two neurologists. The modified Hoehn and Yahr (H and Y) scale was used to evaluate the severity of PD. Serum levels of TNF-α and IL-27 were measured by Elisa. Correlation of H and Y scale with serum levels of these cytokines was evaluated.

Results: : The serum levels of TNF-α were increased and serum levels of IL-27 were decreased in patients with PD compared to those in healthy subjects ($P < 0.0001$). There was a significant correlation between serum levels of TNF-α and IL-27 with H and Y scale.

Conclusion: : Our study showed that the serum levels of TNF-α and IL-27 may be important prognostic biomarkers of PD.

1. Introduction

Parkinson Disease (PD) is the second most common progressive neurodegenerative disease with different clinical symptoms such as bradykinesia, hypokinesia, tremor, cognitive dysfunction and depression. Etiology of PD is unknown, but it is clear that impairment in dopaminergic neurons of the substantia nigra is the main factor (1–3). Recently, some scientists have pointed to IL-1β (4), IL-6 (5), IL-10 (6) as possible immunological factors in pathogenesis and mortality risk of the disease.

IL-27, a cytokine with inflammatory and anti-inflammatory effects, is a member of IL-12 family. Binding to its receptor composed of glycoprotein 130 receptor and IL-27 *receptor* α chain (IL-27Rα) (7–9) on monocytes/macrophages, mast cells, and natural killer cells (10), IL-27 inhibits the production of tumor necrosis factor-α (TNF-α) (11); and in this way it induces its anti-inflammatory effects. IL-27 has an essential role in induction of Th1 differentiation and phosphorylation of STAT1 and STAT3 in $CD4^+$ T cells (12,13). The phosphorylation of STAT3 plays a pivotal role in the inhibition of inflammatory cytokines (14). Many studies have shown that IL-27 plays an important role in the pathogenesis of some inflammatory diseases such as hepatitis B (15), hepatitis C (16) and psoriasis (17). In a study, low serum level of this cytokine was observed in patients with multiple sclerosis (18).

TNF-α, an pro-inflammatory cytokine produced by macrophages, lymphoid cells and neurons (19), binds to its receptors, TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2) (20) and activates the transcription factors of nuclear factor kappa-B (NF-κB) and c-jun N-terminal kinase (JNK). Such signaling pathways lead to inflammation as well as

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Table 1
Basic and clinical characteristic of patients with PD and health subjects.

	PD patients	Healthy subjects	P. value
Number of subjects	83	83	–
Male/female	52/31	38/45	0.029
Age (years)(Mean ± S.D)	65.73 ± 11.20	64.20 ± 12.61	0.5
Disease duration (years)	4.94 ± 3.92		
Treatment duration (years)	3.79 ± 3.55		
H and Y scale (Mean ± S.D)	2/24 ± 0/73		
TNF-α serum levels(pg/ml)	6 ± 3.32	3.22 ± 2.47	0.0001
IL-27 serum levels(pg/ml)	2.79 ± 1.55	4 ± 2.54	0.0001

cell apoptosis (21–23). Many studies have revealed the pathogenic role of TNF-α in inflammatory diseases such as psoriasis (24), prostate cancer (25), rheumatoid arthritis (RA) (26) and multiple sclerosis (MS) (27). Several studies have recently been published dissecting the role of TNF-α in pathogenesis of PD. So that, increased (28,29) and no changes (30) of TNF-α serum level has been reported in PD. However, there has been a direct relationship between serum level of such cytokine with some clinical symptoms of PD including anxiety, depression, fatigue (30) and non-motor symptoms (31).

Serum level of TNF-α has shown some contradictions in previous studies on patients with PD. In addition, according to our knowledge, there are no studies evaluating the serum levels of IL-27 in such patients. The other matter is that changes in serum levels of TNF-α and IL-27 may have close relationship with severity of the disease. Considering such concepts, we aimed to correlate serum levels of TNF-α and IL-27 to PD severity. Such evaluation may suggest their prognostic value and also may render some therapeutic clues.

2. Material and methods

2.1. Study subjects

In our case-control study, 83 patients with PD and 83 healthy volunteers were enrolled. The diagnosis of PD was fulfilled in accordance with clinical diagnostic criteria of the UK Parkinson Disease Society Brain Bank by two neurologists (32). All patients were treated with L-dopa. The exclusion criteria were any other chronic inflammatory/autoimmune diseases. The severity of the disease was assessed by modified Hoehn and Yahr staging (H and Y). Our study was approved by the local Ethics Committee and informed consent was obtained from all participants.

2.2. Blood sample

Peripheral venous blood samples were collected from the patients

Table 2
Values of TNF-α and IL-27 according to different varieties in patients with PD.

Variables		TNF-α (pg/ml)	P. value	IL-27 (pg/ml)	P. value
H and Y	Mild	4.65 ± 1.68	0.0001	2.1 ± 0.71	0.0001
	Moderate	7.65 ± 4.07		3.58 ± 1.79	
	Severe	11.43		6.87	
Sex	Male	5.54 ± 3.08	0.1	2.6 ± 1.38	0.24
	Female	6.77 ± 3.6		3.15 ± 1.8	
Age	< 60	6.51 ± 4.29	0.36	2.7 ± 1.62	0.77
	≥60	5.78 ± 2.82		2.84 ± 1.54	
Disease duration (years)	0-6	5.63 ± 2.94	0.05	2.41 ± 1.23	0.032
	7-12	6.25 ± 3.18		3.43 ± 2.02	
	13-18	9.36 ± 6.22		4.07 ± 1.56	
Treatment duration (years)	0-6	5.63 ± 2.98	0.13	2.47 ± 1.24	0.56
	7-12	7.2 ± 3.84		3.57 ± 2.07	
	13-18	8.42 ± 8.31		3.94 ± 1.79	

Table 3
Correlation between serum levels of TNF-α and IL-27 with different parameters in patients with PD.

	TNF-α		IL-27	
	Correlation coefficient	P. value	Correlation coefficient	P. value
Age	−0.094	0.399	−0.004	0.976
Sex	0.18	0. 1	0.169	0.241
H and Y scale	0.674	0.0001	0.782	0.0001
Disease duration	0.321	0.003	0.442	0.001
Treatment duration	0.318	0.003	0.427	0.002

Table 4
Linear multiple regression analysis evaluating the effect of different variables on the serum levels of TNF-α and IL-27 in patients with PD.

	Variables	Coefficients		T	Sig. P	Adjusted R Square
		B	Std. error			
TNF-α	H and Y scale	3.262	0.365	8.941	0.0001	0.504
	Sex	−0.834	0.534	−1.563	0.122	
	Age	−0.071	0.024	−3.008	0.004	
IL-27	H and Y scale	1.595	0.19	8.409	0.0001	0.593
	Sex	0.036	0.304	0.117	0.908	
	Age	−013	0.15	−0.847	0.401	

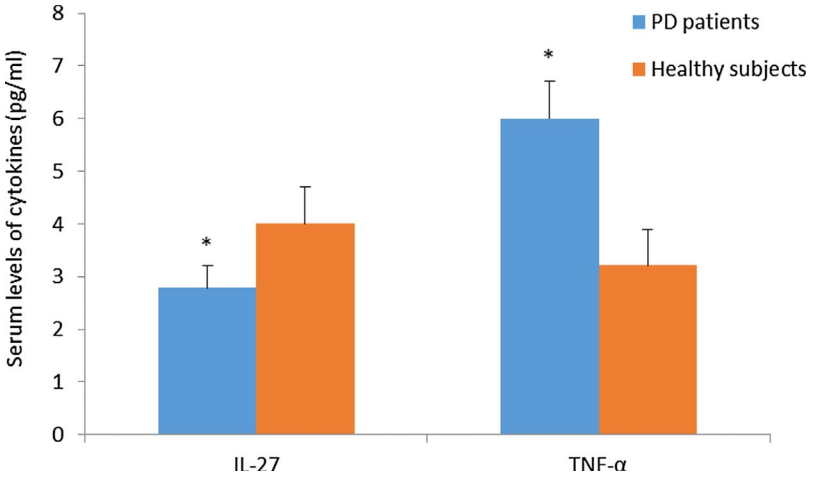

Fig. 1. Mean and 95% confidence interval of serum levels of IL-27 (pg/ml) and TNF-α (pg/ml) in patients with PD and healthy subjects. * represents P < 0.0001; vs. values in the healthy subjects.

and healthy controls. Blood samples were allowed to be clotted and then centrifuged (Hettich D-78532, Tuttlingen, Germany) at 3500 rpm for 10 min and the serum was separated. Then, stored frozen at −80 °C. Serum levels of TNF-α and IL-27 were measured by commercially available enzyme-linked immune sorbent assay (ELISA) kit (My Biosource, USA) (33).

2.3. Statistical analysis

The serum level of TNF-α and IL-27 were analyzed by independent t and chi-square tests. Correlations between variables were calculated by Pearson's correlation coefficient, and simultaneous effects of various factors on these cytokines were analyzed by multiple linear regressions with backward method. Adjusted R Squared was determined as a criterion of goodness-of-fit test, and $P < 0.2$ was considered for exclusion from the model. $P < 0.05$ was considered statistically significant.

3. Results

The clinical characteristics and laboratory findings of the patients and controls are summarized in Table 1. The mean serum levels of TNF-α in patients with PD were significantly higher than those in healthy subjects ($P < 0.0001$). However, serum levels of IL-27 in patients with PD were significantly lower than those in healthy subjects ($P < 0.0001$) (Fig. 1).

Different values of TNF-α and IL-27 serum levels according to different variables are shown in Table 2. Serum levels of TNF-α and IL-27 were significantly higher in severe forms of PD than those in mild and moderate forms ($P < 0.0001$) (Table 2). They were also significantly higher in patients suffering longer times from the disease than those suffering shorter times ($P \leq 0.05$) (Table 2).

The correlation between the serum levels of TNF-α and IL-27 with different parameters are shown in Table 3. There were significant correlations between the serum levels of both TNF-α and IL-27 with disease duration, treatment duration and severity of PD according to H and Y scale (Table 3).

Linear multiple regression analysis showed that increase in TNF-α serum levels is positively associated with severity of PD and age ($P \leq 0.004$). In addition, the serum levels of IL-27 were found to be associated with severity of PD ($P < 0.0001$) (Table 4).

4. Discussion

Considering the severity of the PD, we demonstrated a close correlation between serum levels of TNF-α and PD severity in line (30,31,34) and against (29) with other studies. Comoglu et al. found no correlation between levels of TNF-α and severity of motor and non-motor symptoms in PD patients according to mini-mental scale examination (MMSE), H and Y, and unified Parkinson's disease rating scale (UPDRS) criteria (35).

Confirming (28,31,34,35) and in contrast (29,30) to others, we reported an increased serum levels of TNF-α in PD. TNF-α has been shown to be related to the pathogenesis of other neurodegenerative diseases such as Alzheimer disease (36) and Multiple sclerosis (27). Actually, the neuronal death occurred in dopaminergic neurons through apoptosis (37) is induced by TNF-α in PD (22,38). Enhancing the inflammation, TNF-α may also play some roles in induction of IL-8 through histone acetylation and activation of NF-κB signaling pathway (23).

We believe that our study is the first report on serum level of IL-27 in patients with PD. In recent studies, conflicting results from the point of serum levels of IL-27 in different autoimmune diseases have been reported. Increased serum level of IL-27 has been reported in patients with systemic sclerosis (39) and rheumatoid arthritis (40) and its reduced serum level has been reported in systemic lupus erythematous (SLE) (41,42). In the latter study, there was no correlation between serum levels of IL-27 with disease severity (42). Babaloo et al. reported lower serum levels of IL-27 in the neurodegenerative disease of MS (43). Mechanistically, IL-27 regulates secretion of IL-10 as an anti-inflammatory cytokine (44), and in this way it may have an important role in control of inflammation in PD. Moreover, IL-27 induces inhibitory effects on T helper 17 (Th17) cells. Such effect may introduce IL-27 as a therapeutic target for autoimmune/inflammatory states (45,46) such as PD. A previous study showed that lower expression of IL-27 associated with an increased Th17 response leads to an autoimmune response in Vogt-Koyanagi-Harada disease (47). Therefore, reduction of serum levels of IL-27 in our study may contribute to increased inflammatory action of Th17 and autoimmune responses which may be related to pathogenesis of PD. Our findings showed a close relationship between serum levels of IL-27 with severity of PD. Although serum level of IL-27 in patients with PD is totally lower than that in healthy subjects, it is likely that more production of IL-27 in more severe forms of PD is a compensatory mechanism that tries to resolve the malicious inflammatory condition of the disease during the time.

Our study had some limitations. We did not assess gene expression levels of TNF-α and IL-27 in PD. In addition, we did not evaluate the molecular mechanisms of the function of such cytokines in PD.

Overall, our finding showed that serum levels of TNF-α increase and IL-27 reduce in patients with PD. Also, there was close correlation between disease severities of PD with changes in serum levels of TNF-α and IL-27. Such cytokines may be important prognostic biomarkers of PD.

Declaration of interest

The authors declare no conflict of interest.

Author contributions

O-RT and HN contributed in the conception or design of the work, analysis and drafting of the manuscript. EK, RD-K, O-RT, ED, MB and HA. contributed in conception and manuscript drafting.

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