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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	

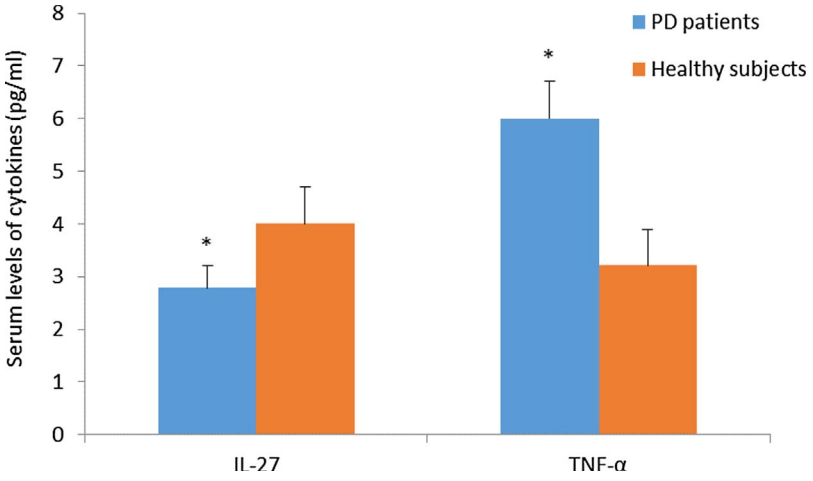

Fig. 1. Mean and 95% confidence interval of serum levels of IL-27 (pg/ml) and TNF-α (pg/ml) in patients with PD and healthy subjects. * represents P < 0.0001; vs. values in the healthy subjects.