EXPERIMENTAL METHODS FOR CLINICAL PRACTICE

Impaired Production of Plasma Interleukin-6 in Patients with Parkinson's Disease

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 133, No. 1, pp. 94-97, January, 2002
Original article submitted September 17, 2001

The contents of interleukin-6 in the plasma from patients with Parkinson's disease and endogenous depression were compared by enzyme immunoassay. Interleukin-6 content in the plasma increased in the early stage of idiopathic parkinsonism complicated by depressive syndrome. A correlation was found between interleukin-6 content and changes in higher mental activity estimated by neuropsychological tests.

Key Words: *Parkinson's disease; interleukin-6; depressive syndrome; frontal lobes*

An important aspect in the studies of Parkinson's disease (PD), or idiopathic parkinsonism, is evaluation of the type of progression of this pathology. Recent observations revealed independent factors that affect the mortality rate and progression of this disease. These factors include the severity of initial extrapyramidal symptoms, dementia, and duration of treatment with L-DOPA derivatives [4,14]. Clinical and experimental observations indicate that depression plays an important role in clinical manifestations and course of parkinsonism [1,6].

Autoimmune disorders play a role in the pathogenesis of PD [13]. In patients with PD, considerable amounts of reactive HLA-DR microglia are found in the zone of pronounced neurodegeneration in the substantia nigra. The role of impaired production of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), in the pathogenesis of PD is poorly understood. Previous studies suggest that these substances can be involved in cascade reactions that cause death (in particular, apoptosis) of nerve cells in the substantia nigra [8,12]. The concentration of proinflammatory IL-6 increases in the striatum and liquor during the early stages of PD, which correlates with the severity of this disease [7]. In patients with PD, plasma concentrations of IL-6 and TNF-α increase to a level observed in 10 years older humans [8]. Plasma IL-1β and IL-6 contents increase in patients with dysthymia and major depression [2,5]. IL-6 is involved in the synthesis of acute-phase proteins, differentiation, and proliferation and enhances the survival of catecholaminergic and cholinergic neurons. Recent studies showed that cholinergic neurons in the frontal lobe can serve as the target for IL-6 [11].

Here we compared plasma levels of IL-6 in patients with PD with different clinical manifestations and duration of the disease.

MATERIALS AND METHODS

Clinical and biochemical tests were performed on 45 patients with PD (25 women and 20 men, 48-75 years). Plasma IL-6 concentration was measured by enzyme immunoassay using commercial DRG kits. Sex- and age-matched patients with endogenous depression (n= 23) comprised a reference group. The control group included 15 healthy individuals of comparable age, sex, and body weights.

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0007-4888/02/1331-0081$27.00

The diagnosis of PD was made by international clinical criteria. The degree of neurological deficiency was estimated by the Unified Parkinson's Disease Rating Scale (UPDRS). Cognitive functions were studied by the Mini-Mental State Examination (MMSE) and method of Luriya [3]. The Tower of London test was used to evaluate planning deficiency in patients with damaged frontal lobes. In the Tower of London planning test, we estimated the total time of performance, latency (total time spent for decision of each of 12 tasks), and number of errors. The diagnosis of depressive syndrome (DS) was made by DSM-IV criteria and Beck Depression Inventory. Anxiety was measured by the Spielberg State-Trait Anxiety Inventory. Patients with endogenous depression were examined at the Psychosomatic Department (N. I. Pirogov Moscow Hospital No. 1). The results were analyzed by medical statistical tests.

We used the criteria of definite, probable, and possible diagnoses of PD [9]. The diagnoses of probable and possible PD were made in 30 and 15 patients, respectively.

RESULTS

The mean plasma concentration of IL-6 in patients with PD did not differ from the control (8.71±2.78 pg/ml). Plasma IL-6 content in 18 patients with PD complicated by DS (more than 18 points by Beck Depression Inventory) significantly differed from that in 27 patients with uncomplicated disease (less than 18 points by Beck Depression Inventory, respectively, Table 1). These patients differed in the degree of affective and mnestic disorders (Beck Depression Inventory, UPDRS-1, $p<0.05$). Patients with severe affective disorders and high IL-6 content in the plasma were characterized by marked disturbances in higher mental activity, which was manifested in the impaired performance of tasks, increased impulsiveness, considerable number of errors ($p<0.01$), and long latency period in the Tower of London test ($p<0.01$).

Plasma IL-6 content most significantly increased in patients with PD complicated by severe DP (more than 28 points by the Beck Depression Inventory) and surpassed not only that in controls, but also in patients with parkinsonism not complicated by DS. IL-6 content in these patients was comparable with that in patients with depression not accompanied by parkinsonism (Table 2).

TABLE 1. Clinical Characteristics of Patients with PD Accompanied by Depressive Disorders of Different Severity ($M\pm m$)

Parameter	PD without DS (n=27)	PD with DS (n=18)
Age, years	69.70±8.93	65.89±8.28
Beck Depression Inventory, points	11.52±3.54	29.11±11.32*
MMSE, points	28.3±1.3	27.13±1.99
L-dopa dose, mg	429.7±225.2	578.1±305.7
UPDRS, points including:	42.7±17.1	58.0±23.5
part I	2.88±1.65	6.50±3.45*
parts II and III	40.16±18.27	51.41±22.24
IL-6, pg/ml	7.59±0.56	9.5±2.9*

Note. *$p<0.01$ compared to PD without DS.

A comparative study of plasma IL-6 concentrations in healthy donors and patients with PD and endogenous depression revealed a correlation between cytokine content and severity of depressive disorders.

A direct correlation was found between the increase in plasma IL-6 concentration in patients with PD (n=26, period before the decrease in L-DOPA efficiency) and severity of DS (Beck Depression Inventory; r=0.64, t=4.42, $p<0.001$) or reactive anxiety (Spielberg State-Trait Anxiety Inventory; r= 0.65, t=4.81, $p<0.001$). Changes in IL-6 content correlated with disturbances in higher mental activity, including performance of the frontal fist-finger test (r=0.6, t=4.15, $p<0.01$; n=16), capacity of short-term memory (r= 0.75, t=6.38, $p<0.01$; n=14), dynamic praxis (r=0.59, t=4.09, $p<0.01$; n=16), and impulsiveness in the Tower of London test (r=-0.42, $p<0.05$; n=26). These data indicate that IL-6 content increases in patients with pronounced mental disorders associated with extensive

TABLE 2. Plasma IL-6 Contents in Healthy Donors and Patients with PD and Endogenous Depression ($M\pm m$)

Parameter	Control (n=15)	Endogenous depression (n=23)	PD without DS (n=27)	PD with severe DS (n=5)
Age, years	62.45±8.60	58.70±8.54	69.70±8.93	69.80±7.98
Beck Depression Inventory, points	7.28±3.14	37.20±7.24^{+}	11.52±3.50	46.50±9.98*$^{++}$
IL-6, pg/ml	7.87±0.65	11.19±5.57^{++}	7.59±0.50	11.68±4.93*$^{+++}$

Note. *$p<0.001$ compared to PD without DS; $^{+}p<0.001$, $^{++}p<0.01$, and $^{+++}p<0.02$ compared to the control.

TABLE 3. Dependence of Changes in IL-6 Production on the Rate of PD Progression in Untreated Patients (1-3 Years, *M*±*m*)

Parameter	Group 1 (*n*=10)	Group 2 (*n*=8)
History of PD, years	2.12±1.12	2.20±1.03
UPDRS, points	43.85±8.61	30.70±9.73**
Beck Depression Inventory, points	17.7±4.9	11.97±5.15**
MMSE, points	28.10±1.83	28.12±1.96
IL-6, pg/ml	8.62±0.87	7.34±0.54*+

Note. *p<0.01 and **p<0.05 compared to group 1; +p<0.05 compared to the control (7.87±0.65 pg/ml).

involvement of the frontal lobes, their relationships and, probably, the limbic system.

The dependence of changes in IL-6 production on the rate of PD progression in untreated patients (1-3 years) was studied to reveal the relationship between clinical manifestations of the disease and plasma cytokine content. The limit points characterizing motor deficiency in patients suffering from PD for more than 1, 2, and 3 years were 30, 40, and 45 points, respectively (UPDRS). Group 1 patients with rapidly progressing disease had high UPDRS points (more than 30, 40, and 45 points after 1, 2, and 3 years, respectively, *n*=10). Group 2 included 8 patients with slowly progressing progredient disease.

Plasma IL-6 content in patients with rapidly progressing disease was higher compared not only to the control, but also to patients with slowly progressing disease (even at the same duration of PD, Table 3).

Recent functional studies by positron emission topography revealed deceleration of metabolic processes in various zones of the orbitofrontal cortex, medial areas of the prefrontal cortex, and cingulate gyrus in patients with endogenous depression and PD complicated by DS (compared to patients with PD not complicated by DS) [15]. These data suggest that endogenous depression and DS in patients with PD have the common biological substrate [6]. However, immunological assays showed that DS in patients with PD is associated with immunological hyperreactivity and accompanied by the increase in activated T cell count and intensive secretion of C-reactive protein, prostaglandin E_2, IL-1β, and IL-6 by mitogen-stimulated T cells [5].

The increase in plasma IL-6 content in some patients with PD reflects systemic immune hyperreactivity and probably contributes to the development of higher mental disorders. During progression of PD these disturbances do not depend on motor disorders and are probably realized via the impairment of sympathetic and cortical neurons in medial areas of the limbic system and frontal lobes and hyperactivity of the hypothalamic-pituitary-adrenal system [4,13]. Autoimmune disorders initially play a regulatory role, but then impair systemic and local homeostasis, which probably affects PD progression [5]. The role of cytokines in clinical manifestations of PD requires further investigations. Published data show that the impairment of neuroimmune interactions mediated by IL-6 plays an important role in the clinical course of PD. Serotoninergic preparations do not attenuate the symptoms of disturbances in the cytokine status in patients with depressive disorders. At the same time, selegilin and midantan possess immunomodulatory and antidepressive properties [10]. Studies of the cytokine status would allow us to develop new approaches to immunomodulatory therapy of PD.

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