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Cytokines in the Pathogenetic Development of Parkinson's Disease

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Abstract This study investigates the role of pro-inflammatory and anti-inflammatory cytokines in the pathogenesis and progression of different clinical subtypes of Parkinson's disease (PD). A total of 160 PD patients were examined, with subgrouping based on clinical phenotype (tremor-dominant and akinetic-rigid-dominant forms), disease stage, and duration. Levels of cytokines including IL-1β, IL-6, IL-10, IL-1RA, and TNF-α were measured in serum and cerebrospinal fluid (CSF). Results revealed elevated IL-1β and IL-6 levels and decreased IL-1RA in PD patients compared to controls, indicating a shift towards a pro-inflammatory state. These changes were particularly significant in patients with advanced stages and in the akinetic-rigid subtype. A correlation was also found between cytokine levels and various clinical features, including non-motor symptoms, depression, and disease lateralization. The findings support the involvement of chronic neuroinflammation in PD pathogenesis and highlight cytokine profiling as a potential biomarker for differentiating PD subtypes and monitoring disease progression.

Keywords Parkinson's disease, Cytokines, IL-1β, IL-6, IL-10, IL-1RA, TNF-α, Neuroinflammation, Disease subtypes, Cerebrospinal fluid, Disease progression, Non-motor symptoms

1. Introduction

Parkinson's Disease (PD) is a chronic, progressive neurodegenerative disorder primarily characterized by dopaminergic degeneration of the substantia nigra. Its clinical manifestations include hypokinesia, muscle rigidity, tremors, postural instability, as well as various non-motor symptoms [9].

The clinical picture of the disease is diverse, typically presenting in combinations of the following symptom types: akinetic-rigid, tremor-dominant, and mixed forms, with differences in progression rate and a range of motor and non-motor features. Lateralization of symptoms is also a distinctive characteristic.

Due to the clinical heterogeneity of PD, there are both general pathophysiological mechanisms common to the disease and unique pathogenic chains associated with specific clinical variants. Beyond phenotypic differences, biochemical identification of clinical forms of PD holds significant fundamental and practical importance, serving as a basis for targeted symptomatic therapy.

Recent studies on the pathogenesis of PD have paid special attention to the immunological mechanisms involved in disease progression [1], particularly the role of pro-inflammatory and anti-inflammatory cytokines in the neurodegeneration process [2].

The akinetic-rigid and tremor-dominant forms of PD differ in terms of epidemiology, pathomorphology, and pathophysiology. Some researchers even propose that these described clinical forms may represent independent nosological variants of primary parkinsonism [3].

During the progression and treatment of PD, gradual changes in the clinical picture are observed, with the emergence of new symptoms and the intensification of existing ones. These include iatrogenic and neurogenic symptoms that often do not respond well to therapy and exert a growing impact on patients, leading to a complex clinical picture. This complexity necessitates adjustments to treatment algorithms based on the form and course of the disease [4].

Although cytokine profiles in PD have been studied, most research is limited by the duration of observation, the number of clinical studies on the topic, and varying concentration data. There are conflicting and scattered findings regarding cytokine levels in blood and cerebrospinal fluid. For instance, Stypula et al. (1996) reported significantly elevated levels of interleukin (IL)-1β, IL-2, and IL-6 in the blood of PD patients [5].

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However, many studies do not consider the impact of the medications patients are taking. In recent years, researchers have focused not only on the changes in cytokine levels but also on their association with the clinical manifestations of PD [6]. For example, Lindqvist D. et al. found that elevated levels of IL-6 and tumor necrosis factor-alpha (TNF-α) in PD patients were positively correlated with certain non-motor symptoms [7].

Despite these findings, the full interrelation of cytokine profile markers with the phenotypic heterogeneity and pathomorphosis of PD remains unclear. Questions remain regarding cytokine levels in blood and cerebrospinal fluid in relation to disease subtype, stage, age of onset, progression speed, symptom lateralization, and severity of motor and non-motor manifestations, as well as the specific response to anti-parkinsonian therapy.

Research Objective: To improve the diagnosis of cytokine metabolism and oxidative stress markers in different forms and variants of Parkinson's disease, and to optimize therapy accordingly.

2. Research Subjects and Methods

From 2023 to 2025, a total of 160 patients diagnosed with this syndrome were examined. Patients meeting the diagnostic criteria for parkinsonism were selected for the study. The clinical-biochemical correlation group consisted of 87 patients. Among those with PD, there were 47 (54%) females and 40 (46%) males. The age range of participants was 43 to 82 years, with a mean age of 65 (range 57–73) years. The distribution of patients by age and sex is presented in Table 1.

Table 1. Distribution of patients by gender and age (n=155)

Age of patients	Men, n-87	Women n-68
40-49 years old	11	9
50-59 years old	32	12
60-69 years old	39	37
>70	5	10
Total:		

The inclusion criteria for the study were as follows: the presence of Parkinson's disease at stages 1.0 to 4.0 according to the Hoehn and Yahr scale [8], and informed consent signed by the patient for participation in the study. The control group consisted of 20 individuals (11 women and 9 men) aged between 46 and 75 years (mean age 64 [9] years), matched to the main group by sex and age, with no chronic inflammatory diseases and no history of central nervous system disorders.

As can be seen from Table 2, the majority of participants in the study were patients with Parkinson's disease at stages 1.5 to 2.5 according to the Hoehn and Yahr scale, totaling 63 individuals (72%). The clinical form of PD was determined based on the predominant symptom of parkinsonism. According to the clinical classification, 7 patients (8.1%) were diagnosed with the tremor-dominant form, 21 patients (24.1%) with the akinetic-rigid form, and 59 patients (67.8%) with the mixed form of PD (akinetic-rigid with tremor) (Figure 1). The leading symptom of parkinsonism was used as the basis for classification.

Table 2. Distribution of patients with PC by age and severity (n=87)

PD stages According to the scale of Hen and Yaru	Age groups of patients				
1	40-49 age	50-59 age	60-69 age	>70	total
1,5	1	2	1	0	4
2,0	1	9	9	3	22
2,5	2	0	5	9	16
3.0	0	8	5	12	25
4.0	0	0	6	4	15
	0	5	5	2	5

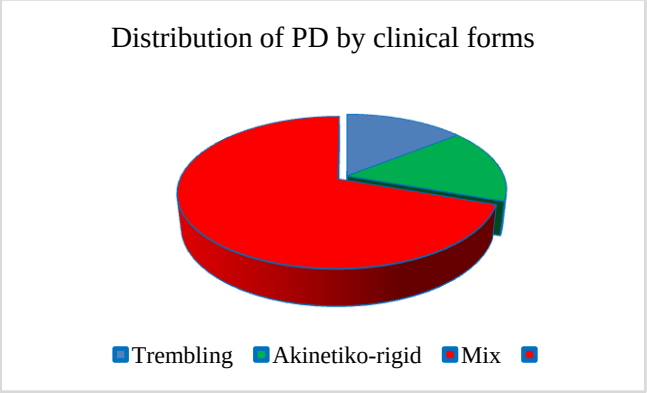

Figure 1. Distribution of patients according to clinical forms of Parkinson's disease (n=87)

Thus, among patients with Parkinson's disease, the mixed form was diagnosed more frequently; however, based on the predominant component, we identified two subgroups: tremor-dominant (TD), comprising 41 patients (47%), and akinetic-rigid-dominant (ARD), comprising 46 patients (53%). Patients with the akinetic-rigid form of the disease were generally at a higher average stage compared to those with the tremor-dominant form.

The duration of the disease ranged from 2 to 16 years. Table 3 presents the number of patients with varying durations of illness.

Table 3. Duration of PD

Duration of PC	Number of patients (%)
Less than 5 years	31 (35,6%)
5 to 9 years	34(39,1%)
10 years or more	22 (25,3%)

Thus, in the studied group, the duration of Parkinson's disease ranged from 5 to 9 years, and the age of disease onset varied from 33 to 76 years, with a mean age of 57.7 (51; 67) years. Early-onset Parkinson's disease (onset before the age of 45) was identified in 7 patients (8.1%), and a positive

family history was found in 2 patients.

Table 4. Comparative characteristics of ARD and TD in groups of patients with PC

Clinical indications	TD group	ARD Group
Age of onset	53 (49-66)	60 (52-68), p=0,04
UShOBP I	2 (1-3)	3 (1-5), p=0,02
UShOBP II	6 (4-10)	10 (7-13), p=0,03
UShOBP III	29 (17-40)	33 (26-46), p=0,02
UShOBP IV	0 (0-2)	1 (0-2)
PIGD	1 (0-3)	3 (1-5), p=0,006
NMS	11 (7-23,5)	20 (10-34)
KShOPS	28 (27-29)	27 (25-28), p=0,009
TRCh	10 (9-10)	9 (8-10)
BLD	16 (15-17)	16 (15-17)
HADS ≪A≫	6 (4-7)	7 (6-9)
HADS ≪D≫	8 (7-9)	9 (8-10)
Beck Depression Scale	15 (13-16)	17 (14-19), p=0,01

Overall, patients in the ARD (akinetic-rigid-dominant) group were at a more advanced stage of the disease — 2.5 (2.0–3.0), compared to the TD (tremor-dominant) group — 1.5 (1.0–2.5), p=0.004. The greatest difference between the groups was observed in the expression of clinical deficits according to the UPDRS scale. On the UPDRS part III subscale, patients in the ARD group had a mean score of 37 (26–46), significantly higher than the TD group — 27 (14–40), p=0.009. The total UPDRS score was 47 (38–68) in group 1, and 37 (19–56) in group 2, p=0.004.

Serum IL-1β levels in patients ranged from 0.8 to 70.6 pg/mL. The median IL-1β level was 6.0 (3.9–8.0) pg/mL, significantly higher than in the control group — 2.0 (1.8–2.4) pg/mL, p=0.001. IL-1β levels were significantly elevated in patients with stages 3 and 4 on the Hoehn and Yahr scale compared to those in stages 1–1.5 and 2–2.5 (p=0.01). However, no correlation was found between IL-1β levels and motor deficits as measured by UPDRS part III. Higher IL-1β concentrations were observed in patients with faster disease progression compared to slow-progressing cases (p=0.040). No significant associations were found between disease onset age, duration, or clinical form and IL-1β levels (p=0.18). CSF IL-1β levels were higher than in serum, with a median of 6.0 (4.0–7.0) pg/mL. Levodopa therapy had no significant effect on IL-1β levels in either serum or CSF.

Serum IL-1RA levels ranged from 0 to 3344 pg/mL. The median level in patients was 120.0 (48.5–358.5) pg/mL, significantly lower than in the control group — 969.5 (831.5–1526.5) pg/mL, p=0.002. In CSF, IL-1RA was 29.0 (9.5–45.5) pg/mL. No correlation was found between IL-1RA levels and disease severity, duration, or symptom burden. However, a negative correlation was observed between serum IL-1RA levels and amantadine daily dosage (UPDRS part I: r = –0.69, p = 0.04). IL-1RA levels were slightly higher in the TD group than in ARD, though this difference was statistically significant only in patients at stages 3 and 4 (p=0.04).

Serum IL-10 concentrations ranged from 2.0 to 29.0 pg/mL. The median was 5.9 (4.8–7.9) pg/mL, slightly lower than the control group — 6.5 (5.5–12.3) pg/mL, p=0.3. No gender differences or associations with age, disease stage, duration, or symptom lateralization were found. However, in patients not receiving medication, IL-10 levels showed a significant inverse correlation with Hoehn and Yahr stage (r = –0.67, p = 0.04). A positive correlation was also found between IL-10 and uric acid levels (r = 0.44, p = 0.04). IL-10 was significantly lower in ARD patients — 5.3 (3.6–6.4) pg/mL compared to TD — 6.4 (5.5–8.1) pg/mL; p=0.03. A direct correlation was observed between IL-10 levels and anxiety/depression severity assessed via HADS (both subscales r = 0.4, p = 0.01), but no differences between TD and ARD groups were observed on HADS: 9 (4–9) vs. 8 (7–9) points, respectively. No correlation was found between IL-10 levels and total scores on SCOPA, BLD, or TRC.

For assessing levodopa's effect on IL-10 levels, three subgroups were compared. In patients treated with levodopa (n=18), IL-10 was 6.0 (3.8–7.1) pg/mL. In those receiving low doses (75–375 mg/day; n=41) — 5.7 (4.4–6.3) pg/mL, and in high-dose users (500–1000 mg/day; n=28) — 7.9 (5.4–19.4) pg/mL. In CSF, IL-10 ranged from 2.6 to 7.7 pg/mL, with a median of 6.8 (4.2–7.3) pg/mL. No significant serum differences were noted. Of note, patient K., with early-onset PD and not on levodopa, had a CSF IL-10 level of 2.6 pg/mL — 2.7 times lower than median IL-6 levels.

Serum IL-6 ranged from 0 to 9.5 pg/mL. Median concentration in patients was 0.7 (0.3–1.4) pg/mL, significantly higher than in controls — 0.3 (0–0.9) pg/mL (p=0.03). A significant negative correlation was found between IL-6 and UPDRS II daily activity scores (r = –0.24, p = 0.04). IL-6 levels decreased with longer disease duration (r = –0.3, p = 0.01). A direct correlation was found between IL-6 and IL-10 (r = 0.3, p = 0.04). No association was found between IL-6 and disease stage or motor symptom severity overall. In TD patients, IL-6 was not associated with depression, but in ARD patients, a direct correlation between IL-6 and depression severity was observed (r = 0.33, p = 0.005). Levodopa dose and duration had no significant effect on serum IL-6 (p=0.13), though a downward trend in IL-6 was observed with higher levodopa doses.

Median CSF IL-6 was 1.4 (1.1–6.7) pg/mL — higher than in serum. Unlike serum, CSF IL-6 showed strong negative correlations with Hoehn and Yahr stage (r = –0.6), disease duration (r = –0.6), and UPDRS II scores (r = –0.6): the more advanced the disease and functional decline, the lower the CSF IL-6. A significant negative correlation was observed between CSF IL-6 and daily levodopa dose (r = –0.7). CSF IL-6 levels differed across levodopa dosage groups: untreated patients — 15 (6–16) pg/mL; low-dose (<375 mg/day) — 1.65 (1.35–4.75) pg/mL; high-dose (>400 mg/day) — 1.0 (0.9–1.2) pg/mL (p=0.01).

Serum TNF-α levels ranged from 0 to 10.9 pg/mL. Median TNF-α was 2.4 (0.8–4.7) pg/mL, not significantly different from the control group — 2.5 (1.5–4.7) pg/mL (p=0.9). TNF-α was higher in men than women (p=0.03). However,

sex-based cytokine differences were not a target of this study and were not further analyzed. No differences were found in TNF-α levels between early-onset and other PD groups. A significant association was found between TNF-α and clinical lateralization: patients with predominantly right-sided symptoms had significantly higher TNF-α — 3.1 (1.6–5.4) pg/mL compared to those with left-sided symptoms — 1.8 (0–3.2) pg/mL (p=0.04).

Finally, in evaluating the severity of non-motor symptoms, only IL-10 showed a direct correlation with HADS anxiety and depression scores (r = 0.4, p = 0.01 for both subscales). No differences were observed between TD and ARD groups in this regard. No correlations were found between IL-10 and SCOPA, BLD, or TRC scores.

Table 5. Cytokine levels in cerebrospinal fluid of patients with PD

indicators	Amount in cerebrospinal fluid, pg/ml
IL-1	6,0 (4,0-7,0)
IL-1PA	29,0 (9,5-45,5)
IL-10	6,8 (4,2-7,3)
IL-6	1,4 (1,1-6,7)
TNF-α	7,2 (5,4-10,1)

Table 6. Cytokine levels in serum of patients in ARD and TD groups

indicators	Amount in cerebrospinal fluid, pg/ml TD group	Amount in cerebrospinal fluid, pg/ml ARD group
IL-1	5,0 (4,0-7,0)	7,0 (4,0-8,0)
IL-1PA	130 (60-450)	118 (35-280)
IL-10	6,4 (5,5-8,1)	5.3 (3,6-6,4) D=0,03
IL-6	0,7 (0,1-1,4)	0,8 (0,3-1,4)
TNF-α	3Д (2,3-7,4)	1,7 (0;5,6)

Taking into account the stage of the disease (according to the Hen and Yar scale), the following values of interleukin levels were determined (Table 7).

Table 7. Cytokine levels in the blood of patients with PC at different stages (Hen and Yar scale)

indicators	Stage 1-1.5	Stage 2-2.5	Stage 3-4
TNF-α, pg/ml	3,2 (1,8-5,6)	1,6 (0-3,1)	4,0 (2,1-7,1) *
IL-1β, pg/ml	4,6 (4,5-8)	5,4 (3,5-8,0)	7,0 (5,0-12,0)
IL-6, pg/ml	1,0 (0,5-1,9)	0,8 (0,2-1,4)	0,4 (0,3-0,9)
IL-10, pg/ml	6,3 (5,4-8,0)	5,3 (3,7-6,4)	6,2 (5,7-8,5) #
IL-1RA, pg/ml	250 (57-435)	116 (45-206)	280 (80-880)

p=0.03 - differences between the groups of patients with PDstages 1-1.5 and 3-4 # r=0.02 - differences between the groups of patients with PD stages 2-2.5 and 3-4.

In addition to the differences in IL-10 levels observed at stages 3 and 4 of Parkinson's disease, significant differences were also found in serum IL-6 and IL-1RA concentrations among patients with the akinetic-rigid form of the disease compared to those with the tremor-dominant form (p=0.04; p=0.05, respectively).

Parkinson's disease (PD) is not characterized by gross blood-brain barrier (BBB) disruption, unlike conditions such as multiple sclerosis. In all patients, serum albumin levels remained within reference ranges (35–50 g/L), and total protein levels in cerebrospinal fluid (CSF) were also within normal limits (0.22–0.45 g/L for CSF). Considering that albumin accounts for approximately 80% of total CSF protein, it is possible to indirectly conclude that CSF albumin levels were preserved. Therefore, the content of interleukins such as IL-6, IL-1β, and IL-10 in serum may reflect similar trends in CSF, especially since lumbar puncture — a traumatic procedure — poses certain risks for patients.

3. Conclusions

Our study provides more precise insights into cognitive impairment among patients with the akinetic-rigid dominant (ARD) form of PD. This association is supported by studies investigating brain activity in PD. For instance, J. Prodoehl (2013) showed that patients with ARD have reduced activity in the prefrontal cortex and globus pallidus compared to those with the tremor-dominant (TD) form, based on MRI data using voxel-based analysis [10]. Similarly, Rosenberg-Katz et al. (2013), using voxel-based morphometry, demonstrated distinct regions of atrophy in different PD subtypes in gray matter [3].

The leading pathogenic mechanisms in PD include oxidative stress and the excessive accumulation of neurotoxic substances, such as reactive oxygen species (ROS), inflammatory mediators, and iron ions. Pro-inflammatory and anti-inflammatory cytokines present in biological fluids of PD patients are believed to play dual roles — both promoting neurodegeneration and exerting neuroprotective effects.

According to our study, the concentration of IL-6 in the serum and CSF of PD patients was significantly elevated compared to controls, consistent with findings by T.N. Torgan (2013), D. Lindqvist (2012), and R. Scalzo (2010). Earlier reports by Stypula G. et al. (1996) and Blum-Degen D. et al. (1995) also confirmed increased IL-6 levels in the blood of PD patients [7].

No significant differences in IL-10 concentrations between patient and control groups were found overall. However, in the TD group, IL-10 levels were higher than in the ARD group. This aligns with findings by Rentzos M. et al. (2009), who reported that IL-10 levels were approximately 1.5 times higher in the tremor-dominant form of PD compared to the akinetic-rigid form [205]. This elevated IL-10 in the TD form may reflect distinct immune-pathogenic mechanisms underlying PD subtypes. Prior studies have demonstrated not only clinical, but also pathomorphological and epidemiological differences between ARD and TD phenotypes [4].

Regarding the effect of IL-10 on motor dysfunction in PD, our findings are consistent with Menza et al., who reported a correlation between UPDRS motor scores and IL-10 levels. According to our data, IL-1β levels in serum were significantly higher in PD patients than in controls, regardless of disease

onset age, duration, or clinical form, indicating that elevated IL-1β may be a general marker of PD pathology.

In our study, serum TNF-α concentrations did not differ significantly from the control group (p=0.9), consistent with findings by D. Lindqvist [6]. Interestingly, we observed a sex difference in TNF-α levels, with higher levels in men — a phenomenon not previously described. While no direct relationship was found between TNF-α levels and CSF concentrations or affective symptoms, we did observe that TNF-α levels were lower in patients with cognitive impairment compared to cognitively intact PD patients. This pattern was more pronounced in those with ARD and mild dementia, suggesting that TNF-α may be related to cognitive deficits. Moreover, a significant association was found between TNF-α levels and clinical lateralization: patients with right-dominant symptoms had higher TNF-α concentrations (3.1 [1.6–5.4] pg/mL) than those with left-dominant symptoms (1.8 [0–3.2] pg/mL) (p=0.04).

A strong relationship between disease stage (Hoehn and Yahr) and cytokine levels was observed only for first-generation pro-inflammatory cytokines such as IL-1β and TNF-α, which act as upstream regulators of cytokine synthesis. These cytokines stimulate the expression of MHC complex antigens, cytokine receptors, chemokines, prostaglandins, and leukocyte recruitment to inflammatory sites.

Although we observed a trend toward a relationship between disease stage and IL-6 levels — another key first-generation cytokine — this did not reach statistical significance. The absence of strong associations with second-generation cytokines may be due to the long premotor phase of PD (10–15 years), during which initial pro- and anti-inflammatory activity is modulated by numerous compensatory mechanisms. Over time, as the pathological process spreads, these mechanisms are exhausted, leading to chronic neuroinflammation.

Therefore, our study confirms the presence of alterations in cytokine profiles in both serum and CSF of patients with PD. Across all clinical subtypes, elevated levels of IL-1β and IL-6 and reduced levels of IL-1RA were observed. These consistent immune shifts suggest that increased pro-inflammatory cytokines and insufficient anti-inflammatory compensation (e.g., low IL-1RA) contribute to the chronic, progressive neuroinflammatory process underlying PD pathogenesis.

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