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Neuroinflammation Mediators are Reduced in Sera of Parkinson's Disease Patients with Mild Cognitive Impairment

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ABSTRACT

Introduction: Cognitive impairment is common in Parkinson's disease (PD) and PD patients with mild cognitive impairment (PD-MCI) are at increased risk of developing Parkinson's disease dementia (PDD). Reliable biomarkers are required for objective identification of cognitive decline in PD. In this pilot study, serum levels of well-known mediators of neuroinflammation were measured in PD patients with or without MCI to find out the involvement of neuroinflammation and microglial activation in PD-MCI.

Methods: 36 PD-MCI, 25 PD patients with normal cognition (PD-NC) and 19 healthy controls were recruited. Serum levels of NLR family pyrin domain containing 1 (NLRP1), NLRP3, caspase-1, NF-kB, IL-1b and IL-18 were measured by ELISA and a panel of neuropsychological tests was administered.

Results: PD-MCI patients showed significantly reduced levels of NF-kB, IL-1b and IL-18, whereas NLRP1, NLRP3 and caspase-1 levels were comparable among PD-NC and PD-MCI patients. IL-18 levels were positively correlated with Addenbrooke's Cognitive Examination-Revised and Symbol Digit Modalities Test scores.

Conclusion: Levels of several microglial activation mediators are reduced in PD-MCI patients inferring a protective role to certain inflammation factors against cognitive decline in PD.

Keywords: Parkinson's disease; neuroinflammation; mild cognitive impairment; inflammasome; IL-18

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INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disorder, characterized by predominance of motor symptoms. Nevertheless, patients may present with non-motor symptoms such as mild cognitive impairment (MCI) (1). MCI diagnosis may be affected from motor and behavioral symptoms and arbitrary selection of neuropsychological tests. Therefore, well-characterized molecular biomarkers are required for objective identification of cognitive decline in PD.

In animal models of PD, a-synuclein released by brain cells has been shown to activate microglia to produce inflammatory molecules such as IL-1b, which exerts detrimental effects on neurons. Production of these cytokines is primarily regulated by NF-kB and multi-protein inflammasome complexes that include caspase-1, NLR family pyrin domain containing 1 (NLRP1) and NLRP3 (2). Although neuroinflammation is known to be among the triggers of neurodegeneration, inflammation pathways contributing to cognitive dysfunction in PD have been vastly understudied.

In this pilot study, serum levels of well-known mediators of neuroinflammation were measured in PD patients with or without MCI to find out the involvement of neuroinflammation and microglial activation in PD-associated cognitive deterioration.

METHODS

Participants

Consecutively selected 36 PD-MCI patients, 25 PD patients with normal cognition (PD-NC) and 19 healthy controls (HC) were recruited. PD-MCI, PC-NC groups and healthy controls were matched for age and gender (Table 1). PD patients were diagnosed according to UK Parkinson's Disease Society Brain Bank Criteria at the Behavioral Neurology and Movement Disorders Unit at Istanbul Faculty of Medicine (3). This study was approved by the Ethics Committee of Istanbul University. Written informed consent was obtained from all patients and healthy controls. Individuals with dementia, immunomodulating/immunosuppressant drug treatment, any psychiatric and other neurological disease were excluded. Disease severity was evaluated with the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and Hoehn-Yahr (H-Y) staging. All PD patients were under dopaminergic drug treatment and L-dopa equivalent daily doses (LEDD) were calculated.

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Neuropsychological Assessments

PD-MCI patients were identified by Addenbrooke's Cognitive Examination-Revised (ACE-R) using a cut-off level of ≤83, as previously determined (4). ACE-R comprises Mini Mental Status Examination (MMSE) and evaluating 5 cognitive domains (attention and orientation, memory, verbal fluency, visuospatial and language abilities). In addition to ACE-R, attention-executive and visuospatial functions of all participants were assessed comprehensively. Symbol Digit Modalities test (SDMT), Wisconsin Card Sorting test (WCST), Stroop color-word test were used to assess attention-executive functions; Judgement of Line Orientation test (JLO) was used to assess visuospatial functions.

ELISA

Serum levels were measured using ELISA kits (Yehua Biological Technology, Shanghai, China) for human NLRP1, NLRP3, caspase-1, NF-κB, IL-1b and IL-18 according to the manufacturers' protocols. Optical density was measured at 450 nm and concentrations were calculated by referring to a standard curve.

Statistical Analyses

Demographic, clinical, neuropsychological data and inflammasome factor levels were compared using one-way ANOVA and post-hoc Bonferroni test, chi-squared test and Student's t-test, as required. Correlation studies were conducted by Pearson's correlation test. $p<0.05$ was considered as significant.

RESULTS

Clinical and Neuropsychological Features

There were no significant differences between ages and gender ratios of study groups. Likewise, PD-NC and PD-MCI patients displayed comparable disease duration, LEDD and H-Y values. By contrast, PD-MCI patients showed significantly worse MDS-UPDRS-total, MDS-UPDRS-III, ACE-R ($p<0.001$), MMSE ($p<0.001$), Judgement of Line Orientation Test (JLO) ($p=0.036$), Stroop test ($p=0.033$) and Symbol Digit Modalities Test (SDMT) ($p=0.001$) scores than PD-NC patients (Table 1). PD-NC patients differed from HCs by worse SDMT ($p=0.013$) scores only.

Inflammation Factors are Suppressed in PD-MCI

PD-MCI patients displayed significantly reduced serum NF-kB, IL-1b and IL-18 levels than HCs and PD-NC patients. They also showed lower caspase-1 levels than HCs but not PD-NC patients. PD-NC, PD-MCI and HC groups showed comparable serum NLRP1 and NRLP3 levels (Figure 1). There were no significant differences among HCs and PD-NC patients. Significant correlations were found only between IL-18 levels vs ACE-R ($p=0.008$, $R=0.434$) and SDMT ($p=0.004$, $R=0.373$) scores. No significant correlation could be found between serum levels of other inflammation factors, neuropsychological test scores, demographic-clinical features and LEDD values.

DISCUSSION

Due to previously established neurotoxic action of inflammatory cytokines, an appealing assertion could be that PD-MCI is generated by increased neuronal death induced by excessive production of IL-1b and IL-18. By contrast, serum levels of inflammatory mediators were decreased in PD-MCI. Moreover, PD patients with higher IL-18 levels were more likely to display preserved attention, cognitive and executive functions. Our results are in line with previous studies showing reduced IL-1b and TNF-a levels in MCI patients with or without PD (5, 6).

Overall these results might imply a potential neuroprotective action for NF-kB, IL-1β and IL-18. Although complex interactions between inflammatory cytokines and NF-kB are well known to induce neurotoxicity, under unique circumstances they may also play a neuroprotective role (7). PD-MCI and PD-NC patients showed comparable levels of inflammasome complex factors suggesting that the inflammasome pathway is presumably not the main culprit in PD-associated cognitive decline. Thus other pathways influencing NF-kB and inflammatory cytokine expression levels need to be investigated.

A likely explanation for our results could be suppressed inflammation activity due to prolonged exposure of PD-MCI patients to dopaminergic medications. However, LEDD levels were comparable among PD-NC and PD-MCI patients and were not correlated with levels of inflammatory mediators ruling out this assertion.

Table 1. Demographic and clinical characteristics of participants

	HC (n=19)	PD-NC (n=25)	PD-MCI (n=36)	p
Age (years)	59.6±7.2 (46–72)	60.4±9.1 (44–81)	64.1±8.6 (45–79)	0.108[a]
Gender (female: male)	7:12	9:16	8:28	0.389[b]
GDS	4.5±3.5	5.4±3.7	6.5±3.8	0.162[a]
Disease duration (years)	NA	5.5±3.2	6.7±3.8	0.198[c]
LEDD	NA	687.3±365.5	818.4±377.8	0.184[c]
MDS-UPDRS-total	NA	42.1±15.7	53.8±20.1	0.018[c]
MDS-UPDRS-III	NA	24.6±9.2	31.5±12.3	0.021[c]
H-Y	NA	1.7±0.5	1.9±0.5	0.197[c]
ACE-R	93.4±4.8	89.9±3.7	76.9±5.8	<0.001[a]
MMSE	29.8±0.5	29.4±0.8	28.1±1.5	<0.001[a]
JLO	25.4±2.9	24.0±4.0	21.0±5.3	0.002[a]
Stroop test	47.6±16.5	54.5±18.5	75.1±40.8	0.003[a]
SDMT	40.4±13.6	31.2±9.3	20.7±8.9	<0.001[a]
WCST	15.8±7.9	19.5±8.7	24.7±10.5	0.005[a]

[a]ANOVA.
[b]Pearson's chi-squared.
[c]Student's t-test.
MMSE, mini mental state examination; H-Y, Hoehn-Yahr stage; GDS, geriatric depression scale; MDS-UPDRS, movement disorder society-unified Parkinson's disease rating scale; LEDD, L-dopa equivalent daily dose; ACE-R, Addenbrooke's cognitive examination-revised; JLO, judgement of line orientation test; Stroop test, Stroop color-word test (interference scores), SDMT, symbol digit modalities test; WCST, Wisconsin card sorting test.
Perseverative errors (%).
NA: not applicable.
Continuous variables are denoted as mean ± standard deviation.

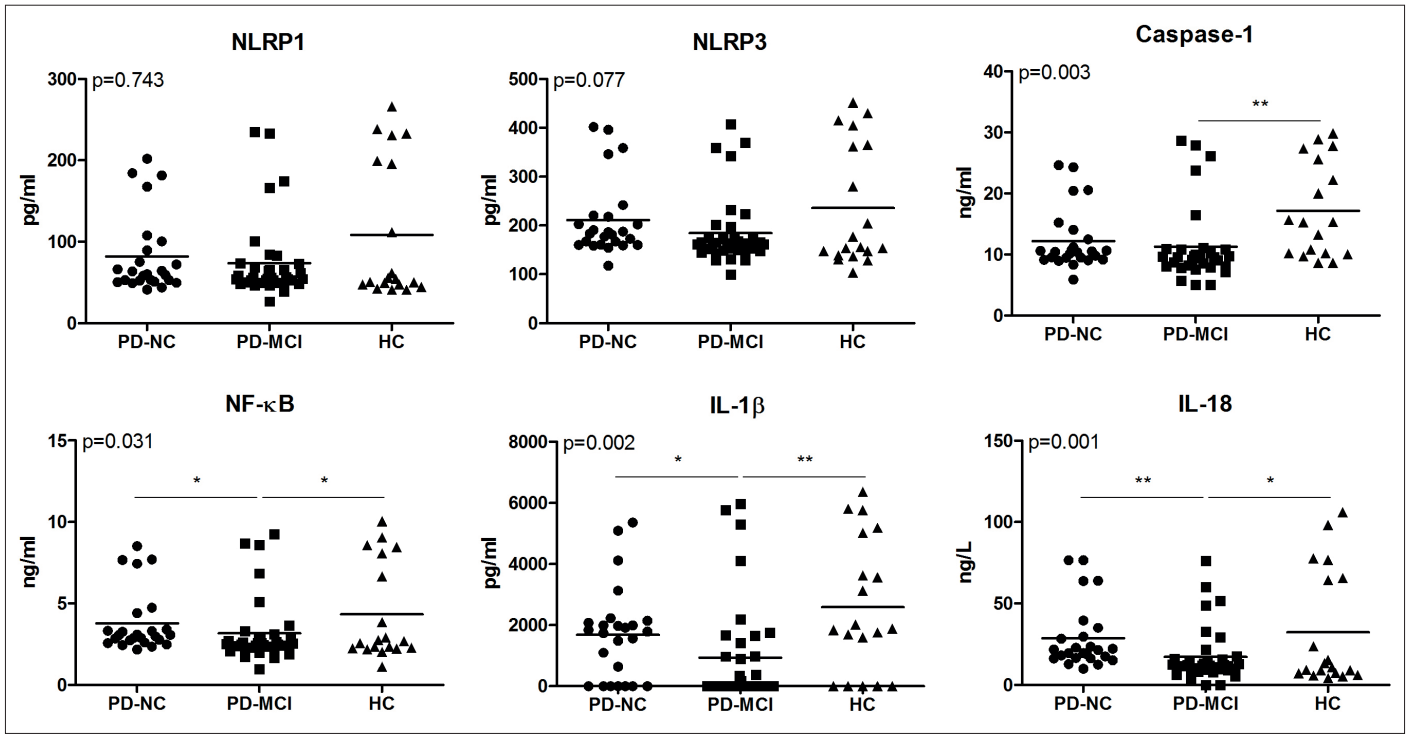


Figure 1. Comparison of serum levels of inflammatory mediators among healthy controls (HC), Parkinson disease patients with normal cognitive functions (PD-NC) and mild cognitive impairment (PD-MCI). p values on the upper left corner of each panel are obtained by ANOVA (Horizontal lines indicate mean values. *, p<0.05; **, p<0.01).

In conclusion, we herein have shown for the first time that PD-MCI patients exhibit reduced levels of certain mediators of neuroinflammation and microglial activity. Our results also bring forward IL-18 as a potential biomarker for early detection of cognitive decline in PD.

Ethics Committee Approval: This study was approved by the Ethics Committee of Istanbul University. Written informed consent was obtained from all patients and healthy controls.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - AK, ET; Design - AK; Supervision - AK, ET; Resource - EÖI, ET; Materials - AK, ZT; Data Collection and/ or Processing - HH, BB, AK, EE, ZT, HG; Analysis and/or Interpretation - AK, HG; Literature Search - AK; Writing - AK; Critical Reviews - HH, BB, EÖI, ZT, EE.

Conflict of Interest: The authors have no potential conflicts of interest to disclose.

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