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MOVEMENT DISORDERS - ORIGINAL ARTICLE

Is C-reactive protein level a marker of advanced motor and neuropsychiatric complications in Parkinson's disease?

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Abstract C-reactive protein (CRP) is a plasma protein involved in inflammation. While its levels have been associated with stroke, cognitive impairment and depression, the association with clinical characteristics of Parkinson's disease (PD) is unknown. A total of 73 consecutive patients with PD (46 males, age 68.8 ± 11.5 years) were evaluated regarding motor as well as cognitive and psychiatric features of PD. Plasma CRP levels were determined and tests for associations with disease parameters were performed. The average level of CRP was 3.9 ± 4.1 μmol/L, and 45.2% of the patients ($n = 33$) had a level above 3.0 μmol/L. Patients in the high CRP group tended to be older (71.4 ± 9.2 vs. 66.7 ± 12.9 years; $p = 0.08$) and coronary artery disease (CAD) was more common (36 vs. 10%, $p < 0.05$) in the high CRP group, but no differences were found between the groups regarding gender, disease duration, levodopa dose, motor scores or most of the neuropsychiatric complications such as severity of depression, psychosis, dementia, cognitive decline or frontal lobe dysfunction. Reported depression (at present or in the past) was more common in the high CRP group (54.5 vs. 25%, $p = 0.01$). CRP levels in patients with PD are associated with a higher prevalence of CAD, but are not associated with PD duration or severity, or with neuropsychiatric complications other than reported depression.

Keywords Parkinson's disease · Inflammation · C-reactive protein · Risk factor · Neuropsychiatric complications

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder primarily characterized by a motor disorder consisting of tremor, bradykinesia, rigidity and postural instability. The main pathological hallmark is a loss of dopaminergic neurons of the nigrostriatal pathway and Lewy body pathology consisting of α-synuclein deposition. The etiology of PD is unknown, and both genetic and environmental factors are involved in the pathogenesis (Litvan et al. 2007).

In recent years, there has been an accumulation of data supporting a possible role for neuro-inflammatory

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processes in the cascade of events leading to neuronal degeneration in the substantia nigra (SN) (Hirsch and Hunot 2009). These mechanisms comprise microglial activation, astrogliosis and lymphocytic infiltration, and several lines of evidence suggest that they are not mere nonspecific markers of neurodegeneration, but rather might be involved in the progression of neuronal degeneration (Teismann et al. 2003). Microglial inflammation has been found to accompany SN degeneration and de-pigmentation in the brains of deceased patients with PD, and activated microglia (Greenamyre et al. 1999), reactive astrocytes (Damier et al. 1993) and increased levels of inflammatory mediators have been detected in their striatum (McGeer et al. 1988). Additionally, several animal studies have also pointed to a contributory role of inflammation in dopaminergic cell loss (Teismann et al. 2003). Microglia participate in an inflammatory response and the number of activated microglial cells in SN increases with age and even more in the SN of patients with PD (McGeer et al. 1988). In animal models of PD, activated microglia have been shown to increase in parallel with the neurodegenerative process and demise of dopaminergic neurons (Cicchetti et al. 2002).

C-reactive protein (CRP) is a plasma acute phase protein that participates in the systemic response to inflammation, and its plasma concentration increases during inflammatory states. It is a pentameric protein produced by the liver in response to induction of hepatic gene expression by cytokines, primarily interleukin-6 (IL-6). A high concentration of CRP has been shown to be a cardiovascular risk factor. In a meta-analysis of studies with long follow-up, it has been shown that the risk for stroke in healthy individuals with the highest quartile of CRP concentrations increased nearly 70% compared to those with the lowest quartile and that high concentrations of CRP were predictive of cognitive decline and dementia (Kuo et al. 2005).

CRP has been detected in the senile plaques and neurofibrillary tangles of patients with Alzheimer's disease (Iwamoto et al. 1994; Duong et al. 1997), and higher plasma concentrations of CRP have been associated with depressive disorders (Berk et al. 1997; Miller et al. 2002). CRP seems to be directly involved in atherogenesis (Paul et al. 2004) and it has been shown to have direct neurotoxicity in vitro (Duong et al. 1998). Microglia can be activated by products of the classical complement cascade and by CRP. Thus, elevated CRP levels could contribute to the ongoing pathological process in PD and might correlate with markers of disease severity, such as cognitive decline and depression. The association between levels of CRP with PD has rarely been studied to date.

A recent study has shown that the levels of CRP in patients with de novo PD were higher than in healthy controls, similar to that in patients with acute ischemic cerebrovascular disease (Song et al. 2009). The aim of the study was to assess the clinical significance of elevated plasma CRP in PD by determining its association with clinical characteristics and measures of progression of PD, as well as with neuropsychiatric complications and cardiovascular co-morbidity.

Methods

Consecutive patients with PD were prospectively recruited from the PD and Movement Disorders Clinic and the Neurology Service at Sheba Medical Center between September 2003 and January 2004. All patients were diagnosed with idiopathic PD according to the UK bank criteria (Hughes et al. 1992). The study protocol was approved by the local ethics committee, and all patients had to give their informed consent prior to their inclusion in the study. Exclusion criteria included patients who were not fluent Hebrew speakers or having other CNS disorders (e.g., normotensive hydrocephalus, brain tumor), psychiatric disorder (e.g., major depression, schizophrenia), prominent cerebrovascular disease and patients after functional neurosurgical procedures for PD.

All patients underwent systematic assessments of demographics, vascular risk factors and atherothrombotic manifestations (stroke, transient ischemic attack, ischemic heart disease and peripheral vascular disease). PD duration, predominant motor manifestations, presence of motor complications and types of medications were recorded, as well as drug regimen including dose and duration of levodopa treatment. The severity of the motor symptoms was measured using the Unified Parkinson's Disease Rating Scale (UPDRS) part III (patients with motor fluctuations were examined in the "on medication" state) and the Hoehn and Yahr scale.

Neuropsychiatric disturbances were evaluated using the Beck Depression Inventory (Leentjens et al. 2000), an apathy scale for PD and the Parkinson Psychosis Rating Scale (PPRS) (Friedberg et al. 1998). Patients were asked about having had depression, hallucinations or delusions, and about the presence of visual impairment. Sleep disturbances and daily somnolence were also documented.

Global cognitive functioning was assessed using the Mini-Mental State Examination (MMSE) (Folstein et al. 1975). Attention was assessed using the digit-span forward and backward tests (Wechsler 1997), the Trail Making *A* and *B* tests and the Number Cancelation test (Lezak 1995). Verbal memory was examined using the Hebrew version of Rey Auditory Verbal Learning Test (AVLT) (immediate recall, leaning and delayed parts) (Vakil and Blachstein 1997). Visual memory was assessed using the Rey–Osterrieth Complex Figure test (RCFC), including

copy, and immediate and delayed parts (Lezak 1995). The frontal lobe functioning was examined using the Frontal Assessment Battery (Dubois et al. 2000) as well as tests for phonemic and semantic word fluency (Lezak 1995).

Laboratory methods

Fasting blood samples from each participant were collected in tubes containing citrate. The blood was immediately centrifuged at 3,000*g* for 6 min, and the plasma was stored at −80°C until analysis. CRP levels were measured with a highly sensitive CRP kit (Olympus AU-2700 analyzer, Germany).

Statistical methods

The patients were divided into two groups according to CRP ≤3 μmol/L and CRP >3 μmol/L, as CRP levels higher than 3 μmol/L are regarded as a cutoff defining high risk for cardiovascular disease (Pearson et al. 2003). Frequencies of dichotomous variables were compared using χ^2 tests. Means or medians of continuous or ordinal variables were compared using *t* tests or Mann–Whitney tests, respectively.

Analyses were also made by tertiles of CRP (1st tertile ≤1.248 μmol/L, 2nd tertile 1.248–3.684 μmol/L, 3rd tertile >3.684 μmol/L) and Mantel–Haentzel χ^2 analysis was performed for analysis of trends through the tertiles of CRP. Further analyses were done to examine adjustment to age also using Mantel–Haentzel tests.

Results

A total of 73 patients with PD (46 males and 27 females) were recruited. Their mean age was 68.8 ± 11.5 years (range, 42–96 years) and mean PD duration was 6.7 ± 4.7 years (range 0.5–18 years). The patient characteristics for all sample and by CRP groups (CRP ≤3 μmol/L, $n = 40$, 54.8% and CRP >3 μmol/L, $n = 33$, 45.2%) are shown in Table 1. The average plasma CRP concentration was 3.9 ± 4.1 μmol/L. Comparisons according to CRP level did not show any difference between the CRP groups regarding gender, disease duration, levodopa dose, motor UPDRS score and Hoehn and Yahr stage. The average age tended to be higher for the elevated CRP group (66.7 ± 12.9 vs. 71.4 ± 9.2, $p = 0.08$), and coronary artery disease (CAD) was more prevalent in the elevated CRP group (36 vs. 10%, $p < 0.05$). There were no significant differences between the groups in terms of psychiatric complications, except for a trend toward a higher apathy

Table 1 Patient characteristics and neuropsychiatric results

	All	CRP ≤3 μmol/L	CRP >3 μmol/L	*p* value
Number of patients	73	40	33	
Age	68.8 ± 11.5	66.7 ± 12.9	71.4 ± 9.2	0.08
Gender (male)	63% (46)	65% (26)	60.6% (20)	0.70
Coronary artery disease	21.9% (16)	10% (4)	36.4% (12)	0.01
Duration of Parkinson disease (years)	6.7 ± 4.7	6.5 ± 5.5	6.9 ± 3.4	0.70
Hoehn und Yahr stage	2 (2–3)	2 (2–3)	2 (2–2.5)	0.62
Motor UPDRS	24.2 ± 12.3	23.5 ± 12.8	25.0 ± 11.8	0.64
Levodopa treatment duration (years)	6.6 ± 4.4	6.6 ± 4.9	6.5 ± 3.8	0.94
Levodopa therapy	86.3% (63)	80% (32)	93.9% (31)	0.08
Depression in the past/present	38.4% (28)	25% (10)	54.5% (18)	0.01
Mini-Mental Status Examination	26.1 ± 3.4	26.0 ± 3.7	26.1 ± 3.0	0.89
Frontal assessment battery	13.9 ± 3.3	14.1 ± 3.6	13.6 ± 3.1	0.56
Beck Depression Inventory	11.2 ± 5.0	11.8 ± 7.7	16.3 ± 13.7	0.14
Patients with psychosis (PPRS score >8)	42.7% (29)	39.5% (15)	46.7% (14)	0.55
Hallucinations at present	20.5% (15)	20% (8)	21.2% (7)	0.90
Delusions at present	19.2% (14)	20% (8)	18.2% (6)	0.84
Hallucinations in the past/present	27.4% (20)	27.5% (11)	27.3% (9)	0.98
Sleep disturbances	54.8% (40)	47.5% (19)	63.6% (21)	0.17
Daily sleepiness	54.8% (40)	47.5% (19)	63.6% (21)	0.17
Apathy scale	17.0 ± 4.5	16.1 ± 4.7	18.2 ± 4.0	0.06

Dichotomous variables are given as % (*n*) and compared using χ^2 tests. Continuous variables are expressed as mean ± SD and compared using *t* tests. Ordinal scale variables are expressed as median (IQR) and compared using Mann–Whitney tests

CRP C-reactive protein, *UPDRS* Unified Parkinson Disease Rating Scale, *PPRS* Parkinson Psychosis Rating Scale

score and a significantly higher prevalence of depression in the present or past (but no association with the BDI score) in the elevated CRP group. There were no differences between the groups regarding global cognitive functioning or specific aspects of frontal lobe functioning as well as attention, verbal and visual memory and word fluency. Adjustment for age using Mantel–Haentzel tests did not change the non-significant results for the neuropsychiatric measures (data not shown).

Further analyses were made also by tertiles of CRP, and Mantel–Haentzel χ^2 analysis was performed for analysis of trends through the tertiles of CRP, but no significant associations were found.

Discussion

While elevated blood concentrations of CRP have been shown to be a cardiovascular risk factor and predictive of stroke, cognitive decline and dementia (Kuo et al. 2005), in our PD cohort plasma CRP was found to be higher with increasing age and was associated with a higher prevalence of CAD, but not with PD duration or any measures of disease severity. Except for higher prevalence of reported depression, there were no associations found with late complications of the neuropsychiatric type, such as severity of depression, dementia, global cognitive decline, frontal lobe cognitive dysfunction or psychosis.

Several molecular and cellular changes are implicated in the pathogenesis of PD, including abnormal protein handling, oxidative stress, mitochondrial dysfunction, excitotoxicity and apoptotic processes. It has been suggested that neuro-inflammatory mechanisms comprising microglial activation, astrogliosis and lymphocytic infiltration are also contributory (Litvan et al. 2007). While these mechanisms are not specific for PD, several lines of evidence suggest that they might be involved in the progression of neuronal degeneration by producing deleterious pro-inflammatory molecules (Hirsch and Hunot 2009).

While CRP has been shown to be an important risk factor for Alzheimer's disease and dementia, it has not been implicated in PD research as of yet. Concentrations of pro-inflammatory cytokines such as IL-1b, IL-2, IL-6 (the main regulator of CRP in plasma) and tumor necrosis factor (TNF-α) were found to be elevated in the brain and cerebrospinal fluid of patients with PD (Nagatsu and Sawada 2005), and elevations in the plasma levels of some of these cytokines have been suggested on comparing PD patients with controls (Chen et al. 2008). As the levels of CRP are not associated with any of the disease-related factors, it might be that the relevance of CRP to the pathogenesis of PD or its late complications is limited; however, the absence of a meaningful systemic inflammatory response does not rule out local CNS inflammatory processes.

Our study is limited mainly due to the relatively small sample size and due to its cross-sectional design. A limitation of any cross-sectional study is the bias introduced by studying only those eligible subjects who survive long enough to be ascertained. Also, a possible age-related variable effect of CRP, as suggested by a positive association of CRP with memory in the very old, (Silverman et al. 2009) might reflect antagonistic pleiotropy, which refers to gene and other effects that may be favorable at one point in life and unfavorable at another.

In conclusion, while high blood levels of CRP are associated with age and vascular co-morbidity, we did not observe an association with progression of PD nor with late complications of the neuropsychiatric type. These findings do not support the contribution of a systemic inflammatory process. However, given the evidence for the involvement of neuro-inflammatory processes in the cascade of events leading to neuronal degeneration in the SN, further research on the contribution of systemic and local inflammatory factors and the disease process in PD is warranted.

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