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The Role of Inflammatory Cytokines in Cognition and other Non-Motor Symptoms of Parkinson's Disease

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Abstract

Parkinson disease (PD) affects patients' lives in a broader sense then merely by physical impairment. Many of the non-motor aspects of PD, such as cognitive impairment, depression and sleep disturbances are common and are associated with a variety of poor outcomes. However, at present, the pathophysiology and clinical management of these symptoms are poorly understood. In this study we examined a panel of cytokines (of IL-1β, IL-6, IL-10, TNF-α) and cortisol in a cohort of 52 PD patients with depression. There were a number of significant correlations between the non-motor symptoms and TNF-α. Specifically, we found that TNF-α (but not IL-1β, IL-6, IL-10 or cortisol) was significantly correlated with measures of cognition, depression and disability. In regression analyses, accounting for all variables, TNF-α was consistently significant in explaining variance in cognition, depression, sleep and disability. These data are consistent with a growing body of literature that implicates inflammatory cytokines in neural and behavioral processes and further suggests that TNF-α may be involved in the production and/or maintenance of non-motor symptoms in PD.

Keywords

Parkinson's disease; Cytokines; Cognition; Depression

Introduction

PD is the second most common neurodegenerative illness in the US, affecting between 500,000 and 1 million individuals. Most, but not all, cases begin after the age of 50, with the prevalence increasing to 1.5 to 2.5% of people over 70 years of age. The illness is progressive and leads to significant functional disability and accounts for substantial health care costs.[1]

The physical aspects of Parkinson's disease (PD), such as tremor, rigidity and postural imbalance, are the defining characteristics of the disease and, understandably, they are the focus of most research and clinical care. Nonetheless, PD affects patients' lives in a broader sense then merely by physical impairment. For example, many of the non-motor aspects of

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PD, such as cognitive impairment, depression and sleep disturbances are common and associated with a variety of poor outcomes. These non-motor symptoms are also significant determinants of quality of life (QoL) for these patients and their caregivers.[2]

At present, both the pathophysiology and clinical treatment of these non-motor symptoms are understudied and poorly understood. Recent advances in cytokine research may present an opportunity for progress in this area. For example, the discovery of multiple functions of cytokines in the central nervous system suggests that cytokines may play a critical role in neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease and also may affect complex CNS functions such as cognition, sleep and depression. [3,4]

Of particular importance in PD, where widespread mild cognitive impairment is extremely common early in PD and frank dementia is common late in the illness, [5] is the association of cytokines with cognitive deterioration. Recent cross-sectional and prospective studies of Alzheimer's and vascular dementia have suggested that particular cytokines are associated with cognitive impairment in these patients,[6,7] raising the possibility that the study of inflammatory cytokines in PD may improve our understanding of the associated cognitive impairment.

The selection of cytokines measured in the present study was based on the fact that systemic inflammatory mechanisms impact neural and behavioral processes, generating neurochemical, endocrine and behavioral alterations similar to that observed in response to psychogenic stressors.[8,9] The cytokines most commonly associated with the "inflammatory" response are IL1β, IL-6, and TNF-α, which individually can alter neuroendocrine activity, increase neurotransmitter release, induce regional activation of immediate early genes in the brain, and modify basic behaviors, such as food ingestion, locomotion and sleep,[10] as well as learning and memory and anhedonia.[11]

Tumor necrosis factor, in particular, has well recognized neuromodulatory effects in the brain, [12] and has been shown to play a role in glutamate excitotoxicity, by inhibiting glutamate transporters on astrocytes, as well as glutamate transmission.[13]

Indeed, there is evidence linking elevated levels of TNF-α to PD. For example, TNF-α levels are elevated in the cerebrospinal fluid and postmortem brains of PD patients[14] and nonsteroidal anti-inflammatory drug use has been associated with a lower risk of developing PD in large US cohort studies.[15] Furthermore, in animals there are increases in cytokines, including TNF-α in the substantia nigra after injection of MTPT or 6 –OHDA and multiple studies indicate that TNF is highly toxic to dopaminergic neurons.[16] These studies suggest, despite variability, that cytokines, and TNF-α in particular, are related to the clinical expression of the symptoms of PD.[17]

We recently completed an NIH-funded, randomized, controlled trial of nortriptyline, controlled release paroxetine, and placebo in patients with PD and depression.[18,19] Because of the potential involvement of inflammatory cytokines in the symptoms of PD, we developed a supplement to this study to evaluate the association between inflammatory cytokines and the non-motor symptoms of PD. We hypothesized that there would be a significant association between the inflammatory cytokines and measures of cognition, depression and sleep. In this report we detail the findings on cytokines and the non-motor symptoms of PD.

Methods

The study group was composed of fifty-two patients, between the ages of 35 and 80, who had a confirmed diagnosis of PD by research criteria, as well as diagnosis of either major depression or dysthymia on the Structured Clinical Interview (SCID) for the Diagnostic and Statistical

Manual of Mental Disorders 4th ed. (DSM-IV). Patients were excluded if they had cognitive impairment (MMSE less than 26), were "off" for greater than 50% of the day (by patient report) or had any current DSM-IV Axis I diagnosis other than a depressive or anxiety disorder. All patients were participants in a double-blind, placebo- controlled study of paroxetine CR, nortriptyline and placebo previously described.[1818] All patients signed an informed consent approved by the Robert Wood Johnson Medical School IRB.

The patients were assessed, as previously described, on the Hamilton Depression Rating Scale20 (HAM-D 17-item), the Parkinson's Disease Questionnaire (PDQ-8)21, the Medical Outcome Study Short Form (SF 36)22, the Clinical Global Impression Scale23 (CGI), the Pittsburgh Sleep Quality Index24 (PSQI) and the Unified Parkinson's Disease Rating Scale25 (UPDRS). We also administered a battery of cognitive tests including the MMSE, forward and backward digit span of the Wechsler Adult Intelligent Test-Third Edition (WAIS-III)26, the Boston Naming Test27, the word list recall and recognition subtests of the Wechsler Memory Scale-Third Edition (WMS)28 verbal category fluency, and the Stroop color-word test.29 A composite measure of cognition was also calculated by adding up all of the individual scores (Stroop, digit span, etc) from our battery.

A cytokine panel, consisting of IL-1β, IL-6, IL-10, TNF-α and cortisol was drawn at baseline and eight weeks. The cytokine collection methodology was as follows. Blood was collected into chilled EDTA-treated tubes and centrifuged immediately at 2000 rpm at 4°C. Plasma was aliquotted into separate Nunc cryotubes and kept frozen at −70C until ready for assay. Approximately 0.5 ml volumes was aliquotted and stored, with each aliquot dedicated for each measure to avoid freeze-thawing and potential degradation of protein. Assessment of cytokines was run in duplicate with an in-house ELISA assay using commercially supplied capture and detection antibody-pairs and cytokine standards (BD Pharmingen BD OptEIA™ ELISA Sets) as we have previously described.[30]

Analysis

Correlation coefficients (Pearson *r*) were calculated between each cytokine and each non-motor measure (e.g. cognition, depression, etc.) within the sample. Given that multiple correlation tests capitalize on chance to a considerable degree, the P levels for the seven correlations calculated for each cytokine were adjusted using the Holm method (PROC MULTTEST; SAS version 9.1.) In order to study the role of covariates (e.g. gender, age) in any correlation patterns that emerge between cytokines and non-motor aspects of PD, multiple regression analyses were also performed.

Results

There were 27 women and 25 men; the mean age was 62.8, the mean duration of PD was 6.6 years and the mean Hoehn-Yahr was 2.2. The Hoehn-Yahr is the standard staging instrument for PD and ranges from 1 (mild disease) to 5 (severe disease). Fifty of the patients had major depression, two had dysthymia in addition to major depression and two had only dysthymia. All patients had an MMSE of at least 26.

Significant correlations were found (see Table 1), unadjusted for multiple comparisons, between TNF-α and many of the non-motor aspects of PD. Specifically, a significant correlation was found between TNF-α and the composite measure of cognition (r = −.51, P=.0003), and between TNF-α and sleep (PSQI, r=.347 [worse sleep], P=.02), depression (HAM-D [worse depression], r= .44, P=.002) and QoL (SF-36 total, r = −.329, P=.03). The UPDRS motor score was not significantly correlated with any cytokine, but the Schwab Disability Scale was significantly correlated with TNF-α, (Schwab, r= −.44 [worse disability], P=.002). Adjusting for multiple comparisons (the seven tests examined) with the Holm method, left

significant associations between TNF-α and cognition (P=.002) depression (P=.013) and disability (P=.013)

Correlations between the other cytokines (IL-1β, IL-6, IL-10) and the other non-motor measures were more sporadic, with the exception of the cognition measure, where a significant correlation was found for IL-6 (r=.43, adjusted P =. 0315).

We also performed four multiple regressions on the cognition data, one for each cytokine in order to study the role of covariates (e.g. gender, age) in any correlation patterns that emerge. For example, to explore the relationship of a given cytokine (TNF-α) to cognition, we used multiple regression, relating that cytokine to an overall neuropsychological performance score measured at baseline (adding up the individual scores [Stroop, digit span, etc] from our battery). Patient age, HAM-D, and the motor score on the UPDRS were added as covariates, as was a single dummy variable corresponding to gender. Because we were testing 4 cytokines, an alpha of .01 was set in advance for accepting as statistically significant the multiple regression weight associated with any given cytokine.

The remaining analyses focus on the relationship of cytokines to the other non-motor aspects of PD measured in the study, including depression, sleep, quality of life, and overall functioning. Only TNF-α was examined, given sporadic correlations between the other cytokines and non-motor aspects (see Table 1). A separate multiple regression is used for each non-motor variable. In addition to TNF-α, the covariates were age, gender and UPDRS motor score.

Cognition

The first regression, with composite cognition as the dependent variable and TNF-α, HAM-D, UPDRS, age and gender as the independent variables, yielded a multiple R-squared of 0.51 ($p < .0001$; R-squared adjusted for shrinkage =.45). Regression weights were non-significant for age ($p > .45$), gender ($p < .17$) and HAM-D ($p < .18$). The standardized regression weight associated with TNF-α in predicting cognition scores was −.51 ($p<.001$). That is, increased levels of TNF were associated with worse cognitive performance, controlling for all other predictors in the regression model. TNF-α, then, accounted for 25% of the variance in cognition. Regression weights were significant for UPDRS motor ($P< .001$) and TNF-α ($P<.001$). Increased total motor disability on the UPDRS was also associated with worse cognitive performance (standardized weight = − 0.46).

When the other cytokines (IL-1β, IL-6, IL-10) where analyzed in the same fashion as was TNF-α above, the regression weights were not significant for any of them at the .01 level.

Depression

In the regression analysis for depression, the multiple R-squared, that is, the amount of variance in the HAM-D that is accounted for by all variables in the model, was .29 (P=.007). The standardized weight associated with TNF-α in predicting HAM-D scores was .40 (P=.006). Therefore, TNF-α accounted for 16% of the variance in the HAM-D score. The p-levels for weights for age (.08) sex (.30) and motor score (.74) were not significant.

Sleep

In the regression analysis for sleep (PSQI), the multiple R-squared was .26 (P=.014).The standardized weight associated with TNF-α in predicting total sleep score was .31(P=.03). Therefore, TNF-α accounted for 9% of the variance in the sleep measure. The p-levels for weights for age (.84) and sex (.84) were not significant, whereas motor score was significant (p=.02; weight =-.39).

Schwab

In the regression analysis for disability (Schwab), the multiple R-squared was .32 (P=.003).The standardized weight associated with TNF-α in predicting the Schwab functioning score for PD was - .47 (P=.001). Therefore, TNF-α accounted for 22% of the variance in the Schwab disability score. The p-levels for weights for age (.83) and sex (.43) were not significant whereas motor score was significant (p=.028; weight =-.34).

QoL – PDQ 8

In the regression for quality of life with the PDQ 8, the multiple R-squared was .16 (P=.133). Given this result, regression weights were not examined further.

QoL - SF-36

In the regression analysis for quality of life with the SF-36, the multiple R-squared was .11 (P=.314). Given this result, regression weights were not examined further.

Discussion

Despite the importance of the non-motor aspects of PD, they have not been well studied and little is known about the underlying neurobiological mechanisms involved. We found, in this sample of patients with PD and depression, that higher levels of the inflammatory cytokine, TNF-α, but not other cytokines or cortisol, was significantly related to greater cognitive difficulties, more severe depression, more sleep difficulties and poorer functioning.

The association between TNF-α and cognition was particularly interesting. Not only were there significant correlations with the composite cognitive measure, but, further, in the regression analysis, with other variables entered, TNF-α accounted for 25% of the variance in the composite cognitive measure. It also appeared that the Boston naming and the Stroop word-color test were strongly associated with TNF-α and, therefore, increased TNF-α may be implicated in impairment of both language and executive functions.

This report of an association between TNF-α and the non-motor symptoms of PD is consistent with the current understanding of the role of inflammatory cytokines in complex CNS functions, as reviewed below, and suggests that inflammation may play a role in the production and/or progression of non-motor symptoms in PD.

The results are, however, based on a small sample and may therefore capitalize on chance. Likewise, our negative findings may be a function of low power. In addition, all of the patients in this sample had PD and depression and the results may not generalize to PD patients without depression. For all these reasons the results are clearly exploratory and preliminary. Nonetheless, given the evidence implicating inflammatory cytokines in neural and behavioral processes[31], the results are intriguing and clearly warrant replication as they could point to pathophysiologic processes that are involved in the production of these symptoms.

That increased levels of TNF-α may be involved in these non-motor symptoms is consistent with published evidence that TNF-α, IL-1β and IL-6 and acute phase reactants like CRP are associated with cognitive decline and dementia in cross-sectional and prospective population studies of normal aging as well as in clinical populations of Alzheimer's and vascular dementia. 32 For example, in an early cross-sectional study, Bruunsgaard, et al.[33] reported that the concentration of TNF-α was significantly higher in 126 centenarians compared to younger control groups, with higher concentrations associated with Alzheimer's disease. In fact, trials with etanercept, an inhibitor of TNF-α, reported a significant improvement of the Mini Mental State Examination (MMSE) and other cognitive tests after treatment.[34] And Tobinic, et. al.

have speculated, on the basis of the clinical results observed and the studies cited above, that optimal synaptic function in the human brain requires that TNF-alpha remain within a physiologic range; perhaps analogous to the necessity to maintain serum calcium in a narrow physiologic range to preserve optimal neuronal function.35 While this remains speculative, it does lend some credence to the core concept that inflammatory markers are related to cognition and the progression of cognitive deterioration36, 37

Depression is also common in patients with Parkinson's disease, with prevalence rates approximately 40%[38] and a key aspect of cytokine exposure in animals is the generation of a syndrome called “sickness behavior” which has compelling similarity to the symptomatology of depression.[39] For example, TNF-α and IL-1β elicit fatigue, anorexia, anhedonia and soporific effects, and severe depressive illness is accompanied by signs of immune activation and by elevations of cytokine production or levels. Finally, immunotherapy, using IL-2 or interferon-alpha, promotes depressive symptoms that are attenuated by antidepressant treatment.[40]

Sleep disorders are also common in patients with PD and are a critical factor in the poor quality of life in PD.[41], A neural cytokine network appears to be involved in the regulation of physiological sleep.[42] Inflammatory stimuli may produce a rise in central IL-1β and TNF-α, with resultant somnogenic effects, as seen in the sickness behavior response. In addition to the direct hypnagogic effects of cytokines, sleep promotion is presumed to result from interplay between cytokines and components of the neuroendocrine system. Specifically, IL-1β and TNF-α promote non-rapid eye movement sleep under physiological and inflammatory conditions. Many of the symptoms induced by sleep loss, e.g. sleepiness, fatigue, poor cognition, enhanced sensitivity to pain, can be elicited by injection of exogenous IL1β or TNF-α.[43] Recently, TNF-α has also been shown in animals to impair clock gene functions and circadian rhythms, thus contributing to sleep disruption and fatigue.[44]

In summary, cytokines have been implicated in PD and other neurodegenerative disorders. Furthermore, various cytokines have been related, in non-PD populations, to cognitive deterioration, sleep difficulties and depression, all of which are common in PD. In this study we found significant associations between TNF-α and measures of cognition, depression, sleep and disability in depressed PD patients. The relationship of TNF-α to cognition was particularly strong. These data, therefore, suggest that inflammatory cytokines may be involved in the neurobiology of initiation and/or maintenance of these important non-motor symptoms in PD. Further study of these relationships could yield important clues to the pathophysiology, course and treatment of non-motor symptoms in PD.

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Table 1

Pearson correlation coefficients (r) between four cytokines and non-motor aspects of PD

	IL-1	IL-6	IL-10	TNF-α
HAM-D	0.298	−0.132	−0.094	0.440**
QoL	0.213	−0.223	−0.067	0.328*
PSQI	0.051	−0.147	0.143	0.347*
Cognition	−0.392*	0.434**	0.129	−0.513**
SF-36	−0.389*	0.073	−0.119	−0.297*
Schwab	−0.195	0.063	0.056	−0.446**
UPDRS	−0.066	−0.216	−0.082	−0.115

*P<.05,

**P<.01