Title: An Exploration of the Association of Inflammatory Cytokines and the Non-Motor Symptoms of Parkinson's Disease in Patients in DATATOP

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This is an exploration of the association of inflammatory cytokines and the non-motor symptoms of Parkinson's disease using stored serum samples and assessments from the DATATOP study. We propose to study both the association between baseline levels of inflammatory cytokines and the cross-sectional severity of non-motor symptoms of PD as well as the longitudinal relationship between these cytokines and the course of these non-motor symptoms. The proposal follows our publication of pilot data from 52 PD depressed patients in which we found significant correlations between peripheral TNF-α and measures of cognition, depression and disability. We believe that this study has the potential to improve our understanding of the pathophysiology of non-motor symptoms as well as to facilitate the development of a biomarker for these symptoms.

Introduction

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 PD, such as cognitive impairment, depression and sleep disturbances are common and associated with poor outcomes. These non-motor symptoms are also significant determinants of quality of life (QoL) for these patients and their caregivers.[i] 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 may affect complex CNS functions such as cognition, sleep and depression.[ii,iii]

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,[iv] 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,[v,vi] raising the possibility that the study of inflammatory cytokines in PD may improve our understanding of the associated cognitive impairment.

The cytokines most commonly associated with the "inflammatory" response are IL1β, IL-6, and TNF-α, which individually can alter neuroendocrine activity[vii], increase neurotransmitter release[viii], induce regional activation of immediate early genes in the brain, and modify basic behaviors, such as food ingestion, locomotion and sleep,[ix] as well as learning and memory and anhedonia.[x] Furthermore, systemic inflammatory mechanisms generate neurochemical, endocrine and behavioral alterations similar to that observed in response to psychogenic stressors.[xi,xii]

There is evidence linking elevated levels of TNF-α directly to PD. 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.[xiii] Furthermore, TNF-α levels are elevated in the cerebrospinal fluid and postmortem brains of PD patients[xiv] and nonsteroidal anti-inflammatory drug use has been associated with a lower risk of developing PD in large US cohort studies.[xv] These studies suggest, despite variability, that cytokines, and TNF-α in particular, are related to the clinical expression of the symptoms of PD.[xvi]

We recently completed an NIH-funded, randomized, controlled trial of nortriptyline, controlled release paroxetine, and placebo in patients with PD and depression.[xvii,xviii] 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 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 and disability.[xix]

We are interested in extending these findings and this study will explore the relationship between TNF-α and other cytokines (IL-1β, IL-6, IL-10, IFNγ) and measures of non-motor symptoms in 200 patients in the DATATOP study. We hypothesize that there will be significant associations between TNF-α and measures of cognition, depression and disability. We further hypothesize that baseline TNF-a will be a predictor of the longitudinal course of these symptoms.

Potential impact: We believe that this study has high potential impact as it may help to establish cytokines as important biomarkers for the non-motor symptoms of PD. In addition, it may help to jumpstart a systematic approach to cytokine research in non-motor aspects PD – an area of high public health significance.

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