COMMENTARY

The depressed brain in Parkinson's disease: Implications for an inflammatory biomarker

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The Need for a Biomarker in Parkinson's Disease

Parkinson's disease (PD) is an increasingly prevalent neurodegenerative disorder currently diagnosed solely on the presence of motor symptoms (i.e., tremor, rigidity, bradykinesia, and postural instability) and their response to dopamine replacement therapy. A major unmet need is the limited number and failure of clinical trials with putative neuroprotective agents intended to halt or delay disease progression. Three main reasons account for this development: (*i*) At the time of the clinical diagnosis >50% of dopaminergic neurons in the substantia nigra have degenerated (1) and other neurotransmitter systems (e.g., norepinephrine, serotonin and acetylcholine) have been affected, indicating that the disease is already at an advanced stage (2); (*ii*) some reports suggest low accuracy for a PD clinical diagnosis, with up to 50% misdiagnosis in early disease (i.e., within 5 y of diagnosis) (3); and (*iii*) there is still no objective meaningful endpoint for clinical trials for early PD other than the Unified PD Rating Scale (UPDRS), a rater-based assessment of symptom severity. Thus, there is a need for objective biomarkers that either are neuropathophysiological manifestations of the disease (marker of state), track the speed of its progression (marker of rate), or are present in at-risk PD (marker of trait) (4). Adding complexity to this endeavor is the fact that PD is very heterogeneous in its clinical, neuropathological, and probably also pathophysiological presentation, with various subtyping strategies based on motor and also nonmotor symptoms recently proposed (5). Given the disease's complexity and variability, it is likely that a panel of biomarkers across several modalities will be needed to fully capture all PD subtypes (6). Because of recognition that the disease involves the peripheral as well as the central nervous system, additional biomarkers are needed that can be accessed via blood or peripheral tissue analysis.

Depression is a frequent nonmotor symptom in PD, affecting up to 40% of patients over time, and it adversely impacts quality of life and is associated with more rapid motor and cognitive decline. It can be a prodromal or preclinical feature up to 10 y before diagnosis, is more common in patients at the time of diagnosis than in healthy controls, and increases in frequency throughout the course of the illness (7). Thus, if depression is considered a disease biomarker it might meet criteria to assess state, rate, and trait.

The Role of p11 in Depression in Parkinson's Disease

In PNAS, Green et al., analyze the altered expression of p11 protein in PD using postmortem brain tissue and antemortem peripheral blood from PD patients classified as depressed or nondepressed (8).

P11, or protein S100A10, can form heterotetramer with Annexin A2, which has been found to be upregulated in conditions such as Alzheimer's disease, and is therefore thought to be associated with brain pathology and astrogliosis (9). In addition, recent data strongly suggest that p11 interacts with serotonin receptors and plays an important role in both the development of depression and therapeutic response to antidepressants (10).

P11 levels are reduced in depressed individuals in several brain regions, including the frontal cortex, nucleus accumbens, and hippocampus. Based on these findings, Green et al. (8) quantified mRNA and protein levels in the nigrostriatal system in postmortem brain tissue from PD patients and healthy controls. P11 levels were found to be significantly lower in PD patients compared with controls not only in the putamen and substantia nigra, regions of the midbrain nigrostristal pathway most affected by PD pathology, but also in the cerebral cortex. If p11 is indeed a depression biomarker, its dysregulation in the cortex in addition to the nigrostriatal pathway could partially explain the strong association between depression and cognitive decline in PD, given the role that disease pathology in the cortex plays in PD dementia.

To further confirm this reduction, Green et al. (8) quantified mRNA levels using real-time quantitative PCR in dopaminergic cells from both five advanced PD patients with a mean disease duration of more than seven years and six healthy controls, isolated by laser-capture microdissection, confirming the reduction in

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p11 activity at the mRNA expression level and raising the possible role of p11 as a transcription factor.

To further evaluate a potential biomarker role for p11 in PD, Green et al. (8) measured p11 protein in peripheral blood leukocyte populations from peripheral blood mononuclear cells of 42 PD patients in advanced stage with or without comorbid depression and 15 healthy controls. No significant differences were found between the groups, but higher p11 levels were correlated with: (*i*) increasing PD disease severity (by higher UPDRS score in the ON state and higher Hoehn and Yahr disease staging) and (*ii*) presence of depression determined by the application of a cut-off score on the Montgomery-Åsberg Depression Rating Scale (MADRS). Controlling for age, sex, and disease duration, significant positive correlations were found between p11 expression in $CD14^+$ $CD16^-$ and $CD14^+CD16^+$ monocytes with total UPDRS score and Hoehn and Yahr staging in all PD patients. P11 levels in NK cells were also positively correlated with both severity measures, and in cytotoxic T cells ($CD8^+$) were correlated with UPDRS score. With respect to depression, higher p11 levels in NK cells only (i.e., not T-cell or monocyte populations) were significantly associated with the MADRS score when examining just the depressed PD group. To assess a possible effect as a result of PD medication, p11 was correlated with levodopa equivalent daily dose, and no association was found.

To assess its potential as a diagnostic biomarker, the peripheral p11 levels in the different cell populations were analyzed using receiver operating characteristic to differentiate between all PD patients (i.e., with and without depression) and healthy controls. P11 levels in $CD8^+$ cells showed the best area under the curve of the receiver operating characteristic (0.97), with sensitivity of 87% and specificity of 93% (8).

The interesting findings of this impressive study (8) need replication, especially with less-advanced PD subjects. A possible cellular link between p11 and the immune system (being higher in T-regulatory cells) is intriguing against the background of a possible context of depression (and other PD symptoms) and inflammation. Regarding the depression component of the Green et al. (8) study, limitations of the research are: use of a cut-off score on a rating scale to "diagnose" depression as opposed to a rater-administered diagnostic interview; not conducting secondary analyses excluding antidepressant-treated patients, given that approximately half of depressed patients were taking an antidepressant and antidepressants themselves have putative effects on p11; presence of an outlier [as seen in figure 4 of Green et al. (8)] that may have driven the correlation between depression severity and p11 levels; and not controlling for UPDRS score or Hoehn and Yahr stage in the depression correlation analyses, given the association between these variables themselves and each with p11. The functional role of p11 in PD pathogenesis and neurodegeneration of dopamine and other neurons still needs to be elucidated, but if this finding is replicated by independent groups, p11 could represent one piece of the puzzle in understanding PD pathogenesis and heterogeneity, and most importantly could serve as a biomarker for PD phenotype and progression.

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