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Metabolomics and the Search for Parkinson Biomarkers

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One of the most sought after goals in Parkinson disease (PD) research is establishment of a therapeutic regimen that can slow or halt disease progression prior to onset of significant motor symptom disability. Achievement of this goal will require better strategies for diagnosis in the early or preclinical phases of the disease. Identification of biological markers, or biomarkers, defined as “characteristic(s) that are objectively measured and evaluated as indicator(s) of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”¹ is the most promising approach for early diagnosis of PD. In addition to aiding in early diagnosis, biomarkers also have the potential to better characterize subsets of Parkinson's disease, monitor response to therapeutic or neuromodulatory interventions, identify patients who are more or less likely to respond to such interventions, improve clinical trial design and better define clinical trial entry criteria, and contribute to better understanding of disease pathophysiology². To date, the ideal biomarker, or set of biomarkers, is unknown and the best approach for identifying biomarkers in PD has not yet been established. Potential methods include the use of clinical markers, such as those related to motor or non-motor symptoms; brain or other (e.g., cardiac) imaging; genomics; proteomics; and metabolomics (quantification of small molecular weight compounds)^{2, 3}.

In this issue, Lewitt and colleagues describe the use of metabolomic analysis to compare postmortem lateral ventricular CSF samples from PD patients and controls⁴. Although Bogdanov and colleagues previously reported the use of metabolomics to evaluate blood^{5, 6}, the study of CSF is novel. The authors take advantage of clinically well-characterized samples available through the Arizona PD consortium to compare PD and control CSF using ultra high performance liquid and gas chromatography linked to mass spectrometry (UHPLC-MS). This technique allows for untargeted screening of the samples and is advantageous because it offers high sample resolution and is capable of rapid rates of analysis^{2, 7}. Additionally, there are extensive reference databases available for sample analysis², including the Metabolon reference library employed by the authors of this study. Using these techniques for metabolomic profiling, the authors identified 19 compounds that differentiated between Parkinson's disease and control samples. Among these changes was a reduction in oxidized glutathione, a reassuring result consistent with previous studies^{8, 9}.

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They also found changes in 3-hydroxykynurenine, an excitotoxin previously found to be increased in the tissue samples from the putamen¹⁰. Biomarkers can also be used as a panel, rather than singly, and multivariate analysis using the 19 identified metabolites yielded classifiers with high sensitivity and specificity when applied to the data set.

This study is a first step towards metabolomics profiling in PD CSF, and it is important to recognize the limitations. First, confirmatory studies are needed. The authors performed an extensive internal cross validation; while this is useful, it is not the same as replication of the results in an independent sample. Second, although the brains of PD patients from which the CSF was derived were very well characterized, the samples are post-mortem and it will be important to validate the changes in living patients. Third, even if validated it is likely that these 19 compounds are only the “tip of the iceberg” and that there are networks of alterations in biochemical metabolism in PD. Greater numbers of subjects along with measures to address the heterogeneity of the disease will be needed to reveal the larger picture. Despite these unanswered questions, the findings reported herein are intriguing in that they provide potential direction for further study, particularly with more intensive investigation of not only the compounds with known connections to PD pathogenesis such as glutathione, but also some of the unidentified compounds or those without previously established roles in the disease process.

Although several promising candidates have been proposed, the ideal biomarker or group of biomarkers for PD remains elusive^{3, 11}. Metabolomic analysis has the potential for identification of biochemical pathways and discovery of metabolic profiles that could be used in PD for making preclinical diagnosis, following progression of disease, or monitoring response to therapy. Future study in this field will be needed to determine how biomarker profiles differ among patients with differing disease characteristics and how the profiles change in response to treatment or with progression of disease. It will also be important to determine if biomarkers in CSF can be correlated with biomarkers or profiles in serum². It is also possible, and perhaps likely, that a single method may not identify the ideal biomarker for PD. Rather, achieving this goal may require a combination approach, with information gained from imaging, genetics, proteomics, metabolomics, and potentially some yet unidentified technique¹². Although questions remain, the current study by Lewitt and colleagues opens the door for the use of metabolomics to analyze CSF profiles in patients with Parkinson's disease.

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