Lewy Body Dementia Biomarkers

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USA

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Lewy Body Dementia Biomarkers

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Parkinson's disease & PD-related disorders|Alzheimer's disease & other dementias

Keywords
Research Abstract

Cognitive impairment and dementia are common and disabling problems in patients with neurodegenerations characterized by intraneuronal ?-synuclein (?-Syn) aggregates. These patients are classified clinically as either Parkinson disease with dementia (PDD) or as dementia with Lewy bodies (DLB). This labeling distinction is based on the order of presentation of parkinsonism versus dementia – in PDD, the movement disorder occurs first, while in DLB, the cognitive impairment occurs first or within 1-year of parkinsonism onset. PDD and DLB exhibit virtually identical pathological findings at autopsy. Abnormalities found include

pathological depositions of ?-Syn, A?-amyloid, and tau proteins, the latter as intraneuronal paired helical filaments or “neurofibrillary tangles” (NFT). In individual brains, ?-Syn alone may be present in cell bodies (Lewy bodies) or in synaptic terminals (Lewy neurites). In other brains, ?-Syn deposits are present together with A?-amyloid plaques. In still other brains, ?-Syn, A?-amyloid and tau NFT pathologies are all present, often diagnosed neuropathologically as Alzheimer disease (AD) with PD. The neuropathologic findings do not, however, correlate substantially with subject clinical classification as PDD versus DLB. The future development of effective therapy for dementia in ?-synucleinopathy will likely require targeting of the pathologic pathways involved, and this in turn, necessitates ability to determine the type(s) of pathology present in individual patients and assessment of which pathologies most strongly drive progression of cognitive impairments. To be effective in disease modification, therapies will require testing and application in patients with only mild symptoms. In the present proposal, we will determine endophenotypes of mild dementia in patients with ?-synucleinopathy, employing multi-tracer molecular brain imaging with positron emission tomography (PET). We will determine the presence of ?- Syn neuropathology on the basis of [11C]dihydroteterabenazine (DTBZ) PET imaging of nigrostriatal projection integrity. We will identify the presence of A?-amyloid plaque deposition with [11C]Pittsburgh compound-B (PiB) PET imaging, and the presence of tau NFT pathology with [18F]AV1451 (formerly designated T807) PET imaging. Together, these imaging results will permit classification of each subject as: “pure” synucleinopathy, or synucleinopathy with A?-amyloid, or as synucleinopathy with both A?-amyloid and tau. We will test the hypothesis that the progression of cognitive decline will be more rapid in the synucleinopathy with both A?-amyloid and tau endophenotype, and that the progression of cognitive impairment in subjects with this endophenotype will correlate with the progression of NFT pathology as determined in follow-up [18F]AV1451-PET. The development of reliable trait biomarkers of neurodegenerative pathologies in PDD and DLB will enable progress in the development and assessment of new therapeutic interventions desperately needed in these syndromes.

Lay Summary

Failure of memory and other higher mental functions (dementia) is increasingly recognized as a major source of disability in Parkinson disease and related conditions. Symptoms of these problems do not respond effectively to available medications, and there are no approaches to slowing or preventing their development. A major limitation to discovery of new treatment approaches is the underlying complexity of brain pathology in PD with dementia subjects. Individual patients may have various combinations of abnormal protein depositions, including proteins called alpha-synuclein, beta-amyloid, and tau. These proteins are potentially hallmarks of differing pathways and types of brain injury, and are unlikely all to respond to the same type of treatment intervention. Thus, progress in the field of PD with dementia will require methods to identify involved pathways and protein depositions in individual patients. In the present research proposal, we will apply recently-developed research brain imaging methods that can reveal the major degenerating pathways and protein accumulations in PD with dementia. We will evaluate whether this approach results in differing types of symptoms or of symptom progression in individual patients, depending on their imaging results. Ultimately, we expect this brain imaging approach will permit the future design and testing of new specifically-targeted treatments to slow or halt the development of dementia in PD patients.

Further information available at:

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