POSTMORTEM VALIDATION OF BIOMARKERS FOR IMAGING PARKINSON DISEASE

https://www.neurodegenerationresearch.eu/survey/postmortem-validation-of-biomarkers-for-imaging-parkinson-disease/

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Title of project or programme

POSTMORTEM VALIDATION OF BIOMARKERS FOR IMAGING PARKINSON DISEASE

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,499,642.20

Start date of award

01/02/2016

Total duration of award in years

5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

imaging biomarker, Autopsy, Parkinson Disease, Benzodiazepine Receptor, beta amyloid pathology

Research Abstract
? DESCRIPTION (provided by applicant): Parkinson disease (PD) affects more than one million

people in North America, and no treatment has been proven to slow progression. A reliable imaging biomarker is urgently needed to monitor disease progression and therapy efficacy. Neuroimaging biomarkers have potential to provide unbiased measurements of PD progression, as indicated by loss of nigrostriatal dopaminergic neurons. We previously evaluated three different PET tracers for presynaptic markers of nigrostriatal neurons in MPTP-treated monkeys: [11C]DTBZ (a vesicular monoamine transporter type 2 [VMAT2] marker), [11C]CFT (a dopamine transport [DAT] marker) and [18F]FD (primarily reflects cerebral decarboxylase activity and storage) and demonstrated that striatal uptake of each of these linearly correlates with the number of nigrostriatal neurons but only when the loss of nigrostriatal neurons does not exceed 50%. In contrast, each of these tracers does linearly correlate with striatal dopamine as measured with high performance liquid chromatography. We recently found that direct PET measures of midbrain uptake of DTBZ or CFT does correlate with nigral cell loss. Yet, the relationship of changes in presynaptic neurons with other measures that affect function of this pathway remains unclear. We also recently reported that PD patients with amyloid-beta pathology in addition to cortical synucleinopathy have faster progression to death from either time of PD motor onset or time of dementia onset. This raises questions about whether those with amyloid-beta have different pathologic changes underlying this faster progression. In this R01, we will leverage human brain tissues collected previously, to determine the relationship between postsynaptic dopaminergic markers and related transmitter systems and the loss of nigrostriatal neurons. We propose to conduct quantitative autoradiography measures of the VMAT2, DAT, dopamine receptors (D1, D2, D3 and D4), cholinergic marker vesicular acetylcholine transporter (VAChT) and the peripheral benzodiazepine receptor (PBR) using pathologically well characterized control and PD brains (n=120, 15 each group for 8 groups, male and female cognitively healthy controls without or with amyloid-beta (tau negative), PD with only synuclein pathology and PD with synuclein plus amyloid-beta). Striatal (caudate, putamen and nucleus accumbens) and extra-striatal (substantia nigra, globus pallidus, thalamus and cortex) distribution of these biomarkers will be analyzed systematically to correlate with the PD disease duration and severity for both male and female groups. We then will determine which receptor and radioligand will have the best correlation with the dopaminergic neuron loss, dopamine loss or motor ratings. This study will provide a critical step for further validation of a neuroimaging biomarker of PD progression in clinic. The studies proposed in this grant have great potential on extending our understanding of the functional roles of dopamine receptor subtypes on dopamine transmission and PBR regulation in the PD. This will be the first comprehensive study using a large and pathologically well characterized population of PD and healthy control cases. We are in a unique position to conduct quantitative autoradiography of D2 and D2 receptors, neuroinflammation and evaluate the pre- and postsynaptic dopamine D2 and D3 receptors. This will be the first cross validation and valid comparisons with systematic measures of these biomarkers in the same subjects.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson disease (PD) affects more than one million people in North America, and no treatment has been proven to slow progression. A reliable imaging biomarker is in urgent need for monitoring disease development and therapy output. Without a good biomarker, it’s difficult for us to reach the ultimate goal of retarding the progression or reversing the inexorable decline of PD. The studies proposed in this grant have great potential to extend our understanding of the functional roles of dopamine receptor subtypes on dopamine transmission, the cholinergic system and PBR regulation in the PD. And this research has the

potential to identify a biomarker for PD severity and lead to new therapeutic targets and metrics for assessment of novel PD treatments.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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2016

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