SOCRATES

RESEARCH PROJECT SUMMARY

1. PROJECT TITLE : MASS SPECTROMETRY BASED MULTIPLEX QUANTIFICATION OF PROTEOFORMS FOR DIFFERENTIAL DIAGNOSIS OF NEURODEGENERATIVE DISEASES;

2. PROJECT ABSTRACT

2.1. Scientific background and Project justification

Diagnostic specificity of the core biomarkers, amyloid beta, tau and p-tau, in combination with neuroimaging and clinical evaluation reaches up to 90% for Alzheimer disease. Nonetheless, differentiation of atypical AD with overlapping neurodegenerative disease (ND), is still challenging. Moreover, there is a lack of specific biomarkers for ND, other than AD, such as Lewy body dementia (LBD) and Fronto-lobaire dementia, (FTLD). Promising novel candidate biomarkers are emerging (Tau isoforms, synucleins, neurofilaments..), even though conflicting results are reported depending on clinical studies. Discrepancies could be related to a lack of specificity of antibodies used in immunometric methods (ELISA…) regarding heterogeneous proteins (isoforms, truncation, homologies with other proteins), e.g. α-synuclein. Mass spectrometry offers great potential in the field of neurodegenerative biomarkers. High specificity toward protein isoforms or modifications is generally achieved thanks to high resolution instruments, together with robust and precise quantification for improved diagnosis sensitivity and standardization between labs. Also, ability for multiplex assays allows simultaneous measurement of several biomarkers. In this context, we aim to develop multiplex mass spectrometry based assay for AD and related ND biomarkers, including amyloids, tau isoforms, synuclein neurofilaments, ... Recently, we observed promising results for differential diagnosis of DLB and AD patients by simultaneously measuring CSF tau and synuclein (Viode at el, in preparation). In this project, we wish to further demonstrated the clinical utility of our multiplex mass spectrometry assay in cohorts of highly phenotyped individuals with AD and related disorders, and corroborate our measurement to neuroimaging data and cognitive decline. Our project also include a parallel cross-validation of existing Elisa methods with mass spectrometry in a comparative performance study of the different available plateforms, thus paving the way to improved cut-offs determination for differential diagnosis of ND.

2.2. Precisely defined research questions and goals (10-20 lines)

Our goal is to verify the clinical utility of multiplex mass spectrometry assay using CSF from highly phenotyped individuals with AD and related disorders (Socrates). We aim to corroborate:
a) The accuracy of the MS-based quantification in differentiating AD from other ND, in a cross-sectional study design.
b) The accuracy of MS-based quantification in differential diagnosis of AD, LBD and FTLD
c) The potential cross-sectional correlation of MS-based quantification with plasma level determined by Elisa (when assay is available);
d) The potential cross-sectional correlation of MS-based quantification with brain functional metabolism, as measured by 18F-fluorodeoxyglucose PET;

f) Cross validation between MS and available Elisa platforms, determination of cut-off level with best Elisa platforms.

2.3. Outline of research methods

The clinical utility of individual biomarkers and a combination thereof will be evaluated using CSF from Socrates cohort. CSF samples will be analyzed using a novel, high-specificity MS multiplex assay. We will need CSF samples and access to MRI, 18F-fluorodeoxyglucose PET and cognitive performance results in order to correlate CSF biomarker status with the aforementioned assessments. Cerebrospinal fluid will be analyzed for correlation with blood when assay is available.

2.4. Expected impact / results / significance

Accuracy of mass spectrometry measurement was recently illustrated with CSF and plasma amyloids (Pannee et al, 2013; Nakamura 2018). Here, we aim to extend this work to a panel of core and promising CSF biomarkers in the context of Alzheimer and clinically overlapping degenerative diseases, including β-amyloid, Tau isoforms, synuclein and neurofilaments. This combination of biomarkers can be used for specific diagnosis of AD, FTLD, LBD and other ND based on underlying pathological mechanisms. Moreover, longitudinal follow-up of patients will make it possible to evaluate the prognostic value of these CSF markers.

3. NAME AND AFFILIATION OF THE PROJECT LEADER AND MEMBERS OF THE RESEARCH PROJECT TEAM

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