Evaluating and Extending Our Hypothetical Model of Alzheimers Biomarkers

https://neurodegenerationresearch.eu/survey/evaluating-and-extending-our-hypothetical-model-of-alzheimers-biomarkers/

Principal Investigators

JACK, CLIFFORD R.

Institution

MAYO CLINIC ROCHESTER

Contact information of lead PI
Country

USA

Title of project or programme

Evaluating and Extending Our Hypothetical Model of Alzheimers Biomarkers

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,588,200.92

Start date of award

01/06/1993

Total duration of award in years

24

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Diagnostic Radiology... Epidemiology And Longitudinal Studies... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): A central insight gained from the current cycle of AG011378 is that in someone destined to develop Alzheimer's disease (AD) dementia, different biomarkers become abnormal in a sequential manner. Based on results from the current grant cycle, we proposed a biomarker-based disease model which posits that amyloid biomarkers become abnormal first, perhaps 15 years before the onset of overt clinical symptoms. Neuronal injury biomarkers become abnormal next, followed later by incident mild cognitive impairment (MCI). While we believe the model is largely correct, some in the field dispute this and therefore empiric evaluation is needed. This renewal will evaluate and extend our hypothetical biomarker model by following a large, population- based cohort of cognitively normal (CN) subjects studied with biomarkers for up to 10 years, and thus address major gaps in understanding disease progression. The central objective of this renewal is to understand how imaging biomarkers of AD pathophysiology (AD-P) change in the preclinical and early MCI phases of AD in relation to each other, and then to identify practical implications of sequential biomarker change. A notable strength of this renewal is our large – perhaps the largest in the world – existing cohort of CN subjects from an epidemiologically defined sample who have already undergone all imaging studies at baseline. Subjects for this renewal (n~1500) will be participants in the Mayo Clinic Study of Aging, an epidemiological sample of non- demented subjects in Olmsted County, MN. As outlined in the Introduction, we have significantly revised this A1 application in response to the study section critique. Aim 1. Establish cut-points for amyloid PET, TF-fMRI, FDG-PET, sMRI, CSF A¿42 and tau demarcating normal from abnormal. A major question in the field at present is how to appropriately define AD biomarker cut-points that separate normal from abnormal. Aim 2. Model validation: test the hypothesis that AD imaging biomarkers become abnormal in a specific temporal order. Our initial model was consistent with the amyloid cascade hypothesis in that amyloid biomarkers become abnormal first followed by FDG-PET and MR. However, this has been challenged. We will formally test this hypothesis using three different approaches and will extend and refine our existing model of biomarker evolution based on these findings. These results could alter current notions of AD pathogenesis. Aim 3. To integrate AD-P biomarker evidence with other predictors to enhance risk prediction for incident MCI. This will provide practical guidance for using AD biomarkers for clinical counseling. Aim 4. To provide practical guidance for using AD biomarkers in secondary prevention clinical trials.

Lay Summary

PUBLIC HEALTH RELEVANCE: In the current grant cycle of AG011378, we proposed a hypothetical model describing the order in which biomarkers of Alzheimer's disease (AD) evolve over time. This model has conceptually influenced the development of new diagnostic criteria and also the design of modern disease modifying therapeutic trials. Our goals in this renewal are to test if this model is correct and where indicated, revise it and in so doing provide practicl information for counseling patients regarding the implications of abnormal AD biomarkers and to aid in designing therapeutic clinical trials in preclinical AD.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:

Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

Database Tags:
N/A