Understanding mechanisms and seeking novel biomarkers in Alzheimers disease

https://neurodegenerationresearch.eu/survey/understanding-mechanisms-and-seeking-novel-biomarkers-in-alzheimers-disease/

Principal Investigators

THAMBISETTY, MADHAV

Institution

National Institute on Aging

Contact information of lead PI
Country

USA

Title of project or programme

Understanding mechanisms and seeking novel biomarkers in Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 820,710.09

Start date of award
Total duration of award in years

4

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)... Basic Behavioral and Social Science... Behavioral and Social Science... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Nutrition... Obesity... Precision Medicine... Prevention

Research Abstract

1. Targeted and quantitative metabolomics in combination with global profiling for predicting AD conversion Over the reporting period for the last year, we have performed perhaps the largest

study of metabolite biomarkers of preclinical AD to date through a collaboration between the BLSA and the Age, Gene/Environment Susceptibility (AGES-Reykjavik) Study in Iceland, wherein targeted/quantitative metabolomics was applied to serum samples to ask whether there is a blood metabolic signature predicting conversion to AD in individuals who were previously cognitively normal. The combined sample size in this study is well over 700 serum samples in individuals who have undergone serial cognitive assessments and detailed clinical evaluations. We have since acquired the first tranche of data using a targeted quatitative method to measure serum concentrations of 187 lipid species in the BLSA and AGES-RS samples. We have completed two main analyses on these data. First we attempted to validate a highly cited finding that attracted considerable attention both in the scientific community as well as in the media by Mapstone and colleagues 14. In a small study of 28 individuals, the authors reported that a 10-metabolite panel of plasma phospholipids measured by the BIOCRATES P180 Absolute IDQ platform could predict risk of conversion to AD with >90% accuracy in cognitively normal individuals. As these findings were of immediate relevance to AD patients and older individuals at risk of AD, we set out to test them in the substantially larger combined sample from the BLSA and AGES-RS studies. We were unable to validate the index findings by Mapstone et al and reported that the 10-metabolite panel does not provide clinical utility to predict risk of conversion to AD in cognitively normal older individuals. In this publication, we discussed several methodological and analytical issues relevant to metabolomics-based biomarker discovery studies in AD. As the field of metabolomics matures, we believe that our study provides an important template for subsequent AD biomarker investigations using this technology. Second, we applied data-driven analytical approaches to the targeted/quantitative metabolomics data in serum to ask whether there were distinct metabolite concentrations associated with the pre-clinical and symptomatic phases of AD. This question is of considerable importance to elucidate mechanisms relevant to disease progression in AD. To achieve this goal, we implemented state-of-the-art machine learning methods without any a priori assumptions about the nature or identity of metabolites related to AD progression. Using four machine learning classifiers (Elastic net regularized logistic regression (EN-RLR); Random forest classifier (RF); Support vector machines (SVM); L1 regularized logistic regression (L1-RLR)), we identified two distinct sets of consensus metabolites common across all classifiers that were associated with the preclinical and symptomatic stages of AD. The metabolite classes represented include acylcarnitines, amino acids, phosphatidylcholines and lysophosphatidylcholines. This finding provides strong evidence that perturbations in specific metabolic pathways can be detected in blood during early disease progression in AD. We are currently acquiring the second tranche of targeted/quantitative serum metabolomic data on the BLSA and AGES-RS samples. In these assays, we will measure absolute serum concentrations of approximately 400 metabolites in the following classes: bile acids, oxysterols, phosphatidylethanolamines (PEs), phosphatidylserines (PSs), phosphatidylglycerols (PGs), sphingolioids and ceramides. In parallel with these quantitative assays, we have nearly completed data acquisition on the same BLSA serum samples using global metabolic profiling with UPLC-MS. We anticipate that together with the longitudinal metadata on virtually every physiological system associated with these samples, we will be uniquely positioned to apply a systems level, integrated approach to understanding the metabolic bases of disease progression in AD. 2. Targeted and quantitative metabolomics in combination with global profiling to understand the molecular basis of resilience to AD pathology Although the presence of amyloid plaques and neurofibrillary tangles in the brain are the defining hallmarks of AD and provide confirmatory evidence at death to support a clinical diagnosis of AD, several studies have shown that these pathological features may be present in

upto 50% of older individuals who did not show any signs of cognitive impairment during life. In the BLSA, these individuals have previously been characterized as asymptomatic AD (ASYMAD) to denote the presence of significant AD pathology in the brain without accompanying clinical features of AD during life. While the majority of mechanistic studies in AD have been directed towards understanding the molecular basis of AD risk, surprisingly few studies have attempted to characterize the biological basis of resilience to AD pathology. We have initiated a series of studies using multiple omics methods to better understand the molecular mechanism(s) underlying cognitive resilience in the presence of AD pathology. Through the autopsy program of the BLSA, we have examined frozen brain tissue samples from individuals in three groups controls i.e. cognitively normal during life with no evidence of AD pathology at autopsy, Alzheimers disease i.e. with a clinical diagnosis of probable/possible AD during life with autopsy confirmation and ASYMAD i.e. without cognitive impairment during life but with significant AD pathology at autopsy. We sampled three brain regions (middle frontal gyrus (MFG), inferior temporal gyrus (ITG) and the cerebellum). Our rationale was to study brain regions both vulnerable (i.e. MFG and ITG) as well as resistant to AD pathology (i.e. cerebellum). In these samples, we have now completed data acquisition using the following methods: i) Quantitative and targeted metabolomics: BIOCRATES P180 Absolute IDQ platform. ii) Global, untargeted metabolomic profiling: UPLC-MS, hydrophilic interaction-chromatography (HILIC-MS) and Gas chromatography-mass spectrometry (GC-MS). iii) Global, untargeted proteomic profiling: Tandem mass tagging (TMT)-proteomics with two labeling approaches i.e. intact protein and intact peptide-level labeling (peptide-level TMT data acquired through collaboration with Nicholas Seyfried and Allan Levey, Emory University). Together, these data allow us to comprehensively study molecular mechanisms mediating resilience to AD pathology. In ongoing analyses using these data, we have identified novel metabolites that appear to discriminate between these three groups of individuals. Some key findings from these studies were presented at the Alzheimers Association International Conference (AAIC) in July 2016. We anticipate that these results will be reported in full-length publications shortly. 3.We have also studied the relationship between midlife obesity, one of the strongest risk factors for AD, and the AAO as well as severity of AD neuropathology. Using longitudinal body mass index (BMI) measurements in the BLSA, we applied an accelerated failure time (AFT) model to show that each unit of higher BMI at age 50 is associated with a lowering of the AAO of AD by about 6.7 months (Figure 8). Equally importantly, higher midlife BMI was associated with greater neurofibrillary pathology at death 41. Our results provide strong evidence for long-lasting effects of midlife obesity on accelerating the course of AD and severity of associated neuropathology. We believe that these findings are also of considerable public health importance as they reveal a long window of opportunity when lifestyle interventions against obesity.

Lay Summary
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