Vascular Dysfunction in Cerebral Amyloid Angiopathy

https://www.neurodegenerationresearch.eu/survey/vascular-dysfunction-in-cerebral-amyloid-angiopathy/

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Country

USA

Title of project or programme

Vascular Dysfunction in Cerebral Amyloid Angiopathy

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,246,748.62

Start date of award

15/09/2005

Total duration of award in years

12

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease Related Dementias (ADRD)... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Bioengineering... Brain Disorders... Cerebrovascular... Clinical Research... Clinical Research - Extramural... Dementia... Diagnostic Radiology... Neurodegenerative... Neurosciences... Rare Diseases... Vascular Cognitive Impairment/Dementia

Research Abstract

? DESCRIPTION (provided by applicant): Despite growing interest in cerebral small vessel diseases (SVD) such as cerebral amyloid angiopathy (CAA), no effective disease-modifying treatment to prevent SVD- related vascular cognitive impairment (VCI) has been identified. We propose to use novel MRI-based analyses of subjects with advanced CAA to test the hypotheses that SVD-related neurologic dysfunction represents the sum of many pathologically heterogeneous, anatomically distributed, and often undetectably small lesions, and that the collective effect of these brain injuries is best measured at the larger scale of whole- brain structure and connectivity. Three complementary quantitative measures of large- scale cortical structure and connectivity will be evaluated: high-resolution T1 mapping of cortical gray and subcortical white matter tissue by multi-echo multi-flip angle FLASH sequences, structural connectivity by diffusion-tensor imaging-based network methods and functional connectivity by resting-state functional MRI methods. Specific experiments will analyze differences in these three measures between 60 non demented CAA subjects and 30 healthy elderly controls (SA1a), and within the 60 CAA subjects, the relationships of the three measures with each other (SA1b), with defined focal lesion types such as microbleeds, white matter hyperintensities, and foci of amyloid deposition on amyloid PET imaging (SA2), and with clinically meaningful cognitive and gait outcomes (SA3). Each analysis of CAA subjects will be performed globally in the brain as a whole, locally in individual brain regions, and longitudinally across time points, and each will control for accompanying Alzheimer Disease pathology by tau PET imaging. The proposed experiments build on the PI’s ground-breaking success in establishing CAA as a disease that can be diagnosed and analyzed during life, his highly productive record of influential publications in the field (including 20 published/in-press original reports over the fist 3.5 years of the current funding cycle), and strong preliminary data supporting the feasibility and promise of the proposed neuroimaging methods. The impact of the proposed studies will be further leveraged by comparison to harmonized studies performed in a hereditary CAA cohort and a non-CAA sporadic SVD/VCI cohort and by extension of the in vivo results to separately proposed ex vivo imaging and histologic examination. Successful completion of these aims has very high potential for identifying biological mechanisms linking SVD to clinically meaningful neurologic dysfunction and directly translating to efficient clinical trials of candidate SVD treatments.

Lay Summary

PUBLIC HEALTH RELEVANCE: We propose to use novel MRI-based methods to determine how the small injuries to the brain from diseases of the small blood vessels interact to produce impairments in important brain functions such as memory, information processing speed, executive function, and walking ability. These studies of large-scale properties of brain structure and connectivity will be performed in individuals with cerebral amyloid angiopathy, a currently untreatable age-related degenerative condition of the small blood vessels in the brain that occurs in a substantial proportion of older people. These studies will create a strong foundation both for understanding the links between small brain injuries and impaired brain function and for efficient drug trials aimed at preventing disability in our aging population.

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