Vascular breakdown in Alzheimers Disease with cerebrovascular disease

https://neurodegenerationresearch.eu/survey/vascular-breakdown-in-alzheimers-disease-with-cerebrovascular-disease/

Principal Investigators

WILCOCK, DONNA M.

Institution

UNIVERSITY OF KENTUCKY

Contact information of lead PI
Country

USA

Title of project or programme

Vascular breakdown in Alzheimers Disease with cerebrovascular disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,497,423.85

Start date of award

01/07/2012

Total duration of award in years

1

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

vasogenic edema, Cerebrovascular Disorders, APP-PS1, Alzheimer's Disease, Matrix Metalloproteinases

Research Abstract
DESCRIPTION (provided by applicant): Microhemorrhages and vasogenic edema are

pathological phenomena that occur in both cerebrovascular disease (CBVD) and Alzheimer's disease (AD). In CBVD these can occur throughout the brain, yet are most frequently subcortical. In AD they usually occur at sites of vascular amyloid deposition. Given that CBVD and AD are not always mutually exclusive but often co-exist it is important that we understand the mechanisms of microhemorrhages and vasogenic edema. We hypothesize that inflammatory-mediated activation of matrix metalloproteinases leads to degeneration of tight junction proteins and basement membrane proteins resulting in vascular leakage producing microhemorrhages and/or vasogenic edema. Our goal for this proposal is to model CBVD in mouse models of amyloid deposition to produce vasogenic edema and microhemorrhage and determine the role of the MMP system in their onset and the impact CBVD has on response to amyloid-targeted therapies. We will assess inflammatory changes and activation of the MMP systems as mechanisms for these abnormalities. Importantly, we propose to acquire MR FLAIR and Susceptibility Weighted (SWI) images to assess vasogenic edema and microhemorrhage as well as any other brain changes occurring through the course of the studies. Immediately prior to tissue harvest we will acquire arteral spin label (ASL) scans to measure brain perfusion and thus enable a comparison of the density of microhemorrhages and brain health. Additionally, we will acquire contrast enhanced T1-weighted scans following administration of Magnevist and Galbumin contrast agents to assess vascular leakage. We propose to use AAV and pharmacological agents to inhibit MMPs directly, or inhibit the inflammatory signals thought to be increasing MMP activity. We will also examine whether the efficacy and side-effect profile of two A¿- targeted therapies in trials are influenced by the presence of CBVD in amyloid-depositing mice. The overall goal of our proposal is to determine the time-course of CBVD pathology when we generate CBVD in APP/PS1 transgenic mice, determine the roles of inflammation and MMPs in the generation of microhemorrhage and vasogenic edema, and finally to establish the effect CBVD has on the response to A¿-targeted therapies. We believe that CBVD is common co- morbidity with AD that influences the pathogenesis of AD and response to therapy.

Lay Summary

Cerebrovascular disease commonly occurs with aging, as does Alzheimer's disease. In fact, it is estimated that 40% of Alzheimer's patients also have cerebrovascular disease. Our research proposal will examine the impact cerebrovascular disease has on the progression of amyloid pathology, a brain pathology in Alzheimer's disease. Our overall goal is to enhance our understanding of the relationship between cerebrovascular disease and Alzheimer's disease and how one can affect the other.

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