MRI and CSF Biomarkers of White Matter Injury in VCID

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Contact information of lead PI
Country

USA

Title of project or programme

MRI and CSF Biomarkers of White Matter Injury in VCID

Source of funding information

NIH (NIA)

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30/09/2016

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5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords
Research Abstract

Summary/Abstract Vascular cognitive impairment dementia (VCID) is a heterogeneous disease that is an important cause of dementia. This proposal is in response to a RFA to identify biomarkers to separate patients into subgroups for treatment trials. Although much is known about multiple biomarkers individually, there is a major gap in our understanding of the optimal ones to use in collaborative studies, which is the aim of this proposal. Subcortical ischemic

vascular disease (SIVD) is the progressive small vessel disease (SVD) form that is optimal for treatment trials. MRI modalities and CSF biochemical studies provide the most promising biomarkers. White matter damage is the hallmark of SIVD, and MRI is the optimal method to show the progressive changes. Biochemical studies of CSF show the inflammatory biomarkers of albumin, matrix metaloproteinases (MMPs) and cytokines. In an on-going clinical study of SIVD, our group has identified microstructural studies with MRI and biochemical studies of MMPs in the CSF as the two most promising biomarkers. This two-phase, milestone-driven proposal is to identify the optimal microstructural and biochemical biomarkers to both identify the SIVD subgroup and to use as surrogate markers of progression. In the first U2 phase, the optimal method to measure CSF MMPs will be determined for patient classification and the optimal MRI biomarkers to show progression will be determined. Normal-appearing white matter (NAWM), which is a region with normal FLAIR signal, often has abnormal diffusion signals, indicating tissue at risk (prodromal). The hypothesis is that CSF and MRI biomarkers can be used for classification of SIVD patients with CSF for primarily classification and MRI for both classification and as a surrogate marker for predicting disease progression that can be used for patient treatment decisions. There are three specific aims: 1) to demonstrate that the growth of white matter hyperintensities (WMHs) as defined by FLAIR images can be predicted based on biomarkers calculated from multi-shell, high b-value diffusion MRI (dMRI); 2) to identify functional brain connectivity, structural brain connectivity and gray matter atrophy biomarkers that predict cognitive decline (executive and memory function) in VCID subjects over a period of two to three years; and, 3) to compare MMP measurements made with zymography with two novel methods, including an ELISA-based method and an activity assay based on immunocapture and fluorescent peptide cleavage in order to optimize the biochemical studies. This proposal will fill a gap in knowledge as to the optimal biomarkers to use for collaborative studies. The major aims are related to refining the set of biomarkers for patient selection, which will be done in the U2 phase by increasing the size of the existing University of New Mexico (UNM) cohort from 100 to 200 patients, and to perform the CSF studies for patient classification and the dMRI studies longitudinally to define surrogate markers to use for outcome measures in clinical trials in the U3 phase. The long-term goal is to have the biomarkers in place by the time the future treatment trials are planned in the fifth year.

Lay Summary

Narrative Dementia is a major health concern due to cost and increasing prevalence. Vascular cognitive impairment dementia (VCID) is the second most important cause of dementia by itself and an accelerator of Alzheimer’s disease (AD). The small vessel form of VCID, subcortical ischemic vascular disease (SIVD), is a progressive process that is optimal for treatment trials. Biomarkers can be used to identify patients with SIVD. This proposal is to optimize the two most promising biomarkers based on MRI modalities and biochemical studies of CSF. These will identify those patients at risk for enlarging the white matter damage (MRI diffusion studies) and for neuroinflammation (CSF MMP studies). The milestone-driven proposal will optimize these biomarkers in the first two years (U2 phase), and expand them to other centers in the next two years (U3 phase), making them available for clinical trials in the last year.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

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Alzheimer's disease & other dementias

Years:
2016

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N/A

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