Biomarkers for White Matter Injury in Mixed and Vascular Cognitive Impairment

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Country

USA

Title of project or programme

Biomarkers for White Matter Injury in Mixed and Vascular Cognitive Impairment

Source of funding information

NIH (NIA)

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€ 2,235,877.06

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01/02/2006

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4

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

subcortical ischemic vascular disease, Vascular Cognitive Impairment, white matter injury, White Matter Hyperintensity, vasogenic edema

Research Abstract
DESCRIPTION (provided by applicant): Vascular cognitive impairment (VCI) is a heterogeneous

disease that is a major cause of intellectual loss in the elderly. Pathological studies indicate that subcortical ischemic vascular disease (SIVD) due to hypertension, diabetes, and amyloid angiopathy is the major subgroup of VCI. Both the 2002 and 2011 Stroke Progress Review Group Reports identified VCI as a major target for research and treatment. Because of the progressive course of SIVD, it is considered the optimal type for clinical trials, and white matter hyperintensities (WMHs) on MRI are suggested as a surrogate marker. However, SIVD has an insidious onset, making it difficult to separate from other forms of dementia, particularly Alzheimer's disease (AD), which overlaps pathologically with VCI. Therefore, biomarkers are sought that could aid the differentiation of the various types of VCI and separate out the overlap or mixed syndromes at an early stage when treatment is possible. During the prior grant, the PI used MRI and CSF studies to identify several novel biomarkers for VCI, and showed that they can aid in diagnosis. The current grant is to use these mechanistic biomarkers prospectively to diagnose the SIVD. The central hypothesis is that progressive injury to the deep white matter is due to inflammation with expression of MMPs, disruption of the BBB, vasogenic edema, and oligodendrocyte death. Studies in animals indicate that hypoxia drives the molecular injury cascade, but that proteases are the final common pathway of blood vessel damage and break down of myelin. Since a large proportion of patients with dementia have both VCI and AD pathological processes, using a multi-modal approach to diagnosis may be the only way to identify the pure forms and separate them from the mixed forms. Aim 1: This aim is to determine a set of biomarkers that can be used in an algorithm to diagnose patients with the SIVD form of VCI early in the disease course. The overall goal of this study is to identif the optimal set of biomarkers from clinical, neuropsychological, imaging and CSF studies to accurately separate patients for treatment trials..Aim 2: This aim is to identify biomarkers for vascular disease and Alzheimer's disease that will aid in selection of mixed patients. This aim is focused on determining the implications of amyloid and tau proteins in the CSF of SIVD patients. Large autopsy studies of patients with AD, VCI and non-demented normal subjects show that pure forms of either AD or SIVD are less common than finding both present, and that evidence of both types of pathology is often present in normal subjects and identifying both AD and VCI biomarkers will improve diagnosis. Aim 3: To determine the role of inflammation in the growth of WMHs and cognitive decline and to test the predictive ability of a SIVD Scale. Data collected in Specific Aims 1 and 2 will be used in Aim 3, which is to determine a set of biomarkers that separate patients and that can be tested against the final diagnoses, and which can be used to indicate the natural history. The overall goal is to identify a minimal set of biomarkers from clinical examination, neuropsychological testing, MRI and CSF that could be obtained at an initial evaluation, and which will best predict the natural history and which can be used to select a more homogeneous group of clinical trials.

Lay Summary
Vascular cognitive impairment (VCI) is an important cause of dementia in the elderly and accelerates the most common form, Alzheimer's disease (AD). Both the 2002 and 2011 Stroke Progress Review Group Reports identified lack of understanding of the pathophysiology and treatment of VCI as a major target for research. We have proposed that the small vessel form of VCI is an inflammatory disease due to hypoxia- driven white matter injury. This proposal will use a unique set of biomarkers for VCI and AD to test the hypothesis. The importance is that early identification of VCI patients will facilitate treatment trials.

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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