Pathophysiology of SNAP in individuals with mild cognitive impairment

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Name of Fellow

Dr. S.J.B. Vos

Institution
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ZonMw

Contact information of fellow
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The Netherlands

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Pathophysiology of SNAP in individuals with mild cognitive impairment

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Alzheimer's disease & other dementias

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Research Abstract

Suspected Non-Alzheimer's disease Pathophysiology (SNAP) is a novel biomarker-based concept representing individuals with a normal amyloid marker but at least one abnormal Alzheimer's disease (AD) neuronal injury marker. The term "non-AD" in SNAP refers to the absence of an abnormal amyloid marker, which is considered essential for AD and followed by neuronal dysfunction. In a recent study, I found that a substantial number of individuals with mild cognitive impairment (MCI) have SNAP (29%). A subgroup however appears to progress to AD-type dementia at the short-term (24%). This relative high prevalence and poor outcome of SNAP makes it an intriguing and clinically relevant concept. The neuronal injury markers of SNAP (e.g. tau in cerebrospinal fluid (CSF) and hippocampal volume on magnetic resonance imaging (MRI)) are abnormal in AD but also in non-AD diseases. This raises questions about what SNAP exactly is and what could explain its biomarker profile.

Aim

The overall aim of this project is to unravel the pathophysiology of SNAP in a large cohort of individuals with MCI. My objectives are twofold:

1) To investigate the molecular mechanisms of SNAP by CSF proteomics
2) To examine the pattern and severity of neurodegeneration and vascular burden of SNAP using MRI

SNAP likely comprises distinct pathophysiological subtypes. I will test several competing hypotheses on potential causes that are reflected in CSF proteomic and imaging profiles:

1) SNAP as non-AD pathology
2) SNAP as pre-AD pathology
3) SNAP as AD subtype with less amyloid pathology
4) SNAP as AD subtype with different aggregated beta amyloid

Approach

We will select CSF samples, MRI scans, and clinical data of 170 subjects with MCI and 40 cognitively normal subjects from biobanks of Alzheimer centers in the Netherlands.
We will perform CSF multiplex analyses including a large panel of CSF proteins and peptides related to AD and non-AD using a Tandem Mass Tag (TMT) technique and we will measure CSF beta amyloid isoforms using reaction monitoring (SRM) mass spectrometry (MS). Furthermore, we will measure global regional atrophy and regional cortical thickness profiles as well as white matter lesions and lacunar infarcts on MRI. We will investigate whether the CSF proteomic and imaging profiles of SNAP differ from those of MCI-typical AD (abnormal amyloid and neuronal injury markers in MCI subjects) and the normal groups (normal amyloid and neuronal injury markers in cognitively normal and MCI subjects) using a theory-driven as well as data-driven random forest method for classification. Further characterization of SNAP will be performed using systems biology approaches including pathway and network methods building on the obtained measurements, Random Forest results, and information from existing knowledge sources. Stakeholders, including a scientific advisory board as well as patients and caregivers, will be involved in the overall molecular, imaging, and clinical characterization of SNAP.

Expected findings and potential importance

This project will provide novel insights in the pathophysiology of SNAP. I expect to identify CSF proteins, patterns of neurodegeneration and vascular burden, and clinical factors that can characterize SNAP or SNAP subtypes at the MCI stage. The classification of subjects with MCI

and SNAP according to all these features will help to improve early diagnosis and personalized treatment of SNAP.

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