Cerebrospinal fluid biomarkers for differentiating between Alzheimer's disease and Vascular dementia

Maria Bjerke
Institute of Neuroscience and Physiology
Gothenburg University

ABSTRACT

Patients suffering from mild cognitive impairment (MCI) run a higher risk of developing dementia, with Alzheimer's disease (AD) being the most common form. Vascular dementia (VaD) is proposed to be the second most common dementia entity, and it includes the clinically relatively homogenous subgroup of subcortical vascular dementia (SVD). Varying degrees of concomitant vascular lesions represent a link between AD and VaD, comprising a state of mixed dementia (MD). Biochemical markers provide important information which may contribute to differentiating between dementias of different etiologies, and in combination with the clinical assessment may improve diagnostic accuracy. The overall aim of this thesis is to provide for better separation between patients suffering from SVD and AD with the aid of biochemical markers.

The cerebrospinal fluid (CSF) biomarkers T-tau, P-tau$_{181}$, and Aβ_{1-42}, have proven useful in distinguishing MCI patients who ultimately develop AD (MCI-AD) at follow-up from those who remain stable. However, less is known about the biomarker pattern in MCI patients who develop SVD (MCI-SVD). An elevated baseline level of NF-L was found in MCI-SVD patients compared with stable MCI patients, while MCI-AD had decreased levels of Aβ_{1-42} and increased levels of T-tau and P-tau$_{181}$ compared with MCI-SVD patients and stable MCI patients.

The biomarkers NF-L, MBP, MMPs and TIMPs together with T-tau, P-tau$_{181}$, HFABP, and Aβ_{1-42} were assessed with the aim of improving discrimination between patients with SVD and AD as well as controls. Biochemical fingerprints representative of subcortical (NF-L, MBP and TIMP-1) and cortical alterations (T-tau, P-tau$_{181}$ and Aβ_{1-42}) provided for high discrimination between patients with SVD and AD, respectively, and between patients and healthy controls.

Enzymatic processing of the amyloid precursor protein (APP) was investigated on the basis of possible divergences in CSF APP metabolites in patients with SVD, MD, and AD as well as controls. A correlation between the levels of the soluble APP metabolite cleaved at the β site and the activity of an as yet unknown β-site cleaving metalloproteinase was found in all examined groups indicating similarities in processing pathways but dissimilarities in pathological mechanisms.

A multicentre study could be an important step to verify these results. However, high inter-centre variability is a problem for both Tau and Aβ_{1-42} measurements making such an enterprise difficult. Confounding factors affecting the stability of Aβ measurements were investigated and a major contributing factor seems to be assay specific, due to variation in antibodies and standards.

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Maria Bjerke

Fakultetsopponent: Professor Marianne Schultzberg,

Institutionen för neurobiologi, Karolinska institutet, Stockholm.

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I. Bjerke, M; Andreasson, U; Rolstad, S; Nordlund, A; Lind, K; Zetterberg, H; Edman, Å; Blennow, K; Wallin, A. Subcortical Vascular Dementia biomarker pattern in Mild Cognitive Impairment. *Dement Geriatr Cogn Disord*. 28(4): 348-356, 2009

II. Bjerke, M; Portelius, E; Minthon, L; Wallin, A; Anckarsäter, H; Anckarsäter, R; Andreasen, N; Zetterberg, H;Andreasson, U; Blennow, K. Confounding factors influencing amyloid beta concentration in cerebrospinal fluid. *Int J Alzheimers Dis*. 15:1-11, 2010

III. Bjerke, M; Zetterberg, H; Edman, Å; Blennow, K; Wallin, A; Andreasson, U. Cerebrospinal fluid matrix metalloproteinases in combination with markers reflecting subcortical and cortical alterations differentiate between Vascular dementia and Alzheimer's disease. Submitted

IV. Bjerke, M; Zetterberg, H; Edman, Å; Magdalena Nutu; Blennow, K; Wallin, A; Andreasson, U. A novel β-secretase activity correlates with amyloid precursor protein metabolites in cerebrospinal fluid of Vascular dementia and Alzheimer's disease. Manuscript

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