Cerebrospinal fluid biomarkers reflecting
β-amyloid and axonal pathology in Alzheimer's disease and related conditions

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs Universitet kommer att offentligen försvaras i Mölndalsaulan, V-huset, SU/Mölndals sjukhus, fredagen den 9 december 2011 kl 13.00

av

Niklas Mattsson

Fakultetsopponent:
Associate Professor Norman Relkin, PhD, MD
Weill Cornell Medical College, Cornell University, NY, USA

Avhandlingen baseras på följande delarbeten:

I: **Mattsson N**, Zetterberg H, Hansson O et al. CSF biomarkers and incipient Alzheimer disease in patients with mild cognitive impairment. JAMA 2009; 302(4): 385-393.

II: Johansson P[§], **Mattsson N**[§], Hansson O et al. Cerebrospinal fluid biomarkers for Alzheimer's disease – diagnostic performance in a homogeneous mono-center population. Journal of Alzheimer's Disease. 2011; 24(3): 537-46. [§]These authors contributed equally and should both be considered first authors.

III: **Mattsson N**, Rosén E, Hansson O et al. Age and diagnostic performance of Alzheimer's disease CSF biomarkers. Neurology. In press.

IV: **Mattsson N**, Andreasson U, Persson S et al. The Alzheimer's Association external quality control program for CSF biomarkers. Alzheimer's & Dementia. 2011; 7(4): 386-395.

V: **Mattsson N**, Rajendran L, Zetterberg H et al. BACE1 inhibition induces a specific cerebrospinal fluid β-amyloid pattern that identifies drug effects in the central nervous system. Manuscript.

VI: **Mattsson N**, Zetterberg H, Bianconi S et al. γ-Secretase-dependent amyloid β is increased in Niemann-Pick type C. A cross-sectional study. Neurology 2011; 76(4): 366-72.

VII: **Mattsson N,** Bremell D, Anckarsäter R et al. Neuroinflammation in Lyme neuroborreliosis affects amyloid metabolism. BMC Neurology 2010; 10: 51.

UNIVERSITY OF GOTHENBURG

Cerebrospinal fluid biomarkers reflecting
β-amyloid and axonal pathology in Alzheimer's disease and related conditions

Niklas Mattsson

Institute of Neuroscience and Physiology
Department of Psychiatry and Neurochemistry
The Sahlgrenska Academy
University of Gothenburg

Abstract

Cerebrospinal fluid (CSF) biomarkers may be used to identify and monitor pathological processes in the central nervous system. CSF biomarkers in Alzheimer's disease (AD) include β-amyloid 42 (Aβ42), total-tau (T-tau) and phosphorylated-tau (P-tau), reflecting brain amyloid, axonal and tangle pathology, respectively. This dissertation aims at defining and validating CSF biomarkers for amyloid and axonal pathology in AD and related conditions.

We found that CSF Aβ42, T-tau and P-tau identified early-stage AD patients in a uniquely large multi-center study, and achieved very high diagnostic performance in a well-controlled mono-center study, with careful standardization of clinical procedures, sample handling, and laboratory performance. The distribution of CSF Aβ42, T-tau and P-tau levels differed across age groups, likely reflecting age-dependent prevalence of AD-like pathology in cognitively stable individuals.

In the multi-center study, differences in the measured CSF biomarker levels were seen across laboratories. To monitor this, we established an external quality control program for CSF biomarkers. This program continues to grow and currently includes over 70 laboratories world-wide.

BACE1 is a key enzyme for Aβ production, and therefore an attractive therapeutic target in AD. CSF biomarkers were studied to measure pharmacodynamic effects of BACE1-inhibitors. A panel of novel biomarkers was identified that may be used to track treatment effects in clinical trials.

Finally, CSF biomarkers of amyloid and axonal pathology were studied in the lysosomal disease Niemann-Pick type C and in Lyme neuroborreliosis. Both these diseases had distinctly altered markers of amyloid metabolism and axonal pathology, and the biomarkers responded to treatments.

In summary, this dissertation indicates that CSF biomarkers are useful in early AD diagnosis, identification of treatment effects and monitoring of amyloid and axonal pathology across neurological diseases. It introduces a quality control program to facilitate global biomarker implementation. With the advancement of biomarkers as components of novel diagnostic criteria, knowledge of CSF biomarker alterations in different diseases will support optimal patient management.