Göteborg, 2022

CSF biomarker panels - Focus on synaptic pathology

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i hörsal **Arvid Karlsson**, Medicinaregatan 3, fredagen den **9de September** 2022, klockan **9:00**

av **Johanna Nilsson**

Fakultetsopponent:
Matthijs Verhage, PhD
Vrije Universitet, Nederländerna

Avhandlingen baseras på följande delarbeten

I. **Johanna Nilsson,** Johan Gobom, Simon Sjödin, Gunnar Brinkmalm, Nicholas J. Ashton, Johan Svensson, Per Johansson, Erik Portelius, Henrik Zetterberg, Kaj Blennow, Ann Brinkmalm. *Cerebrospinal fluid biomarker panel for synaptic dysfunction in Alzheimer's disease.* Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring. 2021. 13(1), e12179.

II. **Johanna Nilsson***, Katheryn AQ Cousins*, Johan Gobom, Erik Portelius, Alice Chen-Plotkin, Leslie M Shaw, Murray Grossman, David J. Irwin, John Q Trojanowski, Henrik Zetterberg, Kaj Blennow, Ann Brinkmalm. *Cerebrospinal fluid biomarker panel of synaptic dysfunction in Alzheimer's disease and other neurodegenerative disorders.* Manuscript.

III. **Johanna Nilsson**, Julius Constantinescu, Bengt Nellgård, Protik Jakobsson, Wagner S. Brum, Johan Gobom, Lars Forsgren, Keti Dalla, Radu Constantinesc, Henrik Zetterberg, Oskar Hansson, Kaj Blennow, David Bäckström, Ann Brinkmalm. *CSF biomarkers of synaptic dysfunction are altered in Parkinson's disease and related disorders.* Manuscript.

IV. Aitana Sogorb-Esteve*, **Johanna Nilsson***, Imogen J Swift, Carolin Heller, Lucy L. Russel, Georgia Peakman, Rhian S. Convery, John C. van Swieten, Harro Seelaar, Barbara Borroni, Daniela Galimberti, Raquel Sanchez-Valle8, Robert Laforce Jr, Fermin Moreno, Matthis Synofzik, Caroline Graff, Mario Masellis, Maria Carmela Tartaglia, James B. Rowe, Rik Vandenberghe, Elizabeth Finger, Fabrizio Tagliavini, Alexandre de Mendonça, Isabel Santana, Chris R. Butler, Simon Ducharme, Alexander Gerhard, Adrian Danek, Johannes Levin, Markus Otto, Sandro Sorbi, Isabelle Le Ber, Florence Pasquier, Ann Brinkmalm, Johan Gobom, Kaj Blennow, Henrik Zetterberg, Jonathan D Rohrer on behalf of the GENetic FTD Initiative. *Differential impairment of cerebrospinal fluid synaptic biomarkers in the genetic forms of frontotemporal dementia.* Alzheimer's Research & Therapy. 2022: Accepted.

V. **Johanna Nilsson**, Nicholas J. Ashton, Andrea L. Benedet, Laia Montoliu-Gaya, Johan Gobom, Tharick A. Pascoal, Mira Chamoun, Erik Portelius, Andreas Jeromin, Muriel Mendes, Henrik Zetterberg, Pedro Rosa-Neto, Ann Brinkmalm, Kaj Blennow. *Quantification of SNAP-25 with mass spectrometry and Simoa: a method comparison in Alzheimer's disease.* Alzheimer's Research & Therapy. 2022. 14.1: 1-10.

VI. **Johanna Nilsson**, Ann Brinkmalm, Sebastian Palmqvist, Wagner Brum, Alexa Pichet Binette, Shorena Janelidze, Nicola Spotorno, Erik Stormrud, Johan Gobom, Henrik Zetterberg, Kaj Blennow, Oskar Hansson. *Cerebrospinal fluid biomarker panel for synaptic dysfunction in a broad spectrum of neurodegenerative diseases.* Manuscript.

*Delad första författare

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INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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Abstract

Fluid biomarkers of neuropathological features are important clinical tools in diagnostics and patient monitoring of neurodegenerative diseases. One area which has gained recent attention is biomarkers reflective of synaptic pathology, which is an early and central part of the pathophysiology of many neurodegenerative diseases, including AD, and clinically relevant since synaptic function is the foundation of cognition. Synaptic biomarkers are thus of interest not only in the routine clinical assessment of neurodegenerative diseases to facilitate diagnosis, disease staging, and progression, but especially to monitor the efficacy and endpoints of treatments in drug trials which commonly aim to halt or reduce synaptic damage. The goal of this thesis was to develop mass spectrometry (MS) methods for quantifying biomarkers of synaptic pathology, to evaluate their potential in AD and across neurodegenerative diseases, and to examine concordance and discordance between biomarker results and other measures of synaptic dysfunction. A synaptic panel assay was successfully established, quantifying 17 synaptic proteins, including several SNARE proteins, neurogranin, synucleins, neuronal pentraxins, and 14-3-3 proteins. Together with an in-house-established MS assay quantifying SNAP-25 and synaptotagmin-1, the panel method was used to study synaptic proteins across neurodegenerative diseases in several studies included in this thesis.

One of the main findings is that almost all of the potential synaptic biomarkers showed specifically higher concentrations in the AD continuum in contrast to other neurodegenerative diseases. Indicating that higher levels of synaptic proteins are possibly generally a specific feature of AD and thus a marker of AD-specific synaptic dysfunction mechanisms compared with other neurodegenerative diseases. The possible exemption to this seems to be 14-3-3 ζ/δ, the higher levels of which might indicate that it is a general biomarker of synaptic degeneration mechanisms across neurodegenerative diseases. Particularly, SNAP-25, neurogranin, and β-synuclein, as well as 14-3-3 ζ/δ, seem to be promising AD-specific biomarkers able to both predict disease progression as well as cognitive decline. Furthermore, this thesis work demonstrated that the neuronal pentraxins are present at lower concentrations across neurodegenerative diseases, indicative of synaptic dysfunction and degeneration mechanisms equally affected across diseases. The neuronal pentraxins were also found to be associated with cognitive status in AD dementia and Parkinson's disease, the latter in which they were also associated with cognitive decline and the progression of motor symptoms and might be useful to predict disease severity. This thesis establishes that the neuronal pentraxins are possible prognostic and monitoring biomarkers for synaptic dysfunction/degeneration that associate with cognitive and motor symptoms across neurodegenerative diseases. Additionally, novel differences in synaptic proteins were found in both parkinsonian disorders and genetic frontotemporal dementia (FTD), with differential synaptic impairment represented by different synaptic proteins. Interestingly, multiple abnormalities were shown in the symptomatic patients with MAPT mutations indicating specific synaptic dysfunction in regard to the underlying proteinopathy found in each genetic FTD mutation. The results demonstrate that differential patterns of synaptic protein alterations across neurodegenerative diseases exist, probably due to differences in synaptic pathology mechanisms.

In conclusion, several of the studied synaptic proteins show promise as possible complements to other CSF and imaging markers as diagnostic, prognostic, stage, or monitoring biomarkers of cognitive decline and synaptic pathology. Furthermore, this thesis provided novel insight into synaptic pathology in neurodegenerative diseases. A better understanding of the mechanistic pathways of synaptic dysfunction across and between diseases may thus contribute to improving diagnostics and potentially also to the development of new therapeutic strategies targeting said pathways. The work included in this thesis demonstrates the importance of MS-based biomarker discovery, allowing for the simultaneous quantification and exploration of multiple biomarkers leading to knowledge that can drive the development of biomarkers as well as new, highly precise methods and increase the availability of biomarker quantification.

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