Göteborg, 2019

CSF biomarkers in idiopathic normal pressure hydrocephalus
Diagnostics and pathophysiology

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, den 14 juni 2019, klockan 13.00

Av Anna Jeppsson

Fakultetsopponent:

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Avhandlingen baseras på följande delarbeten

I. Jeppsson, A, Zetterberg, H, Blennow, K, Wikkelsø, C. Idiopathic normal-pressure hydrocephalus- Pathophysiology and diagnosis by CSF biomarkers. *Neurology 2013;80:1385-1392.*

II. Jeppsson A, Holtta M, Zetterberg H, Blennow K, Wikkelsø C, Tullberg M. Amyloid mis-metabolism in idiopathic normal pressure hydrocephalus. *Fluids Barriers CNS 2016;13:13.*

III. Jeppsson, A, Wikkelsø, C, Blennow, K, Zetterberg, H, Constantinescu, R, Remes A M, Herukka, S-K, Rauramaa, T Nägga, K, Leinonen, V, Tullberg, M. CSF biomarkers distinguish idiopathic normal pressure hydrocephalus from its mimics. *Accepted for publication in Journal of Neurology, Neurosurgery & Psychiatry*

IV. Jeppsson, A, Bjerke, M, Hellström, P, Blennow, K, Zetterberg, H, Kettunen, P, Wikkelsø, C, Wallin, A, Tullberg, M. CSF biomarkers highlight pathophysiological similarities and differences in idiopathic normal pressure hydrocephalus and subcortical small vessel disease. *Manuscript*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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CSF biomarkers in idiopathic normal pressure hydrocephalus
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Abstract

Idiopathic normal pressure hydrocephalus (iNPH) is a disease of the elderly with enlarged ventricles despite a normal CSF pressure. Clinically, iNPH presents with gait- and balance disturbances, cognitive decline and incontinence. As the symptoms are reversed by shunt surgery, precise diagnostics is of essence. As of today, the etiology of the disease is largely unknown and specific diagnostic and prognostic tests are lacking.

The overall aim of this thesis project was to explore the diagnostic and prognostic potential of CSF biomarkers in iNPH. By measuring markers reflecting different pathophysiological aspects, we also wanted to elucidate underlying pathophysiologic mechanisms of iNPH.

In ***paper I***, we showed that NFL was elevated and amyloid precursor protein (APP)–derived proteins and tau proteins were lower in patients with iNPH than in healthy individuals (HI). Post-surgery, there was an increase of NFL, APP-derived proteins, p-tau, and albumin in ventricular CSF, whereas levels of MBP and T-tau decreased. In ***paper II*** the concentrations of all soluble forms of APP, all Aβ isoforms and APL1β28 were lower, whilst APL1β25 and APL1β27 were higher in CSF of iNPH patients compared to HI. No difference could be seen in biomarker concentrations between patients who improved after surgery and those who did not. In ***paper III***, iNPH patients had lower concentrations of tau and APP-derived proteins in combination with elevated MCP-1 compared to HI and the most important differential diagnostic disorders. A prediction algorithm consisting of T-tau, Aβ40 and MCP-1 was designed as a diagnostic tool showing high discriminating ability. In ***paper IV*** all soluble forms of APP and all Aβ isoforms were lower in both subcortical small vessel disease (SSVD) and iNPH in comparison to HI, albeit with a more pronounced reduction in iNPH. INPH and SSVD had elevated concentrations of NFL, MBP and GFAP compared to HI.

Our findings indicate that patients with iNPH have a CSF biomarker profile that distinguishes them from HI of the same age as well as from their mimics. The profile is characterized by a downregulation of APP-proteins, CSF biomarkers reflecting destruction to the white matter and astrocyte activation but no substantial cortical damage. Analysis of CSF biomarkers may provide an important tool for diagnosing patients with iNPH.

Keywords: Idiopathic normal pressure hydrocephalus, cerebrospinal fluid, biomarkers

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