

The role of insulin-like growth factor-I in Alzheimer's disease and vascular dementia

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligen försvaras i sal Arvid Carlsson, Academicum, Medicinaregatan 3, fredagen den 19 april 2024, klockan 13:00.

av Alexandra Horvath

Fakultetsopponent:
Docent Per Dahlqvist
Umeå Universitet

Avhandlingen baseras på följande delarbeten

- I. Quinlan, P., Horvath, A., Nordlund, A., Wallin, A., Svensson, J. 2017. Low serum insulin-like growth factor-I (IGF-I) level is associated with increased risk of vascular dementia. *Psychoneuroendocrinology*. 86: 169–175
- II. Horvath, A., Salman, Z., Quinlan, P., Wallin, A., Svensson, J. 2020. Patients with Alzheimer's disease have increased levels of insulin-like growth factor-I in serum but not in cerebrospinal fluid. *Journal of Alzheimer's Disease*. 75: 289–298
- III. Horvath, A., Quinlan, P., Eckerström, C., Åberg, ND., Wallin, A., Svensson, J. 2022. Low serum insulin-like growth factor-I is associated with decline in hippocampal volume in stable mild cognitive impairment but not in Alzheimer's Disease. *Journal of Alzheimer's Disease*. 88: 1007–1016.
- IV. Horvath, A., Quinlan, P., Eckerström, C., Åberg, ND., Wallin, A., Svensson, J. 2024. The associations between serum insulin-like growth factor-I, brain white matter volumes, and cognition in mild cognitive impairment and Alzheimer's disease. Accepted. *Journal of Alzheimer's Disease*.

**SAHLGRENKA AKADEMIN
INSTITUTIONEN FÖR MEDICIN**



The role of insulin-like growth factor-I in Alzheimer's disease and vascular dementia

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Abstract

Background and purpose: Insulin-like growth factor-I (IGF-I) is involved in normal brain function, but little is known whether IGF-I activity affects the cognitive continuum of dementing disorders. The overall purpose of this thesis was to examine whether changes in IGF-I concentrations are linked to the development and progression of Alzheimer's disease (AD) and vascular dementia (VaD).

Methods: Study participants derived from the prospective Gothenburg Mild Cognitive Impairment study, which is performed at a single memory clinic. IGF-I was analyzed in serum (Study I-IV) and cerebrospinal fluid (Study II). Magnetic resonance imaging-estimated brain volumes were investigated in Study III and IV. In Study IV, neuropsychological test performance was also assessed.

Results: Patients with subjective or objective cognitive impairment (SCI/MCI) having low circulating IGF-I levels had a doubled risk of developing VaD (Study I). In AD, serum but not cerebrospinal fluid concentrations of IGF-I were higher than in the cognitively intact controls (Study II). In stable MCI, but not in AD, higher serum IGF-I was related to larger baseline volumes of the hippocampus and amygdala, and several brain lobes. Furthermore, in stable MCI, lower serum IGF-I was associated with accelerated loss of hippocampal volume over time (Study III). In SCI/MCI, the positive relationships between baseline IGF-I and white matter volumes at baseline and after 2 years were no longer present following correction for multiple variables. However, in the adjusted analyses, lower serum IGF-I was associated with decreased processing speed and executive function in both SCI/MCI and AD patients (Study IV).

Conclusion: Low serum IGF-I levels in SCI or MCI patients were associated with reduced neurocognitive performance and volumes of the gray but not the white brain matter. Low IGF-I was related to an increased risk of developing VaD in SCI and MCI patients. Conversely, in AD, IGF-I serum concentrations were elevated, which supports the hypothesis of IGF-I receptor resistance in the AD brain.

Keywords: IGF-I, mild cognitive impairment, Alzheimer's disease, vascular dementia

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