

# Endocrine and diagnostic aspects of cognitive impairment

with special reference to Alzheimer's disease

Akademisk avhandling

som för avläggande av medicine doktorsexamen  
vid Sahlgrenska akademien vid Göteborgs universitet kommer att offentligen  
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av

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Leg. läkare

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Avhandlingen baseras på följande delarbeten:

**I. Cerebrospinal fluid biomarkers for Alzheimer's disease – diagnostic performance in a homogeneous mono-center population.**

Johansson P<sup>§</sup>, Mattsson N<sup>§</sup>, Hansson O, Wallin A, Johansson JO, Andreasson U, Zetterberg H, Blennow K, Svensson J.

<sup>§</sup>Contributed equally.

*J Alzheimers Dis.* 2011; 24(3): 537-546.

**II. Serum but not cerebrospinal fluid levels of insulin-like growth factor-I (IGF-I) and IGF-binding protein-3 (IGFBP-3) are increased in Alzheimer's disease.**

Johansson P, Åberg D, Johansson J-O, Mattsson N, Hansson O, Ahrén B, Isgaard J, Åberg ND, Blennow K, Zetterberg H, Wallin A, Svensson J.

*Psychoneuroendocrinology.* 2013; *Epub ahead of print.*

**III. Reduced cerebrospinal fluid level of thyroxine in patients with Alzheimer's disease.**

Johansson P, Almqvist EG, Johansson J, Mattsson N, Hansson O, Wallin A, Blennow K, Zetterberg H, Svensson J.

*Psychoneuroendocrinology.* 2012; *Epub ahead of print.*

**IV. Mild dementia is associated with increased adrenal secretion of cortisol and precursor sex steroids in women.**

Johansson P, Johansson JO, Labrie F, Mattsson N, Hansson O, Blennow K, Zetterberg H, Wallin A, Ohlsson C, Svensson J.

*Clin Endocrinol (Oxf)* 2011; 75(3):301-308.

**V. Leukocyte telomere length (LTL) is reduced in stable mild cognitive impairment but low LTL is not associated with conversion to Alzheimer's disease: a pilot study.**

Movérare-Skrtic S<sup>§</sup>, Johansson P<sup>§</sup>, Mattsson N, Hansson O, Wallin A, Johansson JO, Zetterberg H, Blennow K, Svensson J.

<sup>§</sup>Contributed equally.

*Exp Gerontol* 2012; 47(2):179-182.



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## Abstract

Hormones like insulin-like growth factor-I (IGF-I), thyroid hormones, and sex steroids decrease with normal aging. It is, however, unclear whether low hormone levels are related to age-related conditions such as Alzheimer's disease (AD) or whether hormone levels are associated with markers of aging like leukocyte telomere length (LTL). The aims of this thesis were to validate cerebrospinal fluid (CSF) biomarkers in AD and to investigate whether hormonal aberrations might contribute to reduced cognitive function.

Consecutive patients undergoing primary evaluation of cognitive impairment (n=60) and healthy controls (n=20) were included. The patients had AD dementia or mild cognitive impairment (MCI) that was later diagnosed as AD dementia upon follow-up (n=32), stable MCI (SMCI, n=13), or other dementias (n=15). The same physician examined all subjects. Serum and CSF samples were collected and LTL was analyzed using quantitative PCR technique.

In *Paper I*, the core AD biomarkers in CSF (amyloid  $\beta$  [ $A\beta$ ]<sub>1-42</sub>, total-tau [T-tau], and phosphorylated tau protein [P-tau]) demonstrated a very high ability to diagnose AD compared to combined groups of controls and SMCI (area under the receiver operating characteristic curve [AUROC]=0.97 [95% CI 0.93–1.00, P<0.0001]). The addition of other biomarkers only marginally increased the diagnostic accuracy. In *Paper II*, serum IGF-I was higher in patients with AD or other dementias compared to healthy controls (P=0.01 and P<0.05, respectively), whereas CSF IGF-I remained unchanged. In *Paper III*, AD patients showed marginally increased serum thyroid-stimulating hormone (TSH). CSF total thyroxine (T4) level was lower both in patients with AD and other dementias compared to controls (both P=0.001). In *Paper IV*, both male and female patients showed increased serum concentrations of estrone (E1) and estrone sulfate (E1S) compared to controls of similar gender, but serum levels of other precursor sex steroids and cortisol were increased only in female patients. In *Paper V*, SMCI patients showed reduced LTL compared to AD patients (p=0.02) and controls (p=0.008).

In conclusion, the CSF biomarkers  $A\beta$ <sub>1-42</sub>, T-tau, and P-tau were highly accurate to diagnose AD in a well-defined study population. There were multiple alterations in hormonal levels in AD. There might be reduced passage of IGF-I and thyroxine through the blood brain barrier and aberrations in sex steroids and cortisol were more apparent in female patients. Low LTL might indicate more marked biological aging in SMCI patients whereas low LTL does not appear to be a risk factor for conversion to AD.

Keywords: hormones, aging, cerebrospinal, Alzheimer

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