

White matter changes in patients with cognitive impairment - clinical and pathophysiological aspects

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Avhandlingen baseras på följande delarbeten:

- I. Jonsson M, Edman Å, Lind K, Rolstad S, Sjögren M, Wallin A. Apathy is a prominent neuropsychiatric feature of radiological white-matter changes in patients with dementia. (*International Journal of Geriatric Psychiatry* 2010 Jun;25(6):588-95).
- II. Jonsson M, Zetterberg H, van Straaten E, Lind K, Syversen S, Edman Å, Blennow K, Rosengren L, Pantoni L, Inzitari D, Wallin A. Cerebrospinal fluid biomarkers of white matter lesions – cross-sectional results from the LADIS study (*European Journal of Neurology* 2010, 17: 377-382).
- III. Jonsson M, Zetterberg H, Rolstad S, Edman Å, Gouw A, Bjerke M, Lind K, Blennow K, Pantoni L, Inzitari D, Wallin A. Low cerebrospinal fluid sulfatide predicts progression of white matter lesions – the LADIS study. (*Submitted*).
- IV. Bjerke M, Jonsson M, Nordlund A, Gouw A, Blennow K, Zetterberg H, Pantoni L, Inzitari D, Schmidt R, and Wallin A. Cerebrovascular biomarker profile is related to white matter hyperintensities and ventricular atrophy in a LADIS substudy. (*Manuscript*).



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ABSTRACT

Cerebral white matter changes (WMC), detected with computed tomography (CT) or magnetic resonance imaging (MRI), represent a common condition in elderly people. However, the prognostic, symptomatological and biochemical constituents of WMC are only partially known. The aim of the present study was to evaluate WMC in relation to clinical manifestations in patients with mild cognitive impairment (MCI) and dementia and, by means of cerebrospinal fluid (CSF) analyses, to study different structural biomarkers possibly reflecting the pathophysiological process of WMC in non-disabled patients.

In study I, significant associations were found between WMC and age, sex, hypertension, ischaemic heart disease and TIA/minor stroke. Furthermore there were significant associations between WMC and apathy, mental slowness, disinhibition, gait disturbance and focal neurological symptoms, but not with depressed mood.

In study II, CSF was analysed for biomarkers known to be related to Alzheimer's disease [AD; the 1-40 and 1-42 fragments of amyloid- β , α - and β -cleaved soluble amyloid precursor proteins (sAPP α , sAPP β), total tau (T-tau), hyperphosphorylated tau (P-tau)] and vascular dementia [VaD; neurofilament protein light subunit (NFL), sulfatide, and CSF/S-albumin ratio]. NFL and sulfatide but not the AD biomarkers were related to WMC.

In study III, low CSF levels of the myelin lipid sulfatide but not biomarker deviations associated with axonal degeneration (NFL), or AD were found to be related to progressive WMC.

In study IV it was found that WMC were associated with ventricular atrophy which in turn was associated with neuropsychological dysfunction. Furthermore, tissue inhibitor of metalloproteinase 1 (TIMP-1), NFL and sAPP β were related to both ventricular atrophy as well as WMC. Matrix metalloproteinase 9 (MMP-9) was the only marker representing WMC progression.

The results indicate that WMC in patients with cognitive impairment are independently related to a dysexecutive-related behavioural symptom profile, vascular disorders and a non-AD biochemical profile associated with vessel-wall pathology and demyelination. The findings may have implications for definition and nosological knowledge of AD and vascular cognitive disorder.

Key words: white matter changes, vascular factors, cognitive impairment, neuropsychiatric symptoms, cerebrospinal fluid biomarkers, demyelination, axonal degeneration