



**Karolinska
Institutet**

Institution för klinisk neurovetenskap

Markers of inflammation and neurodegeneration in multiple sclerosis

AKADEMISK AVHANDLING

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av

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ABSTRACT

The main line of my thesis projects is searching for biomarkers and evidence of optimal correlation with clinical and para-clinical outcome measurements in multiple sclerosis (MS):

- investigating the **biochemical biomarker** in blood/plasma (cerebrosterol) and in cerebrospinal fluid (CSF) (oligoclonal bands (OCB)) and the correlation with MRI lesion load (paper I and paper IV);
- investigating the **genetic biomarker** (*CYP46A1*) for susceptibility and disability progression in MS (Paper III);
- comparison of the well-known positron emission tomography (PET) ligand and peripheral benzodiazepine receptor (PBR) antagonist, [^{11}C]PK11195, and a new PET-ligand [^{11}C]vinpocetine (**tissue receptor biomarker**). Both ligands denote areas of active ongoing inflammation in MS (paper II).

Paper I: How levels of cerebrosterol – a brain specific cholesterol metabolite - correlate with inflammatory and neurodegenerative markers on brain MRI.

Paper II: PET ligand and PBR agonist, [^{11}C]vinpocetine, facilitates cholesterol delivery to the mitochondrial membrane; a pilot study to investigate whether the new [^{11}C]vinpocetine is a better marker of MS inflammatory lesion areas compared to the old PET -PBR marker [^{11}C]PK11195.

Paper III: A study of how a single nucleotide polymorphism in the gene *CYP46A1*, coding for cholesterol hydroxylating enzyme 24S-hydroxylase, influences susceptibility and prognosis in MS singly and in synergism with another gene variant implicated in cholesterol turnover, *APOE ε4*.

Paper IV: Investigation of a CSF inflammation biomarker –OCB, and carriership of specific HLA gene alleles and the correlation with MRI outcome measures: total T1 and T2 lesion load, as well as T2 lesion load extension in MS specific compartments.

The **most important findings** are:

Paper I: results in this paper support the possibility that cerebrosterol in plasma is a potential marker of neurodegeneration in the relapsing remitting MS group.

Paper II: PET ligand [^{11}C]vinpocetine is a marker of activated glia in MS lesions and binds in different ways compared to [^{11}C]PK11195.

Paper III: *CYP46A1* alone or in combination with *APOE ε4* does not affect susceptibility for MS; men, as carriers of both the *CYP46A1* SNP rs754203 –AA variant and *APOE ε4* need walking assistance 17 years earlier compared with non-carrier men. However, results are lacking statistical significance, due to small sample size.

Paper IV: OCB in CSF, *HLA-DRB1*15*, and *HLA-DRB1*04* affect neither T1 lesion load on brain MRI at MS specific localizations nor total T2 lesion load. This paper supports the possibility that infratentorial T2 lesion load is associated with OCB in CSF.