Biomarkers in Multiple Sclerosis
Monitoring disease activity and treatment efficacy

Akademisk avhandling

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Biomarkers in Multiple Sclerosis
- Monitoring disease activity and treatment efficacy

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Abstract
The pathophysiology of multiple sclerosis (MS) is complex with the presence of inflammation and neurodegeneration in all stages of the disease. The disease course, treatment response and outcome are highly variable in MS. There is a need for reliable biomarkers reflecting different parts of the pathophysiology of MS that may improve the decision-making between various treatment options. The aim of the thesis was to investigate the influence of different therapies on biomarker levels in cerebrospinal fluid (CSF) and blood, explore the relationships between inflammatory and degenerative biomarkers, their diagnostic value and the value of measuring brain atrophy, i.e. brain parenchymal fraction (BPF) and the thinning of retinal nerve fibre layer (RNFL) to detect signs of early degeneration.

In study I, treatment with natalizumab reduced 24S-hydroxycholesterol concentrations in CSF and serum and 27-hydroxycholesterol concentrations in CSF.

In study II, relapsing-remitting MS patients had higher levels of neurofilament light (NFL), CXCL13, chitinase-3-like-1 (CHI3L1), and chitotriosidase 1 (CHIT1) than controls. Subgroup analysis revealed higher levels of NFL, CXCL13 and CHIT1 in patients treated with first-line therapy compared to second-line therapy. NFL and CHIT1 levels correlated with relapse status, and NFL and CXCL13 levels correlated with the formation of new lesions on MRI.

In study III, the levels of NFL, CXCL13, and CHI3L1 decreased after treatment with fingolimod.

In study IV, high correlation between serum and CSF NFL was found. Serum concentrations of NFL were significantly higher in MS patients than in healthy controls and treatment reduced serum NFL levels. Patients with relapse or with radiologic activity had higher serum NFL levels than those in remission or those without new lesions on MRI.

In study V, all phenotypes of MS had increased NFL compared to HC. Increased glial fibrillary acidic protein (GFAP), lower BPF and RNFL were associated with progressive MS but not with other phenotypes of MS. Lower BPF and RNFL, indicating neurodegeneration, were associated with longer disease duration.

We showed that CSF biomarkers that represent different parts of the pathophysiology of MS were related to both clinical and radiological measures. The correlation between neurodegenerative and inflammatory biomarkers, and the lack of signs of neurodegeneration in the earliest phases of relapsing-remitting MS, confirms the hypothesis regarding inflammatory-induced degeneration. The most important finding is that the blood-based biomarker NFL can reflect the disease activity and treatment efficacy. This finding is based on a large set of paired serum and CSF samples from a real-life cohort of patients across a wide clinical and therapeutic spectrum. Therefore, repeated serum NFL measurements may represent new possibilities for the monitoring of MS.

Keywords: biomarkers, multiple sclerosis, neurodegeneration, inflammation, treatment

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