Biochemical markers in dementia

Exploring Swedish registry data and the human proteome

Akademisk avhandling


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Abstract
Cerebrospinal fluid (CSF) biomarkers of neurodegenerative diseases have a wide scope of applications in diagnostics, prognosis assessment, disease staging, treatment evaluation and more. In this PhD project we aimed to expand the understanding of the properties of known CSF biomarkers of Alzheimer’s disease (AD) and other neurodegenerative diseases, including the most prevalent dementia disorders.

In study I, we explored CSF concentrations of three hallmark biomarkers of AD (amyloid β 1-42 [Aβ1-42], total tau [T-tau] and phosphorylated tau [P-tau]) in samples collected in clinical routine from 5676 patients, and found that the most clear-cut AD-like biomarker pattern was found in patients diagnosed with AD, but that large proportions of patients with other dementia disorders also had an AD-like profile.

In study II, we studied CSF concentrations of neurofilament light (NfL), a biomarker of general neurodegeneration, in 3356 patients with different dementia diagnoses. We found that CSF NfL is especially high in dementias with vascular engagement, but also in frontotemporal dementia. We also found that high CSF NfL concentrations are linked to short survival.

In study III, the biomarkers T-tau and P-tau were evaluated as biomarkers ofCreutzfeldt-Jakob disease (CJD), a rare rapid neurodegenerative disease. We could conclude that the combination of increased T-tau levels and increased T-tau/P-tau ratios in patients with CJD has a very high specificity for CJD. We further concluded that CJD patients exhibit rising T-tau concentrations as the disease progresses.

In study IV, we developed a new strategy for analyzing data output from explorative mass spectrometry. We were able to prove the validity of this concept by identifying and validating a new biomarker of AD, a peptide from the protein pleiotrophin (PTN151-166). We concluded that quantification-driven proteomics aided by clustering is a viable way of hypothesis generation in biomarker discovery studies, and that PTN151-166 is a promising AD biomarker candidate.