CSF biomarkers in patients subcortical vascular disease; overview of results from Gothenburg MCI and dementia studies

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The Gothenburg mild cognitive impairment (MCI) and dementia studies are prospective, observational, single-center cohort studies suitable for both cross-sectional and longitudinal analysis that outline the cognitive profiles and biomarker characteristics of patients with Alzheimer’s disease (AD), subcortical vascular disease with white matter involvement, and other cognitive disorders. The studies, the first of which started in 1987, comprise inpatients with manifest dementia and patients seeking care for cognitive disorders at an outpatient memory clinic. Cerebrospinal fluid (CSF) markers, a key focus in the Gothenburg studies, are assumed to reflect pathogenic events as they occur in the brain directly in living patients. One of the first biomarker findings that spoke in favor of the white matter involvement in patients with subcortical vascular disease was the increased levels of neurofilament light subunit (NFL) found in both overt subcortical vascular disease and also in its incipient form. Sulfatide, a component of myelin, was decreased in patients with white matter damage even before disease onset. Blood–brain barrier (BBB) dysfunction, visualized through an elevated albumin ratio, is another hallmark of subcortical vascular disease, whereas BBB has been shown to be normal in patients with AD without vascular disease. In a pivotal study with carefully defined groups of patients using a multivariate analytic method it was found that patients with overt subcortical vascular disease displayed elevated levels of myelin basic protein (MBP), NFL, matrix metalloproteinase 9 (MMP-9), and tissue inhibitor of metalloproteinase-1 (TIMP-1), whereas in AD the CSF levels of phosphorylated tau and total tau were increased reflecting degeneration of cortical regions affected by AD pathology. Interestingly, MMP-9 is believed to be involved in the regulation of the BBB opening and its activity is counterbalanced by TIMP-1. Our CSF results indicate a characteristic neurochemical pattern for subcortical vascular disease that is different from that of AD. The findings provide opportunities for trials in subcortical vascular disease and better definition of AD in AD trials.

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