Biochemical, morphologic and clinical markers at different stages of multiple sclerosis (MS) and their dynamics over time

Summary

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Description

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Background: Despite extensive research, the mechanisms and factors influencing multiple sclerosis (MS) disease progression have not yet been fully clarified and prediction of an individual patient’s prognosis still remains difficult. This is unfortunate for several reasons: In clinical routine, such understanding would help to improve patient counselling and could help to identify patients in need for specific treatment regimes. Likewise, such knowledge could serve to identify targets for novel therapeutic approaches.

However, thus far only very few clinical, morphologic and biochemical markers have been identified to indicate more rapid disease progression. To date, these markers are applicable only to the earliest clinically detectable phases of MS. They consist mainly of factors related to inflammatory aspects of MS such as the number of T2-hyperintense and contrast enhancing lesions and the presence of oligoclonal bands in cerebrospinal fluid (CSF) at disease presentation and subsequent relapse activity over the first few years of the disease. For later stages of the disease, there is also some evidence for the importance of T2 lesion accumulation, but this aspect does not reflect clinical disability of many patients in the long run.

Hypothesis and Objectives: It has recently been suggested that the inflammatory demyelinating disease process might trigger a cascade of events that further lead to neurodegeneration and are amplified by pathogenic mechanisms related to brain aging and accumulated disease burden such as microglia activation, chronic oxidative injury, accumulation of mitochondrial damage in axons, and age-related iron accumulation. Pathologically altered mitochondrial function and increased iron accumulation in MS-patients might further add to this process. These lines of evidence have been derived and followed mainly in a selective manner, i.e. by focussing on specific techniques and tools from immunohistopathology, magnetic resonance imaging (MRI), biochemistry and genetics. Thus far, this has produced only limited answers and could not make use of the synergistic potential of complementary information. Therefore this project aims to disentangle the obviously very complicated interaction of the various factors involved in MS disease progression and their contribution to disease prognostication by a multi-centre setting.

Methodology: This project is part of multi-centre study in collaboration with the Medical Universities of Vienna and Innsbruck. The PhD student will focus on investigating biochemical markers in the CSF and blood. The student will learn to perform immunophenotyping of CSF and blood cells by Flow Cytometry. CSF cytokine and chemokine levels (like soluble CD27 or CxCL13) will be analyzed using multiplex bioassays. The cytoskeletal protein neurofilament light (NFL) represents a candidate to indicate axonal damage and neurodegeneration and CSF NFL will be determined by ELISA. Increased CSF immunoglobulin free light chains (FLC) have consistently been demonstrated in MS, but their role for disease prognostication is still unclear. Therefore, Immunoglobulin Kappa and Lambda FLC will be determined by nephelometry. The student will further learn to perform diagnostic CSF work up, including determination of CSF white
cell count, total protein, lactate, albumin CSF-serum quotient, calculation of immunoglobulin G, A and M indices, determination of oligoclonal bands by isoelectric focusing followed by immunoblotting, as well as isolation of DNA and peripheral blood mononuclear cells. Obtained results will then be set into relation to morphologic and clinical data in a cross-sectional and longitudinal manner.

References:
Romme Christensen, J. et al. CSF inflammation and axonal damage are increased and correlate in progressive multiple sclerosis. Mult Scler 19, 877-84 (2013).

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