Medical University of Graz

The role of neuronal and glial biomarkers to indicate disease worsening in multiple sclerosis

Summary

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Supervisor:	Prof. Dr. Michael Khalil
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 03, 2022 00:00 and September 20, 2022 23:59 (Europe/Zurich)

Description

Background:

Multiple sclerosis (MS) is a chronic autoimmune mediated disease that is characterized by episodes of focal inflammation in the brain and spinal cord that affects both the white and grey matter.[1] The disease typically starts with a relapsing-remitting MS (RRMS) phase and after approximately 10 to 20 years, a progressive clinical course develops in many of the persons affected, eventually leading to impaired mobility and cognition.[1] The clinical presentation is very heterogeneous and related to the spatiotemporal dissemination of lesions and ongoing neurodegeneration within the central nervous system (CNS). These lesions are a hallmark of multiple sclerosis and are caused by immune cell infiltration across the blood–brain barrier (BBB) that promotes inflammation, demyelination, gliosis and neuro-axonal degeneration, leading to disruption of neuronal signaling.[2]

In the RRMS disease course, inter-relapse intervals have long been considered a “silent” phase that bears no clinical evidence of disease activity. The transition time from RRMS to a secondary progressive MS (SPMS) is variable and the diagnosis of SPMS can still only be done retrospectively.[3] However, there is mounting evidence that disability accumulation occurs even in RRMS, which is not related to overt relapses. This indicates an underlying progression even in typical RRMS populations and challenges the current clinical distinction of relapsing and progressive forms of the disease.[4,5]

There is a strong unmet need to develop reliable tools to indicate and monitor such processes. In this respect, body fluid biomarkers in particular for neuro-axonal injury (serum neurofilament light and heavy chain)[6,7] and astroglial markers (glial fibrillary acidic protein – GFAP)[8] have gained increasing attention, as they have been related to disease activity and progression in pwMS. With the advent of an ultra-high sensitive single molecule array (SiMoA),[9] it became possible to reliably quantitate also the compared to the CSF generally lower levels of NfL and GFAP in the peripheral blood, facilitating to perform repeated measurements and therefore studying this marker also in a longitudinal manner.

Hypothesis and Objectives:

Recent studies in persons with MS (pwMS) have shown that serum NfL (sNfL) reflects acute disease activity (relapse and lesion formation) in people, to correlate with therapy response and to predict the course of disability worsening.[6,10] Apart from NfL, some evidence also exists for blood GFAP to reflect, and potentially also predict worsening of disability in pwMS.[8] However, it is still unclear if combined analysis of sNfL and GFAP may more precisely allow to indicate and eventually predict disability worsening in pwMS.

Therefore, in this project we aim to longitudinally investigate, if combined analysis of sNfL and GFAP and their change over time may indicate disease worsening in MS, including clinical and brain imaging measures.

Methodology:

The PhD student will focus on investigating Nf and GFAP proteins in serum in pwMS and relate them to longitudinal clinical and MRI data. The student will learn to use the ultrasensitive Simoa platform for sNfL measurements. The

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student will further learn to perform diagnostic cerebrospinal fluid (CSF)/serum 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.

The student will also learn to handle larger clinical data sets and merge them with biochemical and MRI data prior to statistical analyses.

References:

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4. Kappos, L. et al. Contribution of Relapse-Independent Progression vs Relapse-Associated Worsening to Overall Confirmed Disability Accumulation in Typical Relapsing Multiple Sclerosis in a Pooled Analysis of 2 Randomized Clinical Trials. JAMA Neurol. 77, 1132–1140 (2020).

5. Cree, B. et al. Silent progression in disease activity-free relapsing multiple sclerosis. Ann. Neurol. 85, 653–666 (2019).

6. Khalil, M. et al. Neurofilaments as biomarkers in neurological disorders. Nat. Rev. Neurol. 14, 577–589 (2018).

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8. Abdelhak, A. et al. Blood GFAP as an emerging biomarkerin brain and spinal cord disorders. Nat. Rev. Neurol. 18, 158-172 (2022).

9. Rissin, D. M. et al. Single-molecule enzyme-linked immunosorbent assay detects serum proteins at subfemtomolar concentrations. Nat. Biotechnol. 28, 595–9 (2010).

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