Medical University of Graz

Clinical relevance of serial sNfL testing 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 March 24, 2021 00:00 and May 05, 2021 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] From pathological studies it is known that apart from focal demyelination, diffuse inflammation and grey matter pathology occurs leading to axonal injury and loss.[2] This is highly relevant as neuro-axonal damage and loss is believed to be the pathological substrate of permanent disability. Reliable quantification and longitudinal follow-up of such damage are important for assessing disease activity, monitoring treatment responses, facilitating treatment development and determining disease prognosis.[3,4] In this respect the neurofilament proteins have gained much attention in recent years as their levels rise in the cerebrospinal fluid (CSF) und also blood upon neuro-axonal damage.[4,5] Until recently, measurements of the neurofilament protein that is most promising as a biomarker, neurofilament light chain (NfL), in patients with neurological disorders could only be performed with CSF samples, mainly because assay sensitivity was insufficient for reliable quantification of NfL levels in the blood.[4] This has changed with the advent of an ultra-high sensitive single molecule array (SiMoA),[6] allowing to reliably quantitate also the generally lower NfL levels 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) was higher during acute phases of the disease, in patients with higher Expanded Disability Status Scale (EDSS) scores and in untreated patients.[7] Further studies, investigating NfL in blood samples collected during phase III trials have proven that sNfL may serve as a biomarker of MS disease activity and treatment response.[8] Another study on sNfL could demonstrate that this marker predicts disease worsening and brain and spinal cord atrophy in MS.[9] However, in most longitudinal studies on blood NfL performed so far, the time-interval between baseline and follow-up blood sample collection was quite long, in general one to two years. Based on a most recent report, the average of 2-5 serial sNfL measures within 12 or more months, derived from a clinical trial with long-term follow-up, appear superior to single measures in prognosis of disability worsening in patients with RRMS.[10] The rationale is that singular measures coinciding with a relapse or formation of an acute lesion may be over-predictive for the overall disease progression. The sustained post-relapse elevation of sNfL levels relative to the levels prior to the relapse appear to be more critical for long-term progression than short-term peak levels. This complication may be overcome in a clinically meaningful way by integral measures.

Therefore, in this project we aim to investigate the potential clinical value of repetitively assessing short-term changes in sNfL (blood sampling at least every three months) in patients with MS in a Real-World-Setting. To this end we aim to elucidate if serial sNfL assessment within a period of 12-24 months may add value to monitoring and/ or predicting disease activity, disease progression and response to disease modifying treatments. This shall ultimately serve to investigate if sNfL may be applied also on an individual patient level. The present project shall be performed as collaborative study between the Medical Universities Innsbruck, Vienna and Graz.

Methodology:

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

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

References:

1. Reich, D. S. et al. Multiple Sclerosis. The New England Journal of Medicine, 378(2), 169–180 (2018).

2. Kutzelnigg, A. et al. Cortical demyelination and diffuse white matter injury in multiple sclerosis. Brain 128, 2705–12 (2005).

3. Teunissen, C. E. & Khalil, M. Neurofilaments as biomarkers in multiple sclerosis. Mult. Scler. 18, 552–6 (2012).

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

5. Khalil, M. et al. Serum neurofilament light levels in normal aging and their association with morphologic brain changes. Nat. Commun. 11, 812 (2020).

6. 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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