Universität Basel

Research Project

Towards development of neurofilament light chain as precision medicine biomarker for multiple sclerosis

Third-party funded project

Project title Towards development of neurofilament light chain as precision medicine biomarker for multiple sclerosis
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Project start 01.10.2019
Probable end 30.09.2023
Status Completed

Multiple sclerosis (MS) is a disease that has neuroinflammatory and neurodegenerative features. The neuroinflammatory component appears to be driven by the immune system in the 'periphery', while in parallel, and partly independent, a CNS-compartmentalised neurodegenerative processes takes place (1). The advent of highly efficacious therapies like natalizumab, alemtuzumab and rituximab/ocrelizumab has led to a near complete control of relapse activity in most patients. In contrast, progression (disability worsening independent of relapses) as the clinical manifestation of neurodegeneration remains an unmet medical need as even the most effective compounds fall short in controlling steady progression (2;3). There are two major barriers for the development of more effective therapies for progressive MS (PMS) as well as for other neurodegenerative disease: i) in the clinic, the disease process is manifest only when the functional reserve begins to be exhausted, i.e. at a time point when neuronal loss is already in an advanced stage, and ii) no surrogate biomarker is available that allows to detect and monitor the subclinical neurodegenerative processes.In our previous project (320030_160221 / 1), we developed and validated the concept that the concentration of serum or plasma neurofilament light chain (NfL) in MS is a biomarker of a) disease activity, b) drug response, and is c) predictive of long-term disease course. Based on collaborations with other research groups, we also contributed significantly to the validation of NfL as a biomarker of neuro-axonal damage and loss in primary neurodegenerative diseases such as Alzheimer's disease (AD) and other forms of dementia, spinal cord injury, stroke, or neonatal brain injury. The ability to quantify, for the first time, neuro-axonal injury from a blood-derived specimen marks a breakthrough for biomarker research in neurology. The goal of our new project is to bring our knowledge of NfL biology to a level at which it can be utilised as precision medicine tool for individual patients.First, we aim to elucidate mechanisms that lead to the NfL increases observed in stable relapsing forms of MS and in PMS, and to determine the impact of acute versus chronic active lesions on the levels of NfL. This will be achievable based on our collaborations with MRI research teams at the Centre Hospitalier Universitaire Vaudois (CHUV) and the University Hospital Basel (USB). Furthermore, based on preliminary data from the Swiss MS Cohort Study (SMSC), we have a unique opportunity to identify individual patients that exhibit a suboptimal treatment response, and who would have benefited from a personalised therapy scheme. In these cases, it is our hypothesis that the increased NfL blood levels signal the presence of continuous subclinical disease activity and indicates that these patients are likely to benefit from therapy escalation. We have the ability to address these issues now because we were able to create the SMSC - a well-characterised cohort of more than 1300 MS patients with long-term

follow-up (FU). Furthermore, the collaboration between the Swiss MS Registry (SMSR) and the SMSC will allow us to investigate the association of serum NfL (sNfL) with patient reported outcome measures of quality of life.Second, we will develop highly sensitive assays for myelin components (myelin basic protein and myelin oligodendrocyte glycoprotein) to quantify demyelination in MS based on Single Molecule Array (SIMOA) technology, building on our vast previous experience with this technique and allowing to contextualise the sNfL biomarker signal in MS.Third, we want to determine the turnover rate and half-life time of blood NfL in rodent models of MS (collaboration with the Dept. of Pharmacology, University of Oxford), as the lack of its knowledge is a main hurdle for using of sNfL for individualised monitoring purposes.Lastly, based on international collaborations with academic centres in Switzerland, Germany and the USA, we will establish a normative data base (NDB) including more than 11'000 healthy persons to correct for the age-dependency of the sNfL signal, and to evaluate the impact of comorbidities, which is a prerequisite for accurate interpretation of individual measuring results. In addition, the size and available clinical, samples and MRI FU within the NDB collaborations will allow us to evaluate the predictive value of sNfL on future pathology detected clinically or by MRI in currently 'healthy persons'.The successful completion of these work packages is essential if sNfL levels are to be established as the first biofluid marker to quantify present and to predict future neurodegenerative processes in MS, and to support therapeutic decision making in individual patients for personalised medicine.

Financed by
Swiss National Science Foundation (SNSF)

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