Detection of disease specific aggregates of TDP-43 in cerebrospinal fluid of ALS patients for disease specific diagnosis

Acronym: Aggregated- TDP43

Principal Investigator: Markus Otto

Grant: 80 000€

Duration: one year

Summary of the research project

"We and others could show that the measurement of neurofilaments in cerebrospinal fluid and blood is a promising tool to support the clinical diagnosis and prognostic evaluation of ALS. We already organize round-robins to establish a similar quality of analysis in several European labs. Additional candidate markers await further validation. However, none of these markers seem to be specific and results have to be interpreted always in the differential diagnostic context.
For a specific diagnosis we aim to detect aggregated TDP-43 in cerebrospinal fluid (CSF) of patients with sporadic ALS. TDP-43 seems to be the most straightforward candidate biomarker for ALS due to its involvement in the pathogenesis. Monomeric TDP-43 could be detected by us and others in blood and CSF. However, data about monomeric TDP-43 in CSF is inconsistent as a considerable fraction of TDP-43 is serum-derived.
It has been shown for other neurodegenerative diseases that the aggregated form of the disease-related protein (e.g. alpha-synuclein, prion protein) in CSF reflects the disease pathology. For this detection only minute amounts are used as seeding core. Initially, the protein misfolding cyclic assay (PMCA) was used to detect these minute amounts of pathological prion protein by a technique conceptually analogous to DNA amplification by PCR: small amounts of aggregated prion protein act as template for the conversion of normal prion form which is added in excess. By repetitive ultrasound application newly formed aggregates are broken down to form new seeds for further conversion and amplification.
Subsequently, the RT-QuIC (real-time quaking-induced conversion) assay has been developed which is a microplate reader-based method for the quantitative detection of misfolded prion in CSF and other fluids/tissues. With this assay, the conversion of normal prion and growth of aggregates is detected by thioflavin T staining. This assay is already established in our lab for the detection of pathological prion protein.
Within this project we will adopt this method for TDP-43 in CSF and serum. As prerequisite for this analysis we will use our established biomaterial bank with more than 500 CSF samples of ALS patients. "

Markus Otto is Prof. for Neurology, head of the outpatient unit, Vice-chair Department of Neurology, head of the research laboratory for Neurodegenerative Diseases Diagnostics, Department of Neurology, at Ulm University

Publications

(1) Weydt, P., **P. Oeckl**, A. Huss, et al. **M. Otto** (2016). "Neurofilaments levels as biomarkers in asymptomatic and symptomatic familial ALS." Ann Neurol Jan;79(1):152-8
(2) **Steinacker, P**., E. Feneberg, J. Weishaupt, et al. **M. Otto** (2016). "Neurofilaments in the diagnosis of motoneuron diseases: a prospective study on 455 patients." J Neurol Neurosurg Psychiatry 87(1): 12-20.
(3) **Steinacker, P**., K. Blennow, S. Halbgebauer, et al. **M. Otto** (2016). "Neurofilaments in blood and CSF for diagnosis and prediction of onset inCreutzfeldt-Jakob disease." Scientific Reports Dec 8;6:38737.