

premodiALS

Identification of a disease signature for presymptomatic and early ALS

Poster number: 27

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Aims, research questions and working hypothesis

Even in industrialized countries with advanced medical service, it takes on average 12 months after the first symptoms to be diagnosed with ALS. Because of the rapid and fatal progression of ALS, a timely diagnosis is crucial to start therapy early and allow for inclusion in clinical trials. Although several ALS diagnostic biomarkers have been proposed, including neurofilaments in serum and cerebrospinal fluid (CSF) and soluble p75ECD in urine, a multi-modal signature might be more sensitive to detect early or even pre-symptomatic disease. About 10-15% of ALS patients have a genetic cause. Genetic testing of their family members can identify subjects, who carry the disease-causing mutation, but have not yet developed symptoms of the disease, so-called "pre-symptomatic gene mutation carriers" (PGMC).

Means/methods implemented by the consortium

For this study, 10 different countries join forces (Germany, France, Switzerland, Turkey, Slovakia, Israel, Sweden, Poland, Australia and USA). We plan to recruit PGMC (n=110) and patients with pure motor symptoms (classified after follow-up as either having early ALS or ALS mimics, n=110). Control healthy participants will also be included for comparison (n=110). PGMC, controls and patients with either early ALS or ALS mimics will be assessed longitudinally at two visits with a one-year interval (baseline visit V0 and follow up visit V1). Assessments include an environmental and medical history questionnaire, a neurological examination, a brief smell test examination (B-SIT), a cognitive examination (ECAS), and the collection of biological samples (serum, plasma, urine, tear fluid, and CSF). Proteomic, metabolomic and lipidomic profiles will be analyzed by mass spectrometry and targeted immunoassays. Data will be processed by standardized protocols and consecutively integrated to identify clinical and molecular fingerprints of PGMC and early ALS.

What are the outcomes of the project?

The premodiALS recruitment started in Q1/2023. As of end October 2024, a total of 175 participants were recruited, including 45 controls, 41 PGMC and 84 early ALS/mimics individuals. Recruitment is still ongoing. Parts of the biomaterial collected is available for yet undetermined collaborative projects and future analyses not specified in the initial study protocol. The premodiALS project has been presented at several international conferences as well as during patients days, on the TV and other media of the country members.

Significance and impact of the work on the field

The identification of a panel of presymptomatic biomarkers would enable 1) The identification of individuals at risk of developing ALS before manifest motor symptoms, and 2) confirm ALS diagnosis when the presence of motor symptom are not sufficient. An early detection of the disease would result in a timelier diagnosis offering the opportunities of earlier intervention, earlier inclusion in clinical trials and will facilitate the development of disease-modifying treatments for ALS.

Next steps and future challenges

A manuscript detailing the premodiALS protocol is prepared for submission aiming to promote collaboration and encourage harmonization of protocols across presymptomatic ALS studies. Plasma, serum and CSF samples from the baseline visit (V0) from 110 participants are currently being analyzed via the multiplex NULISA targeted immunoassay. We aim to extend the premodiALS study by an additional three years to 1) extend the recruitment period to include as many participants as originally planned, or even more, and 2) add additional follow-up visits (V2, V3, and V4), each visit separated by one year and ensure a more detailed longitudinal follow-up of the disease evolution.