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BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS IN AMYOTROPHIC LATERAL SCLEROSIS

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Akademisk avhandling

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Biomarkers for diagnosis and prognosis in amyotrophic lateral sclerosis.

Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by loss of upper and lower motor neurons, leading to paresis, muscle atrophy, and respiratory failure. ALS can be difficult to diagnose and prognosticate early.

Aim: To investigate the diagnostic and prognostic characteristics of biomarkers in cerebrospinal fluid (CSF), plasma, and skeletal muscle tissue in patients with ALS.

Paper I: Neurofilament light chain (NFL) and phosphorylated neurofilament heavy chain (pNFH) were analyzed in CSF using enzyme-linked immunosorbent assay (ELISA), and NFL in plasma was analyzed using single-molecule array (SIMOA). CSF NFL, CSF pNFH, and plasma NFL concentrations can differentiate ALS patients from ALS mimics, and were significantly negatively correlated with the disease duration in ALS patients.

Paper II: Myosin heavy chain (MyHC) isoforms in extraocular muscles were investigated using immunofluorescence. Control donors had significantly higher proportion of myofibers containing MyHCIIa and significantly lower proportion of myofibers containing MyHCeom in the global layer compared to spinal-onset ALS and bulbar-onset ALS donors. Disease duration in the spinal-onset ALS donors was significantly correlated with the proportion of myofibers containing MyHCIIa in the global layer and MyHCeom in the orbital layer.

Paper III: The study combined the neurofilament concentrations from Paper I, with cytokines previously analyzed in CSF and plasma using SIMOA, to investigate distinct molecular phenotypes in ALS. Patients with bulbar-onset ALS had significantly higher concentrations of CSF tumor necrosis factor α (TNF- α) compared to ALS mimics. TNF- α and NFL were significantly correlated with each other in both CSF and plasma in ALS patients. Combined analysis of NFL and IL-6 in plasma identified molecular prognostic subgroups in ALS patients.

Paper IV: Creatine kinase (CK), high-sensitivity cardiac troponin T (hs-cTnT), hs-cTnI, and cystatin C (CysC) were analyzed in plasma in a fully accredited laboratory. CK and hs-cTnT concentrations were significantly elevated in limb-onset ALS compared to controls and bulbar-onset ALS. hs-cTnT concentrations were significantly elevated in truncal-onset ALS compared to controls and bulbar-onset ALS. Multivariable Cox proportional hazards models indicated elevated concentrations of CysC as a significant marker for worse prognosis in ALS.

Conclusions: The papers report diagnostic and prognostic characteristics of biomarkers in CSF, plasma, and muscle tissue in ALS patients. The significant findings for biomarkers in plasma could be of value since plasma sampling does not involve a lumbar puncture.

Keywords

amyotrophic lateral sclerosis, biomarkers, neurofilaments, cytokines, troponin, cystatin C

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