Neurogenetic, biochemical and cognitive aspects of familial and sporadic forms of amyotrophic lateral sclerosis in the Czech population

Abstract

This thesis aims to highlight the pitfalls and risks of diagnosis and misdiagnosis in ALS and to evaluate the profile of genetic variants among Czech ALS patients. These data are still completely lacking and current therapeutic trends are directed towards gene-targeted treatment. The first main objective of the study is to evaluate the diagnostic parameters of tests determining the levels of light (NfL) and phosphorylated heavy (p-NfH) neurofilament chains in the cerebrospinal fluid and serum; especially in clinically difficult-to-distinguish situations. A secondary objective is to define the determinants of neurofilament levels. The second main objective is a pilot study on the frequency of genetic variants among Czech patients. A secondary objective is to find clinical predictors of a causal mutation. Our results have shown that in patients with a typical ALS phenotype, the diagnostic performance of both neurofilaments in the cerebrospinal fluid is very good and comparable to each other, and, therefore, can be used to support the diagnosis. On the other hand, variants with incomplete ALS phenotype or slow progression are associated with lower neurofilament levels. Conversely, in relevant alternative diagnoses (compression of roots or myelon), extensive axonal damage leads to their marked elevation, limiting their use in difficult-to-distinguish situations. The study on genetic variants in Czech patients showed the highest frequency of hexanucleotide repeat expansion in C9orf72, as in other European cohorts. Bulbar region of development or comorbid FTD is associated with a higher probability of detecting this variant in sporadic patients.

Keywords

Amyotrophic lateral sclerosis, biomarkers, *C9orf72*repeat expansion, cerebrospinal fluid, frontotemporal dementia, gene variants, neurofilaments, neurogenetics, next-generation sequencing