

Untangling neuroinflammation in amyotrophic lateral sclerosis

Strapline

Chitinase levels are linked to rate of progression and provide a new foothold on optimizing therapeutic targeting of neuroinflammatory pathways.

Main text

A broad body of evidence supports both pathogenic and neuroprotective roles for inflammation in ALS¹ but trials of several immunomodulatory drugs have not yielded a beneficial effect in an increasingly complex disorder with multiple upstream cellular causes². There has been interest in proteins involved in the microglial response as potential biomarkers for well over a decade^{3,4}. Recently this has focused on a group of three chitinase proteins, thought to be macrophage-derived, identified in proteomic analysis of cerebrospinal fluid (CSF) taken from ALS patients^{5,6}. Chitinases have also been studied the pathologically-related disorder frontotemporal dementia (FTD)^{7,8}. Although chitin is not produced by mammals, it is suggested that chitinases might act upon *N*-acetylglucosamine-containing extracellular matrix polymers, such as hyaluronan or keratan sulphate, present in the mammalian central nervous system. Chitotriosidase 1 (CHIT1) is an active chitinase, whilst YKL-40 (Chitinase-3-like protein 1, CH3L1) and YKL-39 (Chitinase-3-like protein 2, CHI3L2) are inactive chitinases involved in innate immunity.

In this issue, Gille, De Schaepdryver et al measured CSF levels of CHIT1, YKL-40 and macrophage chemoattractant protein-1 (MCP-1) in 105 ALS patients, 102 patients with neurological diseases distinct from ALS, and a group of 16 patients initially suspected to have ALS in whom the diagnosis was subsequently excluded (termed ALS mimics). The finding of elevated levels of the three proteins in ALS patients compared with other groups is in keeping with the published literature^{3-6,9-11}. The unimpressive classifier performance of CHIT1 and YKL-40 in distinguishing ALS from mimics is similar to previous studies^{6,9,10}; MCP-1 also performed poorly as an independent classifier. CHIT1 and YKL-40 levels were linked to rate of disability progression, though a previously-identified weak correlation of MCP-1 with rate of progression was not observed³. The study also demonstrated survival associations with both MCP-1 and YKL-40 in multivariate models, but not CHIT1, in contrast to a previous study which reported an association only with CHIT1¹⁰. Levels of all proteins correlated inversely with survival from in univariate analysis. The authors also noted higher CHIT1 levels in those with greater regional burden of disease, so that there appears to be consistency across studies for CHIT1 levels as a marker of absolute disease progression. The present study did not screen for the presence of a *CHIT1* polymorphism which can lead to reduced CHIT1 activity¹², though a previous study reported that this did not appear to influence the severity of ALS⁷. As noted in previous studies, serum levels of CHIT1 and YKL-40 were not significantly elevated.

CSF CHIT1 levels have been linked to the degree of microglial activity within the spinal cord⁹. YKL-40 levels have been correlated with the burden of cognitive dysfunction and extent of clinical upper motor neuron involvement in ALS¹⁰. In a study comparing FTD patients and controls there was marked elevation of CSF YKL-40 and the astrocytic protein glial fibrillary

acidic protein, but not CHIT1⁷. Pathological data in Alzheimer's disease suggest that YKL-40 may be predominantly astrocytic rather than microglial in origin¹³. Taken together, these findings attest to the multi-dimensional nature of the neuroinflammatory component of neurodegeneration in ALS, in which CSF CHIT1 levels reflect microglial activity within the spinal cord and YKL-40 levels represent astroglial activity within the brain. Immunomodulatory therapeutic approaches must necessarily be highly nuanced. Measuring the CSF inflammatory profile in ALS may have unrealised value in the stratification and appropriate selection of participants for future trials, leading the way in an era of increasingly personalised therapy.

References

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