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Editorial Commentary

Serum neuronal pentraxin-2 is unlikely to serve as a synaptic biomarker for survival prediction in ALS

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Editorial commentary

We were interested to read the article by Alali *et al*. on serum levels of neuronal pentraxin-2 (NPTX2) as a predictor of disease severity in amyotrophic lateral sclerosis (ALS) [1]. The study is remarkable, but requires discussion.

We disagree with the assertion that the study identified NPTX2 as a promising synaptic biomarker for predicting survival in ALS [1]. A prognostic biomarker is a measurable clinical or biological characteristic of a patient that is used to monitor and predict disease progression and provides information about the likely outcome of a disease, regardless of treatment [2]. A biomarker should be easily accessible, specific to a disease, sensitive to change, reliable and clinically relevant [3]. However, NPTX2 did not fulfill these criteria as it was not specific for ALS but was also elevated in the control group (DC) [1].

NPTX2 is predominantly expressed in cortical neurons, in the pituitary gland, in islet cells and the adrenal gland [4]. At the cellular level, it is localized to the Golgi apparatus, the centrosome and actin filaments [4]. Since ALS is characterized by neuronal degeneration, it is conceivable that NPTX2 is mainly found in cerebrospinal fluid (CSF), but not in serum as measured in the index study [1]. NPTX2 in serum could originate predominantly from tissues that are not affected in ALS, which would lead to false-positive results. Accordingly, the determination of NPTX2 in CSF might reflect neuronal degeneration and synaptic plasticity more accurately than NPTX2 in serum. To assess the relationship between serum and CSF NPTX2, it might be useful to determine both values simultaneously.

The explanations for the discrepancy between the results of the index study and the study by Oh *et al*. [5] are not comprehensible [1]. Differences in the measurement technique cannot explain the controversial results of the two studies, as the results would remain the same even if different methods of determination were used. Differences in the biological properties of serum and cerebrospinal fluid also cannot explain the divergent findings. The sample size is also not an argument for the discrepancy, as Oh *et al*. examined CSF samples from 20 ALS patients, while serum from 43 patients was examined in the current study. No statement can be made on the heterogeneity of the disease, as the cohort was not specified in either study.

Several details are missing [1]. There is no mention of the criteria used to diagnose ALS. Knowledge of the diagnostic criteria is crucial for comparison with other studies. It is also not mentioned whether only sporadic ALS or also familial ALS was included in the study. It was not reported how many patients had bulbar involvement and muscular respiratory failure. Since serum levels of NPTX2 may also depend on disease duration, it may be helpful to include disease duration in the analysis.

Before concluding that NPTX2 is a potential biomarker of ALS severity, the requirements for an appropriately designed study must be met. Prediction of survival in ALS may not be reflected by a single biomarker, but rather by the degree and progression of respiratory and bulbar muscle involvement.

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