DOI:10.4274/tnd.galenos.2019.97720
Turk J Neurol 2019;25:187-188

Prognostic Value of Serum Neurofilaments in Patients with Clinically Isolated Syndromes

Klinik İzole Sendromlu Hastalarda Serum Nörofilamentlerinin Prognostik Değeri

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Keywords: Multiple sclerosis, clinically definite multiple sclerosis, clinically isolated syndrome, neurofilament light chain
Anahtar Kelimeler: Multipl skleroz, klinik kesin multipl skleroz, klinik izole sendrom, nörofilament hafif zincir

Syndromes

Neurofilament light chains (NfL) are protein components of the neuron structure that are released in the extracellular space subsequent to neuronal damage. Previous studies have shown that NfL concentrations are high in cerebrospinal fluid (CSF) in patients with clinically isolated syndrome (CIS) and multiple sclerosis (MS), and that NfL might act as a biomarker for conversion from CIS to MS. Indeed, measuring this structural protein in serum at the first demyelinating clinical episode of patients may make NfL an ideal biomarker for assessing prognosis. From this idea, Dalla Costa et al. (1) evaluated serum NfL concentrations in patients with CIS in addition to CSF, magnetic resonance imaging (MRI), and clinical data, and analyzed the prognostic value of serum NfL in conversion from CIS to MS in their study "Prognostic value of serum neurofilaments in patients with clinically isolated syndromes" published in "Neurology".

In this study, 222 patients with a diagnosis of CIS (mean follow-up: 100.6±58.0 months) who were admitted to the Neurology department between 2000 and 2015 for a first demyelinating event, and who met the inclusion criteria were analyzed retrospectively. During the two-year follow-up, 45 patients (20%) were diagnosed as having clinically definite MS and 141 patients (63.5%) were diagnosed as having MS according to the McDonald 2017 criteria. At the end of the total follow-up period, 152 patients were diagnosed as having clinically definite MS or MS according to the McDonald 2017 criteria, and 70 patients remained as CIS. It was found that patients who subsequently developed MS were younger, had a greater likelihood of reporting multifocal symptoms, and had a greater chance of having CSF OCBs, and a greater number of T2 lesions and gadolinium (Gd)-enhancing lesions.

In the study, NfL levels were measured using a previously validated electrochemiluminescence immunoassay method, and a serum NfL concentration of 3.91 pg/mL was accepted as analytical sensitivity. The median concentration of serum NfL was 22.0 pg/mL [interquartile range (IQR) 11.6-40.4] in all patients. Serum NfL levels in patients with CIS who subsequently developed MS (median 30.2, IQR 16.4-48.7 pg/mL) were higher than in patients who did not develop MS (median 9.7, IQR 5.5-18.1 pg/mL) ($p<0.001$).

The median CSF NfL concentration in patients with CIS was 731.3 pg/mL (IQR 346.9-1194.6) and they were directly related with serum NfL concentrations, and this relationship was statistically significant, particularly in patients with Gd-enhancing lesions. In line with these data, it was noted that serum NfL concentrations might mirror CSF levels in patients with blood-brain barrier damage as evidenced by the presence of Gd-enhancing lesions. On the other hand, it was emphasized that serum biomarkers might be prognostic for a second attack in parallel with MRI findings closely related to disease activity, and therefore early recurrent episodes.

For serum NfL concentrations measured during the first demyelinating clinical attack, patients' age, time interval from

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Received/Geliş Tarihi: 04.03.2019 **Accepted/Kabul Tarihi:** 04.03.2019

time interval from clinical attack to sampling, baseline T2 and Gd-enhancing lesions, and Expanded Disability Status Scale (EDSS) were found to be predictive.

Consistent with the previous studies, the higher serum NfL concentrations measured in the early period of a clinical attack supported the close relation of serum NfL with inflammation.

EDSS scores and serum NfL levels were correlated at the time of attack; however, no association was found between baseline NfL concentrations and disability progression in 35 patients who experienced EDSS worsening during follow-up.

Serum NfL concentrations were found to be prognostic for both clinically definite MS and MS according to the McDonald 2017 criteria. According to serum NfL concentrations evaluated in five different percentiles, it was found that the risk of conversion was reduced in patients with low and very low NfL concentrations, and increased in patients with high and very high NfL values. This association remained unchanged after adjustments were made for the presence of CSF OCBs and T2 and Gd-enhancing lesions at baseline MRI, which are known to have an effect on conversion to MS.

In conclusion, serum NfL has been shown to have a prognostic value for conversion to MS in patients with CIS. On the other hand, with the available data, it has been speculated that peak level measurements of serum NfL can act as a quantitative marker of serious inflammatory activity and also with steady-state levels, serum NfL can reflect baseline metabolic processes of the central nervous system as well as neurodegenerative and chronic inflammatory processes.

Ethics

Peer-review: Internally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Reference

1. Dalla Costa G, Martinelli V, Sangalli F, et al. Prognostic value of serum neurofilaments in patients with clinically isolated syndromes. Neurology 2019;92:733-741.