NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

EDITORIAL

Arch Neuropsychiatry 2021;58:255–256
https://doi.org/10.29399/npa.28019

Phosphorylated Neurofilament Heavy Chain (pNFH) in Clinically Isolated Syndrome and Multiple Sclerosis

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Neurofilaments are specifically expressed in neurons as cytoskeleton proteins. They are separated into three categories as neurofilament light (NFL), medium (NFM) and heavy (NFH) chains based on their molecular weights. Their expression and phosphorylation levels determine axonal diameter, myelination and conduction velocity of neurons (1). Following neuronal damage, neurofilaments are released into the interstitial fluid, cerebrospinal fluid (CSF) and finally peripheral circulation (2). NFL and phosphorylated NfH (pNFH) have been widely implemented as prognostic biomarkers in neurological disorders with neurodegeneration emerging as a primary or secondary event. These disorders include Alzheimer's disease, amyotrophic lateral sclerosis (ALS), frontotemporal dementia, traumatic brain injury and multiple sclerosis (MS) (2, 3). Neurofilament levels can be measured by enzyme-linked immunosorbent assays (ELISA), electrochemiluminescence (ECL) assays or single molecule array (SIMOA) platform (4). While CSF levels of NFL can be measured by ELISA, ECL or SIMOA is required for assessment of serum levels. By contrast, both serum and CSF levels of pNFH can be measured by ELISA.

CSF and serum levels of NFL are increased in MS patients and clinically isolated syndrome (CIS) patients that later convert to MS (5). NFL levels are correlated with the lesion load on MRI (6) and are reduced in response to disease modifying treatments (7). Thus, NFL levels predict both long-term prognosis and treatment response in MS.

NFH and pNFH levels have been widely used in ALS for prognostic and diagnostic purposes due to very high levels of both parameters in ALS and significant correlation with disease activity and NFL levels (8). In contrast, the relationship of NFH/pNFH with measures of MS has been understudied. Similar to NFL, levels of NFH appear to be elevated in MS and CIS and correlate with MRI lesion load (5). In a recent report, serum and CSF NFH levels were found to be elevated in progressive MS and RRMS patients and correlated with expanded disability status scale (EDSS) scores and peripapillary retinal nerve fiber layer (pRNFL) thickness (9). We recently showed higher levels of pNFH in baseline (first attack) CSF of CIS patients that converted to RRMS in a follow-up period of 3 years as compared to CIS patients, who did not convert in the same time frame. Moreover, CIS patients with higher baseline CSF pNFH levels showed higher EDSS scores and displayed faster conversion to MS. Intriguingly, CSF pNFH levels showed positive correlation with CSF levels of cAMP response element-binding protein (CREB), an element of the CREB-signaling pathway and a marker of neuroregeneration (doi: 10.4103/nsn.nsn_144_21, Neurological Sciences and Neurophysiology, in press). As a matter of fact, during axonal growth, expression levels of neurofilaments and CREB are increased simultaneously (10). Therefore, at least in the earlier stages of MS, neurofilaments (particularly pNFH) may not be only a harbinger of neuroaxonal degeneration but also neuronal regeneration. This assertion needs to be further validated by future experiments.

As another intriguing feature, there is evidence suggesting that NFL and NFH act as an antigenic target in MS, anti-NFL and anti-NFH levels correlate with EDSS scores and thereby contribute to central nervous system autoimmunity and influence clinical progression and disability accumulation (11).

Overall, recent research suggests that neurofilaments are involved in disease activity of MS in a multimodal fashion. The exact physiopathological and biomarker value of NFH/pNFH should be further scrutinized through patient and animal model studies. These efforts might in due time result in novel therapeutic interventions for MS.

Cite this article as: Tüzün E, Şanlı E, Akbayır E, Türkoğlu R. Phosphorylated Neurofilament Heavy Chain (pNFH) in Clinically Isolated Syndrome and Multiple Sclerosis. Arch Neuropsychiatry 2021;58:255–256.

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Received: 16.09.2021, **Accepted:** 23.09.2021, **Available Online Date:** 15.11.2021

Conflict of Interest: The authors have no potential conflicts of interest to disclose.

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