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EDITORIAL

Tackling the usefulness of neurofilament light chain in multiple system atrophy: diagnostic and prognostic perspectives

Daniel G. Di Luca[1] · **Patricio Millar Vernetti**[2]

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Multiple system atrophy (MSA) is a rapidly progressive fatal neurodegenerative disease characterized by parkinsonism and/or cerebellar ataxia accompanied by cardiovascular and urogenital autonomic dysfunction, with no available disease-modifying treatments to date [1]. Among the many challenges in the field, obtaining a reliable biomarker for diagnostic and prognostic purposes remains a challenge. This also leads to significant difficulty in objectively characterizing disease progression in MSA, and potentially evaluating treatment response for prospective disease-modifying therapies. Several biomarkers have been explored in the recent past, with neurofilament light chain (NfL) being a potential candidate due to its association with rapid disease progression or a significant amount of neuronal injury. As a marker of axonal degeneration, both plasma and cerebral spinal fluid (CSF) concentrations of NfL have been described as potentially useful in distinguishing MSA from other parkinsonian syndromes, such as Parkinson's disease (PD). Additionally, a large multicenter European study by Chelban et al. demonstrated that plasma NfL (NfL-p) could be useful in tracking MSA progression, and correlated with survival [2].

With these challenges in mind, Singer and colleagues set out to investigate the usefulness of NfL as a biomarker of disease progression and its diagnostic utility in differentiating MSA and PD [3]. When evaluating 32 individuals with early MSA at multiple time points over 3 years, NfL-p and NfL in the CSF (NfL-c) did not correlate with disease progression. Nevertheless, the results were in agreement with previous studies reporting that NfL-p and c might be reliable biomarkers in differentiating MSA from PD [4, 5].

The study has significant strengths and differences when compared to the previous multicenter European study. Specifically, in the study by Singer and colleagues, individuals were extensively evaluated with imaging and autonomic function tests. Additionally, there was a relatively high number of patients with neuropathological confirmation of MSA in postmortem studies when compared to the study by Chelban et al. (12 patients or 38% of all MSA individuals vs. 18 or around 8.5% of all initial 212 MSA patients). On the other hand, there are certain noteworthy limitations that might limit the generalizability of this study's results. To begin with, while both NfL-c and NfL-p showed exceptional reproducibility across assay platforms, the data come from a single center with a relatively small number of MSA individuals. Another issue, which remains an overall challenge in clinical research, is the lack of a racially and ethnically diverse cohort, with a disproportionately high number of white patients.

What are the clinical and research implications of this study to the field? This prospective and longitudinal study provides an extra level of confidence and moves the field forward in the role of NfL as a supportive biomarker in the diagnosis of MSA, which has been recently added to the 2022 Movement Disorder Society criteria [6]. This may be particularly helpful in patients in the prodromal stages of disease, such as those with rapid eye movement (REM) sleep behavior disorder (RBD) and pure autonomic failure (PAF) [7, 8]. However, other studies have also reported high NfL-c levels in patients with progressive supranuclear palsy (PSP) [9, 10], and to a lesser extent in dementia with Lewy bodies (DLB) [11, 12], which could represent up to 30% of MSA misdiagnosis in autopsy series [13, 14]. In these cases, depending on the disease stage, the combination with other testing modalities such as brain imaging and seed

✉ Daniel G. Di Luca
dilucadaniel@wustl.edu

[1] Department of Neurology, Washington University in Saint Louis, St. Louis, MO, USA

[2] Neurology Department, New York University Grossman School of Medicine, New York, NY, USA

amplification assay (SAA) may provide better diagnostic accuracy [7, 9].

These results might have implications beyond the clinic, with significant changes in selection criteria for clinical trials. By refining the MSA diagnosis and supporting it with laboratorial biomarkers, a more well-defined cohort of individuals can be selected, therefore making the results more reliable. Potentially, the main implication of this paper is the disagreement in respect to the usefulness of NfL-p or c in MSA progression. Although early to say, considering the lack of replicability in terms of the longitudinal properties of this biomarker, it remains uncertain how this biomarker can be reliably implemented or interpreted for progression of disease. This final question of progression remains unanswered, and larger studies will likely have to confirm or refute this hypothesis.

Additionally, the study raises important questions that still need to be answered by future studies. First, the role of peripheral and axonal contribution in patients with peripheral neuropathy or other diseases with neuronal and axonal degeneration remains uncertain, which could further complicate the interpretation of the already wide variability of this test. Moreover, it suggests the possibility that perhaps serum measurements should be improved by concentrating NfL, with distinctive approaches such as exosomes or immune capture of NfL in serum [15].

The study by Singer et al. highlights some of the obstacles in the field of biomarkers in MSA. Although it challenges the possibility of its effectiveness in evaluating progression, setting the stage for future larger and multicenter studies to confirm this hypothesis, it brings some optimism by confirming the usefulness of NfL as a supportive diagnostic tool.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Poewe W et al (2022) Multiple system atrophy. Nat Rev Dis Primers 8(1):56. https://doi.org/10.1038/s41572-022-00382-6
2. Chelban V et al (2022) Neurofilament light levels predict clinical progression and death in multiple system atrophy. Brain 145(12):4398–4408. https://doi.org/10.1093/brain/awac253
3. Singer W et al (2023) Neurofilament light chain in spinal fluid and plasma in multiple system atrophy: a prospective, longitudinal biomarker study. Clin Auton Res. https://doi.org/10.1007/s10286-023-00974-6
4. Hall S et al (2012) Accuracy of a panel of 5 cerebrospinal fluid biomarkers in the differential diagnosis of patients with dementia and/or Parkinsonian disorders. Arch Neurol 69(11):1445. https://doi.org/10.1001/archneurol.2012.1654
5. Hansson O et al (2017) Blood-based NfL. Neurology 88(10):930–937. https://doi.org/10.1212/WNL.0000000000003680
6. Wenning GK et al (2022) The movement disorder society criteria for the diagnosis of multiple system atrophy. Mov Disord. https://doi.org/10.1002/mds.29005
7. Singer W et al (2021) Alpha-synuclein oligomers and neurofilament light chain predict phenoconversion of pure autonomic failure. Ann Neurol 89(6):1212–1220. https://doi.org/10.1002/ana.26089
8. Zhang X et al (2023) Neurofilament light protein predicts disease progression in idiopathic rem sleep behavior disorder. J Parkinsons Dis 13(4):485–499. https://doi.org/10.3233/JPD-223519
9. Compta Y et al (2022) Combined CSF α-SYN RT-QuIC, CSF NFL and midbrain-pons planimetry in degenerative parkinsonisms: From bedside to bench, and back again. Parkinsonism Relat Disord 99:33–41. https://doi.org/10.1016/j.parkreldis.2022.05.006
10. Rojas JC et al (2018) CSF neurofilament light chain and phosphorylated tau 181 predict disease progression in PSP. Neurology 90(4):e273–e281. https://doi.org/10.1212/WNL.0000000000004859
11. Barba L et al (2023) CSF synaptic biomarkers in AT(N)-based subgroups of lewy body disease. Neurology 101(1):e50–e62. https://doi.org/10.1212/WNL.0000000000207371
12. Diekämper E et al (2021) Neurofilament levels are reflecting the loss of presynaptic dopamine receptors in movement disorders. Front Neurosci. https://doi.org/10.3389/fnins.2021.690013
13. Miki Y et al (2019) Improving diagnostic accuracy of multiple system atrophy: a clinicopathological study. Brain 142(9):2813–2827. https://doi.org/10.1093/brain/awz189
14. Koga S et al (2015) When DLB, PD, and PSP masquerade as MSA. Neurology 85(5):404–412. https://doi.org/10.1212/WNL.0000000000001807
15. Okuzumi A et al (2023) Propagative α-synuclein seeds as serum biomarkers for synucleinopathies. Nat Med 29(6):1448–1455. https://doi.org/10.1038/s41591-023-02358-9