EDITORIAL

Neurofilaments as Decay Rate Biomarker in Spinocerebellar Ataxia Type 1

Highlighting Key Questions of Application and Future Challenges

Benedetta Nacmias, PhD

Neurology® 2022;98:821-822. doi:10.1212/WNL.0000000000200360

Correspondence
Dr. Nacmias
nacmias@unifi.it

RELATED ARTICLE

Research Article
Levels of Neurofilament Light at the Preataxic and Ataxic Stages of Spinocerebellar Ataxia Type 1
Page 827

A major challenge in the study of neurodegenerative diseases is obtaining objective and easily accessible serum biomarkers for early detection of neurodegeneration. Having them would allow early diagnosis and detection of the effects of disease-modifying therapies. Neurofilament light (NfL) is a candidate biomarker that may address this challenge. NfLs are neuron-specific cytoskeletal proteins that are released on neuronal damage and, as a result of rapid advances in the development of ultrasensitive assays, are reliably quantifiable in peripheral blood. Recent studies provide evidence of the prognostic use of NfL in a variety of neurodegenerative diseases,[1] including amyotrophic lateral sclerosis,[2] dementia,[3,4] Huntington disease,[5] and neuroinflammatory conditions such as multiple sclerosis.[6]

Spinocerebellar ataxia (SCA) refers to a group of rare autosomal dominant inherited conditions caused by repeat expansions or variations in several SCA genes. These conditions are slowly progressive and are associated with atrophy of the cerebellum that is evident on a brain scan. Most of the SCAs are caused by triplet repeat expansions. People carrying a pathogenic expansion have a high probability of developing the symptoms of the disease, and each of their children has a 50% chance of inheriting the expansion in the pathogenic range, regardless of the sex of the parent or the child. A genetic test can confirm the diagnosis of SCA. For most people, it is obtained after the classic symptoms appear, but it can be requested in those at risk because of their family history.

SCA type 1 (SCA1) is a severe neurodegenerative disease characterized by rapid and irreversible decline of motor function starting in midlife. It is caused by a translated CAG repeat expansion in the *ATXN1* gene, leading to a polyglutamine expansion in the ATAXIN-1 (ATXN1) protein. It is one of the most common SCAs. Recent studies in mice show that antisense oligonucleotide therapies lead to targeted reductions of ATXN1 and may suggest a therapeutic approach for preventing SCA1.[7] As new preventive medications that can prevent or delay the onset of the disease become available, it will be important to identify those carrying a pathogenic expansion in the preataxic stage.

In this issue of *Neurology*®, Wilke et al.[8] publish the results of a study in which they evaluated the potential use of serum NfL (sNfL) as a readily accessible biomarker of the disease. The main finding was that in preataxic individuals with SCA1, sNfL correlated with the time to clinical onset, allowing early detection of neurodegeneration even before volumetric atrophy of cerebellum or pons was evident on MRI. They reported significant sNfL elevations 5 years before onset of symptoms. Their results suggest that sNfL elevations may be more sensitive that volumetric MRI in the preataxic stage.[8] The authors propose sNfL as a candidate serum biomarker for clinical trial inclusion. This could extend the number of CAG repeat-expansion diseases that could benefit from a peripheral blood biomarker.

In patients with neurodegenerative diseases, changes in the brain may begin several years before symptoms appear. Waiting for symptoms to appear may delay treatments until after damage to the brain is advanced. The results of the study by Wilke et al.[8] highlight the value of sNfL as a

From the Department of Neuroscience, Psychology, Drug Research and Child Health, University of Florence, Italy.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

biomarker of neurodegeneration that may be useful to determine when therapies may be started. The study has potential clinical implications and offers a first step to fill the gap between clinical and research work in the field of biomarkers and SCA1. Limitations of the study, as pointed out by the authors, are that additional longitudinal measurements of NfL levels in preataxic individuals are needed to model the early intraindividual dynamics of NfL levels in SCA1 in more detail. In addition, validation of their findings (in particular, for example, of the MRI findings) is needed in independent larger multicentric cohorts of individuals with SCA1.

A recent study provided evidence for elevated NfL levels associated with clinical disease severity in individuals with SCA2,[9] thus confirming the growing interest in NfL as a biomarker. Key questions remain. How can these results be extended to the >48 different forms of SCA? Are we at the threshold of a biomarker-based precision medicine approach to SCA? The growing number of diseases caused by expansion of triplets could benefit from NfL.

Study Funding

The author reports no targeted funding.

Disclosure

The author reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

References

1. Ashton NJ, Janelidze S, Al Khleifat A, et al. A multicentre validation study of the diagnostic value of plasma neurofilament light. *Nat Commun.* 2021;12(1):3400.
2. Masrori P, De Schaepdryver M, Floeter MK, et al. Prognostic relationship of neurofilaments, CHIT1, YKL-40 and MCP-1 in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry.* Epub 2021 Dec 20.
3. Preische O, Schultz SA, Apel A, et al; Dominantly Inherited Alzheimer Network. Serum neurofilament dynamics predicts neurodegeneration and clinical progression in presymptomatic Alzheimer's disease. *Nat Med.* 2019;25(2):277-283.
4. van der Ende EL, Meeter LH, Poos JM, et al; Genetic Frontotemporal Dementia Initiative (GENFI). Serum neurofilament light chain in genetic frontotemporal dementia: a longitudinal, multicentre cohort study. *Lancet Neurol.* 2019;18(12):1103-1111.
5. Byrne LM, Rodrigues FB, Blennow K, et al. Neurofilament light protein in blood as a potential biomarker of neurodegeneration in Huntington's disease: a retrospective cohort analysis. *Lancet Neurol.* 2017;16(8):601-609.
6. Kapoor R, Smith KE, Allegretta M, et al. Serum neurofilament light as a biomarker in progressive multiple sclerosis. *Neurology.* 2020;95(10):436-444.
7. O'Callaghan B, Hofstra B, Handler HP, et al. Antisense oligonucleotide therapeutic approach for suppression of ataxin-1 expression: a safety assessment. *Mol Ther Nucleic Acids.* 2020;21:1006-1016.
8. Wilke C, Mengel D, Schöls L, et al. Levels of neurofilament light at the preataxic and ataxic stages of spinocerebellar ataxia type 1. *Neurology.* 2022;98(20):e1985-e1996.
9. Yang L, Shao YR, Li XY, Ma Y, Dong Y, Wu ZY. Association of the level of neurofilament light with disease severity in patients with spinocerebellar ataxia type 2. *Neurology.* 2021;97(24):e2404-e2413.

Neurofilaments as Decay Rate Biomarker in Spinocerebellar Ataxia Type 1: Highlighting Key Questions of Application and Future Challenges

Benedetta Nacmias

Neurology 2022;98;821-822 Published Online before print March 9, 2022
DOI 10.1212/WNL.0000000000200360