NfL as a Potential Biomarker in ATTRv Amyloidosis

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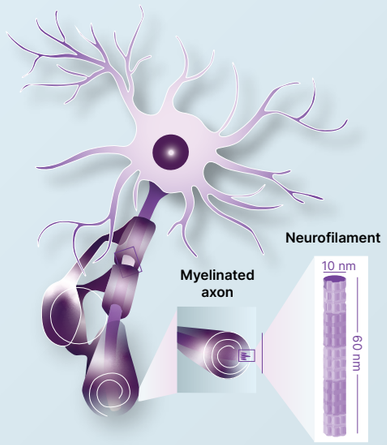
An overview of ATTRv amyloidosis and NfL

ATTRv amyloidosis is a rare, underdiagnosed, progressive and debilitating disease caused by variants in the TTR gene, which leads to the accumulation of dissociated, misfolded TTR as amyloid deposits in organs and tissues.[1-4]

NfL is a well-studied biomarker for neuroaxonal injury across multiple PNS/CNS diseases, that has been suggested to reflect active/continuing neuronal damage in patients with ATTRv amyloidosis.[3,5,6]

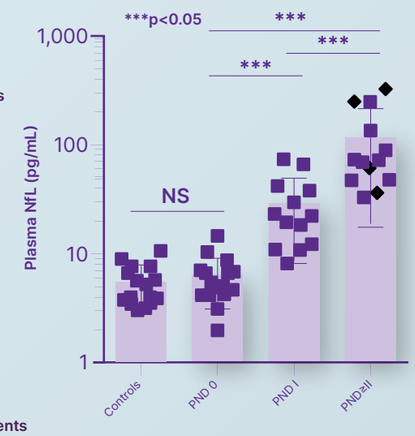


NfL levels are found to be significantly elevated in patients with ATTRv amyloidosis with PN versus healthy controls, and to correlate with disease severity.

60 patients with ATTRv amyloidosis or V30M variant carriers

16 healthy controls

Plasma NfL levels in patients with ATTRv amyloidosis, individuals who are V30M variant carriers, and healthy controls.[7]



Full diamonds represent patients with a PND score of III.

All data are represented as group means ±SD.

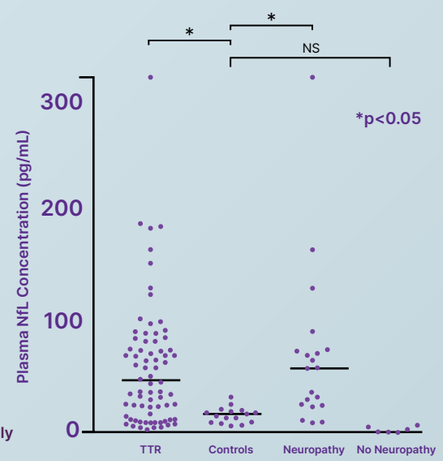
NfL was elevated in patients with ATTRv amyloidosis as a function of disease severity.

NfL differentiated asymptomatic carriers (PND 0) from early symptomatic patients (PND I).

73 patients with pathogenic TTR variants

16 healthy controls

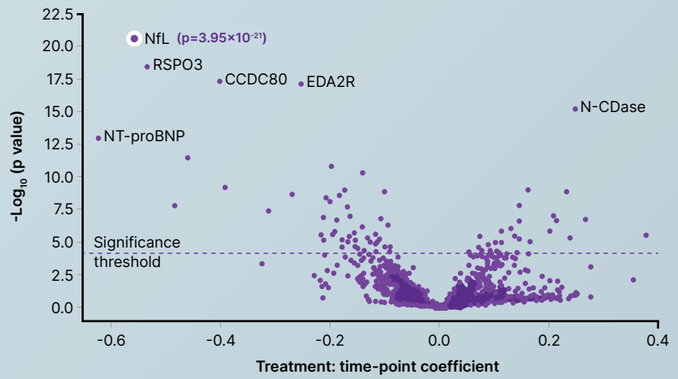
Plasma NfL levels in all patients with ATTRv amyloidosis (TTR), healthy controls, and ATTRv patients with or without neuropathy.[8]



NfL levels were significantly higher in patients with ATTRv amyloidosis with PN versus controls (p<0.001).

NfL levels correlated with disease severity (NIS).

In a post-hoc proteomic analysis from the APOLLO study,[1] NfL was found to be the most significantly changed protein between patisiran-treated and untreated patients with ATTRv amyloidosis with PN.[3]

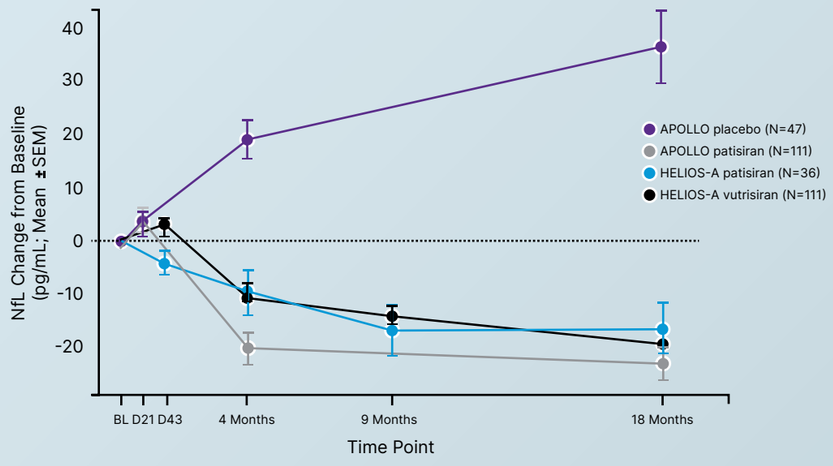


Results from a proteomic analysis conducted to determine the effect of patisiran treatment over time on the plasma level of multiple proteins.

On the volcano plot, each protein is represented with a dot. The y-axis demonstrates the strength of the association ($-\log_{10}$ [p value]) and the x-axis demonstrates the effect size.

Treatment with RNAi therapeutics led to a significant decrease in NfL levels, which was seen as early as 4 months with a sustained response over time.[9]

Change in NfL levels from baseline in APOLLO[1] and HELIOS-A[2] studies



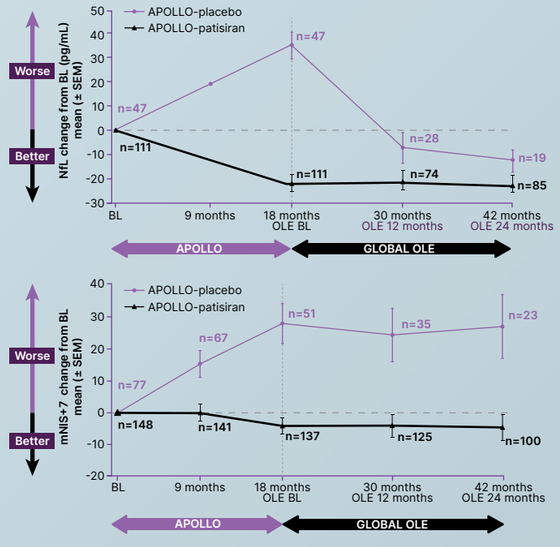
In post-hoc analyses of APOLLO and HELIOS-A studies, NfL levels decreased significantly in patisiran and vutrisiran groups as early as 4 months (p<0.05), and these decreases were maintained to 18 months after treatment initiation (p<0.01).[9]

A positive correlation (R=0.32) was observed between change in NfL levels and change in mNIS+7 in APOLLO and HELIOS-A at 18 months.[9]

A significant decrease in NfL levels with patisiran in the APOLLO study was sustained during the open-label extension period.[4,10]

NfL level significantly decreased after patients receiving placebo began active treatment in the Global OLE (p<0.001).[10]

NfL has been suggested to reflect active or continuing neuronal damage at a specific point in time, whereas mNIS+7 measures the overall clinical burden of neurologic impairment.[3]



Measuring NfL levels may have value in monitoring treatment response in patients with ATTRv amyloidosis.[11]

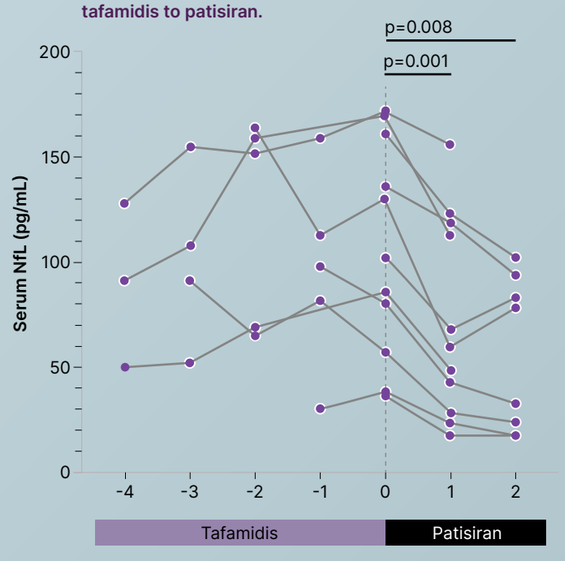
11 patients with ATTRv amyloidosis with PN who switched from tafamidis (20 mg) to patisiran.

Significant decrease in NfL levels was observed at 1 and 2 years following switch

NIS values did not change significantly following switch.

The limitations of this study included the small number of patients and absence of a control group. Further, longer-term studies are necessary to validate the findings.

Serum NfL levels before and after switch from tafamidis to patisiran.



Pre-switch NfL levels are depicted according to the calendar year in which the measurement was made.

Abbreviations

ATTRv amyloidosis: hereditary amyloid transthyretin amyloidosis; BL: baseline; CCDC80: coiled-coil domain-containing protein 80; CNS: central nervous system; EDA2R: ectodysplasin A2 receptor; mNIS: Modified Neuropathy Impairment Score; N-CDase: neutral ceramidase; NIS: Neuropathy Impairment Score; NfL: neurofilament light chain; NS: not significant; OLE: open-label extension; PN: peripheral neuropathy; PND: polyneuropathy disability; PNS: peripheral nervous system; RNAi: RNA interference; RSPO3: R-spondin-3; SEM: standard error of the mean; TTR: transthyretin.

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