Neurofilament-light chain in murine models of neurodegenerative and rare diseases

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BACKGROUND

Neurofilament-light chain (NF-L) is known as a biomarker of many neurodegenerative diseases and their progression. By analyzing amyotrophic lateral sclerosis (ALS) patients CSF or plasma, progression of NF-L levels can forecast conversion from the pre-symptomatic to symptomatic stage and the time of survival. So far, detailed analyses of NF-L expression in neurodegenerative disease patient's samples were performed, while NF-L levels of preclinical mouse models of ALS, Alzheimer's and Parkinson's disease as well as lysosomal storage diseases are still unknown.

MATERIALS and METHODS

We therefore evaluated NF-L levels in the plasma of the ALS model TAR6/6, the Alzheimer's disease model 5xFAD, the Parkinson's disease model Line 61 and the Gaucher disease model 4L/PS-NA as well as CSF of selected models using a commercially available ELISA kit from UmanDiagnostics.

SUMMARY and CONCLUSION

NF-L measurements in the plasma of the neurodegenerative disease mouse models of ALS and Alzheimer's disease are thus a good tool to evaluate disease progression. Compared to analyses in human tissues, our results suggest that murine NF-L levels and their progression have a high translational value. Furthermore, our data indicate that NF-L might also be a good biomarker for diseases that are not classical neurodegenerative diseases but disorders with a neuronal component like some lysosomal storage diseases. Parts of the results are published in Loeffler et al., 2020, Frontiers in Molecular Neuroscience.

RESULTS

Amyotrophic Lateral Sclerosis (ALS)

In TDP43 mice (TAR6/6; Wils et al., 2010) plasma TREM2 levels tended to be decreased at an age of 9 and 17 weeks compared to respective ntg littermates (Fig. 2A). Increased plasma NF-L levels were observed already at an age of 9 weeks (Fig. 2B). ChaT immunolabeling showed a remarkable loss of motor neurons in the spinal cord of TDP43 mice compared to control littermates (Fig. 2C), reflecting the significant increase in NF-L levels.

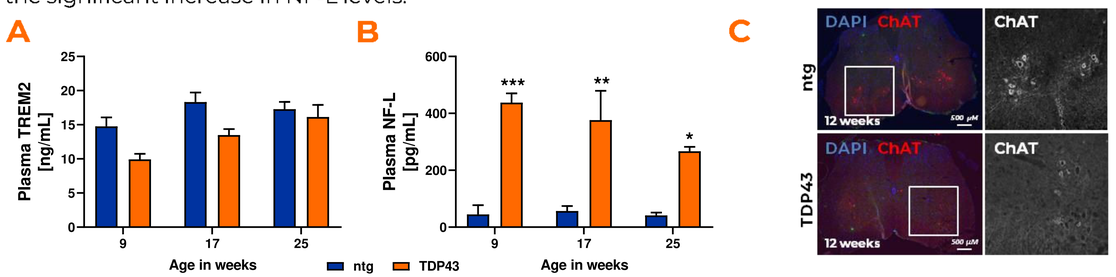

Figure 1. TREM2 and neuronal loss in TDP43 transgenic mice
A: Quantification of TREM2 and **B:** NF-L in plasma of TDP43 transgenic mice compared to non-transgenic (ntg) littermates. TREM2 levels in ng/mL and NF-L levels in pg/mL of mixed sex 9, 17 and 25 week old TDP43 mice compared to ntg controls. Two-way ANOVA with Tukey's *post hoc* test. Mean + SEM. *p<0.05; **p<0.01 ***p<0.001. **C:** Representative images of ChAT and DAPI immunolabeling in 3 month old TDP43 and ntg mice.

Alzheimer's Disease (AD)

In 5xFAD mice (Oakley et al., 2006) an increase in plasma NF-L levels was found already at an age of 6 months compared to ntg controls (Fig. 3A). Additionally, strongly elevated CSF NF-L levels can be detected in 9 month old 5xFAD mice (Fig. 3B). Although, no significant changes in plasma TREM2 levels were observed in 5xFAD mice compared to ntg littermates (Fig. 3C), IBA1, a marker for activated microglia, is highly upregulated in the hippocampus of 5xFAD mice (Fig. 3D).

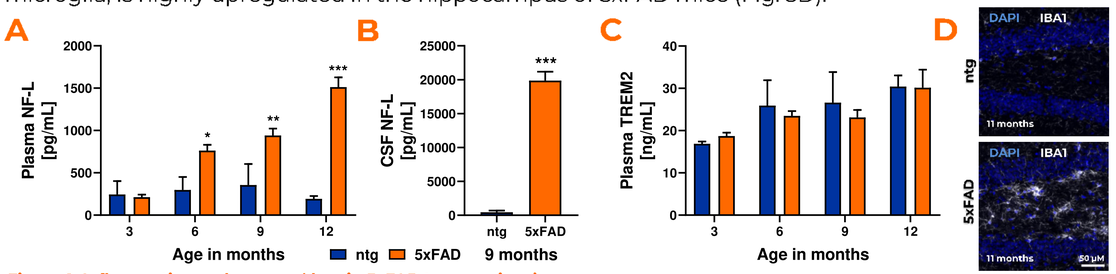

Figure 2. Inflammation and neuronal loss in 5xFAD transgenic mice
A: Quantification of NF-L in plasma and **B:** CSF of 5xFAD transgenic mice compared to non-transgenic (ntg) littermates. NF-L levels in pg/mL of 3, 6, 9 and 12 month old mixed sex 5xFAD mice compared to ntg littermates. **C:** Quantification of TREM2 in plasma of 9 month old 5xFAD mice. **A,C:** Two-way ANOVA with Bonferroni's *post hoc* test. **B:** Unpaired t-test. Mean + SEM. *p<0.05; **p<0.01 ***p<0.001. **D:** Representative images of IBA1 and DAPI immunolabeling in 11 month old 5xFAD and ntg mice.

Parkinson's Disease (PD)

In α-synuclein overexpressing Line 61 mice (Rockenstein et al., 2002) NF-L levels started to rise very late, reflecting data obtained from PD patients (Fig. 4A). Since IBA1 immunolabeling showed no differences between Line 61 and ntg controls, TREM2 levels were not investigated. However, increased astrocytosis was observed in the striatum of transgenic animals (Fig. 4B).

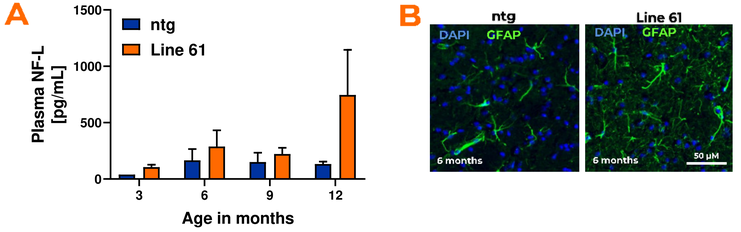

Figure 3. Inflammation and neuronal loss in Line61 transgenic mice
A: Quantification of NF-L in plasma of Line 61 mice compared to non-transgenic (ntg) mice. NF-L levels in pg/mL in the plasma of 3, 6, 9 and 12 month old mixed sex Line 61 mice compared to ntg controls. Two-way ANOVA with Bonferroni's *post hoc* test. Mean + SEM. **B:** Representative images of GFAP and DAPI immunolabeling in 6 month old Line 61 and ntg mice.

Gaucher Disease

In the 4L/PS-NA mouse model (Sun et al. 2005) increased plasma and CSF NF-L levels were found at an age of 18 months compared to 4L/PS+/+NA mice (Fig. 4A,B). In line with these results, a strong neuronal loss in the cerebellum was observed in the 4L/PS-NA compared to 4L/PS+/+NA mice (Fig. 4C).

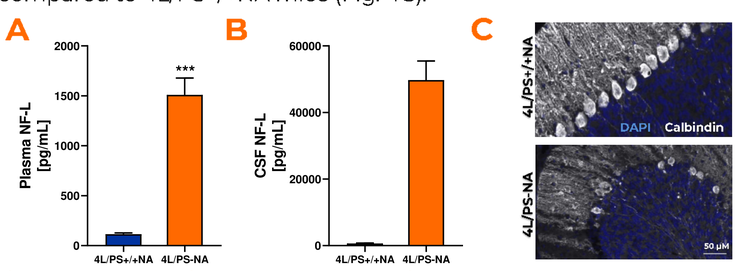

Figure 4. Neuronal loss in 18 week old 4L/PS-NA mice
A: NF-L levels in pg/mL in the plasma and **B:** CSF of 4L/PS-NA mice compared to 4L/PS+/+NA. Unpaired t-test. Mean + SEM. ***p<0.001. **C:** Representative images of Calbindin and DAPI immunolabeling in 4L/PS-NA and 4L/PS+/+NA mice.

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