Characterization of relevant mouse models for new biomarkers

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BACKGROUND

Biomarkers and their use in neurodegenerative disease research may provide an important link between preclinical disease models and evaluation of disease progression in patients. Neurofilament light chain (NF-L), a neuronal cytoplasmic protein, is increased in a variety of neuronal diseases due to axonal damage. Gaetani et al. showed different CSF NF-L levels in humans depending on the type of disease (Fig. 1). Furthermore, TREM2 variants have been associated with the onset of Alzheimer's and other neurodegenerative diseases (PD, ALS).

The aim of this study was to evaluate NF-L as well as TREM2 levels in plasma and CSF of relevant neurodegenerative disease mouse models.

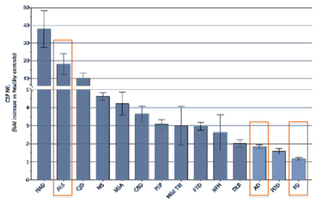

Figure 1. Increase of NF-L in CSF of patients with various neurological diseases.
Adapted from "Neurofilament light chain as biomarker in neurological disorders", by Gaetani et al., 2019.

MATERIALS and METHODS

TDP43, 5xFAD, Line 61 and 4L/PS-NA mice as models of Amyotrophic lateral sclerosis, Alzheimer's, Parkinson's and Gaucher Disease, respectively, were used at different ages. To explore neurofilament light chain levels in CSF and plasma, the NF-Light® ELISA by UmanDiagnostics was used. For the detection of TREM2 an immunosorbent assay specific for mouse TREM2, developed on the MSD (Mesoscale Discovery) platform was used. Additionally, immunohistochemical evaluation of neuronal loss or neuroinflammation was performed.

SUMMARY and CONCLUSION

Evaluation of NF-L and TREM2 levels in various neurodegenerative disease mouse models showed the same trend as in corresponding patients, making these mice suitable model systems with high translational value.

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.

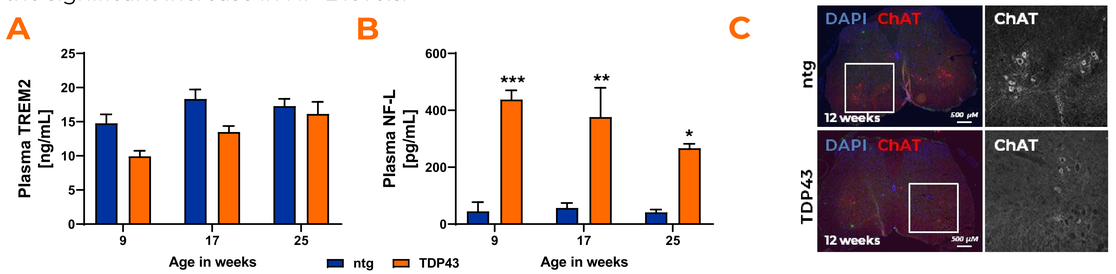

Figure 2. TREM2 and neuronal loss in TDP43 transgenic mice
A: Quantification of TREM2 and **B:** NF-L in plasma of TDP43 transgenic mice compared to non-transgenic (ntg) littermates. TREM2 levels in ng/mL and NF-L levels in pg/mL of mixed sex 9, 17 and 25 week old TDP43 mice compared to ntg controls. 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).

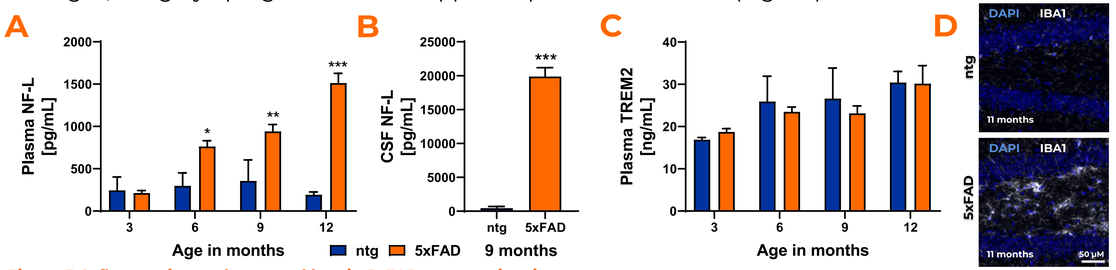

Figure 3. Inflammation and neuronal loss in 5xFAD transgenic mice
A: Quantification of NF-L in plasma and **B:** CSF of 5xFAD transgenic mice compared to non-transgenic (ntg) littermates. NF-L levels in pg/mL of 3, 6, 9 and 12 month old mixed sex 5xFAD mice compared to ntg littermates. **C:** Quantification 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).

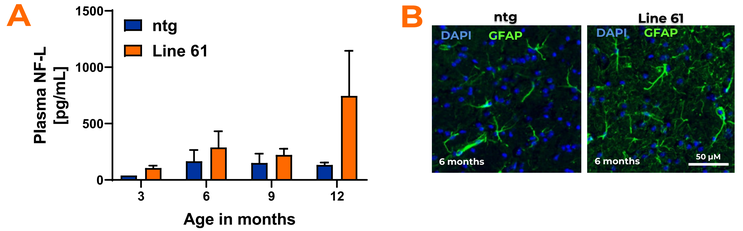

Figure 4. Inflammation and neuronal loss in Line61 transgenic mice
A: Quantification of NF-L in plasma of Line 61 mice compared to non-transgenic (ntg) mice. NF-L levels in pg/mL in the plasma of 3, 6, 9 and 12 month old mixed sex Line 61 mice compared to ntg controls. Two-way ANOVA with Bonferroni's *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 month 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).

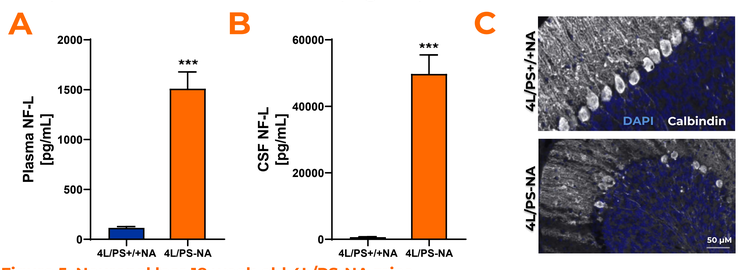

Figure 5. Neuronal loss 18 week old 4L/PS-NA mice
A: NF-L levels in pg/mL in the plasma and **B:** CSF of 4L/PS-NA mice compared to 4L/PS+/+NA. Unpaired t-test. Mean + SEM. ***p<0.001. **C:** Representative images of Calbindin and DAPI immunolabeling in 4L/PS-NA and 4L/PS+/+NA mice.

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