The importance of neurofilament light chain (NF-L) biomarker in 5XFAD Alzheimer's disease and SOD1-G93A amyotrophic lateral sclerosis animal disease models

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BACKGROUND

Neurofilament light chain (NF-L) has gained prominence as a clinical biomarker. The measurement of NF-L levels in CSF and blood holds significant potential for early detection, prognosis, and monitoring of neurodegenerative disorders.

Detecting NF-L in CSF and blood enables early intervention and the formulation of potential treatment strategies. Moreover, NF-L serves as an important biomarker in animal models of Alzheimer's disease (AD) and amyotrophic lateral sclerosis animal disease (ALS). In this study, we aimed to investigate the changes in NF-L levels that may correlate to disease progression and aging in animal models of 5XFAD AD and SOD1-G93A ALS mice. Specifically, we examined NF-L concentration in 5xFAD mice aged 3 to 12 months and SOD1-G93A mice aged 11 to 20 weeks.

METHODS

Animals

- Altogether 43 5xFAD mice and age-matched 33 wildtype (WT) littermate C57BL/6 congenic mice bred from male 5xFAD [B6.Cg-Tg (APPSwFlLon, PSEN1*M146L*L286V) 6799Vas/Mmjax, Jackson Laboratories, USA] and C57BL/6 (Koatech, Korea) were used for experiments.
- Altogether 48 male SOD1 mice and age-matched 24 wildtype (WT) littermate C57BL/6SJL congenic mice bred from male SOD1*G93A (High-copy SOD1*G93A, G1H with 25 TG copies; stock# 002726) and C57BL/6SJL (Koatech, Korea) were used for experiments.

CSF and plasma collection

- The mice were euthanized with terminal dose of pentobarbital, and CSF was collected through the cisterna magna into Eppendorf microtubes. These were frozen on dry ice and stored at -80°C.
- Blood samples were collected by cardiac puncture. Whole blood was collected into lithium-heparin tubes, and plasma was separated by centrifugation (3000 rpm for 15 min) at 4°C. Separated plasma was collected in Eppendorf microtubes, frozen on dry ice and stored at -80°C.

NF-L measurement in both CSF and plasma

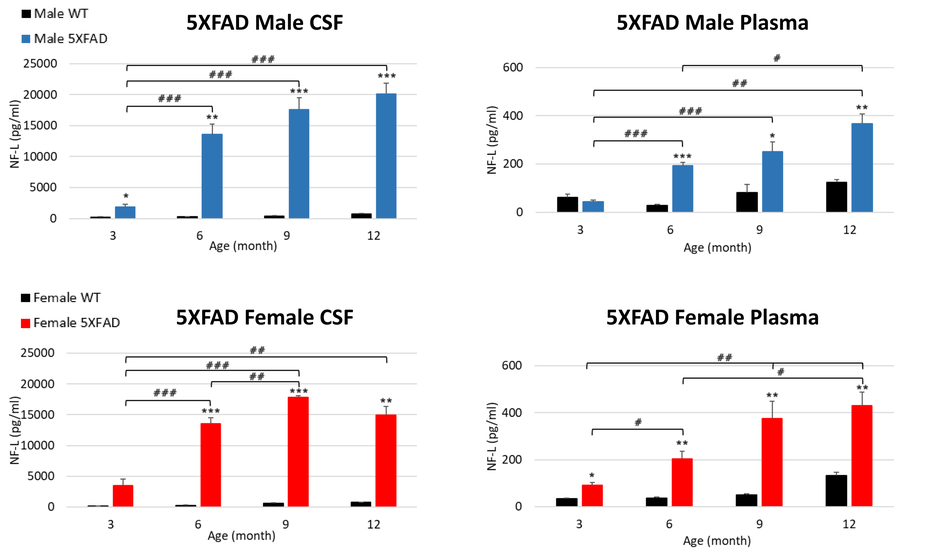
- The level of neurofilament light chain (Nf-L) in mouse CSF was determined using the Simoa® NF-light Advantage Kit (Quanterix Corp, Boston, MA; item 103400).

Disease and neurological score

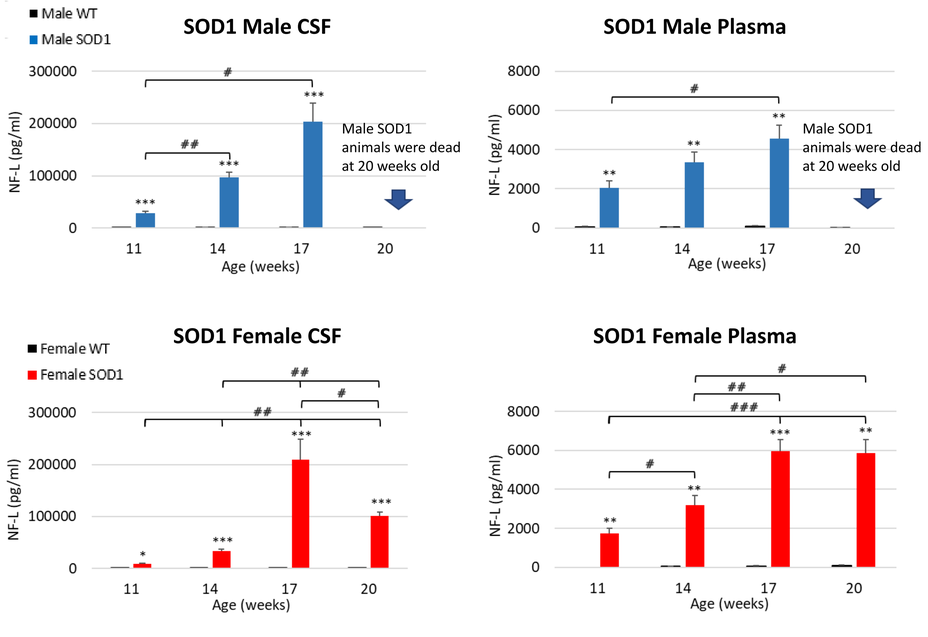
- Mice were evaluated for disease symptoms using Disease Onset Score developed by ALSTDI method (score 0 to 4).
- 30 behaviors for neurological score were evaluated including abnormal gait, tip toe walking, slow careful movements, circling, and sniffing. The assessment is performed as follows: A score of 0 is assigned for normal features (such as locomotor activity) or for the absence of abnormal features (such as absence of piloerection); a score of 1 is given when mild abnormalities are observed; and a score of 2-3 is given when severe abnormalities are observed.

RESULTS

1. NF-L concentrations in CSF and plasma of 5XFAD male and female

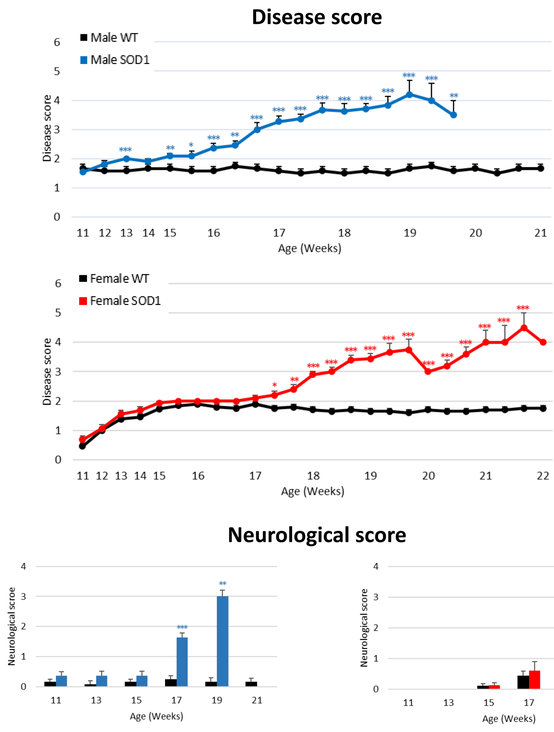


2. NF-L concentrations in CSF and plasma of SOD1-G93A male and female



Mean ± SEM, # : 0.05>p, ## : 0.01>p, ###: 0.001>p ; TG
* : 0.05>p, ** : 0.01>p, ***: 0.001>p ; WT vs TG

3. Disease and neurological scores of SOD1-G93A



Mean ± SEM, * : 0.05>p, ** : 0.01>p, ***: 0.001>p ; WT vs TG

CONCLUSIONS

1. **Concentrations of NF-L exhibited a notable upward trend with advancing age and the progression of diseases in both 5XFAD and SOD1-G39A mice. This observation underscores the potential significance of NF-L as a biomarker for monitoring disease-related changes in these animal models.**
2. **NF-L concentrations were significantly increased at earlier stages of disease development in the CSF and plasma of 5XFAD and SOD1-G93A mice. This finding highlights the sensitivity of NF-L as an early indicator of neurodegenerative disease progression, with one notable exception being male 5XFAD mice, whose plasma showed no significant change before the onset of disease.**
3. **Our study demonstrated a gender disparity in the SOD1-G93A mouse model, with male mice displaying a disease onset approximately 1.5 weeks earlier than their female counterparts and exhibiting a shorter lifespan. This gender-based distinction in disease progression adds an important layer of complexity to our understanding of neurodegenerative diseases and emphasizes the need for tailored research and therapeutic strategies for different patient populations.**