Gender Differences in Alzheimer's Disease Progression and Cognitive Function in 5xFAD Mice

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ABSTRACT

To understand Alzheimer's disease (AD) progression, reliable animal models are crucial. One such widely utilized model is the 5xFAD mice, engineered to express human APP and PSEN1 transgenes bearing five AD-linked mutations. While this model is important for studying AD, discrepancies in research findings underscores the necessity of acknowledging gender differences in disease manifestation.

In both clinical and preclinical research, females are often excluded due to potential pregnancy or hormonal fluctuations. Nevertheless, AD is more prevalent in women, affecting 7.1% compared to 3.3% in men. Despite this gender disparity, preclinical studies frequently use only male mice, primarily due to financial constraints.

This study focuses on investigating gender-specific differences in disease onset and progression in 5xFAD mice, examining amyloid-beta (Aβ) accumulation, inflammatory responses, neurofilament light (NF-L) variations, and cognitive-behavioral functions.

The study found that female 5xFAD mice showed elevated Aβ levels and increased inflammation in the cortex and hippocampus compared to males. Cognitive assessments revealed that differences in cognitive function between wild-type (WT) and transgenic (TG) female mice were more pronounced between 9 and 12 months of age compared to male counterparts. Cognitive disparities were observed as early as 6 months in the Morris Water Maze (MWM) test, while the Y-maze (YM) and novel object recognition (NOR) tests showed significant differences from 9 months onward.

Aβ deposition in the cortex and hippocampus began at 3 months, paralleling NF-L variations in cerebrospinal fluid (CSF) that differentiated WT and TG mice starting at 3 months, reaching a peak at 12 months. Immunohistochemistry disclosed the presence of Aβ in 5xFAD mouse brains from 3 months onward, accompanied by inflammation markers such as GFAP and Iba-1.

Gender-specific cognitive-behavioral assessments showed faster disease progression in females, marked by higher Aβ levels and earlier disease onset compared to males. NF-L measurements in CSF indicated neuronal death due to Aβ accumulation, with greater differences in females than males at 3 months, with noticeable differences in both sexes from 6 months onwards.

Therefore, considering gender disparities is crucial when evaluating AD therapeutics using the 5xFAD model.

METHODS

Animals

- Altogether 5xFAD mice and age-matched 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.

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).

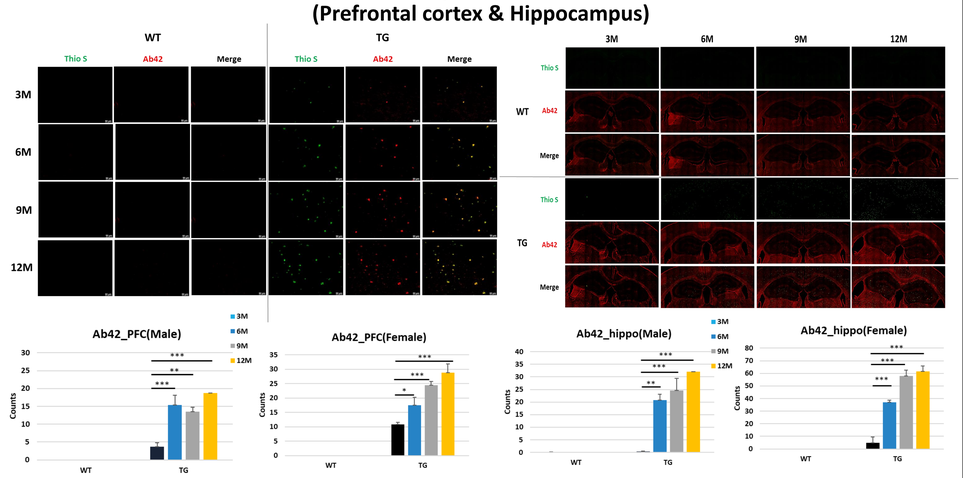
Histology

- 1st Abs
- GFAP(Cell signaling, cat#3670) ,Iba1(Wako, cat#019-19741) , Aβ42 (Millipore, cat#AB5078) ,Thioflavin S (Sigma Aldrich, cat#T1892)
- Sample : Whole brain (PFC, Hippo)
- Imaging: Axio Scan 7 (Zeiss)

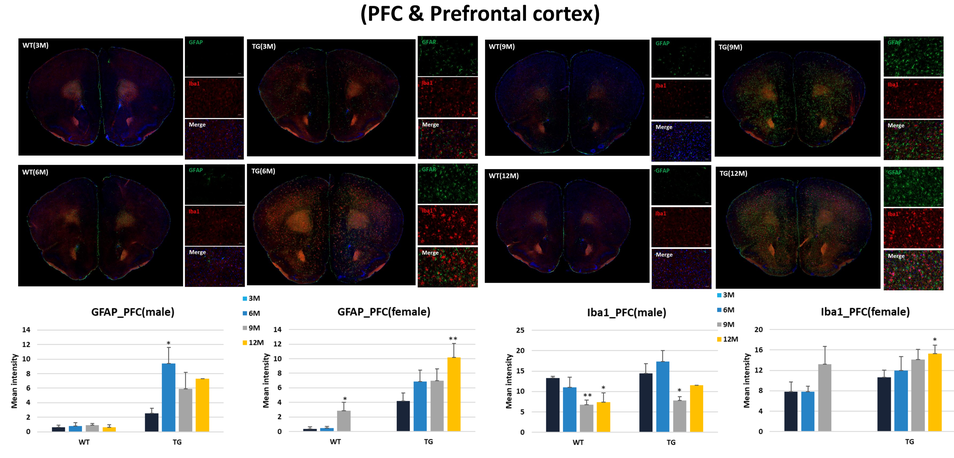
RESULTS

1. Time dependent histological biomarkers change in 5xFAD

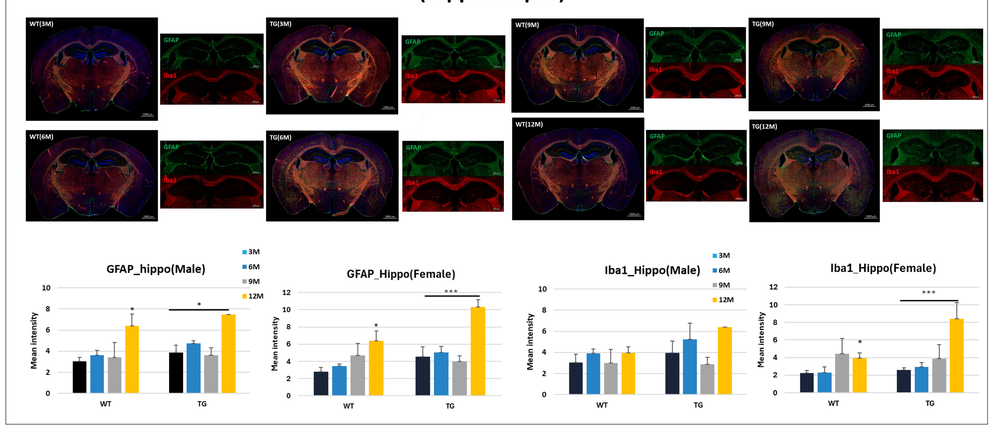
Aβ42/ This
(Prefrontal cortex & Hippocampus)



GFAP and Iba-1
(PFC & Prefrontal cortex)

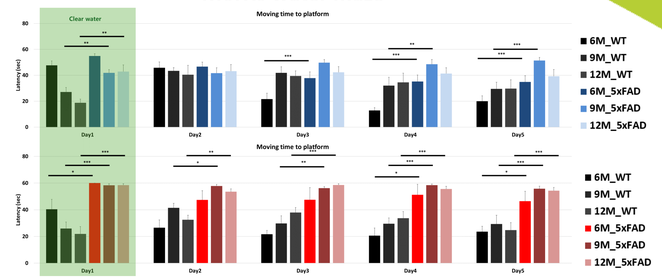


GFAP and Iba-1
(Hippocampus)

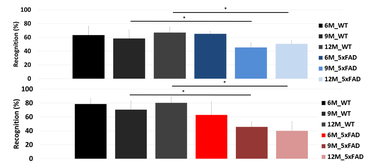


2. Time dependent cognition impairment in 5xFAD mouse.

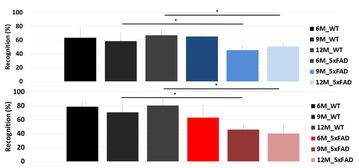
Morris water maze



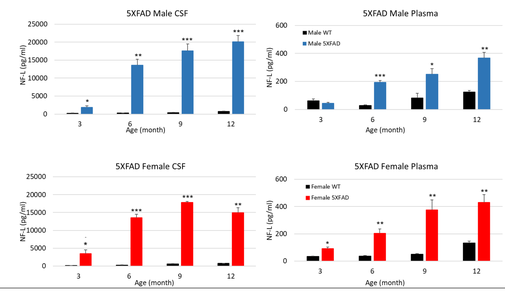
Novel objective recognition



Y- Maze



3. Time dependent Nf-L changes in 5xFAD mouse



CONCLUSIONS

1. This study investigates gender-specific differences in Alzheimer's disease progression using the 5xFAD mouse model, which expresses human APP and PSEN1 mutations linked to AD.
2. These findings show that female mice exhibit elevated amyloid-beta (Aβ) accumulation, increased inflammation, and earlier cognitive decline compared to males.
3. Cognitive impairments in females were more pronounced between 9 and 12 months, while males showed later onset.
4. Neurofilament light (NF-L) variations in cerebrospinal fluid(CSF) & Plasma were detectable from 3 months, with both male and female exhibiting similar progression.
5. The study emphasizes the importance of considering gender differences in preclinical AD research and therapeutic evaluation.