Males vs females: differences in the Aß accumulation

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Abstract

Background: The accumulation of extracellular amyloid-beta (Aß) peptide and intracellular neurofibrillary tangles in the brain are two major neuropathological hallmarks of Alzheimer's disease (AD). For the analysis of Aß-peptide aggregation, different mouse models (single or double transgenic mice) have been used to follow the evolution of AD-amyloidosis, and to test potential treatments. So far, cerebellum tissue has not been deeply analyzed to check the amyloidosis in these transgenic models. Besides, sex influence hasn't been systematically studied in these models, even it has been described important gender differences in the evolution of AD in human population. We have checked whether the progression of amyloidosis in a double transgenic mouse, APP/PS1, is susceptible to aging and differentially affects males and females.

Methods: Aß levels were measured by ELISA in plasma and tissue samples. Cortex and cerebellum tissue of transgenic males and females from 6 to 15 months of age were processed to be analyzed. In addition, fixed hemibrains brain were coronally sectioned and used to perform immunohistochemistry and immunofluorescence studies.

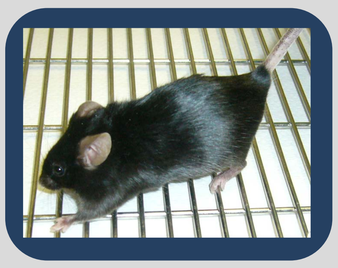
Results: Peripheral levels of Aß presented different levels at 15months-old, being significantly higher in females. This divergence is observed in cerebellum analysis too. The accumulation of amyloid in the cerebellum was 10 fold higher in the females at 15 months. However, cortex results didn't show such differences between sexes. Immunohistochemistry and immunofluorescence analysis confirm ELISA results. Furthermore, the distribution of reactive glial cells showed important differences between cortex and cerebellum. The levels of astrocytes in the molecular layer of the cerebellum were significantly reduced.

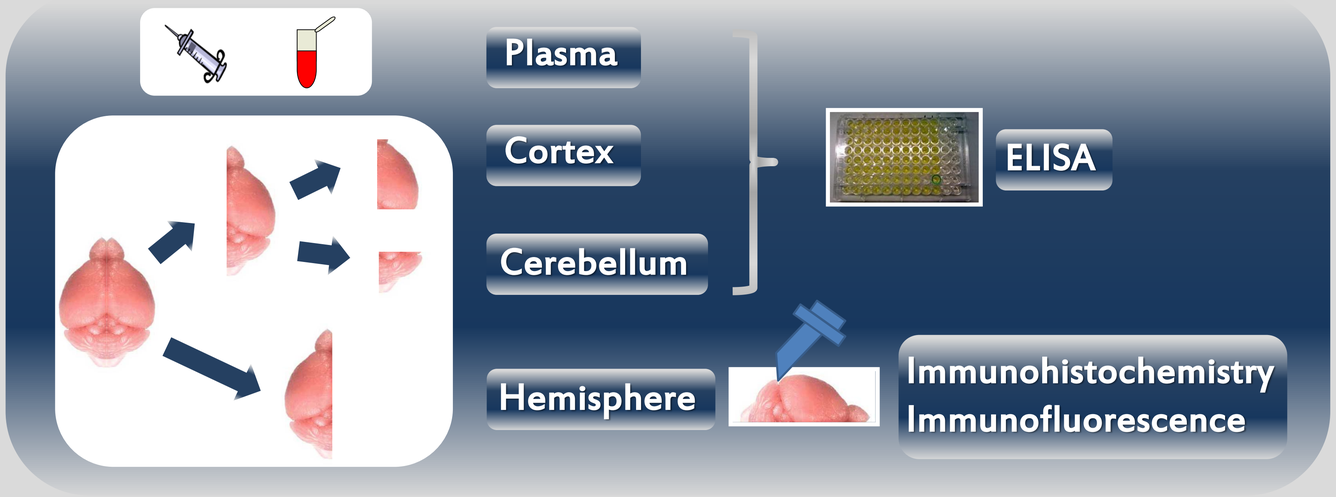
Conclusions: The cerebellum tissue should be deeply analyzed to follow its implications in the evolution of the disease and the developed pathology. Moreover, gender differences could be crucial for a complete understanding of this disease. We suggest that human population could be studied in this way. In addition, sex specific treatment strategies could be developed, even more, differential response after any therapeutic approach could be observed too.

Analyzed groups

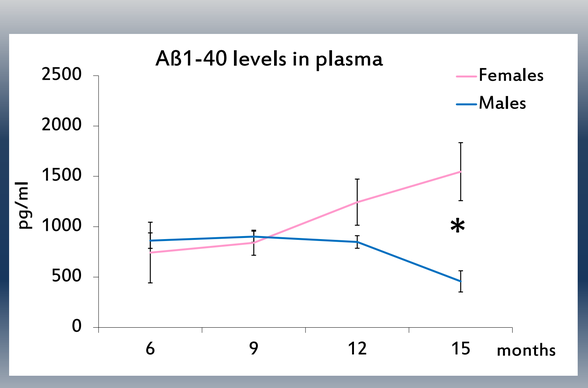
Age	Genotype	n	Sex
6m	Tg	4-6	♂
6m	Tg	4-6	♀
9m	Tg	4-6	♂
9m	Tg	4-6	♀
12m	Tg	4-6	♂
12m	Tg	4-6	♀
15m	Tg	4-6	♂
15m	Tg	4-6	♀

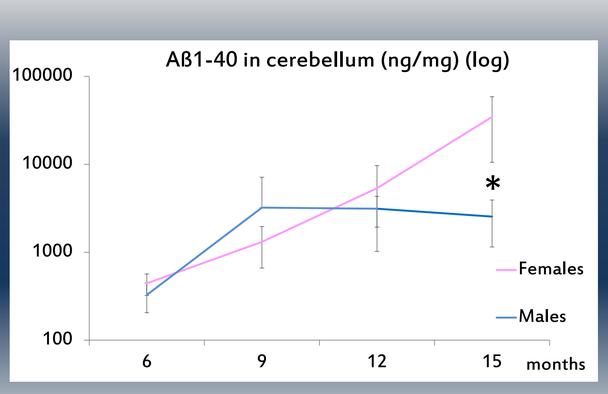
APP/PS1 transgenic mouse model

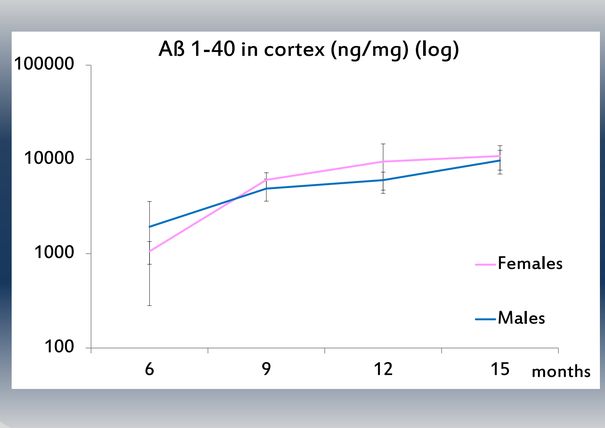




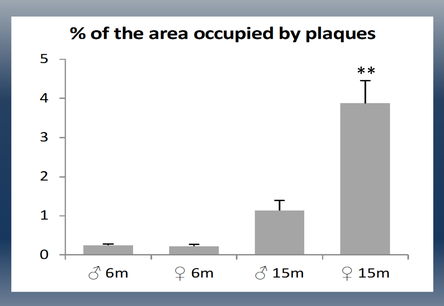
Older females showed increased levels of Aß40 in peripheral plasma and cerebellum, but not in cortex

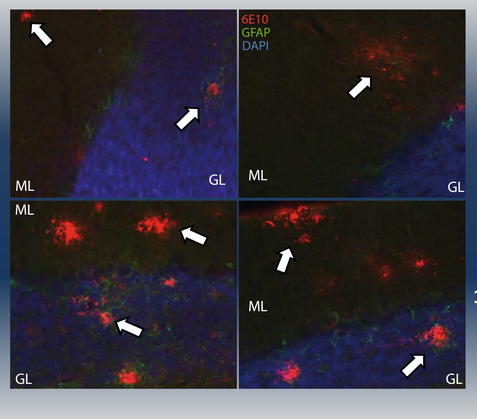




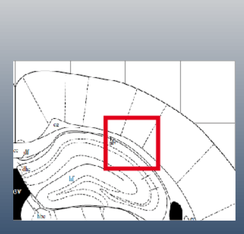


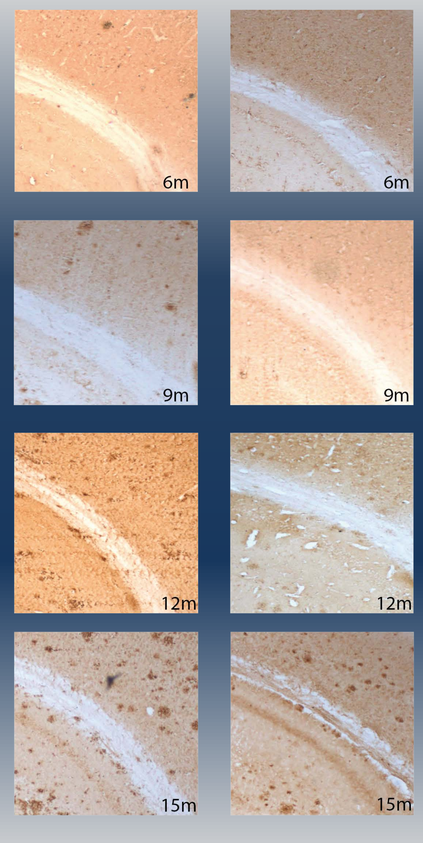
Greater Aß plaques burden in older female's cerebellum
Reduced glia reaction in the cerebellum molecular layer

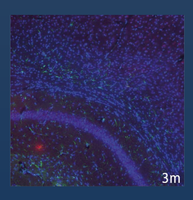


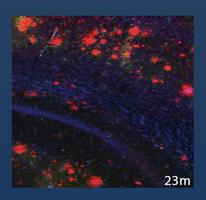


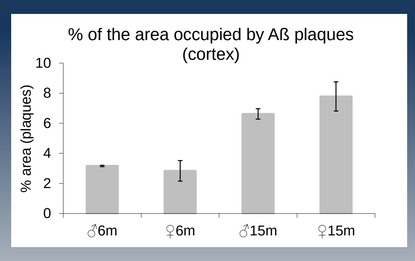
No sex differences in the Aß accumulation in the cortex
Most of Aß plaques are surrounded by reactive glia cells











Conclusions

- The peripheral levels of Aß in old females were greater than those observed in the males at the same age
- Levels of Aß in the cerebellum were higher in 15-month females than in males at the same age
- Not statistically significant differences were found in the Aß burden in the cortex between males and females
- Cerebellum analyses showed an increase in the Aß burden with the age as it occurs in the cortex and hippocampus; developed Aß plaques presented similar structure
- Cerebellum molecular layer presented a very reduced levels of reactive glia cells
- Biochemical analysis (data not shown) confirm gender differences in some important markers; neuronal, survival and autophagic pathways

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