Sex-effect in the treatment response to low-dose radiation therapy for Alzheimer’s disease.

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BACKGROUND

Numerous treatments against AD have been developed to target amyloid, tau or neuroinflammation, without a clear success, highlighting the necessity to develop new therapeutic strategies1. Radiation therapy (RT), one of the mainstay cancer treatments, has been recently studied in AD. It has been postulated that this treatment, applied at low doses (LD), could achieve two important effects for AD: a decrease of amyloid load and neuroinflammation2. Only 6 studies evaluated its impact in the brain of AD mouse models, using different regimens or delay post RT3-4. However, the radiation doses, the delay post treatment, the models and the stage of treatment differ between studies, making difficult to define the effect and the mechanisms of actions of LD-RT in AD.

AIMS

1) The main objective of this study is to assess the clinical relevance of a reference regimen (2 Gy in 5 fractions delivered daily) in an AD rat model applied at a pre-symptomatic stage in males and females.
2) Better understand the sex effect observed in the treatment response.

METHODS

Tg344-AD (TgAD) rats, harboring the hAPPswe and hPS1dE9 transgenes, were treated with 10 Gy in 5 fractions of 2 Gy delivered daily.

Males and females were treated separately at 9-months-old. One or 2 months later, the effect of LD-RT was evaluated postmortem.

In a third cohort, TgAD males were castrated at 6-month-old and analyzed with sham-operated males and females (TgAD and WT) at 12-month-old by PET imaging ([18F]FDG and [18F]Flutemetamol to quantify brain metabolism and amyloid plaques respectively). Postmortem analyses are ongoing.

CONCLUSION

- Low-dose radiation therapy significantly reduced different markers of the AD pathology (amyloid plaques and neuroinflammation) at a pre-clinical stage in males. Interestingly, the same treatment did not impact the pathology in females.
- Females TgAD rats present a more advanced pathology than males.
- We are currently evaluating the effect of sex hormones in the pathogenesis of AD: amyloid, metabolism and brain atrophy in a multimodal imaging study. The difference between both sexes and the effect of testosterone depletion on different amyloid forms, amyloid phagocytosis and neuroinflammation will be evaluated postmortem.

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