Title: Does hypertension contribute to the microbleeds in EFAD mice?

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Abstract:

Background: Hypertension, namely increased blood pressure, has been associated with the presence of microbleeds (MBs) [1]. A study in hypertensive subjects reported that each standard deviation increment in blood pressure was significantly and independently associated with a 1.8- to 1.9-fold higher likelihood for MBs [2], suggesting that hypertension might have an important role in the etiology of MBs. Transgenic mouse models of Alzheimer Disease (AD) resemble the same female excess of brain Aβ and most of the cognitive deficits [3-6]. In this context, microbleeds (MBs) are contributing factor to pre-clinical cognitive decline and an additional clinical burden in AD [7, 8]. We recently showed that this sex bias is inverted when it comes to MBs, with male excess in two human cohorts (KIDS, and ADNI) and female excess in EFAD mice [6].

Method: Using the non-invasive tail-cuff method approach, we measured blood pressure in EFAD mice, targeted replacement of human APO-E3 or -E4 in the contest of the 5XFAD model of AD, at three different ages (2-4-6 months) and their siblings. C57BL/6 were also analyzed for comparison with previous reports. Additionally, we quantified MBs by Prussian Blue Staining and Aβ load by immunohistochemistry with 4G8 antibody in EFAD mice.

Results: In both cross-sectional and longitudinal measurements, female mice showed higher systolic and diastolic blood pressure compared to age matched males at 6mo of age, with no apparent APOE allele interaction. Same trend was observed in siblings without AD transgene. No age or sex bias was observed in C57BL/6 aged matched mice. We additionally compared systolic blood pressure in C57 mice and APOE4 mice. APOE4 carriers showed lower systolic blood pressure compared to C57BL/6 mice. Microbleeds and Aβ load were measured in a separate group of mice. Despite no changes in blood pressure, MBs were detected in 2mo old EFAD mice. Both MBs and Aβ load showed female and APOE4 bias and increased by age.

Conclusion: Our data suggest that hypertension is not a contributing factor for the presence of MBs in EFAD mice. Additional studies are needed for the clarification of a potential interaction MBs-hypertension in older mice.

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