Cross-linking non-amyloid CSVD and CAA

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INTRODUCTION:

In human autopsy studies of the non-demented elderly and Alzheimer's disease non-amyloid cerebral small vessel pathology (CSVD) and cerebral amyloid angiopathy (CAA) are found in the same brain. We here hypothesize a causal link between the two CSVD entities that goes beyond just a simple co-occurrence. We therefore investigated if spontaneously hypertensive stroke-prone rats (SHRSP), a valid non-transgenic animal model of human non-amyloid CSVD, develop CAA as a function of different non-amyloid CSVD stages.

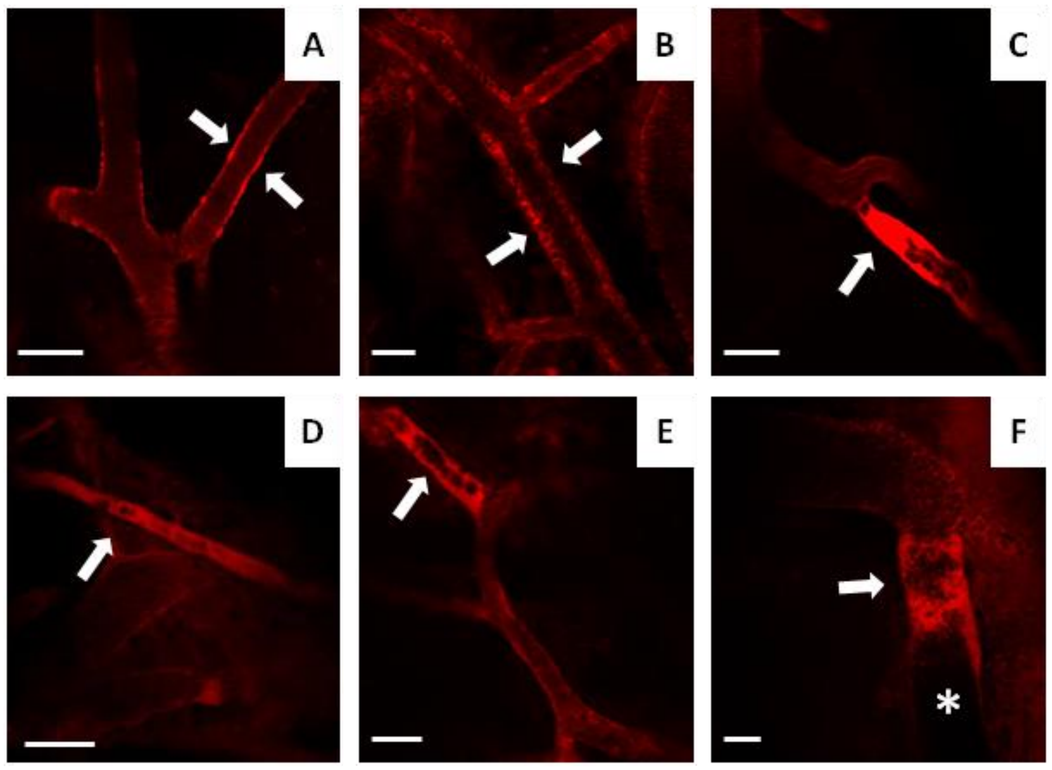

Figure 1: Phenomena of cortical small vessel pathology in SHRSP demonstrated using intravital 2-photon microscopy.
A shows small vessel wall damage indicated by Dextran accumulations in the small vessel walls (arrows). **B** demonstrates erythrocyte accumulations within an arteriolar wall (arrows) and **C** shows Dextran accumulations within the small vessel lumen (arrow). In **D** the luminal formation of non-occlusive erythrocyte thrombi is demonstrated (arrow). Non-occlusive erythrocyte thrombi then transform to occlusive erythrocyte thrombi (**E** & **F**, arrows) or later to occlusive non-erythrocyte thrombi (**F**, asterisk). **A** & **B** refer to CSVD stage 1A (small vessel wall damage), **C** indicates CSVD stage 1B (RBC flow reduction), **D** refers to stage 2 (non-occlusive thrombus formation) and **E** & **F** refer to CSVD stage 3 (occlusive thrombus formation).
Scale bars = 50 µm

METHODS:

Two-photon-microscopy was performed in 21 SHSRP to assess stages of CSVD in vivo. Therefore, the fluorescent dye Dextran was used to label the cerebral vasculature, and cerebral blood flow measures (CBF) were additionally conducted. Furthermore, in 13 out of those 21 SHRSP Methoxy-X04 (Congo red derivate) was used for the intravital CAA detection.

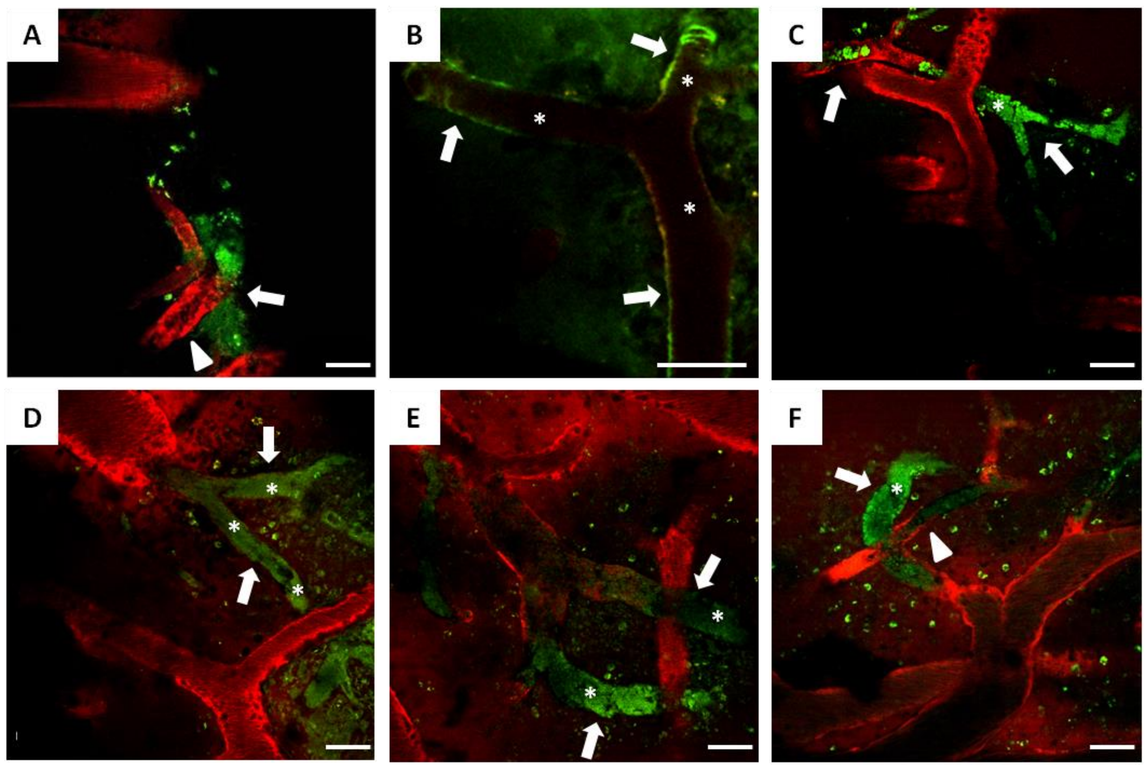

Figure 2: Intravital two-photon microscopy of amyloid pathology in the parietal cortex of SHRSP.
Vascular Methoxy positivity (green) indicative of CAA comprised periarteriolar (**A**, arrow) and wall-adherent amyloid deposits (arrows in **B-F**). CAA was detected next to non-occlusive erythrocyte thrombi (**A, F**, arrowheads) or surround occlusive non-erythrocyte thrombi characterized by long distant Dextran gaps (asterisks in **B-F**) leading to the assignment of all Methoxy-positive SHRSP to either CSVD stage 2 or stage 3. Data refer to the investigation of 13 male SHRSP aged 17-44 weeks. Small vessels and vessel walls are visualized by Dextran (red).
Scale bars = 50 µm

RESULTS:

Non-amyloid CSVD progression occurs in a temporal manner, comprising the following stages: stage 0 – no CSVD pathology, stage 1A – small vessel wall damage, stage 1B – CBF reduction, stage 2 – non-occlusive/ incomplete thrombus formation and stage 3 – occlusive/ complete thrombus formation (Figure 1). Six out of 13 SHRSP (46%) that underwent Methoxy-X04 imaging displayed intravital β-amyloid positivity of the cerebral small vessel walls, i.e. perivascular amyloid deposits and brightly fluorescent arteriolar/small artery wall adherent plane- or circular-shaped amyloid accumulations indicative of CAA. In nearly all Methoxy positive SHRSP amyloid deposits were detected surround thrombotic arterioles characterized by (in)complete small vessel occlusions (CSVD stage 2/3) (Figure 2). A scheme of the cascade of non-amyloid CSVD cascade related CAA development is shown in Figure 3.

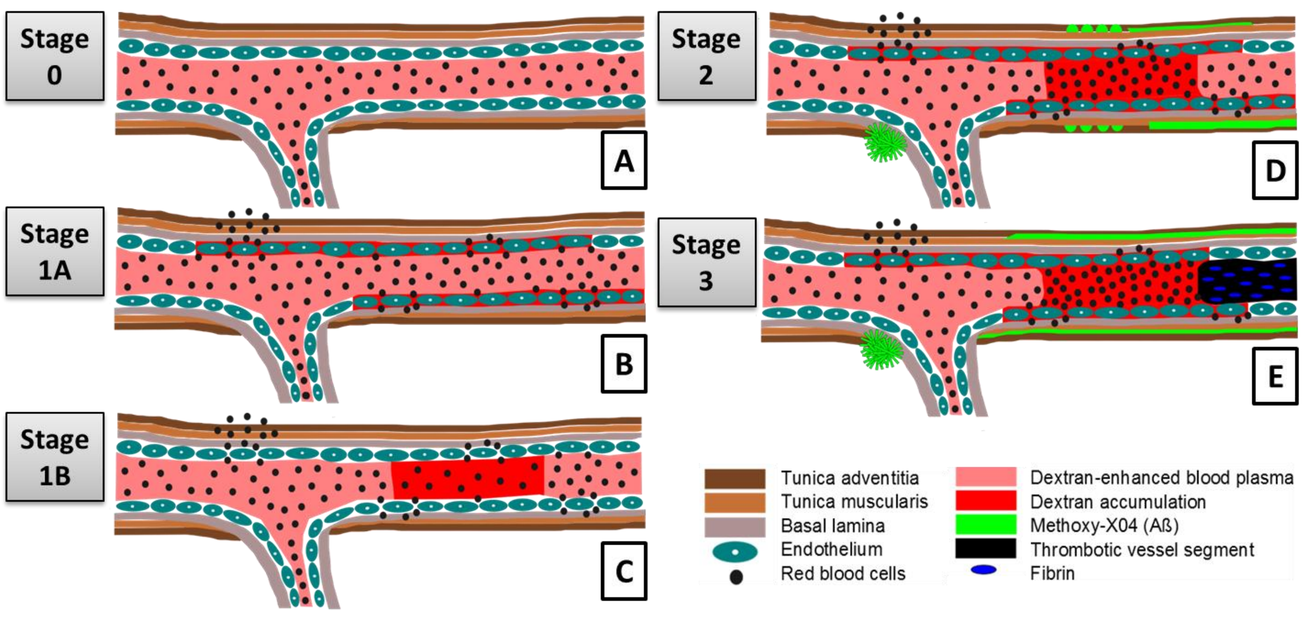

Figure 3: Non-amyloid CSVD cascade related CAA development.
A demonstrates non-pathological vessels without any CSVD phenomena (**A**, stage 0). Non-amyloid CSVD related changes are initiated by small vessel wall damage and blood flow reductions indicated by the accumulation of Dextran and erythrocytes in the small vessel wall (**B**, stage 1A) or Dextran in the small vessel lumen (**C**, stage 1B). The walls of small vessels with subsequent formation of non-occlusive (**D**) or occlusive thrombi (**E**) accompanied by a significant reduction of RBC flow velocity are prone to accumulate (peri)vascular amyloid deposits.

CONCLUSIONS:

Advanced non-amyloid CSVD stages display a condition prone to vascular β-amyloid accumulations, in terms of CAA. Further investigations have to shed light on the pathophysiological interactions between the two small vessel disease entities, especially whether a failure of perivascular Aβ-drainage or disturbances of endothelial Aβ-transport across the blood brain barrier drive the vascular amyloid pathology found in the SHRSP.

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