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In Vivo Longitudinal Monitoring of Blood Flow Alterations in TG2576 Mouse Model of Alzheimer's Disease

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Introduction

One of the cardinal features of pathology of Alzheimer` Disease (AD) includes the occurrence of amyloid β (Aβ) plaques in the brain. Accumulation of different isoforms of this peptide in cerebral vessel walls leads to cerebral amyloid angiopathy (CAA), which is accompanied by a reduced cerebral blood flow. CAA commonly observed in AD patients. A few studies used trangenic mice model of AD to understand how CAA related blood flow abnormalities contributes to the onset and progression of AD [1,2]. In this study we tested whether the frequency of cerebral vascular blood flow artifacts changes over time by longitudinal monitoring of blood flow in cerebral arteries of APP_{Tg2576} transgenic mice by high resolution magnetic resonance angiography (MRA) at 9.4T. To our knowledge, this is the first study which monitors blood flow alterations of the same Tg2576 mice over time by using 3D MRA in vivo. Our results show that blood flow defects are present long before vascular deposition of Aβ takes place in this mouse model, suggesting that non-CAA related changes such as elevated soluble A**β** levels in the vessel wall may be responsible for impair cerebral blood flow, thereby contributing to the early progression of Alzheimer's disease.

Methods

Tg2576 trangenic mouse model of AD were used in this study [3]. Their non-transgenic littermates were used as controls (WT). The N2 generation of mice of both genders (N=10) were studied over time between 8 and 24 months. All measurements were conducted on a vertical wide bore 9.4-T Bruker spectrometer, with a 1000 mTm^{-1} actively shielded imaging gradient insert (Bruker). A birdcage radio-frequency (RF) coil (inner diameter 2 cm) was used. The 3D time-of-flight (TOF) gradient echo sequence was applied with the following parameters: effective echo time = 1.9 ms; repetition time =15 ms ; flip angle = 30°. A resolution of 78x78x78 μm was achieved within an acquisition time of ~16 minutes. A three-dimensional view was obtained by generating maximum-intensity projections. T_2- weigted MR images were acquired using a RARE sequence [4]. Coronal (transverse) images were obtained with a slice thickness of 0.5 mm. A resolution of 78x78 μm was achieved within an acquisition time of ~25 minutes. While inside the probe, the respiration rate of the mouse was constantly monitored (BioTrig BT1 monitoring system).

Results and Discussion

Figure 1 shows the angiogram of WT and Tg2576 mice over time between ages 16 and 23. The overall decrease in the brightness of the arteries was observed in transgenic mice with age which was not visible in WT mice. Flow voids were observed and increased at different places such as in superior cerebral artery, anterior cerebral arteries (Fig. 1) as well as in pterygopalatine arteries (Fig. 2) with age. *In vivo* monitoring of amyloid plaques deposition in the same mouse with age show an increase in plaque load from 16 to 23 months in Tg2576 mice and not in WT mouse (Fig 3). Lastly, we compare the changes in the contrast to noise ratios (CNR) in individual MR slice for anterior cerebral artery (ACA), middle cerebral artery (MCA), and ptergo portion of the pterygopalatine artery in WT and Tg2576 mice at the age of 8, 19 and 23 months. Interestingly the CNR in MCA in Tg2576 mice was significantly lower in the middle cerebral artery reflecting the flow defects in this artery already at the age of 8 months, long before the vascular deposition of Aβ takes place in this mouse model. In ACA the flow alterations were visible at the age of 19 months, which could be correlated with CAA as well as with a high a plaque deposition in the brain tissues at this age.

References: [1] Meyer et al. *Proc. Nat. Acad. Sci.*(2008) 105:3587-3592; [2] Beckmann et al. *J. Neurosci*. (2003) 23:8453-8459; [3] Hsiao K, et al. *Science* (1996) 274:99-103; [4] Braakman et al. JRMI (2006) 24:530-536.

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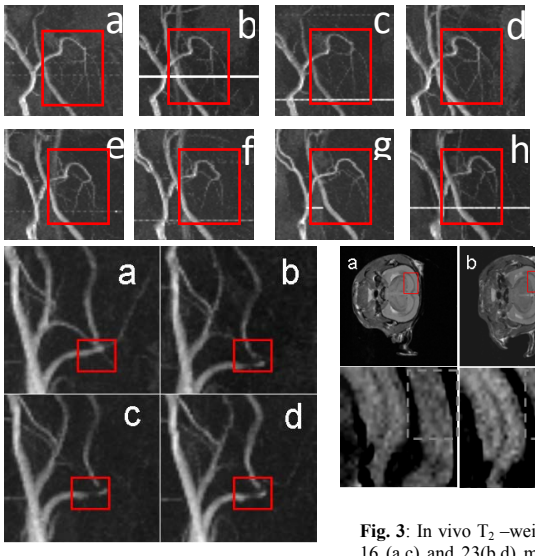


Fig. 1: Angiogram of wt (a,b,c,d) mouse and Tg2576 mouse (e,f,g,h) at different ages (a)16 (b)17 (c)19 (d) 23. Middle cerebral artery (MCA) of wt mouse is longer and has extra brances.

Fig. 2; Angiogram of same Tg2576 mouse at different ages (a)16 (b)18 (c) 21 and (d) 23months,showing severe flow voids at the pterygo portion of the pterygopalatine artery after 16 months.

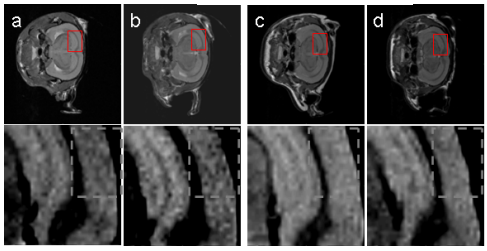
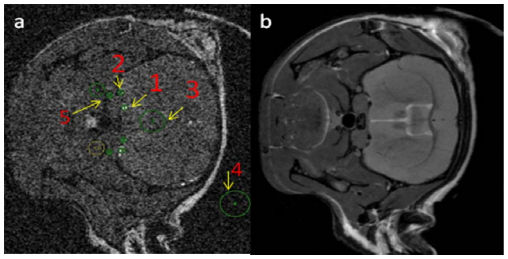


Fig. 3: In vivo T_2 –weighted MR images of the brain of a 16 (a,c) and 23(b,d) month old Tg 2576 mouse(a,b) and wild type mouse (c,d), respectively. Hypointense regions corresponding to Aβ plaques exist in Tg2576 mouse (a,b) but not in wild-type mouse (c, d).



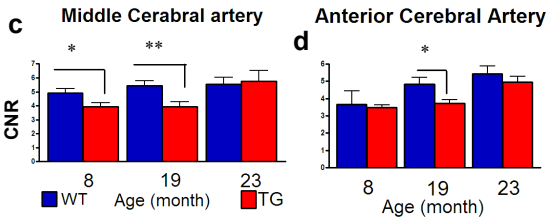


Fig. 4: The 3D angio slice data (a) indicating the regions for the signal intensity evaluation; (b) corresponding T2-weighted MR images of a mouse; (c,d) graphical analysis of CNR. Region of interest (ROI) 1, 2, 5, represent ACA, MCA, ptergo portion of the pterygoplatine artery respectively and ROI (4) represents the background signal. The CNR was determined by subtracting the background signal (ROI 3) from the signal intensity of interest and dividing the difference by standard deviation of noise (ROI 4). Number of animals: 4-6 (WT); 3-4 (Tg). *P<0.05,** P<0.01, one tail student T test was used.