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MRI assessment of blood flow artifacts in a transgenic mouse model of Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly with no effective treatment or definitive antemortem diagnostic test. The neuropathologic features of AD include the occurrence of amyloid β (Aβ) containing plaques, neurofibrillary tangles, decreased synaptic density, and loss of neurons. In AD, the deposition of Aβ peptide in the cerebral vessel walls, known as cerebral amyloid angiopathy (CAA) is frequently observed, leading to blood flow abnormalities. However, its contribution to the onset and progression of dementia is unknown. The evidence for blood flow disturbance during AD comes mainly from postmortem studies. Direct non-invasive *in vivo* methods to probe blood flow disturbance during AD are highly challenging. A previous study [1] has shown that magnetic resonance angiography (MRA) is a useful method to identify changes of vascular function in APP23 mice model of AD. In this study we optimized high resolution MRA at 9.4T in combination with strong gradients to monitor morphological changes in cerebral arteries in APP_{Tg2576} transgenic mice which is one of the most widely used mouse model of AD. Our preliminary data showed significant morphological changes in large and medium sized arteries in APP_{Tg2576} mice.

Methods

The transgenic mice used in this study (Tg2576) contain as transgene the Swedish double mutation of the human amyloid precursor protein (APP_{695}), as developed and described previously by Hsiao et al [2]. The transgene is expressed in C57B6 breeders. The N2 generation mice of both genders were studied at ages between 8 and 23 months. Age-matched non-transgenic littermates served as controls (WT). MRA measurements were conducted at 9.4-T vertical wide-bore imaging systems equipped with a Bruker Avance console and 1000-mT/m gradients. The imaging coil used was a 25-mm volume coil. Time-of-flight (TOF) angiograms were obtained using a 3D gradient echo sequence. The parameters used were TE_{eff} = 1.9 ms, TR =15 ms, flip angle 30° and average = 1. 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 (MIP's).

Results and Discussion

It is well known that vascular abnormalities coexist with other pathological features of AD. Recent vascular corrosion casts studies in APP23 transgenic AD mice have shown significant alteration of the microvasculature [3]. Small to medium-sized arteries and arterioles are most frequently affected vessels by CAA in AD [4]. To compare the vascular architecture of living APP_{Tg2576} transgenic and WT mice, we applied high resolution MRA at 9.4T. With 3D TOF sequence, which is sensitive to fast-flowing blood, cerebral arterial structures of living mice can be selectively probed (Fig. 1). Due to high field strength and use of strong gradients, the large and medium sized arteries were very clearly imaged upto the level of the pial vessels. Overall decrease in the brightness of the arteries was observed in transgenic mice as compared to wild-type suggesting an overall decrease in cerebral blood flow. Flow voids were observed at different places such as in superior cerebral artery, anterior cerebral arteries as well as in pterygopalatine arteries (Fig. 2). However, these voids were not restricted to only these locations in transgenic mice. The presence of plaques and CAA in the brain of same APP_{Tg2576} was confirmed by histology (Fig. 3). Our results suggest that MRA at high magnetic field is useful method to monitor CAA-related structural changes in cererbral arteries and arterioles in mouse models, providing a powerful tool to study the contribution of CAA to AD in vivo in animal models.

References: [1] Beckmann N, Schuler A, Mueggler T, et al. *J. Neurosci.* 2003;23:8453-8459; [2] Hsiao K, Chapman P, Nilsen S, et al. *Science* 1996;274(5284):99-103; [3] Meyer EP, Ulmann-Schuler A, Staufenbiel M, Krucker T. *Proc. Nat. Acad. Sci.* 2008;105:3587-3592; [4] Herzig MC. Inaugural dissertation, Universität Basel 2004.

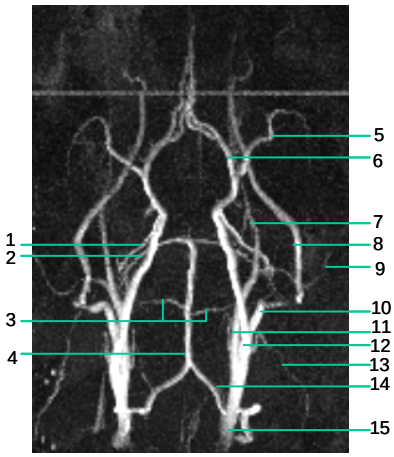

Fig. 1. MIP of 3D TOF MRA month- old wild type mouse. The arteries are identified as: 1, posterior cerebral artery; 2, superior cerebellar artery; 3, caudal cellebellar artery; 4, basilar artery; 5, middle cerebral artery; 6, anterior cerebral artery; 7, facial artery; 8, palatine portion of pterygopalatine; 9, maxillary artery; 10, pterygo portion of pterygopalatine; 11, external carotid artery; 12, internal carotid artery; 14, vertebral artery; 15, common carotid artery.

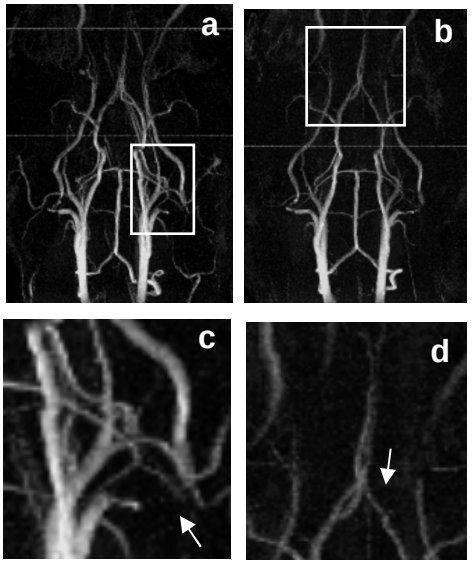

Fig. 2. Angiogram of 23-month-old transgenic mice showing severe flow voids at the pterygo portion of the pterygopalatine artery (a,c) and missing bifurcation of one of the anterior cerebral arteries (b, d). Such changes were not observed in wild-type mice.

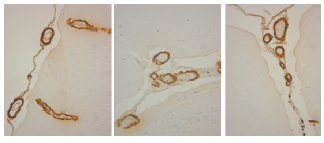

Fig. 3. CAA detected in the brain sections of 23-month old transgenic mice stained with $A\beta_{40}$