MR angiography detects cerebral amyloid angiopathy (CAA) associated with alterations of cerebral blood flow in thalamic vessels of APP23 mice modelling Alzheimer's disease

N. Beckmann[1], E. Capetillo-Zarate[2], S. Larionov[2], M. Staufenbiel[3], S. Zurbruegg[1], and D. R. Thal[2]

[1]Discovery Technologies, Novartis Institutes for BioMedical Research, Basel, Switzerland, [2]Department of Neuropathology, University of Bonn, Bonn, Germany, [3]Neurosciences Research Department, Novartis Institutes for BioMedical Research, Basel, Switzerland

Introduction:

Cerebral amyloid angiopathy (CAA) is a vascular disorder frequently (80-100%) associated with AD [1,2]. Although CAA can also induce cerebral hemorrhage and infarction, usually it is clinically silent. Similarly to senile plaques in Alzheimer's disease (AD), CAA-related vascular amyloid deposits mainly consist of the Aβ-protein [1]. Although the severity and extension of CAA into further brain regions is related to the pathological and clinical progression of the disease [3], it is not clear whether CAA in AD patients has an additional impact on the AD-related degeneration of neurons besides tissue damage due to hemorrhage or infarction. To address this question, we examined by MR angiography (MRA) the flow patterns at the Circle of Willis of 25-month-old APP23 and wild-type mice. Samples from human AD cases were studied to confirm the occurrence of a possible morphological correlative for blood flow disturbances seen in the mouse model to be relevant for human AD.

Methods:

Animals: The generation of APP23 mice containing the murine Thy-1 promoter driving neuron specific expression of human mutated APP_{751} was described in detail in [4]. Female (n=15 APP23, n=18 wild-type) and male (n=15 APP23, n=8 wild-type) were studied.

MRA: Details are provided in [5,6]. Briefly, mice were anaesthetized with forene (1.5%) in a mixture of O_2/N_2O (1:2), administered via a face mask. Measurements were carried out with a Bruker Biospec 47/40 system. Angiograms were obtained using a 3D gradient-echo sequence with the following imaging parameters: TR/TE 40/1.6 ms; matrix 96x192x64; FOV 1.44x1.92x0.64 cm^3, 2 averages. The RF pulse was frequency-selective, thereby exciting a coronal slice 0.64 cm thick. Magnetization transfer contrast was attained by a frequency-selective gaussian pulse of 3500 μs duration, with B_1 = 2 μT and a frequency offset of 2500 Hz with respect to the water resonance, preceding the 3D gradient-echo sequence by 2.4 ms.

Neuropathology: Following MRA the mice were perfusion fixed. CAA was detected immunohistochemically with an antibody raised against Aβ17-24 (4G8). The extent and severity of CAA was determined according to the three stages reported for the development of CAA [3].

Results and Discussion:

MRA displayed all major vessels of the circle of Willis in 85% of the wild-type animals. The four wild-type mice with flow disturbances showed only single-sided changes mostly restricted to the thalamoperforating artery and the distal segment of the posterior cerebral artery. No morphological correlative for these changes was found. By contrast, MRA revealed significant flow disturbances in the thalamoperforating artery and the distal part of the posterior cerebral artery in 93 % of the APP23 mice. Single-sided flow disturbances were more frequently seen but 30% of the APP23 mice demonstrated double-sided flow disturbances. Statistically, blood flow disturbances were prevalent in APP23 but not in wild-type animals regardless of the gender.

Histopathologically, all APP23 mice showed senile plaques and CAA in cortical and subcortical areas including the thalamus. Especially in the thalamus there was a high number of CAA-affected capillaries, arterioles, and venules with an occlusion or severe narrowing of the lumen. The vessel wall of these arterioles and venules was thickened and showed fibrosis as indicated by an accumulation of collagen IV-positive fibers often replacing smooth muscle cells in the media. Hemorrhages were seen in 33% of the transgenic mice, but were most frequently located in the frontal cortex. Thalamic hemorrhage and/or infarction were seen in two APP23 mice only. A reduction of the thalamic capillary density was seen in APP23 mice.

In autopsies, capillary Aβ-deposition narrowing the vessel lumen was more frequently observed in AD cases compared with non-demented controls. Similar to the decrease in capillary density in the thalamus of APP23 mice, human autopsy brains from AD patients and non-demented elderly showed a progressive reduction of capillary density in the occipital cortex with increasing expansion of Aβ plaque pathology.

The occurrence of hemorrhage or infarction was not the primary cause of the flow disturbances as 66% of the mice presenting with flow disturbances were free of hemorrhage and/or infarction. Moreover, when present, hemorrhage occurred mostly in cortical regions whereas flow disturbances detectable by MRA were found in the thalamus. CAA-related vasculitis was likewise seen in only 50% of the APP23 mice exhibiting flow disturbances. Therefore, CAA in the branches of the thalamoperforating artery was the main cause of the flow disturbances seen in APP23 mice by MRA.

Our data suggest that CAA represents the morphological correlative for cerebral blood flow disturbances seen in MRA. In so doing, vascular Aβ-deposition, i.e. CAA, represents a second mechanism of Aβ-toxicity. In addition to its direct neurotoxic effects, Aβ may contribute to the degeneration of neurons in AD by altering cerebral blood flow due to CAA and consecutive chronic hypoxia.

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