Association of Blood-Brain-Barrier Permeability with Future Development of Brain Atrophy: A longitudinal Voxel-Based Morphometry (VBM) Study in A Canine Aging Model

M-Y. Su[1], K. Head[1], L. Vu[1], B. A. Muggenburg[2], O. Nalcioglu[1], and E. Head[3]

[1]Tu and Yuan Center for Functional Imaging, University of California, Irvine, CA, United States, [2]Lovelace Respiratory Research Institute, Albuquerque, NM, United States, [3]Institute for Brain Aging and Dementia, University of California, Irvine, CA, United States

Purpose:

Deposition of beta-amyloid (Aβ) in brain tissue and cerebral blood vessels are pathological hallmarks of Alzheimer´s disease in humans. Dogs naturally develop a similar pathology with aging, and also in parallel develop cognitive impairments. Thus, we have been using the canine as an animal model of human brain aging and dementia. We recently demonstrated that a combination of an anti-oxidant diet and behavioral enrichment can slow cognitive decline and also reduce brain pathology [1]. Based upon our previous imaging studies, dogs also show ventricular enlargement with aging, as in humans, but only subtle signs of cortical atrophy [2]. The deposition of Aβ in the cerebrovasculature (CAA) may impair vascular function. Aβ damages vessel-associated endothelial cells and may lead to the disruption of the Blood-Brain-Barrier (BBB). Further CAA may cause enhanced vasoconstriction leading to chronic cerebral hypoperfusion. In humans it is known that areas with vascular dysfunction (hypoperfusion measured on SPECT imaging) often co-occurs with regional atrophy. We hypothesized that BBB permeability is associated with the future development of atrophy in aging dogs. Images of dogs were grouped into those with higher vascular permeability vs. those with lower vascular permeability. These two groups were compared to detect differences in the extent of cortical atrophy that developed over time in a longitudinal study. Since our initial studies suggest brain atrophy was subtle in aging dogs we applied the most sensitive Voxel-Based-Morphometry (VBM) techniques, which were specifically developed for dogs, to investigate differences [3].

Methods:

The study was conducted on 46 beagles (10 to 12 years old). The MRI studies performed across three years were analyzed. The experiments were performed using a GE 1.5 Tesla mobile scanner with a knee coil. Animal were anesthetized by inhalation of Isoflurane (1.5-2 %). The protocol included anatomic imaging using a SPGR pulse sequence to acquire a set of 3D images across the whole brain, and a dynamic SE pulse sequence (TR/TE= 133/14 ms) to acquire T1-weighted images before and after injection of Gd-DTPA (0.15 mmol/kg). The enhancement kinetics from frontal, parietal, and occipital regions were measured and averaged. The early enhancement ratio (ER, enhancement at 30-45 sec) was used as the vascular volume index, and the late ER at 6.5-7.5 min after contrast injection was an indicator for the contrast leakage through BBB (Fig. 1). The BBB permeability index was defined as the contrast leakage divided by the vascular volume. According to the permeability measured in Year-1, the dogs were separated into 2 groups as being either above or below the median for the entire group. VBM was applied to compare the gray matter and white matter differences based on the 3D anatomic images across groups. A study specific VBM template was generated using all studied dogs, then the GM and WM probability maps were applied for segmentation, then statistical comparisons were made with $p < 0.001$ uncorrected. Two more MRI studies were performed in the next 2 years for follow-up. VBM was again performed using the MRI of the same dogs in each group in Yr-02 and Yr-03, to compare whether the differences increased with time.

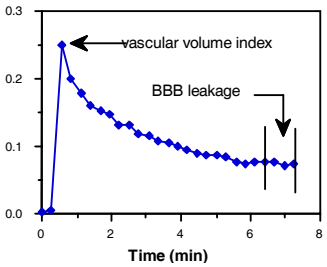

Fig.1 The contrast enhancement kinetics. The ratio between the late enhancement (leakage) to the early enhancement (vascular volume) gives the BBB permeability index.

Results:

Figs. 2 and 3 show the VBM statistical maps comparing dogs with above median (high) vs. below median (low) BBB permeability. The gray matter density in the high BBB group was greater in the parietal lobe, and this same area showed less GM in the low BBB group in Yr-02 and Yr-03, leading a greater difference with time. The GM density in the low BBB group was higher in the anterior left hippocampus, which remained stable during the 2 years follow-up period.

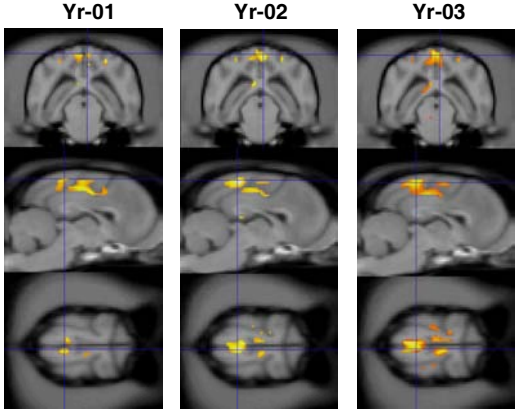

Fig.2 The VBM statistical maps showing the group with above median BBB has a higher GM density in the parietal lobe than the group with below median BBB.

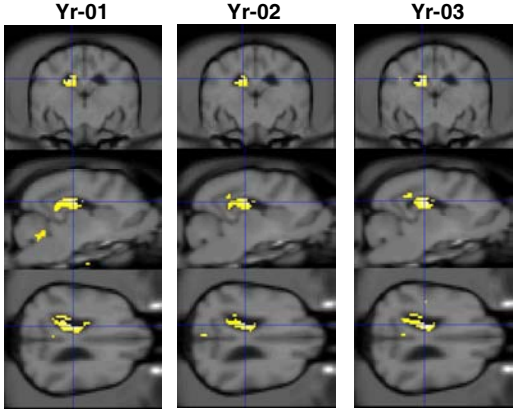

Fig.3 The VBM statistical maps showing the group with below median BBB has a higher GM in anterior hippocampus than the group with above median BBB.

Discussion:

In this study we investigated whether BBB permeability measured by dynamic contrast enhanced MRI predicted the future development of brain atrophy. The working hypothesis was that BBB disruption may cause vascular dysfunction, and the resulting hypoperfusion may lead to neuronal death observed as structural atrophy. If the images acquired in the 3 longitudinal studies over 2 years could be directly compared, it would provide the most robust analysis to investigate longitudinal changes. However, the mobile scanner used to collect data each year was upgraded each time and the image quality could not be directly compared. In this study we used an alternative approach, first to investigate group differences in Yr-01, then compare these same regional differences for changes in Yr-02 and Yr-03. GM in the high BBB group was higher in the parietal lobe, with increasing differences in Yr-02 and Yr-03. In contrast the GM in the low BBB group was higher in the anterior part of left hippocampus, which remained stable over 2 years. Therefore, dogs with a higher BBB permeability did not develop more cortical atrophy with time. CAA may only affect a subset of vessels [4], and neurons could receive nutrients from other compensatory perfusion, which might explain the lack of association between BBB and atrophy. Dogs do not develop significant atrophy at this age suggesting it may be a challenge to study the link between atrophy and vascular dysfunction. The same analysis, however, may be applied to humans, which may better reveal the consequence of vascular dysfunction on subsequent development of brain atrophy.

References: [1] Milgram et al. Neurobiol Aging. 2005; 26:77-90. [2] Su et al. Prog Neuropsychopharmacol Biol Psychiatry. 2005; 29:389-397. [3] Tapp et al. Neuroimage 2006; 29:234-244. [4] Su et al. Fourteenth ISMRM proceedings, 2006; abstract # 109.

Acknowledgement: This work was supported in part by NIH grant No. R01 AG17066.