Evolving White Matter Injury in Alzheimer's Disease Mouse Model Characterized by Diffusion Tensor Imaging

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Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder that results in progressive memory loss and cognitive decline. Pathological changes in AD can be characterized by the presence of amyloid plaques and neurofibrillary tangles that accompany neuronal and synaptic loss. Although AD pathology has been well defined in postmortem histology, longitudinal detection of the progression of AD and its correlation with the extent of the disease in the live brain tissue remains elusive. A feasible and reliable non-invasive imaging modality offering a tractable biomarker in preclinical drug discovery and clinical evaluation of AD is strongly needed.

Magnetic resonance imaging (MRI) has been used to measure atrophy of brain tissues in the patients with AD (1). Additional AD-related metabolic or microscopic structural changes (1-4) also have been found using magnetic-resonance (MR) based techniques, including diffusion tensor imaging (DTI). Considerable evidences suggest that microscopic white matter pathology can be detected (1-4) in AD patients using DTI. Unfortunately, findings in these studies are not consistent. Hanyu, *et al*, and Bozzali, *et al*, have reported both an increase in the diffusion coefficient and a decreased diffusion anisotropy (2, 3), while Kantarci, *et al*, and Bozzao, *et al*, report no changes in diffusion anisotropy in the white matter of AD patients (1, 4).

In order to resolve inconsistent findings in human studies, characterization of rapidly progressing transgenic mouse models of AD provides a focused etiology and may help eliminate sources of variability in the study. In addition, transgenic mouse models allow opportunities for temporal measurement of disease progression in reasonably short periods of time that could add to the understanding of the evolution of AD. The study described herein examines APPsw mice and wild type age-matched control mice at four different ages (8, 12, 16, and 18 months). DTI protocols were used to calculate the trace of the diffusion tensor (Tr (D)), the relative diffusion anisotropy (RA), the axial diffusivity ($\lambda_{\|}$), and the radial diffusivity ($\lambda_{\perp}$) derived from the three eigenvalues of the diffusion tensor (5, 6). Since $\lambda_{\|}$ and $\lambda_{\perp}$ have been shown to be sensitive, non-invasive indices of axonal injury and demyelination (5, 6), examination of these DTI indices provides a sensitive probe of the microscopic changes in brain tissue that may reflect disease progression, and yield new insights into the dysfunction induced by neurodegenerative processes associated with AD.

Materials and Methods

In the current study, four groups of APPsw and age-matched control mice were examined at 8, 12, 16, and 18 months. Eight animals for each strain at each age were assessed. All DTI experiments were conducted in an Oxford Instruments 200/330 (4.7 T, 33 cm clear bore) magnet equipped with a 15 cm inner-diameter, actively-shielded Oxford gradient coil (180 mT/m, 400 μsec rise time). The 6-direction DTI (7, 8) data were acquired with the following acquisition parameters: TR=3 sec, TE=43 ms, Δ=25 msec, δ=10 ms, slth=0.5 mm, FOV-1.5 cm, data matrix 128×128 (zero filled to 256× 256), and b-value = 764 sec/mm^2. ROIs were selected in gray matter for the cortex (CT) and the hippocampus (HP), and in white matter for the anterior commisure (AC), the corpus callosum (CC), the cerebral peduncle (CP), the external capsule (EC), the optic nerve (ON), the optic tract (OT).

Results

No differences exist between gray and white matter when comparing the APPsw and the control mice at 8 months of age. Reduced $\lambda_{\|}$ was observed in most regions of the APPsw mouse brain at ages greater than 8 months, which is consistent with the time that the amyloid plaque begins to accumulate as confirmed by *ex vivo* histology. Various brain regions exhibit different patterns of evolution for the changes in $\lambda_{\|}$ and $\lambda_{\perp}$. The evolution of water diffusion characteristics in EC and CC is shown in Fig. 1. The 10-15% decrease of $\lambda_{\|}$ and $\lambda_{\perp}$ in EC at 12-months is followed by the return to normal values for $\lambda_{\perp}$ at 16 and 18 months. In CC, both $\lambda_{\|}$ and $\lambda_{\perp}$ decrease by 10-15% at 12 months, but $\lambda_{\perp}$ subsequently increases by 31.2% and 14.5% at 16 and 18 months.

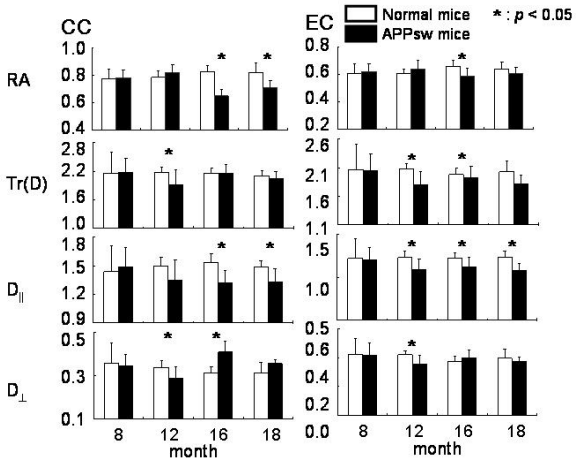

Fig. 1

Discussion

This study demonstrates that DTI can be used to non-invasively evaluate AD pathology in mice caused changes in water diffusion in both gray and white matter. The DTI parameters reported for APPsw and age-matched control animals show varying degrees of change for different anatomical regions of gray and white matter. Our results are similar to those found in clinical studies which report selective white matter damage in the brain of AD patients. As previously described (5, 6), $\lambda_{\|}$ and $\lambda_{\perp}$ in white matter can be used to probe the extent of axonal injury and demyelination. Using similar arguments, the decrease in $\lambda_{\|}$ and $\lambda_{\perp}$ at 12-months for the CC and EC in the current study may suggest the presence of axonal injury, while the subsequent increase in $\lambda_{\perp}$ for CC is consistent with demyelination. All other white matter tracts also exhibit decreased $\lambda_{\|}$ at 12 –months of age, without the concomitant increase in $\lambda_{\perp}$. Hence, these later changes could reflect axonal injury, but not demyelination. The combination of $\lambda_{\|}$ and $\lambda_{\perp}$ and measurements of these parameters could serve as a valuable tool for evaluating white matter pathologies in animal models of AD and eventually enable new insights for the development of new drugs and for potential clinical interventions.

Reference

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