Diffusion kurtosis abnormalities in a pre-symptomatic α-synucleinopathy mouse model.

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Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder. The impaired motor function defining PD is related to the presence of Lewy bodies and abnormal α-synuclein (αSYN). However, recent studies suggest alterations in the brain of pre-symptomatic PD [1]. There is also a growing recognition of prominent cognitive decline in PD which can be linked to hippocampal abnormalities. Here, we used a pre-symptomatic human mutant αSYN overexpressing mouse model for PD [2]. We hypothesized that pre-symptomatic changes are reflected in the diffusion properties of the tissue water. Therefore, we performed Diffusion Kurtosis Imaging (DKI) to evaluate the integrity of the microstructure of brain regions involved in the motor circuit and cognitive function and to assess DKI as a potential non invasive early marker for PD.

Methods

Five month old (Thy-1)-h[A30P]αSYN transgenic (TG) mice (n=7) were compared with age matched wild type (WT) animals (n=7) for changes in diffusion parameters. The imaging protocol included high resolution (0.125mm x 0.125mm) *in vivo* multi-slice fast spin echo imaging with diffusion sensitizing gradients along 15 directions and 3 b-values (0, 1000, 2500 s/mm^2), which was adapted from Mori and Van Zijl [3]. The images were collected to cover the whole brain (24 axial slices; inter-slice distance: 0.6mm) with following parameters: TR/TE=2000/26ms, δ=5ms, Δ=12ms, acquisition matrix=128 x 128, FOV=20mm x 20mm, RARE=4, NEX=4. Accurate tensor estimates for the diffusion tensors and the diffusion kurtosis tensors were obtained by using a constrained maximum likelihood estimator, which includes a Rician noise model. The fixed noise level was estimated from the histogram mode of the image background [4]. The motor cortex, hippocampus and caudate putamen were segmented with AMIRA (Mercury Computer systems, San Diego, USA) and a region of interest analysis was performed for all diffusion tensor and diffusion kurtosis tensor derived parameters (i.e. mean (MD), radial (RD) and axial (AD) diffusion and fractional anisotropy (FA), and mean (MK), radial (RK) and axial (AK) kurtosis and kurtosis anisotropy (KA), respectively). The WT and TG group were compared with non-parametric statistics.

Results

In the caudate putamen of TG mice we observed a significantly decreased RK, AK and MK ($p<0.05$), and an increased RD and MD ($p<0.05$) as compared to WT mice. The hippocampus of TG mice showed a decrease of AK ($p<0.05$) and an increase of AD and MD ($p<0.05$). In the motor cortex, the RD, AD and MD were significantly increased ($p<0.05$) in the TG group as compared to the WT group.

Discussion

At five months of age the (Thy1)-h[A30P]αSYN TG mice are pre-symptomatic, but abundantly express the transgenic protein in the proteinase K labile conformation that characterizes native αSYN. Whereas with DKI we were able to detect subtle microstructural differences in the examined regions. This suggests that microstructural alterations in regions of the motor circuit and cognitive function precede the expression of symptoms. Although the exact nature of the diffusion and kurtosis variations has yet to be resolved, these findings might be an important step toward developing a non invasive pre-symptomatic marker for PD. The ongoing follow up study in 12 month old TG mice will shed light on the evolution of the diffusion and kurtosis parameters in symptomatic mice.

References

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