Diffusion Kurtosis Imaging (DKI) reveals an early phenotype (P30) in a transgenic rat model for Huntington's disease

I. Blockx[1], M. Verhoye[1,2], G. De Groof[1], J. Van Audekerke[1], K. Raber[3], D. Poot[2], J. Sijbers[2], S. von Horsten[3], and A. Van der Linden[1]

[1]Bio-Imaging Lab, University of Antwerp, Antwerp, Antwerp, Belgium, [2]Vision Lab, University of Antwerp, Antwerp, Antwerp, Belgium, [3]Experimental Therapy, Friedrich-Alexander University, Erlangen, Germany

BACKGROUND

Huntington's disease (HD) is the most common polyglutamine disorder, which is characterized by a gradual onset and progression of psychiatric, motor, and cognitive symptoms. Although it is known that HD is a late manifesting disorder, it is reasonable to assume that the pathogenetic mutation of the gene can cause progressive, subclinical alterations in the cellular homeostasis even in very young mutant huntingtin (htt) gene-carriers (1). At least some genetically determined neurodegenerative diseases may even represent an emerging class of developmental disorders (1). Very recently, Diffusion Kurtosis Imaging (DKI) was proposed to quantify the non-Gaussian nature of the diffusion process in biological tissue (2-3). Non-Gaussian diffusion results from diffusion barriers, such as cell membranes, water compartmentalization, etc. and is therefore an indicator of microstructural complexity.

AIM In this study, we used DKI to investigate early developmental brain tissue changes of microstructure and neuroconnectivity of rat pups (postnatal day 15 - P15 and postnatal day 30 – P30) transgenic for HD (4). Together with Diffusion Tensor parameters, DKI was aimed to provide additional information concerning tissue microstructural complexity during development in both transgenic (TG) and wildtype (WT) animals.

METHOD

MRI A total of 23 HD rat pups were used in the present study. In vivo experiments were carried out at the age of P15 (n=6TG/n=6WT) and P30 (n=6TG/n=5WT) on a 9.4T Bruker Biospec scanner (Ettlingen, Germany). DKI images were acquired using a spin echo EPI sequence with an encoding scheme of 15 DW-gradient directions using TR/TE=3000/25ms, δ=5ms/Δ=12ms, NEX=4, acquisition matrix = 128*128, FOV=30mm, slice thickness=1mm. During experiments respiration rate and temperature were continuously monitored, and kept constant. *Data analyses:* DKI data were realigned using the 'diffusion II toolbox' in SPM5 and processed using Matlab routines to generate the DTI (fractional anisotropy - FA, mean diffusivity - MD, Radial diffusivity – RD, axial diffusivity - AD) and DKI (mean kurtosis - MK, radial kurtosis - RK, axial kurtosis - AK, kurtosis anisotropy - KA) parametrical maps. Region of interest analysis (ROI) was performed by a manual segmentation of different grey (*Cortex-Ctx; Hippocampus-HP; caudate putamen-CPu*) and white matter (*Corpus Callosum and Internal Capsula - cc/ce; anterior commissure anterior - aca*) structures. Statistical analyses (non-parametric) testing for differences of the diffusion parameters between HD and control pubs at the age of P15 and P30 were done using SPSS (SPSS; Statistical Package for Social Sciences, version 16.0).

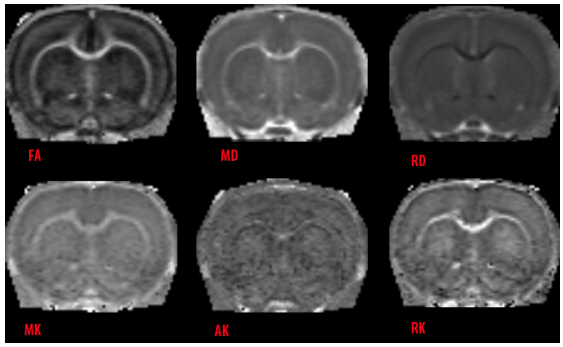

Figure 1: DT (upper row) and DK (lower row) maps of a WT P30 rat.

RESULTS AND DISCUSSION

Representative DT and DK maps, which provide great image contrast, of a WT control P30 rat are shown in ***figure 1***. The diffusion parameters for which a significant difference was found are presented in ***figure 2***. In P15 TG pups, no differences were observed as compared to WT littermate controls. In white matter of P30 TG pups we observed a significantly decreased FA ($p<0.01$) (cc/ce), and increased AK ($p<0.05$) (cc/ce – aca) as compared to WT littermates. In grey matter of P30 TG pups (*CPu*) AK was significantly increased ($p<0.05$) as well as MK ($p<0.01$).

The changes in FA, AK and MK suggest a differential development starting on P30 in several white matter tracts and grey matter structures in pups carrying the mutant htt gene. While anisotropy decreases, microstructural complexity increases in the white matter as indicated by an increase in AK. This might be related to a decreased orientational coherence or packing of fibre tracts. In the CPu we observed a similar increase in complexity as in the white matter which is related to changes in AK. Although, the TG HD rat model closely resembles the late-onset form of the disease, behavioural analyses revealed already an early phenotype. It has been shown that behavioral symptoms precede the appearance of the earliest aggregates at about 6 months of age in this model and can be detected in a very young age. This very early behavioural phenotype is characterized by decreased numbers of isolation induced ultrasonic vocalization calls at P10, a loss of prepulse inhibition at P17 and increased risk behaviour at P21. The DKI changes we could detect in TG HD pups, suggest that neurodegenerative process of HD involves also neurodevelopment defects already detectable at P30 (5). As these data are part of a multimodal study (including, behaviour and histology), ongoing analysis of these measures could reveal possible correlations.

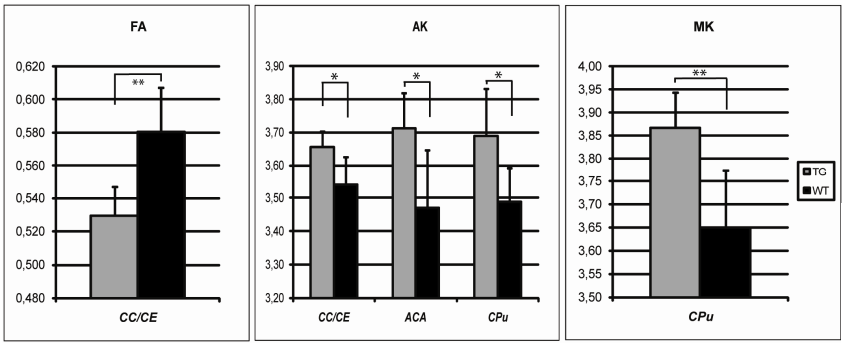

Figure 2: Mean and Standard deviation of diffusion parameters measured in different ROI in P30 rat: (left) FA is significantly lower in the WM of the TG HD group, as compared to the WT controls; (middle) AK values showed a significant increase in WM and GM in TG animals; (right) in addition, an increase in MK was found in GM.

P values < 0.05 are indicated with * and p values < 0.01 are indicated with **.

References: ***(1)****Mehler M Trends Neurosci. 2000 Dec; 23 (12): 599-605. (2) Jensen JH et al., Magn Reson Med. 2005 Jun; 53(6): 1432-40.* ***(3)****Hui ES et al., Neuroimage. 2008 Aug 1; 42(1): 122-34.* ***(4)*** *von Hörsten S et al., Hum Mol Genet. 2003 Mar 15; 12(6):617-24.* ***(5)****Raber KA et al., Neuroscience, November 2008, Washington.*