DYT1 Dystonia of Mice and Men

A. M. Ulug[1], A. Vo[1], M. Argyelan[1], W. K. Schiffer[1], L. Tanabe[2], W. T. Dauer[3], and D. Eidelberg[1]
[1]The Feinstein Institute for Medical Research, Manhasset, New York, United States, [2]Columbia UNiversity, New York, New York, United States, [3]University of Michigan Medical School, Ann Arbor, Michigan, United States

Introduction

Dystonia is a neurological disease characterized by sustained involuntary muscle contractions [1]. Previous studies using positron emission tomography (PET) and magnetic resonance diffusion tensor imaging (DTI) showed metabolic abnormalities in the cerebellum and basal ganglia dystonia patients with DYT1 mutation [2] and implicated the cerebello-thalamo-cortical pathway [3,4]. Here, we studied genetically engineered mice in which human DYT1 mutation has been "knocked in" to endogeneous mouse allele [5], and report metabolic and diffusion abnormalities that are similar to the published human studies. Our study can be considered a reverse translation study from human to mice that explores changes linked to genetic nature of dystonia.

Subjects and Methods

We studied 8 DYT1 heterozygous mice and 6 littermate controls (12 weeks of age) using *in vivo* 3Tesla MRI, FDG microPET and *ex vivo* 9.4 Tesla MR DTI. *In vivo* MRI protocol included T1 and T2w imaging. In T2w imaging image resolution was 0.125mm x 0.125mm x 1mm, TR 4.8 s, TE 100ms, 8 NEX; in T1w imaging, image resolution was 0.156mm x 0.156mm x 0.2mm, TE 2ms, TR 7.8 ms, 6 NEX. The microPET image acquisition parameters included a matrix size of 128x128x95 with a voxel size of 0.949mm x 0.949mm x 0.796mm. After *in vivo* imaging the mice brains were perfusion fixed and later scanned *ex vivo*. 3D volumetric image sets of *ex vivo* diffusion weighted images were acquired in 6 directions. The minimum b-value was 210 s/mm^2 and the maximum b-value was 2138 s/mm^2. The DTI matrix was 136x84x64 which was zerofilled to 272x168x128. The FOV was 17mm x 10.5mm x 8mm. The nominal resolution was 62.5µm x 62.5µm x 62.5µm with a total imaging time of approximately 20 hours. After data acquisition, FA and ADC maps were calculated. A 9-parameter affine registration was applied to each mouse brain to bring it to a common space using SPM Mouse [6]. Micro PET images were processed as in [7].

Results

Metabolic group differences in DYT1 mice when compared to normal littermates with microPET images are shown in Fig. 1 top row. Bottom row shows published metabolic abnormalities from human subjects [2]. In figure 2, left column shows the FA decreases in DYT1 mice group when compared to controls. In the right column published FA decreases in human DYT1 subjects [3] are shown. The correlation between striatal and cerebellar metabolic abnormalities in DYT1 mice are plotted in Fig. 3 below.

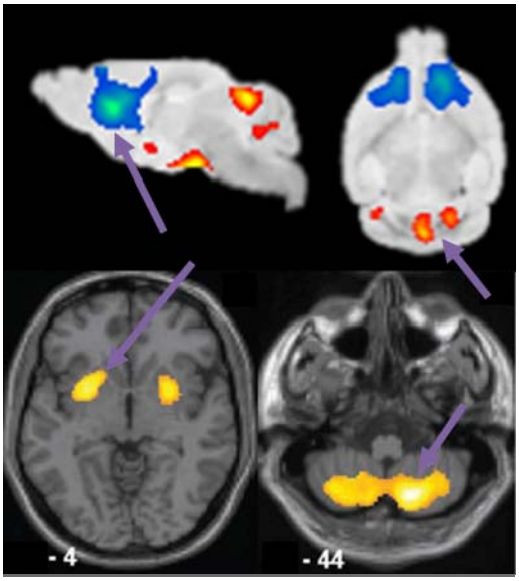

Figure 1: Metabolic pattern in DYT1 mice (top row) and human subjects (bottom row)

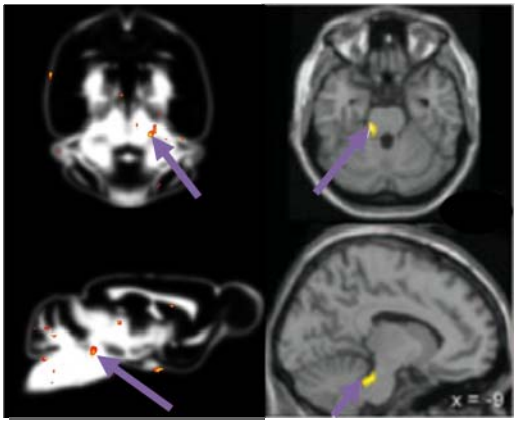

Figure 2: FA group decrease in DYT1 mice (left column) and human subjects (right column) when compared to controls

Discussion/Conclusions

In this translational study, we compared changes in mouse "genecopy" of DYT1 dystonia with their wild type littermate controls using microPET and MR DTI images. Notably these mice express the disease protein at normal levels and with normal profile unlike classical transgenic mice. Our results show that there are significant group differences between DYT1 mice and controls. We found that DYT1 mice exhibit metabolic and FA abnormalities that resemble the DYT1 patients. The correlation between striatum and cerebellum metabolic activity and the correlation between the metabolic activity and the FA abnormalities are also shown.

References:

1. Carbon M, Eidelberg D. Neuroscience, 2009, 164(1), 220-229.
2. Carbon M, Su S, Dhawan V, Raymond D, Bressman S. Eidelberg D. Neurology 2004 62, 1384-1390.
3. Carbon M, Kingsley PB, Tang C, Bressman S, Eidelberg D. Movement Disorders 2008; 23:234-239.
4. Argyelan M, Carbon M, Niethammer M, Ulug AM, Voss HU, Bressman SB, Dhawan V. Eidelberg D. J. of Neuroscience 2009; 29(31):9740-7.
5. Goodchild R, Kim CE, Dauer WT. Neuron 2005; 48: 923-932.
6. Sawiak SJ, Wood NI, Williams GB, Morton AJ, Carpenter TA. In Proc. of ISMRM 17, p.6264, Honolulu (2009).
7. Mirrione MM, Schiffer WK, Fowler JS, Alexoff DL, Dewey SL, Tsirka E. NeuroImage 2007; 38: 34-42.

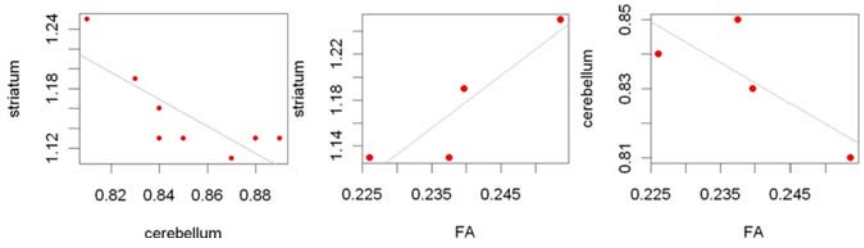

Figure 3: a) Correlation between the regional metabolic activity in mice; b) Correlation between the FA decrease in cerebellar peduncle of mice and metabolic change in striatum, and c) cerebellum