Multimodality Neuroimaging to Study Tourette Syndrome: Correlating AMT-PET and DT-MRI.

A. S. Saporta[1], M. I. Makki[2], B. J. Wilson[1], M. E. Behen[1], O. Muzik[1], C. Juhasz[1], and H. T. Chugani[1]

[1]Pediatrics, Wayne State University, Detroit, MI, United States, [2]Radiology, Wayne State University, Detroit, MI, United States

Introduction: The cortico-striato-thalamic circuitry (CSTC) is known to be affected in Tourette Syndrome (TS). Morphological MRI studies in children with TS have shown volumetric and diffusion effects in the basal ganglia and thalamus (decreased volumes of caudate nucleus [1]; increased fractional anisotropy in thalamus and putamen [2]). In a recently published study of our group, positron emission tomography (PET) with α-[C^{11}] methyl-L-tryptophan (AMT), a labeled precursor of serotonin, showed marked asymmetries of tracer uptake in the caudate nucleus (CN) and thalamus (TH), structures of the CSTC, in children with TS [3]. The usefulness of matching information from 2 complementary neuroimaging modalities (PET and MRI) led us to design the present study which aims to correlate AMT PET uptake to magnitude and anisotropy of water diffusivity measured by diffusion tensor images (DTI) in CN and TH. Our hypothesis was that functional variations measured by the asymmetry index in tryptophan metabolism will be associated with microstructural changes in the CN and TH. (Figure 1)

Methods: Fifteen children diagnosed with TS underwent AMT-PET and DTI scans (Mean age=11 ± 2.5 years; age range: 6-15 years, 3 girls). The diagnosis of TS was established based on DSM-IV TR criteria (Diagnostic and Statistical Manual of Mental Disorders-4th Text revised) [4]. PET studies were performed on a CTI/Siemens EXACT/HR whole body positron tomography (Knoxville, TN) scanner. The tracer AMT (0.1 mCi/kg) was injected IV over 2 minutes. Twenty-five minutes after tracer injection, a dynamic emission scan of the brain (7 frames x 5 minutes) was acquired in 3D mode, thus generating 47 image planes with slice thickness of 3.125 mm and field of view (FOV) of 15 cm. Measured attenuation and decay correction were applied to all images. As all subjects received a standardized dose based on their weight (0.1 mCi/kg), calibrated images (μCi/mL) directly depict the standard uptake value, which represents tissue activity concentration normalized to the injected activity per kilogram of body weight. Patients taking psychoactive medication had to wean it off 4 weeks prior to the scan [5]. DTI scans were performed with double refocusing pulse spin-echo EPI on a 3T scanner (GE Healthcare), using 6 non-collinear diffusion sensitization gradients (b=1000 [s/mm^2]) plus one T2W volume (b~0 [s/mm^2]) and parallel imaging factor of 2, repeated 6 times and magnitude averaged to increase signal-noise-ratio and reproduce more measurements. Water diffusivity in the CN and TH was measured from the tensor *eigenvalues:* λ_1 (parallel diffusion) and λ_{23} (perpendicular diffusion), i.e. the average of λ_2 and λ_3, using DTI studio software [6], as well as fractional anisotropy (FA) and apparent diffusion coefficient (ADC) maps. Furthermore, linear (C*l*), planar (C*p*), and spherical (Cs) indices were calculated to classify the microstructure into geometric criteria and to measure the correspondence to the generic cases: line, plane, and sphere [7]. The second phase of the image processing consisted of automatic co-registration of PET images to the DTI maps using the VINCI software [8]. Manual corrections were done in all cases by an experienced neurologist when the automatic procedure failed to provide an accurate match. Regions of interest (ROI) were manually drawn by 2 observers in order to ensure reliability to delineate the CN and TH bilaterally using FSL software [9]. Following this procedure, the ROI values of each of the DTI indices and the coregistered AMT-PET images were extracted. In order to analyze the asymmetry between left (L) and right (R) sides of CN and TH in AMT and DTI images, we calculated asymmetry indices (AI) for each variable (AMT uptake, λ_1, λ_{23}, FA, ADC, C*l*, C*p* and C*s*) of both structures with the following formula: AI=200x[(L-R)/(L+R)] (%).

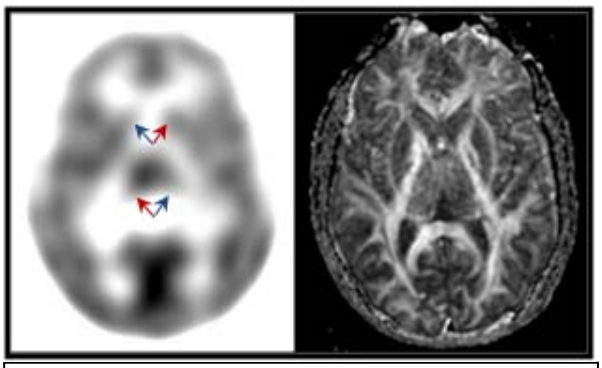

Figure 1: A PET scan image (left) clearly showing typical asymmetric pattern of AMT uptake in caudate nucleus and thalamus seen in TS, and the FA map (right) of the same patient. (Red arrow points the higher uptake side; blue arrow, the lower uptake side)

Results: Intra class correlation (ICC) showed high consistency between the 2 observers (ICC: single measures=0.969-0.997 and average measures=0.984-0.998, p<0.0001). Pearson correlation analyses showed a highly significant negative correlation between the AI of AMT and FA (r = - 0.744; p=0.001) in the caudate nucleus (Figure 2). Also we observed a significant positive correlation between the AI of AMT and Cs (r=0.594; p=0.019) in CN. None of the DTI indices showed any significant correlation with AMT in the thalamus.

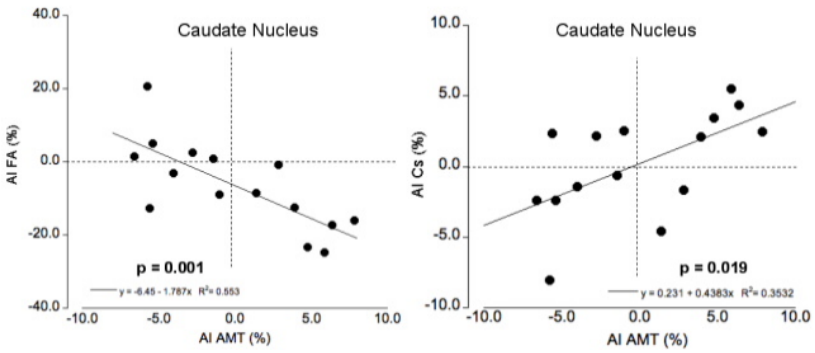

Figure 2: Graphs showing the correlation between the asymmetry index (AI) for AMT PET and the AI for FA (left) and between the AI for AMT PET and the AI for Cs in the caudate nucleus (right).

Conclusion: Our findings demonstrate a relationship between tryptophan metabolism and microstructure changes measurable by AMT-PET and DTI, respectively, in CN of children with TS. The non-concordance of findings in TH might be related to its more complex structure, as well as differences in maturation timing [10, 11] and tryptophan metabolism rate [5] compared to CN. Based on the previous AMT PET study showing higher AMT uptake in basal ganglia in TS patients compared to healthy controls [3], and other studies showing that the levels of serotonin and tryptophan are lower in blood and cerebrospinal-fluid in TS [12], we suggest that the higher AMT-uptake was not related to the serotonin synthesis pathway but to the alternative kynurenine pathway, leading to the synthesis of both neuroprotective and neurotoxic products, the latter contributing to tics. Moreover, the side with higher AMT uptake has lower FA, which can be related to neuronal, axonal or dendrite injuries [13], and higher Cs, which also reinforces the presence of decrease of neuronal density with decrease in anisotropy diffusion as the microstructure changes toward a spherical shape. Based on these findings, our future directions will be to use the AI for AMT and FA/Cs in CN as a trait marker of changes related to TS and to study whether the changes on these parameters will be transitory or permanent, and to obtain more imaging/clinical relationships to determine and understand the different course of the disease.

References: [1]Peterson et al, Arch Gen Psychiatry, 2003; [2] Makki M. et al, Mov Disord, 2008; [3] Behen M. et al, Mov Disord, 2007; [4] American Psychiatric Association, 2000; [5] Chugani, DC et al. Synapse, 1998; [6]Jiang, H.et al. Comput Methods Programs Biomed, 2006; [7] Westin CF et al. ISMRM,1997; [8] Cizek, J.et al. Neuroimage, 2004; [9]Smith, S M, et al Neuroimage, 2004; [10] Lebel C et al. Neuroimage, 2008; [11] Pfefferbaum A et al. Neurobiol Aging. 2008; [12] Comings D.E., Am J Med Genet, 1990; [13]Hasan KM et al. Magn Reson Med, 2008.