Diffusion Tensor Imaging Findings in Rett Syndrome Patients

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Purpose

Rett Syndrome (RTT) is a neurodevelopmental X-linked disease that affects primarily girls. Clinically, these children are normal at birth and then develop progressive autistic-like behavior, neurodevelopmental delay, with loss of motor skills[1].

Cerebral volume loss in RTT was attributed to be due to a decrease in neuronal cell body size and dendritic arborizations, particularly in cortical gray matter with relative preservation of axons and myelin. However recent neuropathologic studies[2] have suggested axonal involvement and our recent magnetic resonance spectroscopic study has also shown more decreased levels of neuronal marker NAA in cortical white matter than gray matter[3,4].

The purpose of our study is to investigate the involvement of specific cerebral white matter tracts in Rett patients by using diffusion tensor imaging (DTI).

Materials and Methods

Twenty RTT patients (age range 2.5 to 15.5 years, mean age of 6.0 years) and 10 controls (age range 5.0 to 15.0 years, mean age of 10.5 years) were examined. DTI data were acquired at 1.5 T by using a single-shot echo-planar imaging sequence with the sensitivity encoding (SENSE), parallel imaging scheme (reduction factor, 2.5). Scanning parameters were: 96x96 image matrix, zero filled to 256x256, 2.5 mm slice thickness, no gap, 30 independent orientations and b max of 700 mm^2/sec. Fifty slices were used to cover the entire brain. The DTI data was corrected, processed and analyzed with in-house softwares (DtiStudio and DSX). Color-coded DTI maps were used to select the regions of interest; fractional anisotropy (FA) and Apparent Diffusion Coefficient (ADC) were measured in 9 tracts in both hemispheres.

Linear regression was used to evaluate the effect of age on FA and ADC in both groups. ANOVA with Fisher's LSD method as a post-hoc test was employed to examine the differences in FA and ADC between RTT and healthy subjects and to evaluate the differences in FA and ADC between the hemispheres in both groups. Age was used as a covariate in the ANOVA evaluations of group differences. Paired t-test was employed to perform comparisons between anterior and posterior regions. Statistical significance was set to $p<0.05$ in all analyses. Data are presented as means ± standard deviations.

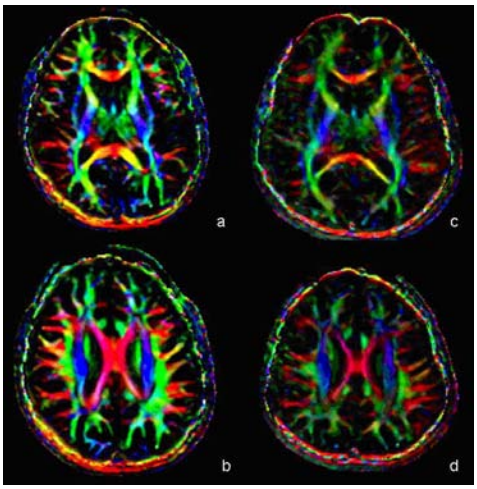

Figure 1 – Color maps a and b for a control (15 years old) and c and d from a RTT patient (10.5 years old) showing thin genu, splenium of corpus callosum and corona radiata and small brain in RTT.

Results

Visual evaluation of the DTI color maps showed prominent difference in the size of head and brain. Some of the white matter tracts such as corpus callosum or corona radiata appeared thinner than controls (Figure 1).

ANOVA revealed a very small but significant effect of age on both ADC ($p<0.0001$, and FA ($p=0.018$). While ADC decreased with a slope of $-3.70 \cdot 10^{-5} mm^2/s^{-1} \cdot year^{-1}$ in controls on average, the slope was $-1.16 \cdot 10^{-5} mm^2/s^{-1} \cdot year^{-1}$ in Rett patients (interaction term age x group: $p=0.017$). No difference in age-dependence of FA between groups was detected; FA increased with a slope of $2.96 \cdot 10^{-3}$ $year^{-1}$ in both groups.

No overall difference in ADC and FA between the hemispheres in the two groups was detected.

ANOVA detected significant regional differences in ADC ($p<0.0001$) and FA ($p<0.0001$) within each group. While no differences in ADC values between the patients and controls were detected, FA values were significantly different between RTT and controls (interaction term group x region: $p=0.001$). Compared to the control group, FA in the Rett patients was lower by 10.5% in the forceps minor (FA=0.410 ± 0.053, $p=0.007$) and by 10.1% in the posterior thalamic radiation (FA=0.517 ± 0.053, $p=0.031$).

In the RTT group, anterior internal capsule showed a lower FA compared to posterior internal capsule [0.54± 0.06 (anterior) vs 0.62±0.03 (posterior), $p<0.0001$]. No differences in FA and ADC were observed between genu and splenium.

Discussion

Significant age related differences in DTI values were found in our study in both patients and controls. FA values showed gradual increase by age with a similar rate in patients and controls. ADC values showed gradual decrease in both patients and controls with a steeper slope in controls than patients. Our findings in controls are in agreement with a study of normal white matter maturation in early childhood[5], although we note that our study also included older children.

Lower fractional anisotropy in major white matter tracts in RTT is consistent with previous findings of white matter pathology in RTT[3,4].

Anterior limb of internal capsule appears to be more affected than posterior limb. Our DTI findings, suggesting prefential involvement of specific white matter tracts in Rett patients, in particular in the frontal lobe, might indicate regions of vulnerability that could be target to treatment strategies in the future.

References

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