Diffusion Abnormalities Detected by Tract-Based Spatial Statistics in Children with Sickle Cell Disease

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Introduction: The central nervous system is a major target for ischemic damage in sickle cell disease. Between 22 and 40% of children with homozygous sickle cell disease (SCD) will have a clinically evident stroke or a more subtle infarct on neuroimaging ("silent stroke") before age 21 (Steen 2003). In addition, children without lesions by conventional MRI demonstrate neurocognitive impairments and have subtle changes in the morphometry of the brain when studied using advanced MRI analysis techniques (Baldweg 2006, Kirk 2009). The current research hypothesizes that subtle white matter injury that is not detected with standard MRI techniques might be visible with diffusion tensor imaging (DTI). To test this hypothesis, we applied Tract-Based Spatial Statistics (TBSS, Smith 2006) to evaluate the diffusion changes in adolescents with SCD.

Methods: A prospective study compared adolescents with SCD and age–matched, healthy siblings or friends. Any subject found to have an abnormal conventional MRI exam by a pediatric neuroradiologist was excluded from their respective group. One of the excluded SCD subjects was judged to have mild gliosis and they were combined with 12 SCD subjects from a separate retrospective study to form a third group, SCD with mild gliosis. The DTI images were obtained on a 3T scanner using a 30-direction EPI-based DTI sequence (b=1000 s/mm^2), along with 5 b=0 scans, with a nominal spatial resolution of 2mm^3 and a parallel imaging factor of 2. The TBSS analysis included preprocessing carried out in the order of eddy-current-correction, brain-extraction and diffusion tensor calculation. The resulting maps of the fractional anisotropy (FA) were then used to find the transformation matrix between each subject and the standard MNI space. The mean FA image is thinned to create a mean FA skeleton which represents the spines of all tracts common to the group. Maps derived from the DTI images (FA, mean diffusivity (MD) and the three Eigen values) and the radial diffusivity derived from the 2nd and 3rd Eigen values were then projected onto this skeleton for voxelwise statistics testing between the SCD, gliosis and control groups.

Results: MRI data was successfully obtained from 13 radiologically normal SCD subjects (15.1±1.7 years) and 13 controls (14.9±2.8 years) in the prospective study and this was combined with the data from the 13 subjects in the mild gliosis group (14.9±2.9 years). The TBSS analysis revealed significant differences (p < 0.05, corrected) between both patient groups (SCD & gliosis) and the control group. Specifically, elevated MD was identified in the subcortical white matter (Figs. A&B) with the gliosis group showing more extensive changes than the SCD group. The SCD group showed only limited changes in the corpus callosum (CC) compared to the controls, while the gliosis group exhibited changes throughout the CC (Figure B). When directly comparing the gliosis and SCD groups no significant changes in MD were seen at p<0.05. Reducing the threshold to p<0.30 showed changes which were in good agreement with those seen when comparing these two groups to the controls (figure C). The FA values for the gliosis group showed a decrease compared to the controls. The spatial extent of the changes was reduced compared to that seen for MD, with most of the FA changes occurring in the CC (figure D). The SCD group showed no significant changes in FA compared to the controls or the gliosis group at p<0.05. Lowering the threshold for the SCD and gliosis group comparison revealed a pattern of changes which were similar to those found between the control and gliosis groups. There were hardly any areas of significant difference for the primary Eigen value (axial diffusivity) between any of the groups. The results for the radial diffusivity (not shown) were very similar to those for the MD. Changes in the radial diffusivity have been reported to be associated with demyelination (Song 2003). However, in a complex disease such as SCD, where in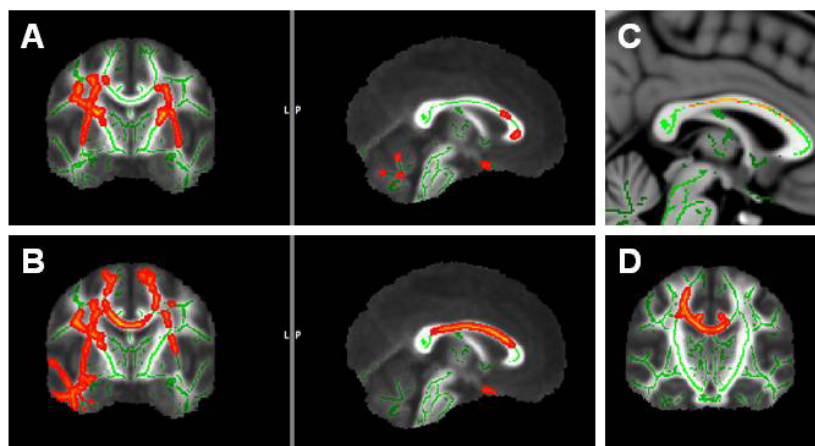flammatory endothelial and tissue injury is an important component of the disease, it is unclear how accurately the directional diffusivities relate to specific pathologies. In addition, care must be taken when analyzing the radial diffusivity since residual misalignment of the tracts or crossing fibers may lead apparent changes in this radial diffusivity (Wheeler 2009).

Figure 1: TBSS comparison (p < 0.05, corrected) for the MD between SCD and control groups (A) and the gliosis and control groups (B). More extensive regions of elevated MD can be seen in B, most notably in the corpus callosum and right temporal lobe. At p<0.05 the comparison of the MD data from the SCD and gliosis groups showed no significant differences, but with p<0.30 changes corresponding to the differences between figures A and B can be seen (figure C – note in this figure the areas of significance have not been thickened). Comparing the FA data between gliosis and control groups (figure D) showed a reduced spatial extent compared to the MD images with changes principally in the corpus callosum.

Conclusions: The current research demonstrates that TBSS analysis of DTI data is a valuable tool in studying and evaluating SCD. While subtle white matter impairments in children with SCD are usually non-detectable with conventional MRI techniques, they appear to strongly modify water diffusion measures, especially the mean and radial diffusivity.

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