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Tract specific analysis in patients with sickle cell disease

Yaqiong Chai^{a,b,c,*}, Julie Coloigner^{a,b}, Xiaoping Qu^{a,c}, Soyoung Choi^b, Adam Bush^{b,c}, Matt Borzage^e, Chau Vu^b, Natasha Lepore^{a,c,d}, and John Wood^b

^aCIBORG laboratory, Department of Radiology, Children's Hospital Los Angeles, CA, USA

^bDivision of Cardiology, Children's Hospital Los Angeles, CA, USA

^cDepartment of Biomedical Engineering, University of Southern California, CA, USA

^dDepartment of Radiology, University of Southern California, CA, USA

^eDepartment of Neonatology, Children's Hospital Los Angeles, CA, USA

Abstract

Sickle cell disease (SCD) is a hereditary blood disorder in which the oxygen-carrying hemoglobin molecule in red blood cells is abnormal. It affects numerous people in the world and leads to a shorter life span, pain, anemia, serious infections and neurocognitive decline. Tract-Specific Analysis (TSA) is a statistical method to evaluate white matter alterations due to neurocognitive diseases, using diffusion tensor magnetic resonance images. Here, for the first time, TSA is used to compare 11 major brain white matter (WM) tracts between SCD patients and age-matched healthy subjects. Alterations are found in the corpus callosum (CC), the cortico-spinal tract (CST), inferior fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC). Based on previous studies on the neurocognitive functions of these tracts, the significant areas found in this paper might be related to several cognitive impairments and depression, both of which are observed in SCD patients.

Keywords

sickle cell disease; white matter; statistical analysis

1. INTRODUCTION

Sickle cell disease (SCD) is an inherited red blood cell disorder, which is caused by single amino acid substitution in the beta subunit of hemoglobin. It is closely associated with overt stroke, chronic vascular damage, anemia and mortality¹. There are more than 90,000 people affected by the disease in the U.S., and as many as 1,000 babies are born with SCD each year². In the U.S., SCD is highly represented by African Americans and Hispanics, representing 90% and 10% of cases as of 2005, respectively³. Because the sickle-shaped red blood cells are rigid, they tend to accumulate along the walls of the larger arteries, damage

* natashalepore@gmail.com; phone 1 323 361 8726; ciborg-lab.com.

the vascular endothelium and further narrow the micro-vascular walls, which can cause cerebrovascular abnormalities.

Despite the potential damage to vital organs in the body, cerebrovascular complications, including intracranial hemorrhage, are the most immediate concern for physicians. Previous imaging studies in SCD have revealed delayed brain development, and grey matter (GM) and white matter (WM) loss compared with healthy control subjects^{6–9}. In the long term, other behavioral and cognitive consequences may occur. These include both the psychological toll of the disease, such as feeling sad or isolated due to limitations in daily activities and frequent medical visits and hospitalizations, as well as neurocognitive consequences. Previous studies have reported changes in neurocognitive functions, lower verbal intelligence quotient scores, poorer math performance, and visuo-motor impairments with increasing age in children with SCD^{10–12}. A higher prevalence of depressive symptoms was previously reported in adult patients^{13–14}. However, few studies have looked at the regional WM alterations that underlie these symptoms.

Brain magnetic resonance imaging (MRI) is commonly used to detect cerebrovascular damage, but clinical imaging protocols do not typically employ diffusion tensor imaging (DTI). It is sensitive to WM microstructure and is a powerful clinical tool for detecting preclinical neurologic ischemia⁵. Tract-based spatial statistics (TBSS), an analysis tool for DTI data that enables the investigation of WM damage in neurological disorders, has been utilized to demonstrate that SCD patients have subtle WM damage in the corpus callosum (CC) and centrum semiovale, two regions for which conventional anatomical MRI scans show only mild abnormalities¹⁵.

A newer method, tract-specific analysis (TSA)¹⁶, has several advantages over the widely used TBSS for finding WM differences across populations using DTI. In TSA, white matter fibers are segmented on a population specific template, and statistical comparisons are performed on DTI derived measures projected on a medial sheet generated from these tracts. By focusing on specific tracts, it provides better localization of areas that are affected by neurological disease. Recently, TSA was shown to outperform TBSS in a comparison of congenitally blind vs. sighted controls¹⁷ and in traumatic brain injury¹⁸, and was also applied to detect white matter abnormalities in children with brain tumors treated with surgery and chemotherapy¹⁹.

Here we will utilize TSA in a pilot study to compare brain white matter microstructure between SCD patients and healthy controls. Our dataset consists of patients without overt or silent strokes on T1- and T2-weighted images, and healthy controls.

2. METHOD

2.1 Dataset and Preprocessing

DTI scans were obtained in 30 directions for 14 subjects on a 3T-Phillips Achieva as part of a study on SCD and its neurocognitive outcomes. All of the DTI scans were obtained using a single shot echo-planar imaging sequence with a b-value of 1000s/mm². Table 1 shows our imaging parameters.

The study was approved by the Institutional Review Board at Children's Hospital Los Angeles. All patients were recruited with consent or assent. Our final dataset consisted of 7 clinically asymptomatic SCD patients' brain MRIs (age=19.0 $\pm$ 4.0; F=5, M=2) that were compared against 7 age and gender matched healthy controls (age=19.9 $\pm$ 5.1; F=5, M=2). Exclusion criteria included previous overt and silent stroke, "moya moya" pattern from other imaging modalities, acute chest syndrome, pregnancy, and pain crisis hospitalization within one month of the study. All subjects recruited are either African American or Hispanic.

2.2 Registrations and 3D Representations

In order to compare WM differences between the two groups, all the preprocessed DTI scans were normalized to a common template. A population-specific template (adult template), publicly available in IXI brain database²⁰, which is morphologically most similar to the subjects in the population of the SCD patients and the healthy group was used to improve the accuracy of spatial normalization.

Firstly, rigid alignment between subject and template was employed to find an initial linear estimation. Then affine alignment was performed to affine the rigid alignment by calculating a more general linear transformation to allow global size and shape matching. Furthermore, a deformable registration was applied to improve alignment quality by removing shape and size differences between local structures. These steps were all achieved using DTI-TK²¹.

After registration, WM and tract-specific attributes were sampled across the whole population. Fractional anisotropy (FA), as a measure of the preponderant directionality of water diffusion, is one of the most frequently used DTI metrics for microstructural tissue damage measurements in patients with brain disease. In TSA, FA values are computed locally and projected onto the medial representation or mesh of the tracts, which is a thin sheet-like structure representing a 3D tract. To be more specific, the maximum FA values along the spokes are projected on the mesh. The 11 tracts of interest that are available as part of the standard release of the software were tested: the corpus callosum (CC), the cortico-spinal tracts (CST), inferior fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), and uncinate fasciculus (UNC).

2.3 Statistical Analysis

The model uses a cluster analysis on the medial surface of each white matter tract. Statistical significance was assessed using a non-parametric permutation-based and supra-threshold statistical model²². The threshold p-value was set to 0.01 in the statistical analysis step, and the number of permutations was set to 1000. Statistically significant findings indicate that SCD patients' FA signal differs significantly from controls in those clusters²³.

3. RESULTS

Seven tracts out of 11 show regions of statistically significant differences, as displayed in Fig. 1–3: in all cases, FA was lower in SCD than controls.

Fig. 2 shows the CST and SLF tracts, respectively. Noticeable areas of difference are shown on each side of CST tracts, located in the mid-body and posterior parts. This finding is

consistent with Balci et al's results, which detected decreased FA values and fewer fiber counts on both CST tracts²⁴. The significant regions shown on the CST are implicated in several cognitive processes, such as information processing, visual-spatial working memory, attention, interference suppression and response inhibition²⁵. Regional differences in cortical thickness from SCD patients were also located on these posterior medial surfaces, the so-called "watershed" areas between the perfusion territories of the anterior cerebral artery (ACA) and the posterior cerebral artery (PCA)²⁶.

Fig. 2 shows areas of significant differences for the CC and ILF pairs. As the largest fiber tract and the main commissure of the human brain, CC is also the most studied tract. The FA decrease found in Fig. 1 is located in the splenium, which connects regions of the parietal, temporal and occipital lobes.

There are also areas of difference on each side of the SLF tract. SLF changes in patients without stroke or cerebral infarct were not detected in previous studies with less sensitive detection methods. The SLF tracts are involved in processing speed and memory in healthy volunteers, and FA decreases are seen in patients with traumatic brain injury¹⁸ and cancer patients treated with chemotherapy¹⁹.

Fig. 3 above shows the left (a) and right (b) IFO. A small area of difference is found on the left tract and two slightly larger ones are shown on the right posterior tract. However, more subjects are needed to confirm this finding. Reduced IFO FA values were also found in a study on patients with sickle cell anemia and with mild gliosis^[28].

4. DISCUSSION

Our analysis detected several areas of difference between the SCD and control groups, all of which are due to lower FA values in the SCD patients. These findings are consistent with previous studies. For example, Chen R. et. al.²⁹ found that total WM volume increased in children with SCD at about half the rate of that of healthy control subjects (age ranges from 9 to 16 years old), which indicates that WM development is affected by SCD pathology.

One possible explanation for the decreased FA values in the SCD patients may be a loss in WM fiber integrity. The sickle shaped blood cells are more likely to cause vaso-occlusive crises. In turn, hemolysis is compensated by an increased cerebral blood flow in order for the brain to be normally oxygenated. The loss of WM fiber integrity may be an effect of chronic hemodynamic complications and subsequent insufficient oxygen delivery to neuronal tissue.

Another noticeable finding of the above work is the slight asymmetry of the areas with significantly decreased FA values on most of the tract pairs. Although we excluded patients with silent infarct and strokes, these asymmetries may be due to microstructural changes secondary to vascular involvement, yielding different severities of microstructural tissue abnormalities between the two hemispheres. Additionally, studies have shown that SCD patients without any cerebral incidents on T2-weighted imaging can still exhibit focal or global brain atrophy^[30,31]. Therefore, SCD patients might have abnormal microstructural tissue secondary to vasculopathy that is not shown on standard T2 MRI.

This study is part of an ongoing grant and we are currently in the process of acquiring more data, which we will use to validate the observed WM alterations and continue this examination on a larger data set. In addition, results will be correlated to neuropsychological testing – which we are also performing on all of our subjects. This will allow us to determine how these WM alterations are related to neurological impairment, and hence inform treatment.

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Figure 1.
Sagittal view of CST and SLF. Color bar indicates p-values ranging from 0.01–0.5.

Figure 2. Sagittal view of the CC and ILF of the (a) left hemisphere and (b) right hemisphere. The color bar indicates p-values ranging from 0.01–0.5.

Figure 3. Sagittal view of IFO of the (a) left hemisphere and (b) right hemisphere. The color bar indicates p-values ranging from 0.01–0.5.

Table 1

Acquisition parameter for DTI scans.

TR	7600 msec
TE	86 msec
FOV	240mm × 240 mm
Size.	2.5×2.5×2.5mm

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