

Diffusion Tensor Imaging in Patients with Hallervorden-Spatz Syndrome and their Siblings

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Introduction: Hallervorden Spatz syndrome (HSS) is a rare autosomal recessive neurodegenerative disorder with core pathological features of iron deposition in basal ganglia, axonal spheroids and gliosis of the pallidum and substantia nigra (SN) (1, 2). The deposition of iron causes bilateral high signal intensity surrounded by a region of low signal intensity on T2-weighted image in the medial globus pallidus (GP) on magnetic resonance imaging (MRI), and recognized as the “eye of tiger sign” (1). Patients with mutated PANK2 gene have this imaging pattern, which was not found in mutation negative patients (3). Pathologically it has been found that the patients with HSS contain both extracellular and intracellular iron in deep gray nuclei (4).

A recent diffusion tensor imaging (DTI) study has reported high fractional anisotropy (FA) values in all stages of hemorrhage when present in brain tumors (HBT). They have suggested that high FA in HBT could be due to the RBCs entangled in fibrin meshwork during acute and early subacute stage of the bleed and metello-anisotropic effect of intracellular hemosiderin in chronic stage (5).

The study aimed to compare the DTI metrics in deep grey matter among HSS patients, their siblings with normal conventional MRI, and age matched controls to look for any differences.

Materials and Methods: In the current study, 4 patients with HSS (mean age±SD=8±3.2), 2 of their siblings (same age group) and 5 age matched healthy controls were prospectively evaluated with conventional MRI and DTI imaging on a 1.5 T GE scanner, using quadrature birdcage head coil. Conventional MRI included T2, T1, fluid attenuated inversion recovery (FLAIR) and T2* gradient recalled echo sequence (GRE) images. DTI data were acquired using a single-shot echo-planar dual SE sequence with ramp sampling. The b-factor was set to 1,000 s/mm², TR=8secs, TE=100ms, NEX=8. All the conventional and DTI images were acquired in axial plane with image matrix size of 256×256, field of view (FOV) of 240×240 mm, slice thickness of 3 mm with no inter-slice gap.

Data processing and analysis: The DTI data were processed as described in detail elsewhere (6). In each subject, five slices were selected for caudate, putamen and GP, and three were selected for SN, where the respective structure was best visualized, were taken for DTI metrics quantification. The size of region of interests (ROIs) varied from 2 × 2 to 4 × 4 pixels. In patients with HSS, in addition to the ROI analysis, hypointense and hyperintense components of “eye of tiger sign” visible on T2* GRE were segmented to obtain DTI metrics from these regions using in-house developed JAVA based software.

Statistical Analysis: To compare the DTI indices among the different groups, one way analysis of variance (ANOVA) using Bonferroni post-hoc multiple comparisons was performed. Student’s independent t test was performed to see difference between hypointense and hyperintense regions of “eye of tiger sign” visible on T2* GRE in patients. A p value of < 0.05 was considered as statistically significant.

Results: The FA and MD values of different regions in all the three groups are summarized in table 1. A significant difference in FA value was observed among all groups in caudate nuclei (CN), GP, and SN. No significant change in FA value was observed among groups in putamen. On MD map significant difference in MD values among groups was observed in GP only. In CN, Putamen and SN; no significant change in MD values was observed.

Significantly high (p < 0.01) FA value in hypointense regions (0.34±0.05) was observed compared to hyperintense region (0.18±0.05) while MD values were significantly higher (p < 0.01) in hyperintense region (0.88±0.06) than hypointense region (0.72±0.03) of “eye of tiger sign” in patient group.

Discussion: In this study we observed significantly high FA values in both patients and their siblings as compared to controls in GP, SN and CN. In addition significantly high FA and low MD values were observed in hypointense as compared to hyperintense regions of “eye of tiger” sign. The earlier pathological studies have provided evidence of iron accumulation in basal ganglia (4). In a recent DTI study in HBT, researchers have shown increased FA. They explained high FA in HBT on the basis of the presence of intracellular iron (hemosiderin laden macrophages), that is a paramagnetic substance and is associated with high susceptibility. The intracellular iron (hemosiderin laden macrophages) introduces local field gradients that have been shown to increase anisotropy (7). We suggest that high anisotropy in GP, SN and CN in patients reflects the presence of intracellular iron in these regions.

On T2 bilateral areas of hyperintensity within a region of hypointensity in the medial GP is known as “eye of tiger” sign, a diagnostic feature of HSS (8). Hypointense region of “eye of tiger sign” on T2* GRE in GP is diagnostic of iron deposition as a result of abnormal iron metabolism. The pathological studies also have shown iron accumulation including regions apart from “eye of tiger sign” (normal appearing on GRE), suggest T2* GRE has sensitivity constraint in the detection of abnormal iron accumulation. T2* effect is field and pulse sequence dependent (3, 9). Though, the anisotropy in GP, CN, and SN in siblings with normal T2* GRE is lower compared to the patients, it was significantly higher in siblings compared to control. It further suggests the siblings with normal conventional imaging including GRE imaging showing high FA in the deep grey matter probably represent the abnormal iron metabolism.

Due to the rarity of the disease, the number of patients studied was small, which may be considered as a limitation of this study. We conclude that FA is a sensitive indicator of abnormal iron metabolism and its accumulation in deep grey matter even in the absence of demonstration on T2* GRE.

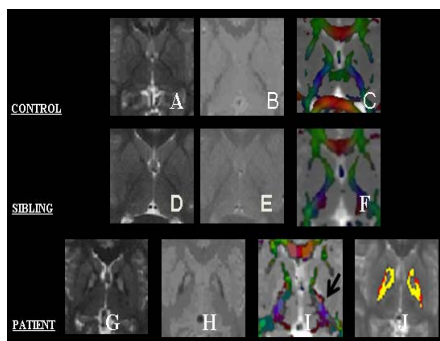


Table 1: Summary of DTI indices collected from grey matter nuclei from patients with HSS, their siblings, and age matched controls.

Group	CN		Putamen		GP		SN	
	FA	MD	FA	MD	FA	MD	FA	MD
Control	0.09±0.01	0.74±0.04	0.08±0.01	0.69±0.03	0.09±0.01	0.69±0.30	0.14±0.01	0.98±0.03
Sibling	0.10±0.01	0.77±0.21	0.08±0.01	0.71±0.05	0.13±0.01	0.74±0.01	0.17±0.01	1.06±0.09
Patient	0.12±0.01	0.77±0.38	0.08±0.01	0.70±0.02	0.21±0.01	0.76±0.05	0.22±0.02	1.06±0.09

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