Voxel based DTI analysis predicts suggestive of MS track in clinically isolated syndrome patients

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Introduction

The ability to early diagnose clinically isolated syndrome (CIS) patients who may convert to clinically definite multiple sclerosis (MS) could potentially allow targeting immuno-modulatory treatment so as to reverse/retard the disease progression. DTI has been demonstrated as a powerful imaging tool in detecting white matter abnormalities in MS patients [1,2,3]. In this study, we hypothesize that DTI parameters will not only be capable of delineating white matter abnormalities in CIS patients but also differentiating CIS suggestive of MS (CIS-MS) from CIS not suggestive of MS (CIS-NMS) patients.

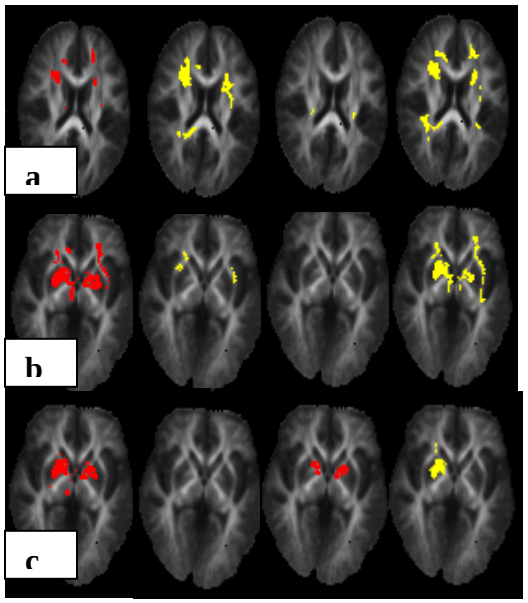
Materials and Methods

This was an IRB approved study and written informed consent was obtained prior to imaging. Patients presenting as CIS (9M and 25F) and 35 healthy control subjects (21F, 14M, Age 38.2±8.8) were recruited and imaged. 3D T1 MP-RAGE (isotropic voxel size 1mm^3) and EPI-DTI images using 6 non-colinear diffusion gradient encoding directions were acquired using a 3T head-only MR scanner (Allegra, Siemens). In order to determine whether or not DTI images acquired at the baseline are capable of differentiating CIS-MS from CIS-NMS patients, clinical evaluation, including EDSS and relapses conducted within ~2yr since the baseline DIT scans was employed to divide CIS patients into CIS-MS (7M,15F, Age 41.5±11.1) and CIS-NMS (2M,10F,Age 38.0±7.2) groups, respectively. A bi-directional 3D B-spline registration approach was used to warp the T1 images from all the subjects towards an arbitrary chosen template. Each subject's DTI image without diffusion gradient encoding was registered towards his/her T1 images with affine registration. By following these two registrations, all DTI parameters from different subjects were spatially normalized towards the common template frame for voxel based statistical analyses. Three quartiles of histograms for all DTI parameters were computed. For each patient, a volume of abnormal white matter tissues (VAWM) for each DTI parameter was computed as the sum of voxels within major white matter whose DTI parameter deviated either positively (ADC,L1,L2) or negatively (FA) more than two standard deviations away from the normal (NORM) mean. To evaluate the variation within the healthy control group, VAWM was obtained with the mean and standard deviation from the rest of the healthy control group excluding the subject of interest. To identify the sub-cortical regions (major white and deep gray matters) demonstrating significant difference among groups, voxel based group comparison was performed between each patient group and NORM. Age and gender factors were programmed as covariates in all the statistical analyses.

Results

All statistical significant findings with histogram and VAWM analyses were summarized in the Table. All three quartiles of FA, ADC, L2 and the 3rd quartile of L1 demonstrated statistical significances when compared with NORM, while non-statistical significance was found for CIS-NMS. CIS-MS patients had significantly elevated ADC and L2 than CIS-NMS patients in histogram analysis. In analysis of VAWM, all four diffusion parameters demonstrated statistical significances in CIS-MS group when compared with NORM, and none such significance for CIS-NMS was observed. Abnormal regions in frontal white matter and internal capsule were found with FA, ADC, L1, and L2 (left to right columns in the figure) in CIS-MS patients (**a)**, while no such significant areas were detected in CIS-NMS patients. Basal ganglia (BG) were found abnormal in both CIS-MS (**b**) and CIS-NMS (**c**). In CIS-NMS, no significant areas were identified with ADC at all, and regions around BG demonstrated reduced L1.

P-values of statistical analysis with spatially normalized histogram			
DTI quartiles	CIS-MS v. Norm	CIS-NMS v. Norm	CIS-MS v. CIS-NMS
FA 1st	P=0.0001*	P=0.06	P=0.05
FA 2nd	P=0.0001*	P=0.07	P=0.10
FA 3rd	P=0.0001*	P=0.05	P=0.17
ADC 1st	P=0.0004*	P=0.17	P=0.11
ADC 2nd	P<0.0001*	P=0.20	P<0.03*
ADC 3rd	P<0.0001*	P=0.21	P=0.03*
L1 3rd	P<0.05*	P=0.66	P=0.24
L2 1st	P<0.0001*	P=0.07	P=0.14
L2 2nd	P<0.0001*	P=0.06	P=0.08
L2 3rd	P<0.0001*	P=0.08	P=0.02*
P-values of statistical anlaysis with VAWM			
DTI parameter	CIS-MS v. Norm	CIS-NMS v. Norm	CIS-MS v. CIS-NMS
FA	P=0.0007*	P=0.69	P=0.02*
ADC	P<0.0001*	P=0.44	P=0.006*
L1	P=0.0017*	P=0.68	P=0.03*
L2	P<0.0001*	P=0.40	P=0.0017*



Discussion

Our results demonstrate that CIS-MS patients exhibit more severe white matter abnormality than CIS-NMS patients. More sub-cortical regions were found abnormal in CIS-MS patients. Even though BG abnormality was common in these two groups, but the underlying clinical implication may differ. L1 in BG was significantly reduced in CIS-NMS but not in CIS-MS. This finding may suggest that BG damage in CIS-NMS may be at an earlier stage, since it was shown in cuprizone model that L1 was reduced in acute phase of axonal injury and was increased afterwards [4]. In conclusion, our results strongly supported that voxel based DTI analysis can differentiate CIS-MS from CIS-NMS patients.

References

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