Correlation of Quantitative Diffusion Tensor Tractography with Clinical Grades of Subacute Sclerosing Panencephalitis

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Introduction: Subacute sclerosing panencephalitis (SSPE) is a progressive degenerative disorder of childhood and early adolescence caused by persistent measles virus. Symptoms of SSPE usually appear after a latent period of approximately 6–8 years of clinical measles infection (1). Diagnosis of SSPE is usually based on typical clinical manifestation, electroencephalography (EEG) findings and laboratory findings including high levels of CSF gamma globulin, and elevated titer of measles antibody in the CSF and serum (2). Early symptoms of SSPE are mild intellectual deterioration followed by the onset of myoclonus, convulsions, and abnormal postures and movements, progressing to optic atrophy, motor weakness, and akinetic mutism and ending in coma and death (3). The correlation between the clinical staging and MR imaging is usually poor. In the early stages of disease, findings of brain MRI studies are usually negative (4,5). Metabolite abnormalities in the normal-appearing white matter of patients with SSPE have been described on in-vivo proton MR spectroscopy (1). Diffusion tensor imaging (DTI) characterizes the apparent diffusion properties of water. A region of interest (ROI)–based morphometric DTI study has shown abnormal fractional anisotropy (FA) values in parietooccipital white matter and splenium in the stage II SSPE patients those were normal on conventional imaging (6). The popular ROI–based morphometric DTI method is limited to 2 dimensional (D) that does not reflects the whole fiber bundle in 3 D space. In brain white matter, the principle diffusion direction corresponds well with orientation of major fiber in each voxel. Diffusion tensor tractrography (DTT) gives 3-dimensional information of white matter fiber tract. The purpose of this study was to look for probable correlation between tract-specific DTI metrics in major white matter pathways and Jabbour classification based clinical grades.

Materials and Methods: We examined 20 children (16 boys and 4 girls) of SSPE (mean age of 9 years) and 11 age and sex-matched controls. The diagnosis of SSPE was based on typical clinical presentation, EEG pattern, and elevated CSF anti-measles antibody titer**.** Patients were graded according to Jabbour classification (2). Out of 20 children, 9 children were in stage II, 6 were in stage III, and 5 patients were in stage IV SSPE. The usual clinical presentation was the myoclonus, altered behavior, and cognitive decline. Whole brain conventional MRI (T2, T1 and FLAIR) and DTI were performed on a 1.5-Tesla GE MRI system. All imaging was performed in the axial plane and had identical geometrical parameters: field of view (FOV) = 240 × 240 mm^2, slice thickness = 3 mm, interslice gap = 0 and number of slices = 36.DTI data were acquired using a single-shot echo-planar dual spin-echo sequence with ramp sampling. Fiber assignment by continuous tracking (FACT) algorithm was used for reconstruction of fibers. Major white matter fiber tracts including corpus callosum (CC), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), cingulam (CNG), superior (SCP), middle (MCP) and inferior (ICP) cerebellar peduncle and anterior (ATR), superior (STR), and posterior (PTR) thalamic radiations were generated and quantified by using in-house developed JAVA based software. The white matter fiber tracts were generated as described in detail elsewhere (7).

Statistical analysis: Multiple comparisons using Bonferroni, Post Hoc test was performed to determine the changes in FA and mean diffusivity (MD) values among controls and clinical grades of patient groups. A p value ≤ 0.05 was considered to be significant. Bivariate analysis of correlation was performed to study the relationship between the white mater tract specific DTI measures and clinical grade of CP with the assumption that there was no correlation between DTI measures and clinical grade (Ho=0). Alternatively, if a correlation of <0.001 is observed at α=0.05 and 90% power of the test, the null hypothesis was rejected.

Results: Significantly decrease FA with increased MD values was observed in all patient groups compared to controls. Successive decrease in FA values and increase in MD values was observed in all white matter pathways (except MCP, SCP and ICP), moving from controls to stage IV SSPE patients through stage II and III (**Table 1**). Significant inverse correlation between clinical grade and FA values was observed in CC (r=-0.811, p<0.001), CNG (r=-0.648, p=0.017), SLF (r=-0.533, p=0.05), ILF (r=-0.776, p=0.001), STR (r=-0.538, p=0.047) and PTR (r=-0.586, p=0.035).

Table 1: Summary of FA values of whole fiber bundles of major white matter pathways from controls and patient groups

	Genu	Splenium	SLF	ILF	CNG	MCP	SCP	ICP	ATR	STR	PTR
Control	0.38±0.01	0.40±0.02	0.30±0.01	0.34±0.02	0.29±0.02	0.41±0.02	0.35±0.01	0.35±0.02	0.30±0.01	0.31±0.01	0.35±0.02
Stage II	0.33±0.03	0.34±0.02	0.25±0.02	0.30±0.02	0.26±0.03	0.37±0.03	0.32±0.02	0.33±0.03	0.27±0.03	0.27±0.03	0.31±0.02
Stage III	0.30±0.03	0.29±0.01	0.24±0.02	0.27±0.02	0.24±0.01	0.37±0.04	0.33±0.03	0.31±0.03	0.26±0.01	0.26±0.02	0.29±0.02
Stage IV	0.27±0.04	0.25±0.02	0.22±0.03	0.25±0.02	0.22±0.02	0.35±0.03	0.32±0.02	0.32±0.02	0.25±0.02	0.23±0.03	0.28±0.03

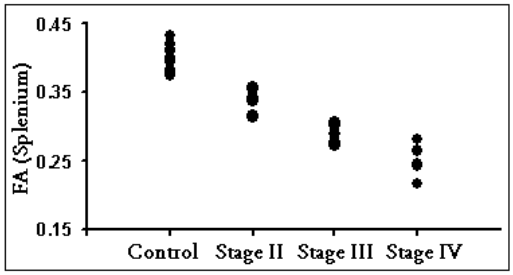

Figure 1

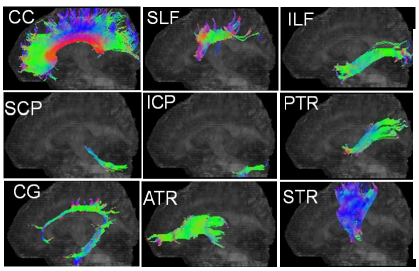

Figure 2

Fig.1: Scatter plot shows distribution of FA values in the splenium of CC in control and different grade of SSPE patient groups.
Fig.2: Projection of major white matter fiber tracts on sagittal plane in 8 years old control.

Discussion: To the best of our knowledge this is the first quantitative DTT study showing major white matter tracts in children with SSPE and their comparision with age/sex matched controls. This study demonstrates the correlation between clinical grades and DTI measures in major white matter tracts in children with SSPE. It is documented that severity of conventional MR changes poorly correlate with the clinical findings. Patients with severe disease may still have normal findings at conventional MR examinations. Significant inverse correlation of FA with clinical grades suggests that FA is a better measure than conventional MRI for the assessment of clinical grade in these patients.

Correlation of FA with clinical grade was much stronger in CC than other white matter tracts, which is in line with previous DTI study in SSPE patients (6). Cognitive decline is the common clinical feature in patients with SSPE (8). CC play an important role in normal vision and cognitive functions. The significant decrease in the corpus callosal FA in patients compared with controls confirms its involvement and may be responsible for the cognitive decline. Quantitative DTT can detect the changes in the major white matter tracts in the patients with SSPE earlier than conventional MR imaging and may be helpful in treatment planning for these patients.

References: 1)Alkan A, et al. Am J Neuroradiol 2003;24:501–06; 2) Jabbour JT, et al. JAMA 1969;207:2248–55; 3) Garg RK.Postgrad Med J 2002;78:63–70; 4) Brismar J, et al. AmJ Neuroradiol 1996;17:761–72 ; 5) Anlar B, et al.Neurology 1996;47:1278–83 ; 6) Trivedi R, et al.Am J Neuroradiol 2006;27:1712–16 ; 7) Trivedi R, et al. Pediatric Research 2009 (Epub ahead of print) ; 8) Ohya T, et al. Neurology 1974;24:211–18.