Assessment of White Matter Damage in Subacute Sclerosing Panencephalitis using Quantitative Diffusion Tensor MRI

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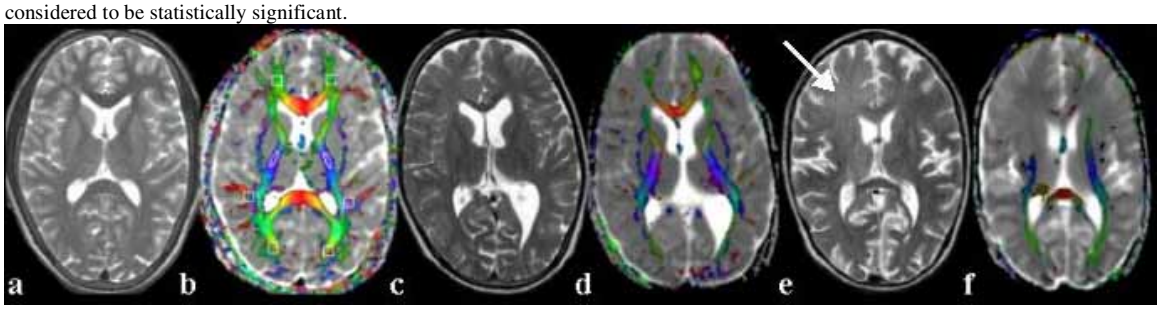
Introduction: Subacute sclerosing panencephalitis (SSPE) is a rare progressive degenerative disease that is caused by persistent infection with a defective measles virus. Symptoms of SSPE usually appear after a latent period of about 6-8 years of clinical measles infection. Diagnosis of SSPE is usually based on typical clinical, electroencephalography (EEG) findings and demonstration of high titer of measles antibody in the cerebrospinal fluid (CSF). Early symptoms of SSPE are mild intellectual deterioration, behavioral changes and poor school performance. It is followed by the onset of myoclonus, convulsions, abnormal postures and movements. Brain biopsy or postmortem brain analysis from SSPE patients shows evidence of astrogliosis, neuronal loss and degeneration, neurofibrillary tangle, and infiltration of inflammatory cells.[1] The correlation between the clinical staging and MRI abnormalities is usually poor.[2] DTI has been shown to be a valuable tool to detect the microstructural changes in clinical situations like multiple sclerosis, brain ischemia, and traumatic brain injury.[3] The aim of our study was to investigate the role of quantitative DTI in patients of SSPE in defining the microstructural changes in the normal and abnormal appearing brain parenchyma and to investigate the possibility to detect the microstructural abnormalities in patients with normal conventional MRI.

Materials and Methods: We examined 12 children (ten boys and two girls) with grade II SSPE (mean age of 8.6 years) and 10 age and sex-matched controls. The diagnosis of SSPE was based on typical clinical presentation, EEG pattern, and elevated CSF anti-measles antibody titer**.** The usual clinical presentation was the myoclonus, altered behavior, and cognitive decline. In addition five of the twelve children had extrapyramidal symptoms, and difficulty in walking.
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. The DTI data were processed as described in detail elsewhere.[4] The DTI-derived maps were displayed and overlaid on images with different contrasts to facilitate the region-of-interest (ROI) placement. ROIs were placed on corpus callosum (genu, mid-body, and splenium), posterior limb of internal capsule, and white matter of frontal, parietal, occipital lobes, and temporal lobe. A student's independent t-test was performed to evaluate the regional differences in the DTI metrics between SSPE patients and healthy controls. A p value of less then 0.05 was considered to be statistically significant.



T2 (a), color-coded FA (b) fused with ADC shows the normal distribution of white matter in 6-years-old healthy control. The rectangular and elliptical ROIs placed (b) on frontal, parietal, and occipital cerebral lobes and posterior limb of internal capsule. T2(c) image appears normal whereas color-coded FA (d) shows widespread bilateral abnormal white matter in 12-years-old-boy with clinical findings of SSPE. A 7-years-old -boy with SSPE shows hyperintensities on T2 (e) image in right frontal (arrow) and parieto-occipital region. Color coded FA (f) shows widespread bilateral white matter abnormalities and thinning of genu and splenium of corpus callosum.

Result: Based on the conventional MRI findings, the patients were grouped into normal (n=6) and abnormal (n=6) conventional imaging for the purpose of quantitative DTI analysis. Motor functions were impaired in five out of six patients as indicated by MRI. Significantly reduced FA values were observed in the corpus callosum (^{a}genu, ^{b}mid-body, and ^{c}splenium), and periventricular white matter of ^{d}frontal, ^{e}parietal, ^{f}occipital, and ^{g}temporal lobes in both the patient with normal ($^{a}0.45 \pm 0.08$, $^{b}0.30 \pm 0.07$, $^{c}0.47 \pm 0.06$, $^{d}0.18 \pm 0.02$, $^{e}0.19 \pm 0.03$, $^{f}0.19 \pm 0.02$, $^{g}0.20 \pm 0.04$) as well as abnormal conventional imaging ($^{a}0.47 \pm 0.05$, $^{b}0.34 \pm 0.04$, $^{c}0.36 \pm 0.12$, $^{d}0.17 \pm 0.02$, $^{e}0.15 \pm 0.02$, $^{f}0.16 \pm 0.02$, $^{g}0.17 \pm 0.00$) as compared to controls ($^{a}0.54 \pm 0.05$, $^{b}0.44 \pm 0.05$, $^{c}0.61 \pm 0.07$, $^{d}0.24 \pm 0.05$, $^{e}0.25 \pm 0.03$, $^{f}0.26 \pm 0.03$, $^{g}0.25 \pm 0.03$). MD values were significantly increased in the ^{h}parieto-^{i}occipital region in patients with normal ($^{h}0.78 \times 10^{-3} \pm 0.06 \times 10^{-3}$, $^{i}0.75 \times 10^{-3} \pm 0.05 \times 10^{-3}$) and abnormal conventional imaging ($^{h}0.78 \times 10^{-3} \pm 0.06 \times 10^{-3}$, $^{i}0.78 \times 10^{-3} \pm 0.03 \times 10^{-3}$) as compared to controls ($^{h}0.70 \times 10^{-3} \pm 0.04 \times 10^{-3}$, $^{i}0.71 \times 10^{-3} \pm 0.04 \times 10^{-3}$). Patients with normal as well abnormal conventional imaging showed no change in MD in genu, mid-body, and splenium of CC as compared to controls. In addition patients with abnormal conventional imaging showed significantly decreased FA in PLIC (0.43±0.03) as compared to controls (0.49±0.06). In patients with normal conventional imaging no change in FA was observed in PLIC (0.46±0.04) as compared to controls.

Discussion: Based on the observations in the present study, it appears that patients with clinical stage II disease showing normal imaging on conventional MRI have widespread microstructural changes in the white matter. These observations of significantly decreased FA in cerebral white matter of patients with normal and abnormal imaging suggest a net loss and disorganization of the structural barriers to molecular diffusion of water, and may be explained by documented pathological characteristics of SSPE like demyelination, neuronal loss, astrogliosis, infiltration of inflammatory cells, and infection of oligodendrocytes by measles virus.[5] Significantly increased mean MD value was observed in parietal and occipital cerebral lobes in patients with normal and abnormal imaging as compared to controls, which suggests that the pathologic changes were more extensive in parieto-occipital region and further confirm the involvement of cerebral hemispheres from posterior to anterior with the disease process. The significantly decreased FA in posterior limb of internal capsule in patients with abnormal imaging as compared to control reflects the presence of motor dysfunction along with pyramidal signs on clinical examination. Demonstration of involvement of parieto-occipital lobe, with or without involvement of splenium on DTI, especially in patients with normal conventional imaging may be used as an early sign of SSPE in young children with the history of childhood viral fever, skin rashes, and poor school performance along with behavioral changes.

References: (1) Hayashi M, et al. J Child Neurol 2002;17:725-730. (2) Brismar J, et al. Am J Neuroradiol 1996;17:761-772. (3) Sundgren PC, et al. Neuroradiology 2004;46:339-350. (4) Hasan KM, et al. J Magn Reson Imaging. 2005;21:735-743. (5) Ohya T, et al. Neurology 1974;24:211-218.