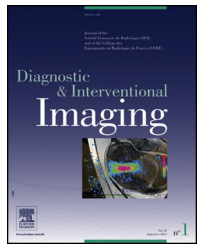
Diagnostic and Interventional Imaging (2016) **97**, 171—176



ORIGINAL ARTICLE /*Neuroradiology*

Brain diffusion tensor imaging in children with tuberous sclerosis

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KEYWORDS
Pediatrics;
Diffusion tensor imaging;
Tuberous sclerosis;
Radial diffusivity;
Axial diffusivity

Abstract
Purpose: To evaluate diffusion characteristics of tubers and white matter lesions in children with tuberous sclerosis (TS) using diffusion tensor imaging (DTI).
Materials and methods: Eighteen children (11 male, 7 female; mean age 9.3 years, age range 1—16 years) with a definite diagnosis of TS were recruited in this study. Apparent diffusion coefficient (ADC), fractional anisotropy (FA), radial diffusivity (RD), and axial diffusivity (AD) values in 89 tubers and 37 white matter lesions were measured and compared with those of contralateral normal regions.
Results: ADC, AD, and RD values were significantly higher and FA values were lower in lesions, than the ones measured in contralateral normal regions for tubers ($P < 0.001$). Similarly RD values were significantly higher and FA values were lower in white matter lesions ($P < 0.05$). ADC and AD measures were detected to increase in white matter lesions, however no statistically significant difference was observed. The increase in the mean values of RD was significantly greater than the increase in the AD values for tubers and white matter lesions ($P < 0.05$).
Conclusion: DTI can provide valuable information about the cytoarchitectural changes in TS lesions beyond morphologic MRI findings alone.

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http://dx.doi.org/10.1016/j.diii.2015.04.002

Tuberous sclerosis (TS) complex, the second most common neurocutaneous syndrome after neurofibromatosis type 1, is characterized by multiple benign hamartomatous lesions involving skin, brain, kidneys, eyes, and heart [1—3]. It occurs in 1 of 6000 newborns and 1.5 million people are estimated to suffer worldwide [1]. This autosomal dominant phakomatosis is caused by a mutation in either one of two tumor suppressor genes called *TSC1* and *TSC2* [1—3]. The typical appearance of TS is epilepsy, mental retardation, and facial angiofibromas; named as ''Vogt's triad''. However, this triad is seen in only 30—40% of patients. The clinical expression of TS has great variability [1,2]. Several neurological symptoms, such as autism, behavioral problems, mental retardation, and seizures may be seen in TS [1,2].

Typical intracranial lesions of TS are tubers, subependymal nodules, subependymal giant cell astrocytomas (all of which are the major features for the diagnosis of TS) and white matter abnormalities [1—3]. Magnetic resonance imaging (MRI) is the main modality to display all these intracranial lesions. Tubers [1,3], which constitute the hallmark of the disease, are hamartomatous cortical-subcortical lesions that are seen in 90% of patients. Tubers have low signal on T1-weighted (T1-W) images and high signal on both T2-weighted (T2-W) and FLAIR images unless they are calcified. The white matter lesions of TS are also hypointense on T1-W images and hyperintense on T2-W and FLAIR images [1,3]. Radial glial bands, also called radial migration lines and periventricular cyst-like lesions are defined as white matter lesions of TS. Radial glial bands are linear or wedge shaped lesions, which may reach from ventricular ependymal surface to the cortex, occasionally terminating at tubers. They are thought to represent heterotopic neuronal and glial elements that arrested during cortical migration [1,3].

Although conventional MR sequences are routinely used for detecting intracranial lesions, they are not able to reveal the subtle microstructural characteristics of TS. Diffusion tensor imaging (DTI) makes investigation of the three dimensional microanatomical structure of brain parenchyma possible [4—6]. This technique evaluates the direction and magnitude of water diffusion in tissues [4—7]. Protons diffuse freely in all directions in an isotropic diffusion (as in cerebrospinal fluid), whereas diffusion is restricted in some directions in an anisotropic diffusion (as in organized biological tissues like cerebral white matter). Diffusion tensor is a second-order matrix that represents direction and magnitude of diffusion at each voxel on the image [5,6]. It is characterized by three eigenvalues ($\lambda1$, $\lambda2$, and $\lambda3$) and three eigenvectors ($\varepsilon1$, $\varepsilon2$, and $\varepsilon3$), which represent the magnitude and direction of diffusion respectively [6,8]. Major eigenvalue ($\lambda1$) also called ''axial diffusivity'' (AD) represents the highest diffusivity parallel to the axon. Intermediate and minor eigenvalues ($\lambda2$ and $\lambda3$ respectively) define diffusivities perpendicular to the axon and the ''radial diffusivity'' (RD) is the arithmetic average of $\lambda2$ and $\lambda3$ [9]. The apparent diffusion coefficient (ADC) evaluates the overall magnitude of water diffusion in the tissue and is equal to the average of the 3 eigenvalues. Another main DTI index fractional anisotropy (FA), which measures the degree of anisotropy and is scaled from 0 (completely isotropic) to 1 (completely anisotropic) [5,7].

In recent years, DTI has been used for investigating several pediatric neurological diseases, like malformations, periventricular leukomalacia, tumors, multiple sclerosis, epilepsy, and phacomatosis [7]. There are few studies described DTI findings of TS up to date. Most of these studies investigated either ADC [10] or ADC and FA both [11—13]. Firat et al. [10] reported higher ADC values in tubers than normal appearing white matter in controls and other studies [11—13] which investigated ADC and FA, found lower values of FA and higher values of ADC in tuberous sclerosis lesions than normal appearing corresponding areas. However the directional diffusivity indices like AD and RD can give additional beneficial information on the microstructure of tubers and white matter lesions [14]. Therefore, in this work, we aimed to characterize water diffusion and its directionality in TS lesions by using DTI method investigating axial and radial diffusivities in addition to apparent diffusion and anisotropy measures.

Materials and methods

Patients

This study was approved by the local ethics committee of our institution. The sample of our study consisted of 18 pediatric patients (11 male, 7 female; age range 2—16 years with mean age 9.3 and standard deviation 5 years) with a definite diagnosis of tuberous sclerosis who were regularly followed up in our pediatric neurology outpatient clinic. Presence of tubers on MRI was identified as selection criteria. All 18 patients suffered from epilepsy and mental retardation. Other clinical manifestations included hypopigmented macules in all patients, facial angiofibromas in 12 patients, shagreen patches and renal angiomyolipomas in 11 patients, cardiac rhabdomyomas in three patients.

Magnetic resonance imaging procedure

Routine cranial MRI and DTI were performed on a 1.5 Tesla MRI device (Siemens Aera; Siemens Medical Systems, Germany). The routine cranial MR imaging protocol consisted of 3-D MP-RAGE T1-weighted imaging (TR = 1900 ms, TE = 2.86 ms, slice thickness (ST) = 1 mm, FOV: 250 × 250 mm, Resolution: 256 × 256), coronal and axial T2-weighted imaging (TR = 4000 ms, TE = 96 ms, Number of slice (NS) = 23, ST = 5 mm, FOV: 230 × 230 mm, resolution: 320 × 320), axial FLAIR (TR = 7000 ms, TE = 84 ms, NS = 23, ST = 5 mm, FOV: 260 × 260 mm, resolution: 256 × 256), and susceptibility weighted imaging (SWI) (TR = 49 ms, TE = 40 ms, ST = 3 mm, FOV: 260 × 260 mm, resolution: 256 × 256). Additionally DTI images with following parameters were acquired by using a single-shot echo-planar pulse sequence: TR = 3500 ms, TE = 83 ms, Resolution = 128 × 128, FOV: 230 × 230 mm, ST = 5 mm and 3 averages. Two *b* values (0,1000 s/mm^2) were applied in 12 non-collinear directions. The total acquisition time for DTI sequence was approximately two and a half minutes.