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Diffusion weighted MR findings of brain involvement in tuberous sclerosis

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PURPOSE
Diffusion Weighted Imaging (DWI) is effective in identifying microstructural cerebral parenchymal changes. We studied the diffusion characteristics of hamartomas and normal white matter in cases with tuberous sclerosis (TS).

MATERIALS AND METHODS
Diffusion weighted images of 6 TS cases (ages between 3 – 15 years, mean 9.0 years, SD 4.4 years) that presented to our center for magnetic resonance (MR) imaging have been retrospectively evaluated. In addition to 56 non-calcified hamartomas of TS patients, apparent diffusion coefficient (ADC) values measured from frontal, parietal normal white matter, and basal ganglions of TS patients were compared with values obtained from 9 normal subjects (ages 1 – 13 years, mean 8.9 years, SD 3.4 years). Hamartomas were divided into 3 subgroups based on their locations, and the ADC values measured in these groups were compared.

RESULTS
ADC values of all hamartomas were between 838 and 2230, with a mean value of 1408 $mm^2/sec \times 10^{-3}$ (SD: 273.2); ADC values of the white matter of normal subjects were between 695 and 857, with a mean value of 776.1 $mm^2/sec \times 10^{-3}$ (SD: 44.23) ($p < 0.0001$). ADC values of subependymal nodules, white matter hamartomas, and subcortical tubers were 838–2230 (mean: 1440.5 $mm^2/sec \times 10^{-3}$; SD: 526.46), 1046–1622 (mean: 1328.6 $mm^2/sec \times 10^{-3}$; SD: 189.4), and 981–1973 (mean: 1417.4 $mm^2/sec \times 10^{-3}$; SD: 219.5), respectively ($p = 0.666$).

CONCLUSION
Diffusion characteristics of white matter hamartomas resulting from TS clearly differ from those of normal white matter, but no significant difference was observed in ADC values of these lesions based on their locations. Moreover, the ADC measurements of normal white matter in these cases did not differ from those of the control group, indicating that the disease does not cause a common explicit damage in white matter and central gray matter, other than hamartomas, which can be detected by DWI. DWI may only be used in the differential diagnosis of hamartomas from secondary lesions with T1 and T2W signal intensities similar to those of hamartomas and with different diffusion characteristics.

Key words: • *diffusion magnetic resonance imaging* • *tuberous sclerosis* • *brain*

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Tuberous sclerosis (TS) is an autosomal dominant phacomatosis. The disease causes hamartomatous lesions, usually in the brain, eyes, skin, and kidneys, and less frequently in other organs (1). Lesions formed in the brain are hamartomas located in cortical grey matter, white matter subependymal regions and subependymal giant cell astrocytomas. Conventional magnetic resonance (MR) imaging is used as the primary method for detecting TS hamartomas. Diffusion weighted imaging (DWI), used in evaluating the microstructure of tissues, is an advanced application of MR imaging. This method can be used in evaluating parenchymal tissue abnormalities, which cannot be detected by current methods (2).

There are a limited number of TS cases studied with DWI (3 - 5). In these studies, the diffusion characteristics of hamartomas were investigated and the role of DWI in the detection of epileptogenic tubers were evaluated.

In the present study, the existence of probable microstructural changes in white matter and deep gray matter, that were evaluated as normal in TS cases with conventional MR imaging, were investigated with DWI. In addition, we aimed to determine if hamartomas exhibit diffusion differences based on their locations.

Materials and method

Six TS diagnosed cases (5 female and 1 male) between 3 and 15 years old (mean: 9.0 years; SD: 4.4 years) were examined with computed tomography (CT) (Secura, Philips, Best, Holland), conventional MR imaging, and DWI in a 1.5 T superconductor scanner (Intera Master, Gyroscan, Philips, Best, Holland). Conventional MR imaging tests consisted of axial T1W (TR/TE = 450/10 ms), T2W (TR/TE = 5304/110 ms), and FLAIR (TR/TE = 6000/110 ms) sequences. Echo-planar imaging (EPI) (TR/TE = 5381/81 ms; slice thickness: 5 mm; space between slices: 1 mm; FOV: 230 x 230 mm; matrix: 256x256; b values: 0, 500, and 1000 s/mm^2) sequence was used for DWI. Apparent diffusion coefficient (ADC) maps were formed with these images.

In total, 56 non-calcified hamartomas were identified by CT and conventional MR inspection. By excluding lesions with calcification from the study, we attempted to avoid the effects of calcification on ADC values. However, the probable presence of microcalcifications, which could not be identified by the methods used for lesions examined, was unavoidable. The non-calcified hamartomas mentioned above were divided into 3 subgroups based on their locations; cortical (41), white matter (7), subependymal (8). ADC values of these lesions were measured using regions of interest (ROI`s) with a minimum of 20 pixels. Magnified conventional images were used to avoid artifacts of cerebrospinal fluid (CSF) in ADC measurements taken from cortical

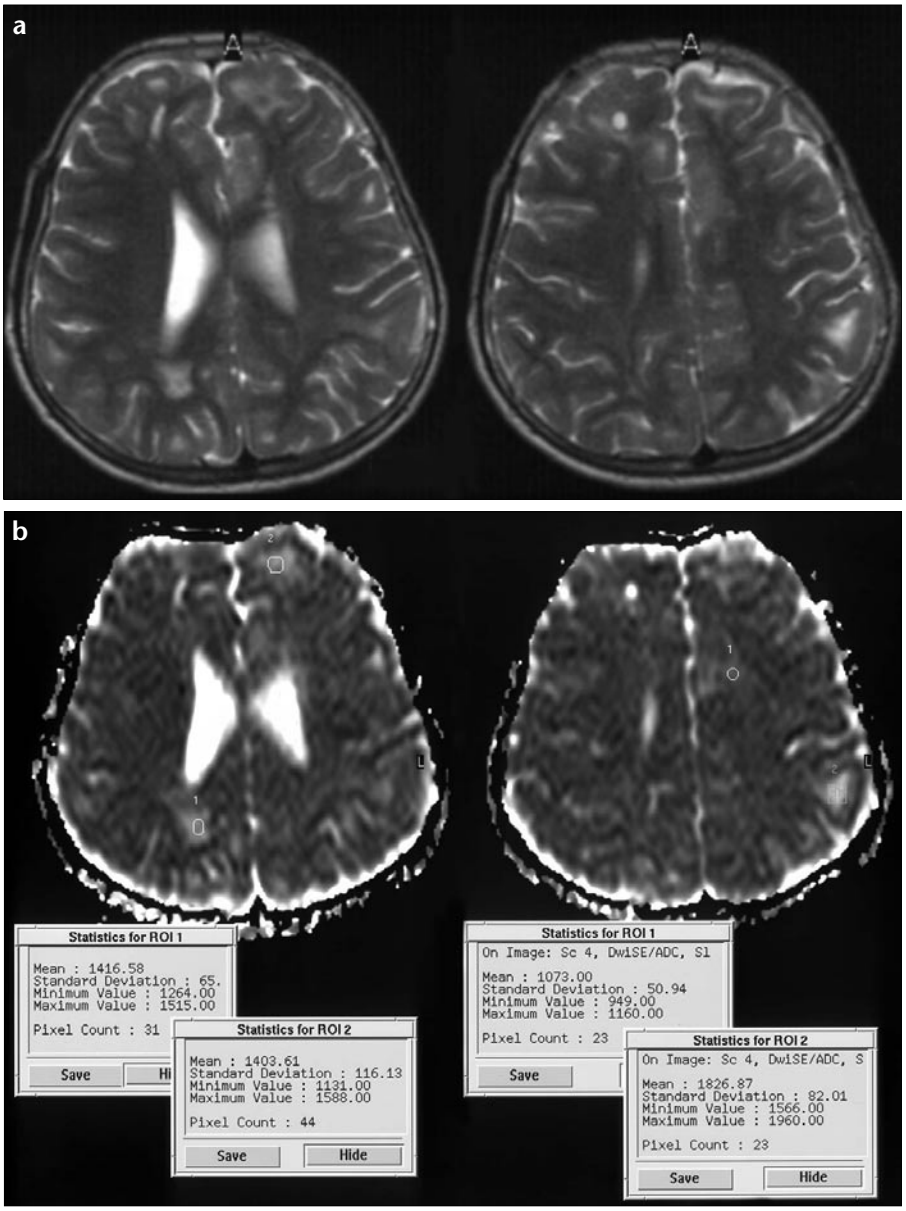

Figure 1. a, b. Sequential transverse T2W images **(a)** and ADC maps **(b)** with ADC measurements from different hamartomas on these maps are seen.

hamartomas (Figure 1a). ROIs were formed on these images and then automatically copied onto ADC maps (Figure 1b). Each lesion was measured 3 times and their mean was used in statistical analysis. Additionally, 6 ADC measurements (3 times each from both hemispheres) were taken from frontal and parietal white matter, and basal ganglions in conventional MR imaging. The mean of these 6 measurements was used in relevant analyses.

The control group was formed of 9 age-matched normal subjects between 1 and 13 years old (mean: 8.9 years; SD: 3.4 years; 5 male and 4 female). This group was examined with the same protocol used in the TS cases. SPSS (Statistical Package for Social Sciences) version 10.0 was used for statistical analysis.

The difference between mean ADC values obtained from normal-looking white and deep grey matter of the subjects in TS and control groups, and the difference between ADC values of hamartomas in TS and of normal white matter in the control group were analyzed with independent variants t test. The difference between ADC values of hamartomas at various locations, in the case group, was tested with variance analysis (ANOVA). In these analyses, $p < 0.05$ was accepted as statistical significance.

Findings

ADC values obtained from normal looking frontal and parietal white matter, and deep grey matter of the subjects in the case group were 730.2-884.3 $mm^2/sec \times 10^{-3}$ (mean: 799.7; SD: 49.6), 745.3-863.3 $mm^2/sec \times 10^{-3}$ (mean: 788.3; SD: 45.8), and 725.6-798.6 $mm^2/sec \times 10^{-3}$ (mean: 751.3; SD: 28.8), respectively. These values of the subjects in the control group were 738.0-857.0 $mm^2/sec \times 10^{-3}$ (mean: 791.5; SD: 40.8), 695.0-856.6 $mm^2/sec \times 10^{-3}$ (mean: 782.5; SD: 47.7), 700.7-783.0 $mm^2/sec \times 10^{-3}$ (mean: 747.4; SD: 32.9), respectively. There was no statistically significant difference between mean ADC values obtained from normal-looking frontal ($p = 0.665$) and parietal ($p = 0.900$) white matter, and deep grey matter ($p = 0.536$) of the subjects in TS and control groups.

ADC values of 56 hamartomas identified in TS group were 838-2230 $mm^2/sec \times 10^{-3}$ (mean: 1408; SD: 273.2). ADC values of cerebral white matter of the control group were 695-857 $mm^2/sec \times 10^{-3}$ (mean: 776.1; SD: 44.2). There was a statistically significant difference between the ADC values of hamartomas in TS group and normal white matter in the control group ($p < 0.0001$).

When hamartomas were grouped as cortical, white matter, and subependymal. based on their location, relevant ADC values were 981-1973 $mm^2/sec \times 10^{-3}$ (mean: 1417.4; SD: 219.5), 1046-1622 $mm^2/sec \times 10^{-3}$ (mean: 1328.6; SD: 189.4), and 838-2230 $mm^2/sec \times 10^{-3}$ (mean: 1440.5; SD: 526.5), respectively.

There was no significant difference between ADC values of hamartomas based on location ($p = 0.666$).

Discussion

TS was first defined by Friedrich von Recklinghausen in 1862. The currently used name for the disease was suggested by Désiré-Magloire Bourneville in 1880. Although the diagnostic criteria were defined under Diagnostic Criteria Report of the National Tuberous Sclerosis Association, definitive diagnosis is made by genetic analysis (6). Mutation or deletion was identified in 2 different genes in the TS cases (7, 8). The classical cerebral lesion of TS is hamartoma. It is suggested that the abnor-

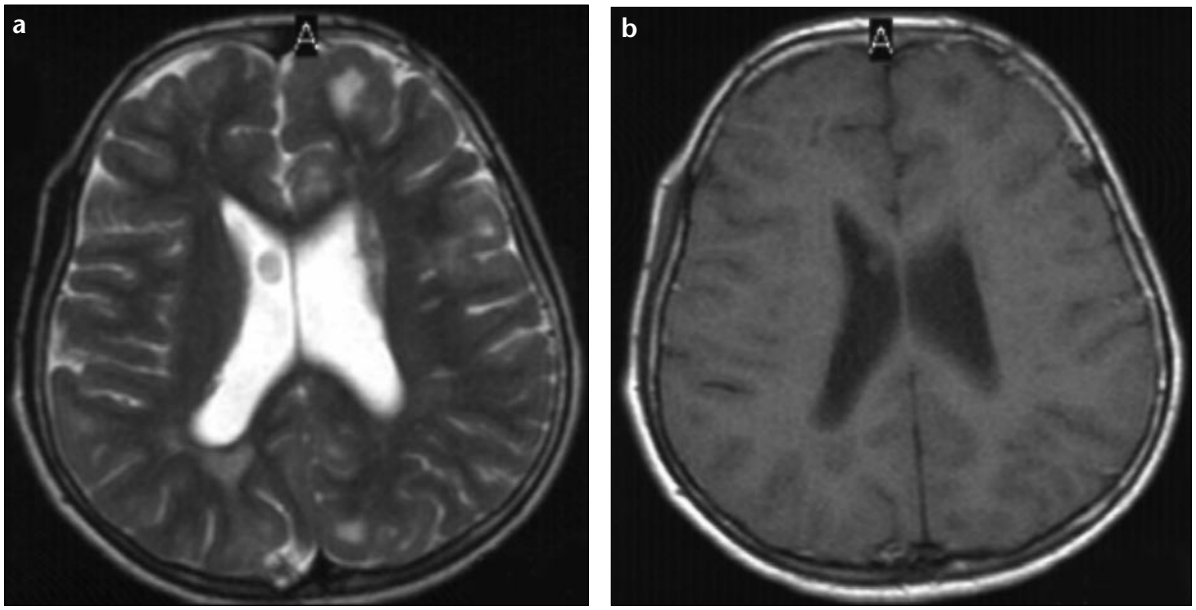

Figure 2. a, b. Transverse T2W image shows hyperintense hamartomas located adjacent to posterior of right lateral ventricle, in the deep white matter and in the left frontal subcortical area **(a)**, with high signal intensity on T1W **(b)** image.

mal stem cells in the germinal matrix cause hamartomas. It is known that the abnormalities in development, migration, and organization phases of these germ cells cause hamartomas. Hamartomas result in symptoms like infantile spasm, convulsion, and mental retardation in 60%-80% of cases (6-9). Another important lesion observed in TS is subependymal giant cell astrocytoma. Astrocytoma occurs in 5%-10% of cases, usually after the age of 10, with increased symptoms of increased intracranial pressure syndrome. Lesions play an important role in the mortality rate of TS (9).

Subependymal lesions may be observed in TS at any stage between subependymal nodules and giant cell astrocytomas. Therefore, it is not easy to distinguish these 2 lesions histologically as they rarely belong to only one of these 2 categories. White matter hamartomas and cortical hamartomas, known as tubers, have similar histopathological characteristics. These lesions are formed of dysplastic cells and hypomyelination areas, showing characteristics of neuronal and glial cells, such as giant neurons and balloon cells (5, 8). In TS, in addition to the macropathologies mentioned above, histopathological studies have shown that microscopic heterotopic cell clusters occur, which cannot be observed with white matter imaging methods. These lesions may calcify over time and become microscopically visible (1, 8).

In the past, CT and MRI findings in TS were studied in detail. Hamartomas are observed as isodense in CT, whereas in MRI, they appear iso-hypointense in T1W sequences and hyperintense in T2W sequences (Figure 2).

Hamartomas have low signal intensity when they are calcified (1, 8). In addition to the imaging results, there may be contrast-enhancing differences between subependymal nodules, and cortical and white matter hamartomas. This difference is believed to be secondary to histological differences (8).

In recent years, MR spectroscopy and DWI findings of TS have been investigated (3-5, 10). ADC values obtained by DWI are believed to provide information regarding the microscopic structure of brain lesions (2, 11, 12). While the mean of ADC values of hamartomas was 1520 $mm^2/sec \times 10^{-3}$ in a study conducted by Şener et al. (3), this value was 840 $mm^2/sec \times 10^{-3}$ for normal white matter obtained from the control group. In the present study, the values mentioned above were 1408 $mm^2/sec \times 10^{-3}$ and 776 $mm^2/sec \times 10^{-3}$, respectively. Increased random molecular movement caused the significant difference between the ADC values of hamartomas and normal white matter. This increase is partially due to the changes in glia and neurons, and is partially due to the demyelinizing process (3, 8). Numeric differences between the results of the 2 studies mentioned are most probably due to scanner and sequence differences.

It was stated at the beginning of the study that dysplastic cell groups and myelination defects defined histologically may cause differences in diffusion measurements, although they cannot be identified by conventional imaging methods. Therefore, for the first time in the literature, diffusion characteristics of normal white matter areas obtained with conventional imaging methods were examined in this study. Nevertheless, ADC values of the white matter of TS subjects were similar to those of control subjects. This can be explained by the fact that diffuse changes are not observed in TS cases. Furthermore, this result demonstrates that DWI cannot contribute to the diagnosis of lesions that cannot be determined with conventional imaging.

Şener et al. (3, 5) have studied hamartomas as a group and found that the ADC values of giant cell astrocytomas are closer to those of white matter than of hamartomas. The present study differed by grouping subependymal, white matter, and cortical hamartomas separately. This grouping is based on the fact that subependymal hamartomas exhibit histological characteristics that are different than other hamartomas (8). However, there was no statistically significant difference between

ADC values of hamartomas at different locations. This result showed that DWI may be utilized for differentiating hamartomas from normal white matter, but it cannot be used for distinguishing histopathological differences between hamartomas.

As a result, DWI does not contribute additionally to conventional MR imaging findings in TS cases. DWI may be used in distinguishing hamartomas from secondary lesions with T1W and T2W signal capacities similar to hamartomas and different diffusion characteristics.

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