Diffusion-Weighted Magnetic Resonance Imaging and Identification of the Epileptogenic Tuber in Patients With Tuberous Sclerosis

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**Background:** Patients with tuberous sclerosis complex and drug-resistant epilepsy may be considered candidates for epilepsy surgery. This demands the unambiguous demonstration of the epileptogenicity of one of the tubers.

**Objective:** To test whether diffusion-weighted magnetic resonance imaging enables differentiation of epileptogenic tubers from inert ones.

**Methods:** In 4 patients with clear unifocal interictal spike activity, fluid-attenuated inversion recovery and diffusion-weighted magnetic resonance imaging were performed. Apparent diffusion coefficient maps were calculated in the identified epileptogenic tuber and compared with those in nonepileptogenic tubers and regions of normal-appearing cortex.

**Results:** A significant increase in the apparent diffusion coefficient was found in the epileptogenic tubers. Furthermore, the apparent diffusion coefficient of the nonepileptogenic tubers was significantly higher than the trace apparent diffusion coefficient of regions of normal-appearing cortex.

**Conclusion:** Diffusion-weighted magnetic resonance imaging may be of clinical importance for the identification of epileptogenic tubers in patients with tuberous sclerosis and intractable epilepsy.

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In patients with tuberous sclerosis complex (TSC), cortical tubers may give rise to epilepsy, mental retardation, and focal neurological deficits. Epilepsy occurs in 80% to 90% of patients with TSC and is refractory to medical treatment in about half of the cases.

In patients with TSC and drug-resistant epilepsy, surgical treatment should be considered. However, as the success of surgery depends on clear identification of the epileptogenic zone, and as most patients with TSC have multiple, potentially epileptogenic tubers, this option is often rejected. Reports on the outcome of surgery in patients with TSC have shown variable results.1,5

Magnetic resonance imaging (MRI) and fluid-attenuated inversion recovery (FLAIR) MRI techniques have proved successful in the detection of even small tubers,6 but do not differentiate epileptogenic lesions from “silent” ones. In patients with clear unifocal interictal activity, simultaneous high-resolution (HR) electroencephalography (EEG) and HR magnetoencephalography (MEG) in combination with MRI has been applied to identify a primary epileptogenic zone matching with a single tuber.7 Disadvantages of MEG, however, are the required cooperation of the patient and its restricted availability.

In patients with partial epilepsy, diffusion-weighted MRI (DWI) techniques have been used to identify focal abnormalities when conventional MRI results were normal. In some of these patients, areas of increased diffusivity concurred with the focus of epileptiform EEG abnormality.8 So far, only limited experience has been obtained with DWI in patients with TSC.9

In this study, we correlated quantified diffusion trace MRI with FLAIR MRI and data obtained from simultaneous HR EEG and HR MEG registrations to test whether DWI enables the differentiation of epileptogenic tubers from inert ones.

**METHODS**

**PATIENTS**

We examined 4 patients who fulfilled the revised TSC diagnostic criteria.10 In 2
patients, the clinical diagnosis was confirmed with detection of a nonsense mutation in the TSC2 gene. All 4 patients had active epilepsy. In all patients, clear unifocal interictal spikes were identified by means of MEG, using 151 axial gradiometers arranged as a helmet (Omega 151; CTF Systems Inc, Port Coquitlam, British Columbia), and simultaneous 64-channel EEG with a sampling rate of 625 Hz. Coregistration of MEG, EEG, and MRI was obtained by identifying common marker positions. Three interictal registrations of 10 minutes each were performed in each patient. An average of 20 spikes per registration was found. Volume conductor models were constructed with Curry V3 software (Neuroscan, Sterling, Va). A multiple signal classification analysis for the localization of the dipole source of interictal spikes was performed. Data from simultaneous EEG and MEG source localization were superimposed on FLAIR images to enable the identification of the epileptogenic tuber.

MRI (FLAIR and DWI) Scanning Protocol and Image Analysis

Magnetic resonance investigations were repeated on a 1.5-T scanner (Philips Gyroscan NT-Intera; Philips Medical Systems, Best, the Netherlands) after informed consent had been obtained. None of the 4 patients had a seizure on the day the MRI was performed. FLAIR scans were performed with a repetition time, echo time, and inversion time of 6000, 100, and 2000 ms, respectively; a section thickness of 4 mm; no intersection gap; a 230 × 230-mm field of view; 2 averages; a 256 × 256 matrix size; and a scan reduction of 8% (ie, 85% of the data points acquired). Corresponding DWI scans were performed with a fat-suppressed (spectral presaturation with inversion recovery), multishot, spin echo and echo planar imaging sequence with repetition and echo times of 5393 and 87 ms, respectively; a section thickness of 4 mm; no intersection gap; a 230 × 230-mm field of view; 1 average; a 256 × 256 matrix; a scan reduction of 75%; and 8 b-values: 0, 240, 480, 720, 960, 1200, 1400, and 1680 s/mm². Apparent diffusion coefficient (ADC) maps of the trace of the diffusion tensor were calculated on the basis of the DWIs that were acquired at each b-value over the 3 principal axes (trace $ADC = \sqrt[3]{xyz}$), thus eliminating diffusion anisotropy effects. On the FLAIR images, tubers were segmented with the use of a previously published protocol. These FLAIR segmentations were registered manually on the matching slices of the trace DWI and ADC maps. The ADC measurements were performed in the epileptogenic and nonepileptogenic tubers and in the normal-appearing cortex on FLAIR images. Differences in ADC between the normal-appearing cortex, the nonepileptogenic tubers, and the epileptogenic tubers were calculated with analysis of variance and Scheffé post hoc tests. The ADC values are expressed as mean, SD, and range.

Patient Characteristics

<table>
<thead>
<tr>
<th>Patient/Age at Onset of Seizures, mo</th>
<th>Time Since Seizure Onset, mo</th>
<th>Type of Seizures</th>
<th>IQ</th>
<th>EEG Focus</th>
<th>Tuber Load*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/22</td>
<td>4</td>
<td>CPS</td>
<td>67</td>
<td>L central</td>
<td>28: 22.4</td>
</tr>
<tr>
<td>2/24</td>
<td>5</td>
<td>CPS</td>
<td>79</td>
<td>R posterotemporal</td>
<td>18: 9.4</td>
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<tr>
<td>3/22</td>
<td>10</td>
<td>SPS, GTCS</td>
<td>78</td>
<td>R frontal</td>
<td>26: 12.2</td>
</tr>
<tr>
<td>4/55</td>
<td>1</td>
<td>SPS, GTCS</td>
<td>&lt;48</td>
<td>R central</td>
<td>13: 6.25</td>
</tr>
</tbody>
</table>

Abbreviations: CPS, complex partial seizures; EEG, electroencephalography; GTCS, generalized tonic-clonic seizures; L, left; R, right; SPS, simple partial seizures.
*Given as total number of tubers and total volume per patient (in cubic centimeters).

The patient characteristics are given in the Table. Seizure semiology corresponded well with the zone of interictal epileptiform activity (eg, spikes). After integration of HR EEG and HR MEG with FLAIR MRI, a single epileptogenic tuber was identified in each of the 4 patients (Figure 1). The FLAIR images, DWIs, and the ADC maps showed multiple tubers (Figure 2 and Figure 3). On the trace DWIs and ADC maps, tubers were characterized by decreased and increased signal intensity, respectively, compared with the surrounding normal-appearing white and gray matter. Although the delineation of tubers on DWIs and ADC maps was in close agreement with that on FLAIR images, small tubers (diameter <3 mm) could not be detected with DWI.

The trace ADC, calculated from 18 nonepileptogenic tubers in these patients, was significantly higher (mean, 926 mm²/s; SD, 69.4 mm²/s; range, 828-1037 mm²/s) than the trace ADC of 16 regions of normal-appearing cortex (mean, 784 mm²/s; SD, 61.7 mm²/s; range, 689-897 mm²/s) (P < .001).

The trace ADC of the 4 epileptogenic tubers was significantly higher (mean, 1099 mm²/s; SD, 35 mm²/s; range, 1049-1141 mm²/s) than that of the 18 nonepileptogenic tubers (P < .001) (Figure 4). Furthermore, when we used each patient as his or her own control, the trace ADC of the epileptogenic tuber was outside the range of the ADC of all other nonepileptogenic tubers with approximately the same size in the same patient. The higher ADC measurement in epileptogenic tubers, compared with that of nonepileptogenic tubers, was not always evident on visual inspection.

Comment

The most important finding of this study is that DWI may be of additional diagnostic value in the detection of epileptogenic tubers in patients with TSC and epilepsy.

Diffusion-weighted MRI is increasingly acknowledged to be a powerful noninvasive technique that enables the evaluation of pathophysiological changes in experimental and clinical epilepsy, as well as the identification of epileptogenic zones in patients with partial seizures. Ictal DWI studies have shown a reduction of tissue-water ADC, most likely as a result of
exitotoxicity-related cell swelling and changes in the intracellular tortuosity, whereas interictal DWI has revealed increases in diffusivity. Recent DWI studies have detected regional decreases in diffusion anisotropy and increases in diffusivity in patients with partial epilepsies that were cryptogenic, acquired, or associated with malformations of cortical development, reflecting microstructural and architectural tissue changes.

In the present study, tubers were detected by means of DWI. Trace ADC values of tubers were significantly higher than those of the surrounding normal-appearing cortex. Similar findings have been reported recently. An increase in diffusivity of tissue water may reflect an increased extracellular space, the loss of structural organization, and poor myelination. This is in close agreement with the histopathological findings in tuberous sclerosis. Tubers are characterized by a disruption of the...
normal cortical lamination and by abnormal cell differentiation.\textsuperscript{16} In addition, the density of myelinated fibers and the number of normal neurons are reduced.\textsuperscript{17}

Tubers and other cortical malformations are generally detected with FLAIR MRI. However, conventional MRI techniques do not distinguish between epileptogenic and nonepileptogenic lesions. Simultaneous HR EEG and HR MEG enables identification of the epileptogenic zone, but not all patients fulfill the criteria of MEG paradigms. In our 4 patients with multiple tubers, in whom a single epileptogenic tuber was identified with a combination of HR MRI, HR EEG, and HR MEG, a significant increase in ADC was found in the epileptogenic tuber compared with the nonepileptogenic tubers. One may speculate that in the epileptogenic tubers the number of neurons is even less and myelination is poorer. Another explanation may be that the seizures have caused more neuronal loss and/or an increase in size of the extracellular water compartment as a result of edema, contributing to the increase of ADC.

In conclusion, this is the first study, to our knowledge, that demonstrates the potential of DWI to detect epileptogenic tubers in patients with TSC. Identification of the epileptogenic tuber with the single and widely available technique of DWI offers many advantages compared with identification with a combination of FLAIR MRI, HR EEG, and HR MEG. If the present findings can be reproduced in a larger number of patients with TSC and intractable epilepsy, DWI may become an important tool for the identification of the epileptogenic lesion. This would greatly facilitate the selection of candidates for epilepsy surgery in this patient group.

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REFERENCES