*Original Article*

# Proton Spectroscopic Findings in Children With Epilepsy Owing to Tuberous Sclerosis Complex

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## ABSTRACT

Tuberous sclerosis complex is an autosomal dominant disorder that often causes refractory seizures. The presence of multiple lesions makes it difficult to identify a single lesion responsible for the epilepsy. Our purpose is to assess the single-voxel proton spectroscopic findings of the tubers in 11 children with tuberous sclerosis complex. Prior to age 4 years, all of the patients had presented with epileptic seizures and multiple bilateral tubers in magnetic resonance images. Single-voxel proton spectroscopy was performed from the tubers especially showing epileptogenic activity using both the long and short echo time and in 14 controls. The results were analyzed using the Mann-Whitney *U*-test. Compared with the control group, the spectroscopic findings of tubers were characterized by decreased *N*-acetylaspartate to creatine ratios (1.43 ± 0.33; $P < .001$) in both the long and short echo time spectra, increased choline to creatine ratios (0.91 ± 0.082; $P < .05$), and *myo*-inositol to creatine ratios (0.97 ± 0.19; $P < .01$) in the short echo time spectra. A lactate peak was detected in the regions corresponding to an epileptic focus on electroencephalography in six patients. Single-voxel proton spectroscopy could be a useful noninvasive method to evaluate epileptogenic tubers. (*J Child Neurol* 2005;20:517–522).


Tuberous sclerosis complex is an autosomal dominant disorder characterized by lesions of the brain, skin, heart, kidneys, and other organs.[1] Two genes cause tuberous sclerosis complex (tuberous sclerosis complex 1 on chromosome 9q34 and tuberous sclerosis complex 2 on chromosome 16p13).[2,3] Several different types of brain lesions result from tuberous sclerosis complex, including cortical tubers, subependymal nodules, giant cell astrocytomas, and focal cortical dysplasias. The individuals who have more cerebral cortical lesions are more likely to develop both severe epilepsy and severe intellectual dysfunction.[4–6] The functional characteristics of the lesions that might be responsible for the epilepsy in tuberous sclerosis complex are not well established.

Single-voxel proton spectroscopy is a novel and noninvasive method to evaluate selected biochemical characteristics of living tissues. It has been used as a sensitive method to evaluate the abnormal function of the structural lesions, especially in epileptic patients.[7,8] Although a few adults with tuberous sclerosis complex have been studied with proton spectroscopy, the technique has not been evaluated in children with tuberous sclerosis complex, especially in those suffering from refractory epilepsy.[9] The purpose of this study is to define the single-voxel proton spectroscopy characteristics and to assess their relationship to electroencephalographic (EEG) findings of the cerebral cortical tubers in children with tuberous sclerosis complex.

## METHODS

We studied 11 children who met the revised clinical diagnostic criteria for tuberous sclerosis complex.[1] The study was approved by the Committee for Human Research of the University of Istanbul, Istanbul Faculty of Medicine, and in each case, a parent or guardian consented to participate in the study. Each child underwent a complete physical and neurologic examination, as well as a psychometric test. The age at seizure onset, seizure types, and the outcome of epilepsy (favorable or unfavorable, defined by whether the child had seizures more than twice per month despite the use of appropriate antiepileptic medications) were recorded for each patient. Scalp EEG was performed on three or more occasions in all of the 11 patients, usually during an interictal period (11 cases) and/or during an ictal period (7 cases). If a consistent epileptic focus was identified, the voxel placement was structured to include this area, and single-voxel proton spectroscopy was performed from tubers without epileptic discharges.

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This work was approved by the Ethics Commitee of Istanbul University, Istanbul Faculty of Medicine (650/08102003).

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**Table 1. Summary of Clinical and MRI/CT Findings**

| *Patient* | *Sex/ Age (yr:mo)* | *Seizure Type (Seizure Onset, yr:mo)* | *Response to Medication* | *Mental Retardation* | *Number of Tubers With Cerebellar Involvement** |
|---|---|---|---|---|---|
| 1 | M/16:0 | Focal motor (2:2); status epilepticus (3:0); GC (5:0); myoclonic (7:0) | Refractory | Severe | Multiple (30↑)* |
| 2 | F/8:0 | IS (flexor) (0:4); tonic (2:0); CPS (3:0); myoclonic/atonic (5:0); GC (7:0) | Refractory | Severe | Multiple (30↑)* |
| 3 | F/3:2 | GC (0:9); IS (flexor) (1:0) | Good | Mild/moderate | Multiple (26) |
| 4 | F/10:0 | IS (extensor) (0:8); GC (9:0); CPS (10:0) | Refractory | Severe | Multiple (30↑) |
| 5 | M/3:1 | IS (flexor) (0:6); focal motor (2:0) | Good | Mild | Multiple (11) |
| 6 | F/11:0 | CPS (4:0); GC (6:0); drop attacks (6:0) | Refractory | Severe | Multiple (30↑) |
| 7 | M/7:6 | CPS (3:6); GC (5:2) | Good | Mild | Multiple (8) |
| 8 | F/11:0 | IS (extensor) (0:3); GC (7:0) | Good | Mild/moderate | Multiple (17)* |
| 9 | M/14:5 | Focal motor (0:7); GC (2:0); secondary GC (2:0); CPS-frontal (5:0) | Refractory | Mild | Multiple (10) |
| 10 | F/16:7 | GC (0:6); status epilepticus (11:0); focal motor (14:0); secondary GC (14:0) | Good/ moderate | Severe/ moderate | Multiple (30)* |
| 11 | F/8:6 | IS (mixed (0:7); GC (4:0); CPS (8:0) | Refractory | Severe | Multiple (30↑)* |

CPS = complex partial seizures; CT = computed tomographic; GC = generalized convulsion; IS = infantile spasms; MRI = magnetic resonance imaging. *Cerebellar lesions.

Each child underwent magnetic resonance imaging (MRI) with a 1.5 Tesla scanner using a spin-echo or fast spin-echo technique with a standard head coil and a slice thickness of 5 mm. The location and number of cortical tubers, cerebellar involvement as a marker of wide distribution of lesions, and other findings were assessed. The children also underwent single-voxel proton spectroscopy using *PROBE/SV* software (GE, Milwaukee, WI), which permitted automated shimming, water suppression, and data processing. $T_2$-weighted axial or fluid-attenuated inversion recovery images were used to properly locate the voxel in the selected hamartomas. The average voxel size was approximately $2 \times 2 \times 2$ cm$^3$. Long echo time spectra were obtained from all of the 11 patients. In addition, short echo time spectra of six patients were recorded using point-resolved spectroscopy (repetition time 2000 milliseconds, echo time 144 or 30 milliseconds, 96 or 64 acquisitions, respectively). Both the long and short echo time spectra were performed in the same locations with equal voxel size; at least two different cortical lesions were studied in each individual, emphasizing lesions that corresponded to prominent interictal epileptic discharges on EEG. After immediate automatic processing of the raw data, spectra from the below peaks were evaluated semiquantitatively by peak area measurement: *N*-acetylaspartate, choline, *myo*-inositol, and creatine.

**Table 2. Single-Voxel Proton Spectroscopic Findings and Presence of Epileptic EEG Foci**

| | | *Long Echo Time* | | *Short Echo Time* | | | | |
|---|---|---|---|---|---|---|---|---|
| *Patient* | *Tuber Region* | *NAA/Cr* | *Cho/Cr* | *NAA/Cr* | *Cho/Cr* | *ml/Cr* | *Lactate Peak* | *Epileptic Foci* |
| 1 | rF | 0.82 | 1.21 | 0.65 | 0.97 | 1.33 | + | + |
| | lP | 1.06 | 0.77 | – | – | – | – | + |
| 2 | rO | 1.54 | 1.29 | – | – | – | + | + |
| | lT | 1.77 | 1.39 | – | – | – | – | – |
| 3 | lF | 1.11 | 1.28 | – | – | – | + | – |
| | lpmF | 1.44 | 1.2 | – | – | – | – | – |
| | rF | 1.39 | 1.29 | – | – | – | – | – |
| 4 | rOP | 1.21 | 1.09 | – | – | – | – | – |
| | rO | 1.88 | 1.12 | – | – | – | – | – |
| | rF | 0.91 | 1.17 | – | – | – | + | – |
| | lOP | 1.68 | 1.04 | – | – | – | – | + |
| | lO | 1.35 | 1.06 | – | – | – | + | + |
| 5 | lOT | 1.3 | 2 | – | – | – | – | + |
| | rT | 1.71 | 1.61 | – | – | – | + | + |
| | lF | 1.78 | 1.35 | – | – | – | – | – |
| 6 | rF | 0.93 | 1.2 | 0.88 | 0.86 | 1.19 | – | – |
| | lT | 0.99 | 1.07 | 0.81 | 0.84 | 0.97 | – | + |
| | lF | 1.33 | 1.06 | – | – | – | – | – |
| 7 | lF | 1.84 | 1.09 | 1.35 | 0.72 | 0.8 | + | + |
| | rOP | 1.55 | 1.12 | 0.81 | 0.99 | – | + | + |
| 8 | lO | 2.27 | 1.09 | 1.48 | 0.77 | 0.7 | – | – |
| | rF | 1.24 | 1.05 | 1.08 | 0.85 | 0.95 | – | + |
| 9 | riF | – | – | 1.68 | 1.07 | 0.94 | – | + |
| | rmF | 2.29 | 1.32 | 1.63 | 1.04 | 0.77 | – | + |
| | lmF | 1.69 | 1.43 | 1.26 | 1.01 | 0.79 | – | – |
| 10 | rF | 1.48 | 1.28 | 1.18 | 0.88 | 0.74 | + | – |
| | lmT | 1.19 | 1.27 | 1.13 | 1.05 | 1.09 | – | – |
| 11 | rF | 0.97 | 1.15 | 0.91 | 0.88 | 1.06 | + | – |
| | lT | 0.97 | 1.08 | – | – | – | + | + |
| | rT | 1.2 | 1.11 | – | – | – | – | + |

Cho = choline; Cr = creatine; EEG = electroencephalographic; F = frontal; i = inferior; l = left; m = middle; ml = *myo*-inositol; NAA = *N*-acetylaspartate; O = occipital; P = parietal; p = posterior; r = right; T = temporal.

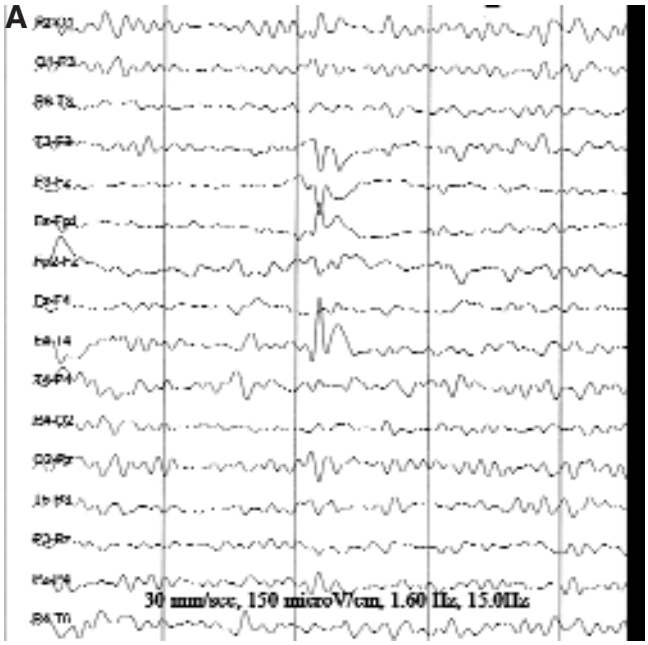


Figure 1. *A,* Epileptic focus in the right frontal area (patient 1). *B,* Axial $T_2$-weighted magnetic resonance image shows the voxel localization for single-voxel proton spectroscopy over a tuber in the right frontal lobe of patient 1. *C,* Long echo time single-voxel proton spectroscopy of patient 1 showing a marked reduction in *N*-acetylaspartate peak (*thin arrow*), an increased choline peak (*thick arrow*), and lactate peak (*punctual arrow*).

The control group included 14 healthy volunteers within the same age range and was evaluated by means of the same single-voxel proton spectroscopy protocol. Ratios of metabolites relative to creatine (*N*-acetylaspartate to creatine, choline to creatine, *myo*-inositol to creatine) were compared with values obtained from the control group, and abnormal peaks were detected. The Mann-Whitney *U*-test was used for the statistical evaluation of the single-voxel proton spectroscopic data.

## RESULTS

Our group of patients consisted of seven girls and four boys (Table 1), whose current ages ranged from 3.1 to 16.7 years (9.93 ± 4.55 years). The follow-up period ranged from 2 months to 7 years (3.18 ± 2.086). In the control group, there were 14 children (5 girls, 9 boys), and their mean age was 10.75 ± 5.50. All of the patients presented with epileptic seizures and were diagnosed before 4 years of age. Ten patients had generalized convulsions, six had infantile spasms, six had complex partial seizures, four had focal motor seizures, and three had myoclonic seizures and/or atonic attacks. In eight individuals (72.7%), the first seizure was noted before 1 year of age. More than two seizure types were identified in seven individuals (63.6%). In six (85.7%) of these seven children, seizures were refractory in nature. Mental retardation was severe in six (54.5%) and mild/moderate in five (45.5%).

Brain MRI revealed multiple bilateral tubers and subependymal nodules in all of the 11 children, subcortical linear heterotopias in 6 children, and a giant cell astrocytoma in 2 children. There were multiple tubers in all of the six children with severe mental retardation. Four of these patients with this condition had cerebellar involvement (66.6%) as well. More than 30 tubers were detected in five of the six children suffering from refractory epilepsy (83.3%). Three of the six children with this condition also had cerebellar involvement. Mild/moderate cortical atrophy was identified in three children. Nine of the 11 children had focal epileptiform activity on EEG (Table 2).

Thirty different voxels were analyzed in our group of patients. In six patients, lactate peaks were recorded from lesions corresponding to an EEG focus in 7 of the 15 regions. Four of these six patients with a lactate peak in the epileptic foci in the spectroscopy had both refractory seizures and severe mental retardation (see Tables 1 and 2 and Figure 1). Four patients (1, 2, 4, and 11) with lactate peaks had a seizure within 2 days prior to spectroscopy. Lactate peaks were also identified in four different tubers from different individuals whose EEG did not reveal focal epileptic activity (see Table 2). But lactate peaks were detected more in the epileptogenic

**Table 3. Spectroscopic Findings of the Control Group**

| | | | | *Long Echo Time* | | *Short Echo Time* | | |
|---|---|---|---|---|---|---|---|---|
| *Control* | *Region* | *Age (yr)* | *Sex* | *NAA/Cr* | *Cho/Cr* | *NAA/Cr* | *Cho/Cr* | *ml/Cr* |
| 1 | rF | 8.2 | M | 2.02 | 1.11 | – | – | – |
| 2 | rF | 6.3 | F | 2.67 | 1.20 | – | – | – |
| 3 | parafalxF | 14.0 | M | 1.83 | 1.15 | – | – | – |
| 4 | postInsula | 4.6 | F | 1.72 | 1.06 | – | – | – |
| 5 | lF | 18.0 | M | 2.01 | 1.09 | – | – | – |
| 6 | rF | 15.0 | F | 2.23 | 0.99 | – | – | – |
| 7 | lF | 11.0 | M | 2.09 | 1.21 | – | – | – |
| 8 | lT | 3.6 | M | 1.90 | 1.13 | – | – | – |
| 9 | lF | 2.4 | F | 2.07 | 1.34 | – | – | – |
| 10 | parafalxF | 7.1 | M | 1.94 | 1.03 | – | – | – |
| 11 | lF | 12.0 | M | – | – | 1.81 | 0.82 | 0.65 |
| 12 | LF | 12.1 | M | – | – | 1.74 | 0.82 | 0.60 |
| 13 | RF | 17.0 | M | – | – | 1.77 | 0.71 | 0.64 |
| 14 | RF | 19.2 | F | – | – | 1.62 | 0.78 | 0.58 |

Cho = choline; Cr = creatine; F = frontal; l = left; ml = *myo*-inositol; NAA = *N*-acetylaspartate; r = right;T = temporal.

foci (46.7%) than in the nonepileptic tubers (26.7%). Single-voxel proton spectroscopic findings of the tubers showed significantly decreased *N*-acetylaspartate to creatine ratios (1.43 ± 0.33) in both the long and short echo time spectra of the experimental group compared with those of the controls (2.04 ± 0.26; $P < .001$). Moreover, single-voxel proton spectroscopic findings showed significantly increased choline to creatine (0.91 ± 0.082) and *myo*-inositol to creatine ratios (0.97 ± 0.19) in the short echo time spectra of the experimental group compared with those of the controls, in whom the values were 0.78 ± 0.05 ($P < .05$) and 0.61 ± 0.03 ($P < .01$), respectively (see Tables 2 and 3).

## DISCUSSION

The neurologic manifestations of tuberous sclerosis complex vary widely but often include mental deficiency, epilepsy, and behavioral disorders.[10] Frequent seizures can contribute to poor neurologic outcome in tuberous sclerosis complex, and MRI data suggest that individuals with more cerebral lesions have a greater likelihood of severe cognitive impairment and intractable epilepsy.[4–6,11]

Proton spectroscopy provides a noninvasive method to investigate the neurochemistry of the brain.[7,12] The technique has been used to study leukodystrophies, developmental malformations, tumors, and other diseases, such as mitochondrial and epileptic disorders.[8,13–16] Phosphocholine, *N*-acetylaspartate, creatine, *myo*-inositol, and lactate concentration can be measured with single-voxel proton spectroscopy. A reduced *N*-acetylaspartate ratio can indicate loss or dysfunction of neurons in lesions such as tumors or infarction, whereas the choline signal tends to be increased in tumors and demyelinating lesions as a marker of membrane turnover. Because creatine is distributed homogeneously and is relatively resistant to change, it can be used as a standard value to compare with the other metabolites. Lactic acid is the end product of glycolysis. A lactate peak can occur in settings with anaerobic metabolism, such as mitochondrial dysfunction, or in tumors, acute ischemia, or the chronic lesions producing refractory seizures.[15] Najm et al suggested that proton spectroscopy can be used to identify specific in situ metabolic markers for seizures and seizure-induced neuronal damage in rat brains.[17] The authors found a significant increase in lactate ratios in rats during and 24 hours after seizure onset. Elevated brain lactate and reduced *N*-acetylaspartate associated with a seizure disorder in humans were first reported by Mathews et al in two patients with Rasmussen's encephalitis.[16] Our findings indicate that lactate peaks can also be detected in patients with tuberous sclerosis complex.

The few previous studies of proton spectroscopy in tuberous sclerosis complex have investigated adults.[9,14] There has been no previous attempt to compare single-voxel proton spectroscopy and EEG from specific cerebral tuberous sclerosis complex lesions in children in such a large number, and our results suggest a pattern of low *N*-acetylaspartate to creatine, high choline to creatine, and *myo*-inositol to creatine ratios in tubers (see Figures 1C and 2B). We detected lactate peaks in one or more brain lesions in 8 of the 11 individuals studied with single-voxel proton spectroscopy, and the area with the lactate peak corresponded to an epileptic focus on EEG in 6 of these 8 individuals (see Table 2 and Figure 1). Four of the six individuals with both abnormal peaks and focal epileptic foci had multiple seizure types, poor seizure control, and severe mental retardation (66.6%). In other words, decreased *N*-acetylaspartate to creatine and increased choline to creatine ratios with a lactate peak in single-voxel proton spectroscopy were more likely in individuals with severe neurologic dysfunction. Four of the six patients who showed lactate peaks had seizures within 2 days before or on the same day of the spectroscopy, but lactate peaks were also detected in four tubers not associated with an epileptic focus, as well as in two individuals (patients 3 and 10) with good seizure control and no interictal spiking on EEG. So, although a lactate peak is not a specific marker of an epileptic generator, abnormal single-voxel proton spectroscopy ratios might reflect dysfunctional neurotransmitters and the changes related to refractory seizures.

The *N*-acetylaspartate to creatine ratio was reduced within a cortical tuber in one adult patient,[14] and another report of 26 adults with tuberous sclerosis complex found a lower *N*-acetylaspartate to creatine ratio but no alteration in the choline to creatine ratio or lactate peak in cortical tubers relative to the contralateral normal brain.[9] Mizuno et al suggested that decreased *N*-acetylaspartate to creatine ratios in the tubers of four children resulted from a reduction in neurons and increased *myo*-inositol to creatine ratios from glial cell proliferation.[18] Children with tuberous sclerosis complex have not been studied, and anecdotal case studies with proton spectroscopy were performed using either long echo time or short

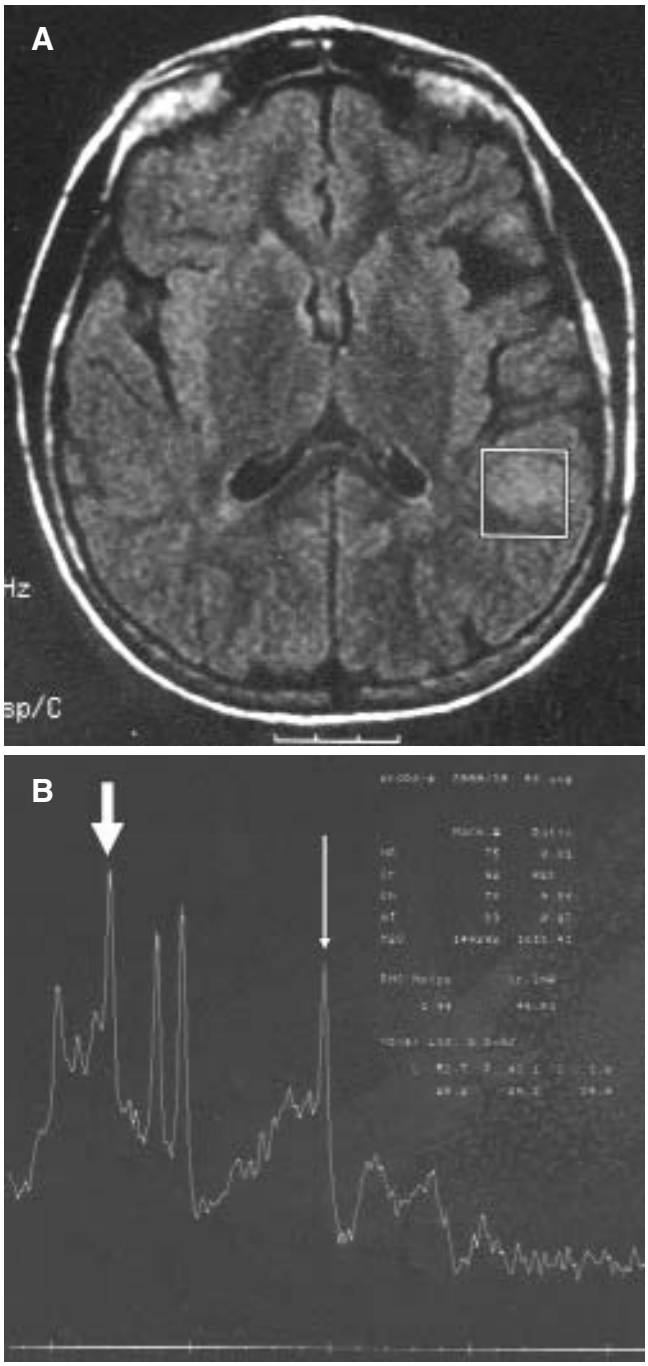


Figure 2. *A,* Axial fluid-attenuated inversion recovery image sequence showing the voxel localization in the left temporal lobe (patient 6). *B,* Short echo time single-voxel proton spectroscopy of patient 6 showing decreased *N*-acetylaspartate (*thin arrow*) and increased *myo*-inositol (*thick arrow*).

echo time spectra.[9,18] With the use of both the long and short echo time sequences, we confirmed not only the increase in *myo*-inositol (Figure 2, A and B) but also the presence of lactate (see Figure 1, B and C).

Kuzniecky and colleagues related EEG abnormalities to the *N*-acetylaspartate to creatine ratio,[8] but Li et al failed to detect a correlation between the seizure severity and *N*-acetylaspartate signal intensity in patients with cortical developmental malformations.[14] Some studies suggest that proton spectroscopy is useful for noninvasive localization of epileptogenic foci in individuals with partial epilepsy.[16,19–21] Surgical resection of one or two cerebral lesions can be effective in patients with tuberous sclerosis complex with intractable epilepsy provided that the responsible lesions can be pinpointed.[22,23] Individuals with medically refractory epilepsy owing to tuberous sclerosis complex typically have numerous cerebral cortical lesions, and the ability to identify the lesions responsible for the seizures could greatly enhance the feasibility of epilepsy surgery in these individuals. The difficulties in obtaining single-voxel spectroscopy on a poorly defined lesion such as a tuber are known. Although our results are encouraging, additional studies will be required to determine if single-voxel proton spectroscopy could help identify the lesions responsible for generating seizures in patients with tuberous sclerosis complex.

In conclusion, single-voxel proton spectroscopy can provide additional information about brain abnormalities detected by MRI in children with tuberous sclerosis complex. Although additional studies with more patients need to be completed, single-voxel proton spectroscopy could improve our ability to identify the tuberous sclerosis complex lesions responsible for epileptic seizures in some of these individuals and thus improve our ability to identify those whose epilepsy might benefit from surgery.

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