Pulsed Arterial Spin-Labeled MR Imaging Evaluation of Tuberous Sclerosis


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BACKGROUND AND PURPOSE: Tuberous sclerosis presents with characteristic cortical hamartomas and subependymal nodules associated with seizures. The purpose of this study was to use pulsed arterial spin-labeling (PASL) to quantify the perfusion of the cortical hamartomas and correlate the perfusion values with seizure frequency.

MATERIALS AND METHODS: A retrospective search yielded 16 MR imaging examinations including conventional MR imaging and PASL perfusion performed in 13 patients (age range, 7 months to 23 years) with a history of tuberous sclerosis. The mean perfusion of each cortical hamartoma greater than 5 mm in size localized with conventional MR imaging sequences was obtained with use of manually drawn regions of interest. Cortical hamartomas were classified as normal, hyperperfused, or hypoperfused on the basis of the mean and SD of the unaffected cortex. Correlation was made between perfusion imaging, conventional imaging, and clinical history.

RESULTS: Of the 245 cortical hamartomas, 227 (92.7%) were hypoperfused, 10 (4.1%) were hyperperfused, and 8 (3.3%) were unchanged relative to the mean gray matter. One patient had a subependymal giant cell astrocytoma with a mean perfusion of 93.5 mL/100 g tissue/min. There was a statistically significant positive correlation between seizure frequency and the number of hyperperfused cortical tubers ($r = 0.51; n = 16; P = .04$), with higher seizure frequency associated with a greater number of hyperperfused cortical tubers. There was no significant correlation, however, between seizure frequency and the overall number of cortical tubers ($r = 0.20; n = 16; P = .47$).

CONCLUSIONS: The PASL technique can assess and quantify the perfusion characteristics of a cortical hamartoma. Most lesions are hypoperfused; however, both normally perfused and hyperperfused lesions occur. The presence of hyperperfused cortical tubers was associated with increased seizure frequency.

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Cortical hamartoma perfusion imaging findings in a series of 13 patients evaluated with pulsed arterial spin-labeling

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (yr)</th>
<th>Seizures per Week</th>
<th>Seizure Frequency</th>
<th>No. Cortical Hamartomas &gt;1 cm</th>
<th>No. Hyperperfused Hamartomas</th>
<th>No. Hypoperfused Hamartomas</th>
<th>No. Normally Perfused Hamartomas</th>
<th>Mean Normal GM Perfusion (mL/100 g/min)</th>
<th>Mean Hyperperfused Lesions (mL/100 g/min)</th>
<th>Mean Hypoperfused Lesions (mL/100 g/min)</th>
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<tr>
<td>1a</td>
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<td>0</td>
<td>None</td>
<td>12</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>63.8</td>
<td>26.5</td>
<td>26.3</td>
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<td>1b</td>
<td>12</td>
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<td>None</td>
<td>12</td>
<td>0</td>
<td>11</td>
<td>1</td>
<td>67.9</td>
<td>26.3</td>
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<td>2a</td>
<td>7</td>
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<td>10</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>116.6</td>
<td>63.9</td>
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<tr>
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<td>0</td>
<td>6</td>
<td>3</td>
<td>123.0</td>
<td>79.8</td>
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<tr>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1 per week</td>
<td>21</td>
<td>0</td>
<td>21</td>
<td>0</td>
<td>173.6</td>
<td>104.6</td>
<td>104.6</td>
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<tr>
<td>4a</td>
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<td>2 per week, left facial twitch</td>
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<td>3</td>
<td>5</td>
<td>1</td>
<td>108.1</td>
<td>155.1</td>
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<td>3</td>
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<td>112.4</td>
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<td>35.3</td>
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<tr>
<td>5</td>
<td>23</td>
<td>4</td>
<td>4 per week, EEG left temporal</td>
<td>23</td>
<td>1</td>
<td>21</td>
<td>1</td>
<td>52.8</td>
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<td>3</td>
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<td>3–4 per week</td>
<td>18</td>
<td>1</td>
<td>17</td>
<td>0</td>
<td>163.2</td>
<td>186.7</td>
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<td>1</td>
<td>21</td>
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<td>18</td>
<td>1</td>
<td>99.6</td>
<td>38.9</td>
<td>38.9</td>
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<tr>
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<td>None last 3 months</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>84.6</td>
<td>22.8</td>
<td>22.8</td>
</tr>
<tr>
<td>12</td>
<td>11</td>
<td>2</td>
<td>1–2 per week</td>
<td>24</td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>60.0</td>
<td>23.8</td>
<td>23.8</td>
</tr>
</tbody>
</table>

Note:—Pt indicates patient; EEG, electroencephalogram; GM, gray matter.

Fig 1. Summary of hamartoma perfusion data for each patient. The average of the hyperperfused lesions is shown in green. The average of the hypoperfused lesions is shown in blue. The mean unaffected gray matter perfusion is shown in red.

with cortical hamartoma perfusion values. Seizure frequency, age, hamartoma burden, average gray matter perfusion, and average hamartoma perfusion values are listed in the accompanying Table. Thirteen patients (mean age, 6.8 years; age range, 7 months to 23 years) were identified with a history of tuberous sclerosis. The mean perfusion values of each patient are summarized in Fig 1. Eight patients had no seizures within the last 3 months. Five patients had 1 to 4 seizures per week.

We generated quantitative CBF maps by using a quantitative imaging of perfusion using a single subtraction with thin-section TI periodic saturation (Q2TIPS) flow-sensitive alternating inversion recovery sequence. This sequence generates 60 tag and control image
pairs. Motion correction is applied, and the control and tagged image pairs are then subtracted to generate relative perfusion signal intensity maps. The perfusion maps are segmented according to the anatomic T1-weighted image and then are scaled by the mean signal intensity (M0) of blood. The segmentation and scaling step allows for voxel-wise computation of absolute CBF maps. The perfusion maps are colorized with a standard scale, and the JPEG of the resulting image series is sent to the PACS.

We localized cortical hamartomas using the conventional T1- and T2-weighted sequences. We cross-referenced the gray-scale PASL images to the conventional sequences to draw regions of interest on the PASL sequence corresponding to the cortical signal intensity abnormality. Mean CBF of the region of interest was recorded. As an internal control, the mean and SD of 20 regions of interest of unaffected gray matter (no cortical or adjacent white matter signal intensity abnormality) in the same patient were recorded. Hyperperfused and hypoperfused lesions were defined as perfusion measurements respectively above and below 1 SD from the mean. Normal perfusion was defined as within 1 SD of the mean. Region-of-interest analysis of 1 patient with subependymal giant cell astrocytomas (SEGAs) was also included but was reported separately from the cortical tubers.

**Statistical Analysis**

The Pearson correlation coefficient was used to investigate the relationship between seizure frequency and total number of cortical tubers, as well as number of normoperfused, hyperperfused, and hypoperfused cortical tubers. The Pearson correlation coefficient was also used to investigate the relationship between the overall number of cortical tubers and the number of normoperfused, hyperperfused, and hypoperfused cortical tubers. We performed all statistical analyses by using the Statistical Package for the Social Sciences 16.0 (SPSS, Chicago, Ill).

**Results**

We identified 245 cortical hamartomas greater than 5 mm in size in 13 patients: 227 (92.7%) were hypoperfused (Fig 2), 10 (4.1%) were hyperperfused (Fig 3), and 8 (3.3%) were unchanged relative to the mean gray matter. The mean CBF of the hypoperfused hamartomas was 46.9 mL/100 g tissue/min.
Tuberous sclerosis complex (TSC) is an autosomal-dominant disorder with a high spontaneous mutation rate. TSC1 or TSC2 gene mutations, which generate the proteins hamartin and tuberin, result in the clinical manifestations of the disorder. The tumor suppressor protein malfunction causes the variety of disease manifestations on the basis of the expression and distribution of the proteins. The more severe the tumor suppressor protein malfunction, the more severe the clinical manifestations. Cortical tuber burden has been correlated to seizure frequency and the number of hyperperfused cortical tubers with normal perfusion had normal blood volumes. Widjaja et al examined 59 tubers and may not have had enough patients to detect the small population of hyperperfused tubers. They also noted that several hamartomas had normal blood volumes. Presumably, lesions in our study were hypoperfused because of decreased blood volume, and those with normal perfusion had normal blood volumes. Widjaja et al examined 59 tubers and may not have had enough patients to detect the small population of hyperperfused tubers. We believe the hyperperfused tubers in our study would show increased blood volume, which may be an intrinsic property of the tuber or reflect epileptogenic activity.

Cortical hamartomas can have an indistinct transition from gray to white matter on histologic examination. The PASL sequence relies on gray and white matter segmentation to quantify perfusion values. If segmentation is inaccurate, erroneous perfusion values can be reported. The PASL sequence still showed that the lesions (arrow and arrowhead) were significantly hyperperfused relative to mean gray matter. A third lesion is partially seen on the contrasted image at the left foramen of Monroe.
pathologic changes that cannot be detected with current neuroimaging techniques.\textsuperscript{30} It is unknown whether the microscopic changes can significantly alter local cerebral perfusion. The internal control was selected because of the age-dependent variability in global pediatric cerebral perfusion.\textsuperscript{31,32}

Gliosis in the white matter adjacent to the hamartoma has been described previously.\textsuperscript{30} This gliotic white matter may be more characteristic of subependymal nodules.\textsuperscript{11} The patients in this series did not show calcifications or susceptibility artifacts in the selected cortical tubers.

Alternating bands of hyperperfusion and hypoperfusion (Fig 3) have also been seen with nuclear medicine SPECT studies.\textsuperscript{18,33} However, the hyperperfused lesions were identified during the ictal acquisition. The patients in our series did not have clinically apparent seizures during or preceding perfusion imaging. In 1 patient with hyperperfusion, the perfusion pattern was stable at 6-month follow-up. We are uncertain if the patient was having subclinical seizures or if the tubers had baseline hyperperfusion. Although the patient population in our study was small, those patients with hyperperfused cortical tubers did have a statistically significant positive correlation with clinical seizure frequency. However, only 3 of the 5 patients with frequent seizures had hyperperfused tubers, and, in a similar fashion, 3 of the 5 patients with hyperperfused tubers had seizures. This means that although there is a statistically significant association between hyperperfused tubers and seizures, a significant population of patients with seizures will not have hyperperfused tubers. In practical terms, the relationship between hyperperfusion and seizure frequency seems to be an association rather causal. We are uncertain if the identified hyperperfused tubers were the epileptogenic focus. Additional long-term studies with multimodality functional imaging and postsurgical correlation would be necessary to make this determination.

Various methods have been used to localize the epileptogenic cortical tuber in cases of focal intractable epilepsy. These include electroencephalography, PET imaging, ictal SPECT, and magnetoencephalography.\textsuperscript{13,15,18,33–40} Each isolated technique had variable success to correctly identify the problematic cortical tuber. However, the favored approach is to use multiple complementary imaging modalities to accurately and confidently localize the epileptogenic focus before surgical resection.\textsuperscript{13,15,18,33–35,37,39–42} When seizures can be localized to a single epileptogenic tuber, surgical resection has proved beneficial, with significant reductions in seizure frequency.\textsuperscript{15,18,33,35–38} Future studies with PASL could localize the epileptogenic tuber by establishing the baseline perfusion values of the cortical hamartomas and evaluating the perfusion change associated with the ictal or postictal state similar to nuclear medicine SPECT examinations.\textsuperscript{18,33}

Conclusions

The perfusion characteristics of cortical hamartomas have not been previously evaluated with PASL perfusion imaging. The stratification of lesions into high, low, and normal groups with use of unaffected gray matter as an internal control shows that most lesions are hyperperfused; however, a significant number of lesions are hyperperfused. The presence of hyperperfused cortical hamartomas is associated with an increased frequency of seizure activity. Future studies may incorporate PASL into the seizure algorithm by use of perfusion changes to complement multimodality localization of the epileptogenic hamartoma.

Acknowledgments

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