Magnetic Resonance Imaging Evidence of Hippocampal Sclerosis in Asymptomatic, First-Degree Relatives of Patients With Familial Mesial Temporal Lobe Epilepsy

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Objective: To investigate the presence of hippocampal atrophy (HA) and other magnetic resonance imaging (MRI) signs of hippocampal sclerosis (HS) in asymptomatic relatives of patients with familial mesial temporal lobe epilepsy (FMTLE).

Methods: We invited first-degree, asymptomatic relatives of patients with FMTLE to participate in our MRI protocol. After obtaining informed consent, all participating individuals underwent an MRI examination. Hippocampal abnormality was determined by qualitative and volumetric analyses, using a standard protocol.

Results: We studied 52 asymptomatic individuals (27 men), with a mean age of 32 years (range, 7-71 years), from 11 families with FMTLE. Volumetric studies showed HA in 18 (34%) of 52 individuals: 11 had left HA and 7 had bilateral HA. In addition, careful visual analysis of T1- and T2-weighted images showed additional classic MRI signs of HS (such as abnormal T2 signal and/or abnormal internal structure) in 14 of these 18 individuals. There was no age difference between individuals with and without HA (t test, P=.80).

Conclusions: Our findings indicate that MRI evidence of HS is not necessarily related to seizure severity and may occur in individuals who never had seizures. In addition, these observations strongly indicate that HS in FMTLE is not a consequence of recurrent seizures and is determined by a strong genetic predisposition. The determination of seizure severity in patients with FMTLE probably depends on the interaction of different factors, both genetic and environmental.

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Familial mesial temporal lobe epilepsy (FMTLE) is a well-characterized syndrome that occurs in a large proportion of affected individuals with magnetic resonance imaging (MRI) evidence of hippocampal sclerosis (HS), including quantitative analyses. The identification of clear-cut hippocampal atrophy (HA) and additional MRI signs of HS in patients with a benign clinical course in these families supports the theory that a genetic factor determines hippocampal pathologic abnormalities in FMTLE. In addition, the finding of subtle hippocampal malformation in asymptomatic relatives of patients who present with complex febrile seizures suggests that inherited dysgenetic abnormalities may lead to a predisposition to seizures in these families. The MRI findings for family members asymptomatic for FMTLE have not been previously reported. The investigation of mesial temporal abnormalities in high-resolution MRI in first-degree relatives of familial patients can be helpful for investigating if these families segregate MRI evidence of HS in individuals without clinical manifestation of the disease. The objective of this study was to investigate whether asymptomatic relatives of patients with FMTLE have MRI evidence of HS.

METHODS

Familial mesial temporal lobe epilepsy was defined as 2 or more family members diagnosed as having mesial temporal lobe epilepsy by clinical and electroencephalographic (EEG) criteria. The MRI findings of affected individuals with FMTLE were reported previously. We invited all asymptomatic, first-degree relatives of these affected individuals to participate in the present study and to undergo an MRI examination. All individuals signed a written consent form, approved by the ethics committee of our institution. All individuals ascertained for this study were questioned about history of febrile or afebrile seizures. Parents and older relatives were also interviewed to corroborate the clinical information.

The MRIs were performed in a 2T scanner (Prestige; Elscint Ltd, Haifa, Israel), with...
T1 and T2 acquisitions in 3 orthogonal planes. The MRI acquisition variables were as follows: (1) sagittal T1 spin echo; 6 mm thick; flip angle, 180°; repetition time (TR), 430; echo time (TE), 12; matrix, 200 × 350; and field of view (FOV), 25 × 25 cm; (2) coronal images, perpendicular to long axis of hippocampus, defined on the sagittal images: (a) T2-weighted and proton density fast spin echo; 3 mm thick; flip angle, 160°; TR, 4800; TE, 108/18; matrix, 256 × 256; FOV, 22 × 22 cm; (b) T1-weighted inversion recovery; 3 mm thick; flip angle, 200°; TR, 2800; TE, 14; inversion time, 940; matrix, 130 × 256; and FOV, 16 × 18 cm; (3) axial images parallel to the long axis of the hippocampi: (a) T1-weighted gradient echo; 3 mm thick; flip angle, 70°; TR, 200; TE, 5; matrix, 180 × 232; and FOV, 22 × 22 cm; (b) T2-weighted fast spin echo; 4 mm thick; flip angle, 120°; TR, 6800; TE, 129; matrix, 252 × 328; and FOV, 21 × 23 cm; and (4) T1-weighted 3-dimensional gradient echo with 1-mm isotropic voxel, acquired in the sagittal plane for multiplanar reconstruction (1 mm thick; flip angle, 35°; TR, 22; TE, 9; matrix, 256 × 220; and FOV, 23 × 25 cm).

Hippocampal formations and total intracranial volumes were manually delineated on coronal inversion recovery images using software developed by the National Institutes of Health (NIH-Image, National Institutes of Health, Bethesda, Md), and anatomic guidelines were obtained from a standard protocol. For determination of normal variables, hippocampal volumes were obtained in a group of 30 healthy volunteers (20 women; mean age, 32 years; range, 18-62 years). We calculated the absolute volumes for each hippocampus, corrected for variation of total brain volume to evaluate unilateral and bilateral volume loss. We also obtained an asymmetry index (AI) for each patient (defined as the ratio of the smaller by the larger hippocampus). Volumes and/or AIs that were 2 SDs below the mean values of control group were indicative of HA.

In addition to volumetric studies, we performed careful systematic visual analysis of all MRIs, including T1- and T2-weighted images, for identification of other MRI signs of HS in these individuals. Visual assessment of hippocampal integrity accounted for hippocampal signal, internal structure and shape of hippocampi, and other mesial temporal structures. Images were analyzed on a Silicon Graphics workstation (O2; Silicon Graphics Inc, Mountainview, Calif) with imaging postprocessing software (Omniprod2; Elscint Ltd) that allows changing windowing (contrast and brightness), realignment of images, and multiplanar reconstruction. We paid special attention to the format of hippocampi along its entire axis and the morphologic findings of the adjacent mesial temporal structures.

Hippocampal volumes and AIs from each subject were transformed into z scores (standardized scores that express the number of SDs away from the mean of the control group). The z scores below −2 (2 SDs below the mean of healthy controls) were indicative of HA. We used the 2-tailed t test to compare the distribution of ages at MRI scan between individuals with and without HA.

RESULTS

We evaluated 11 of 32 families with FMTLE, with a total of 52 subjects (27 men) (mean age, 32 years; range, 7-71 years; with no difference compared with the control group; analysis of variance; \( P = .80 \)). We found HA (Figure 1) in 18 (34%) of the 52 individuals: 11 unilateral (all left) and 7 bilateral (Table). There was no difference in age at MRI between individuals with and without HA (t test, \( P = .80 \)). In addition to HA, we found additional signs of HS in the visual analysis of MRIs in all but 3 individuals (Table). In-
creased T2 signal and/or loss of internal hippocampal structure was found in 14 of the 18 individuals with HA. Abnormal shape and axis of the hippocampal formation were present in 8 individuals (Figure 1). Additional abnormal anatomy of the mesial temporal structures, including enlargement of the fusiform or parahippocampal gyri and the collateral sulcus, was identified in 7 of the 18 individuals (Figure 2).

**COMMENT**

Both HS and HA have been associated with refractory seizures and good postoperative outcome in unilateral mesial temporal lobe epilepsy. The MRI evidence of HS includes HA and other abnormalities, such as abnormal signal intensity, loss of internal structure, and abnormal shape and orientation of hippocampal formation. Hippocampal atrophy is a reliable MRI indicator of HS and easy to quantify, thus allowing a more objective analysis. Furthermore, several studies reported a robust correlation between the degree of HA and histopathologic findings. The real frequency of HA in patients with good seizure control is not yet well established. However, in our series of patients with FMTLE, we observed HA by visual analyses in 57% of individuals studied, including patients with a single episode or seizure remission. In a subsequent multicentric study, we found HA by volumetric study in 77% of affected individuals with FMTLE. This indicates a strong genetic factor in the development of hippocampal pathologic findings in these patients with FMTLE.

The observation of HA by volumetric measurements in first-degree, asymptomatic relatives of patients with seizures in these families further corroborates our previous hypothesis and raises the question of the cause-and-effect relationship between HS and epilepsy. Our findings indicate that MRI evidence of HA is probably genetically determined in these families, and the occurrence and prognosis of seizures may depend on additional environmental factors and possibly modifying.

<table>
<thead>
<tr>
<th>Patient No./Relationship With MTLE Patient/</th>
<th>Age at Study, y</th>
<th>Side of HA</th>
<th>RHV ( z ) Score</th>
<th>LHV ( z ) Score</th>
<th>Al ( z ) Score</th>
<th>Increased T2 Signal</th>
<th>Loss of Internal Structure</th>
<th>Abnormal Shape and Axis</th>
</tr>
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<tbody>
<tr>
<td>1/Sister/36</td>
<td>36</td>
<td>Left</td>
<td>−1.3</td>
<td>−2.0</td>
<td>0.93 (−0.05)</td>
<td>Right</td>
<td>No</td>
<td>R:=L</td>
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<tr>
<td>2/Brother/33</td>
<td>33</td>
<td>Left</td>
<td>−0.5</td>
<td>−2.4</td>
<td>0.85 (−2.79)</td>
<td>Left</td>
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<td>No</td>
</tr>
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<td>3/Sister/43</td>
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<td>Left</td>
<td>1.8</td>
<td>−0.1</td>
<td>0.86 (−2.18)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4/Father/68</td>
<td>68</td>
<td>Bil</td>
<td>−2.0</td>
<td>−2.7</td>
<td>0.92 (−0.35)</td>
<td>Bil</td>
<td>Bil</td>
<td>Bil</td>
</tr>
<tr>
<td>5/Son/15</td>
<td>15</td>
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<td>−1.5</td>
<td>−2.2</td>
<td>0.93 (−0.12)</td>
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<td>Left</td>
</tr>
<tr>
<td>6/Sister/48</td>
<td>48</td>
<td>Bil</td>
<td>−2.9</td>
<td>−3.6</td>
<td>0.91 (−0.55)</td>
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<td>No</td>
<td>No</td>
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<tr>
<td>7/Sister/35</td>
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<td>−0.8</td>
<td>−2.7</td>
<td>0.84 (−2.96)</td>
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<tr>
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<td>Left and abnormal FG</td>
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<tr>
<td>9/Daughter/15</td>
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<td>Left</td>
<td>−0.3</td>
<td>−1.9</td>
<td>0.86 (−2.27)</td>
<td>Left</td>
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<td>Left</td>
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<tr>
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<td>0.80 (−4.39)</td>
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<tr>
<td>11/Brother/18</td>
<td>18</td>
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<td>−3.1</td>
<td>−3.6</td>
<td>0.93 (0.00)</td>
<td>Bil</td>
<td>Bil</td>
<td>Bil</td>
</tr>
<tr>
<td>12/Mother/43</td>
<td>43</td>
<td>Bil</td>
<td>−3.3</td>
<td>−3.5</td>
<td>0.95 (0.63)</td>
<td>Bil</td>
<td>Bil</td>
<td>Bil</td>
</tr>
<tr>
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<td>Bil</td>
<td>−4.8</td>
<td>−4.9</td>
<td>0.96 (0.85)</td>
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<td>Left</td>
<td>Left and abnormal FG</td>
</tr>
<tr>
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<td>−3.4</td>
<td>0.76 (−5.57)</td>
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<td>Left</td>
<td>Left and abnormal FG</td>
</tr>
<tr>
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<td>40</td>
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<td>−5.2</td>
<td>0.93 (0.11)</td>
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<td>No</td>
<td>Bil and abnormal FG</td>
</tr>
<tr>
<td>17/Brother/35</td>
<td>35</td>
<td>Left</td>
<td>−1.1</td>
<td>−2.1</td>
<td>0.90 (−0.92)</td>
<td>Left</td>
<td>No</td>
<td>Left and abnormal FG</td>
</tr>
<tr>
<td>18/Sister/27</td>
<td>27</td>
<td>Left</td>
<td>−1.4</td>
<td>−2.1</td>
<td>0.92 (−0.19)</td>
<td>Left</td>
<td>No</td>
<td>Left and abnormal FG</td>
</tr>
</tbody>
</table>

*MTLE indicates mesial temporal lobe epilepsy; HA, hippocampal atrophy; RHV, right hippocampal volume; LHV, left hippocampal volume; Al, asymmetry index; Bil, bilateral; L, left; R, right; and FG, fusiform gyrus. The \( z \) score is the number of SDs below the mean of the control group.

Figure 2. Mesial temporal abnormalities extending to the parahippocampal and fusiform gyri, as well as the collateral sulcus (small arrow) on the left (A) in a 7-year-old, asymptomatic girl with left hippocampal atrophy (arrow) (B) determined by magnetic resonance imaging volumetric measurements (C) (patient 9 in the Table).
genes. For example, morphologic abnormalities of hippocampal formation may represent mild phenotypes with susceptibility for developing full-blown HS in the presence of some types of injury. On the other end of the spectrum, there may be individual genetic effects strong enough to induce HS and temporal lobe epilepsy with minimal influence of environmental factors.

In addition, we found MRI signs suggestive of mesial temporal lobe dysgenesis in 8 of 18 individuals with HA. This may represent an inherited malformation of the mesial aspects of temporal regions that is not necessarily associated with seizures. The morphologic development of the entire hippocampal formation seems to follow a complex process of rotation and folding. The folding of dentate gyrus is especially marked in higher mammals. In the mature hippocampus, the cornu ammonis and dentate gyrus form 2 U-shaped, interlocking laminae. In normal circumstances, the internal structure of the hippocampus is the same in its different segments. It is reasonable to assume that there might be a developmental basis of HS or some heralds of subsequent HS. This correlates with the finding of subtle hippocampal malformations described in asymptomatic siblings of patients with febrile seizures, indicating a previous, genetically determined abnormality that in the presence of other modifying factors may be associated with different phenotypes.

A recent report provided pathologic confirmation of hippocampal malformation occurring without the presence of widespread cortical dysgenesis in an adult with temporal lobe epilepsy in whom MRI demonstrated bilateral hippocampal abnormalities. Postmortem examination revealed abnormal position and complex convolutional malformations isolated to the hippocampal formation, including verticalization of the hilus of the dentate gyrus and an excessively long and folded CA1.

Seizures are clinical events triggered by abnormal firing of a large number of interconnected neurons. Subclinical EEG seizure discharges and interictal epileptiform discharges have a complex neurobiological substrate and are a common finding in patients with epilepsy. On the other hand, the true incidence of EEG abnormalities in asymptomatic individuals is unknown. One may speculate that these asymptomatic individuals with MRI evidence of HS may in fact have interictal EEG abnormalities and even subclinical EEG seizures. However, given the random nature of these possible EEG abnormalities and the difficulties and cost involved in long-term EEG monitoring, these subclinical phenomena would be difficult to rule out. The absence of difference in age in individuals with HA compared with those who did not have abnormal hippocampi is another important indicator that this abnormality is probably the cause and not the consequence of ongoing ictal discharges. In conclusion, the MRI evidence of HS and hippocampal malformation in unaffected family members is indicative of preexisting predisposition to seizures in FMTEL that is modulated by other modifying factors. Our findings further support the hypothesis of a genetic inheritance of HS in these families with mesial temporal lobe epilepsy.

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