

MAGNETIC RESONANCE IMAGING OF FAMILIAL TEMPORAL LOBE EPILEPSY

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

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PURPOSE: 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 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 seven 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* = 0.80).

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.

COMMENTARY

Two tools for epilepsy research, clinical genetics and neuroimaging, are becoming increasingly complementary. Imaging plays a key role in identifying and defining the features of a variety of genetic disorders associated with malformations of cortical development. More recent studies have begun to reveal familial clusters of “mesial temporal lobe epilepsy” (MTLE) with or without hippocampal sclerosis (HS). This pathologic entity has been thought by many investigators to be an acquired lesion associated with antecedent events such as febrile seizures, as well as clinical factors such as epilepsy duration and seizure frequency (1–4).

In a previous study, Kobayashi et al. (5) described 68 patients from 22 families containing at least two individuals with clinically diagnosed MTLE. Interestingly, hippocampal atrophy was observed in patients with a variety of seizure types including febrile seizures alone, and with well-controlled as well as refractory seizures. This suggested a strong genetic component to mesial temporal sclerosis, but in addition, a complex relation between hippocampal atrophy and epilepsy severity.

In their current study, the authors investigated 52 asymptomatic individuals (mean age, 32 years; range, 7–71 years) from 11 of the families with MTLE they had identified in their previous study. In each family, two or more members had been diagnosed as having MTLE by clinical and electroencephalographic criteria. The investigators performed volumetric magnetic resonance imaging (MRI) studies that showed hippocampal atrophy in 18 (34%), which was bilateral in seven. The criterion of abnormality was either an absolute volume, or a left/right asymmetry, more than two standard deviations below control values. On visual analysis of T₁- and T₂-weighted images, 14 of the asymptomatic relatives had either increased T₂ signal intensity or abnormal internal structure, but none had increased signal intensity without volume loss. MRI signs suggestive of mesial temporal lobe dysgenesis in were found in eight of 18. Age did not affect the results.

This study is particularly interesting, as it showed signs of HS in subjects who had never had seizures. The presence of subtle dysgenesis was detected in some patients with febrile status who went on to develop HS rapidly (6,7). However, it would be helpful in interpretation to know more about the affected family members, particularly the age at seizure onset

and epilepsy duration. Some of the asymptomatic relatives were still quite young and could potentially develop seizures later on. In their previous study of familial MTLE, HS was present in 57%, but not all the families participated in the second study (5).

Several families have been described with lateral TLE and auditory symptoms, some of whom are linked to sites on chromosome 10q; these patients, however, have normal MRIs, as do those with another syndrome, "partial epilepsy with pericentral spikes," mapped to chromosome 4p15 (8–11). So far there is little evidence for linkage of any specific chromosomal marker to familial HS or MTLE.

Careful clinical seizure classification will be very important in ongoing studies of potential familial aggregations of HS and MTLE, particularly as MRI findings are often considered crucial (without perhaps serving as a *sine qua non*) for the syndrome diagnosis. Siblings of patients with HS were more likely to have a variety of seizure types, particularly febrile seizures, than were siblings of control subjects (12). It may be that there will be independent but related familial aggregations of HS and clinical seizures, or as-yet-undefined vulnerabilities to either or both that may or may not become apparent clinically.

It is important to remember that a wide range of etiologies, pathogenic mechanisms, and genetic predispositions probably can produce neuronal injury in patients with epilepsy, and that the etiology of HS and MTLE, even in patients who are part of a familial aggregation, will remain multifactorial and complex. Moreover, many of the patients in the affected families studied so far seem to have a more benign clinical course than the "typical" patient with HS and MTLE, underlining the likely heterogeneity of the condition.

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