Etiology of hippocampal sclerosis

Evidence for a predisposing familial morphologic anomaly

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ABSTRACT

Objective: We sought evidence of a hereditary component for hippocampal sclerosis (HS) by determining whether close relatives of probands with temporal lobe epilepsy (TLE) with HS also had asymptomatic HS or subtle variation in hippocampal morphology.

Methods: First-degree relatives from 15 families in which probands had TLE with HS and 32 age- and sex-matched controls were included in the study. Left and right hippocampal volumes and T2 relaxometry were measured using 3-tesla MRI.

Results: Thirty-two asymptomatic first-degree relatives and 3 relatives with a history of seizures or epilepsy were studied. None of the first-degree relatives had HS on visual analysis and T2 relaxation times were normal, excluding the presence of HS. Mean hippocampal volume was smaller (6.4%) in asymptomatic relatives ($2.94 \pm 0.27 \text{ cm}^3$, 95% confidence interval = 2.87–3.01) than in controls ($3.14 \pm 0.22 \text{ cm}^3$, 95% confidence interval = 3.09–3.19, $p < 0.005$); the effect was greater in relatives of probands with a positive family history of epilepsy. The relatives also had more asymmetric hippocampi (asymmetric index 0.92 ± 0.05) than controls (0.96 ± 0.03 , $p = 0.001$).

Conclusions: Small asymmetric hippocampi in healthy relatives are likely to represent a familial developmental variant that may predispose to the formation of TLE with HS. The underlying histopathology of these small hippocampi is unknown. This observation may provide an imaging marker for future studies seeking susceptibility genes for HS. *Neurology*® 2013;81:144–149

GLOSSARY

AI = asymmetric index; FS = febrile seizure; HS = hippocampal sclerosis; TLE = temporal lobe epilepsy.

Hippocampal sclerosis (HS) is a common pathologic finding in patients with temporal lobe epilepsy (TLE). The etiology of HS is controversial and likely multifactorial. It is widely considered an acquired phenomenon, secondary to postnatal injury such as prolonged febrile seizures (FS). Prospective studies of large cohorts of children with FS have not shown a convincing association,^{1–5} although the recent FEBSTAT study suggests that children with prolonged FS may have acute hippocampal injury and an increased frequency of hippocampal developmental change.⁶ Moreover, several family studies have provided some evidence for a genetic predisposition to HS.^{7,8} These findings appear to be inconsistent with evidence from twin studies in which 4 monozygous twin pairs were all discordant for TLE and HS.^{9,10} The findings from twin studies argue against a strong genetic basis for TLE with HS or HS itself. To further clarify this issue, we studied family members of probands that had TLE with HS to search for evidence of HS or more subtle anatomical abnormalities in relatives.

METHODS Patients and participants. We recruited the families of probands with TLE and HS in which their first-degree relatives lived in proximity to our medical center. Diagnosis of TLE in probands was made based on clinical and electroencephalographic findings. Clinical features such as déjà vu, stereotyped flashbacks of a past event, rising epigastric/visceral sensation, or stereotyped/unpleasant olfactory or gustatory hallucinations at seizure onset were considered as supportive of mesial temporal origin. Interictal EEG showed unilateral or bilateral epileptiform discharges and/or focal rhythmic slowing over the temporal region. HS was diagnosed by an experienced neuroradiologist on routine MRI for diagnosis or presurgical evaluation based on standard radiologic criteria.¹¹ Probands who had other concomitant intracranial pathologies such as malformation of cortical development, tumor, or trauma were excluded. Response to anti-epileptic medications was determined according to the recent International League Against Epilepsy proposal.¹²

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Pedigrees were constructed and all first-degree relatives were invited to participate in the research. Relatives in whom high-field MRI could not be proven safe and those who required anaesthesia were excluded. Participants were interviewed by a neurologist (M.-H.T.) for history of epilepsy or FS. Where available, the mothers of participants were contacted regarding the participant's early history, including CNS infection and head injury. A history of syncope, unexplained loss of consciousness, or symptoms of epilepsy including auras was also sought. Thirty-two sex- and age-matched controls were used for comparison; these were healthy volunteers who had received MRI scans on the same scanner. Volunteers who had a history of seizures or FS identified on a questionnaire were excluded.

MRI scanning. Individuals were scanned with a 3-tesla Siemens TIM Trio MRI scanner (Erlangen, Germany) using our standard protocol optimized for epilepsy.¹¹ Two image acquisitions were used for quantitative analysis: a high-resolution, whole-brain, T1-weighted MRI for hippocampal volumetry, and a multispin echo, T2-weighted MRI scan for hippocampal T2 relaxometry. Image acquisition parameters included the following: T1-weighted MRI: magnetization-prepared rapid acquisition with gradient echo sequence, sagittal acquisition, repetition time = 1,900 milliseconds, inversion time = 900 milliseconds, echo time = 2.6 milliseconds, flip angle = 9°, and 0.9-mm isotropic voxel size; T2-weighted MRI: multispin echo, multicontrast sequence (16 slices; slice thickness = 5 mm; slice gap = 2.5 mm; repetition time = 4,000 milliseconds; 8 echo times: 28.9, 57.8, 86.7, 115.6, 144.5, 173.4, 202.3, and 231.2 milliseconds; matrix size = 256 × 192; 1-mm³ in-plane voxel size). Slices were acquired in the coronal plane and were oriented by aligning with the posterior surface of the brainstem at the level of the cerebellum.

All MRI scans were reviewed by 2 experienced neuroradiologists with special attention to subtle features of HS.

Hippocampal volumetry. Hippocampal volumes were measured by manually segmenting the hippocampi from T1-weighted, whole-brain, structural MRI. Hippocampal segmentation was performed using ImageJ software (version 1.45s; US NIH, Bethesda, MD, <http://imagej.nih.gov/ij/>).

Hippocampi were manually delineated in a posterior to anterior direction. The most posterior slice was selected as the slice in which the fornix was visible in full profile. The hippocampus was outlined on each slice, and the area of each slice was summed to give an estimate of the hippocampal volume in voxels. The volume of the hippocampus was converted to cubic millimeters by multiplying by the voxel size. Usually, 30 to 40 slices were measured.

Asymmetric index (AI) was calculated in each individual to identify the difference between bilateral hippocampal volumes as follows:

$$AI_{HippVOL} = 1 - \{ |HippVOL_{left} - HippVOL_{right}| / 1/2(HippVOL_{left} + HippVOL_{right}) \}$$

Correction for total brain volume. Total brain volumes were measured using the software program BET, provided as part of the FSL software package (<http://www.fmrib.ox.ac.uk/fsl/>). Brain tissue was segmented from nonbrain structures and the results were visually inspected to ensure correct segmentation. In some cases, a portion of nonbrain tissue was included in the brain segment. In these cases, correct segmentation was obtained by providing a center of mass estimate for the brain as input to the BET program to improve the starting estimates for brain segmentation.

Hippocampal volumes were corrected for total brain volume using a covariance model.¹³ Hippocampal volumes of

subjects were adjusted with total brain volume using the following formula:

$$HippVOL_{corrected} = HippVOL_{measured} - \text{gradient} \times (BrainVol_{measured} - BrainVol_{mean})$$

where gradient is the slope of a linear regression fit of the left and right control hippocampal volumes to the control brain volumes, and $BrainVol_{mean}$ is the average brain volume of the controls.

Both hippocampi and total brain volumes were measured on 35 control subjects. The average total brain volume in controls was 1,418 cm³. Linear regression analyses of the left and right hippocampal volume to total brain volume were performed independently because they are statistically significantly different. The gradient was 0.0014 for the left side and 0.0016 for the right side.

T2 relaxometry. T2 maps were generated by fitting a monoexponential decay function to the signal from each voxel in the image (see equation).

$$S = S_0 e^{(-TE/T_2)}$$

where signal (S) is the signal intensity at each voxel for each echo time. Parameters S_0 and T_2 were estimated using nonlinear least-squares estimation. Only even ordered echoes were used (i.e., 57.8, 115.6, 173.4, and 231.2 milliseconds) in order to optimize the precision of the T2 estimate.

An estimate of the average hippocampal T2 was then measured by placing a circular region of interest within the hippocampus, avoiding partial volume of nearby CSF. The slice that contained the maximal surface area of the hippocampal head was used for generation of the T2 map; usually this was the third or fourth slice from the most anterior slice of the acquisition.

AI of T2 relaxation time was also calculated:

$$AI_{T2R} = 1 - \{ |T2R_{left} - T2R_{right}| / 1/2 \times (T2R_{left} + T2R_{right}) \}$$

Statistics. Comparisons of hippocampal volumes and T2 relaxation time between relatives and controls were assessed using Student *t* test. The test-retest reliability was evaluated using an intraclass correlation coefficient. Linear regression analysis was used for correction with total brain volume. Comparisons of hippocampal volumes in relatives according to probands' history of FS, response to antiepileptic medications, side of HS, and family history of seizures were performed using Student *t* test. All statistics were performed using IBM SPSS software (version 20; IBM Corp., Armonk, NY).

Standard protocol approvals, registrations, and patient consents. The protocol was approved by the Austin Hospital Human Research Ethics Committee, and all subjects or their legal guardians, in the case of minors, gave informed consent.

RESULTS Subjects. Thirty-five relatives of 15 probands with TLE with HS who were available to undergo MRI completed the study; this represents 67% (35/52) of all relatives who were available. The 15 probands were unrelated and had electroclinical findings of TLE with HS on MRI (10 right HS; 5 left HS). Fifty-three percent (8/15) had refractory epilepsy and had undergone anterior temporal lobectomy with HS confirmed on histopathology; the remaining 7 were therapy responsive. The diagnosis of HS in drug-responsive patients relied on MRI only. Mean duration of afebrile seizures was

25.2 years. FS had occurred in 8 of 15 probands and were prolonged in 4. A family history of seizures was found in one-third of cases (5/15).

Three of the 35 first-degree relatives had a history of seizures and were therefore not included in the primary analysis: one had unlocalized focal epilepsy, one had an FS, and one had benign TLE in adolescence. The ages of the 32 asymptomatic relatives ranged from 14 to 64 years (mean 39.2 years); 18 were male. None, including the 3 affected relatives, had HS (both hippocampal atrophy and increased T2 signal) on visual analysis.

Hippocampal volume measurements in relatives and controls. The hippocampal volumes corrected for total brain volume of 32 asymptomatic relatives were compared with 32 age- and sex-matched controls; the mean age and total brain volume between the 2 groups did not differ (table). The mean test-retest difference was 0.55 cm³ and the mean percentage difference was 1.8%. The intraclass correlation coefficient was 0.81.

The key finding was that the mean corrected volumes of both the right and left hippocampi were smaller (6%–8%) and more asymmetric in the relatives compared with controls (table), with no side preference for the lesser volume (figure). This degree of volume loss is not detectable by qualitative inspection.

T2 relaxometry in relatives and controls. There was no difference in absolute T2 relaxation time or AI compared with healthy controls ($p > 0.05$) (table).

Probands' characteristics and hippocampal volume in relatives. We compared corrected hippocampal volumes of relatives of probands who had a family history of seizures with those who did not. The relatives of probands who had a positive family history had smaller hippocampi (2.79 ± 0.26 cm³) compared with those who did not have a family history (3.03 ± 0.26 cm³,

$p = 0.02$). Indeed, as shown in the right panel of the figure, the distribution of values in those relatives was shifted to the left and down, with a more circular distribution, indicating smaller and more asymmetric hippocampi. Total brain volume, hippocampal AI, and T2 relaxation time did not differ in relatives with and without a family history of seizures.

Of the 3 affected first-degree relatives, 2 had unilateral (1 left and 1 right) and 1 had bilateral hippocampal atrophy (z score -2.1 to -3.6); all had normal T2 relaxation times. Further comparisons of relatives' hippocampal volumes according to probands' history of FS, response to antiepileptic treatment, and side of HS did not show any differences.

Other hippocampal abnormalities. Among 32 asymptomatic relatives, 12 (37.5%) had hippocampal shape anomaly (based on 2 radiologists' consensus), including 5 bilateral, 6 left, and 1 right. Further comparison of hippocampal volumetry and T2 relaxation time between malrotated and normal hippocampi showed no difference.

DISCUSSION In subjects with HS, it is well established by studies of MRI and histopathology that decreased hippocampal volume correlates with neuronal loss in the hippocampus^{14–17} and increased T2 relaxation time correlates with gliosis in the dentate gyrus.¹⁷ Importantly, increased T2 relaxation time is a sensitive measure of HS.^{18,19}

In this study, we observed that none of the first-degree relatives had HS on careful qualitative and quantitative analyses, consistent with previously published data showing discordance for HS in monozygotic twins.^{9,10} Taken together, these findings suggest that the heritability of HS, at least in our sample, which included a mixture of refractory and drug-responsive cases, is low. The data do not exclude the possibility of susceptibility genes predisposing to HS.

Table	Comparison of hippocampal volumetry and T2 relaxation time between relatives and controls ^a		
	Relatives (n = 32)	Controls (n = 32) ^b	p Value ^c
Sex, male/female	18/14	18/14	—
Age, y	39.2 ± 16.5	37 ± 7.6	NS
Total brain volume, cm ³	1,403 ± 101	1,416 ± 106	NS
Left hippocampal volume, ^d cm ³	3.00 ± 0.29 (2.9–3.1)	3.19 ± 0.23 (3.11–3.27)	0.005
Right hippocampal volume, ^d cm ³	2.89 ± 0.26 (2.8–2.98)	3.09 ± 0.22 (3.01–3.17)	0.001
AI hippocampal volume	0.92 ± 0.05	0.96 ± 0.03	0.001
Left T2R	109.2 ± 6	108.4 ± 6	NS
Right T2R	109.6 ± 5.3	109.2 ± 5	NS
AI T2R	0.97 ± 0.05	0.95 ± 0.03	NS

Abbreviations: AI = asymmetric index; NS = not significant; T2R = T2 relaxation time.

^aData are n or mean ± SD (95% confidence interval of the mean).

^bQuantitative T2 relaxometry was available in only 21 of 32 controls.

^cStudent t test.

^dHippocampal volumes corrected for total brain volume.

Figure Distribution of hippocampal volumes of asymptomatic relatives

Raw data (A) show that the relatives (red) had smaller hippocampi than controls (blue). The same data are shown (B) with 90% confidence ellipse of means of the controls shown in the blue oval (the smaller oval), and 90% confidence ellipse of the relatives of probands with a positive family history (FH) shown in the red oval. The 2 confidence ellipses have different centers and shapes, indicating that the relatives from families with an FH of epilepsy have hippocampal volumes that are smaller and more asymmetric than controls.

Indeed, we found that first-degree relatives of patients that have TLE with HS, who had never had seizures, have smaller and more asymmetric hippocampi compared with age- and sex-matched controls. However, T2 relaxometry measures were normal. Although the pathologic correlation of the smaller hippocampi in asymptomatic relatives is unknown, the normal T2 relaxometry suggests that the smaller hippocampal volumes are not simply a mild version of HS. Rather, we believe it is likely to represent a subtle developmental variation in the hippocampus, although unknown acquired factors are not excluded.

The absolute mean decrement in hippocampal volume was 0.2 to 0.25 cm³ (6%–8%) compared with controls. Previous quantitative studies showed that visibly abnormal hippocampi are at least 15% smaller than normal,^{20–23} explaining why the subtle differences found here were not detectable on careful visual analysis.

The smaller hippocampus, which we infer to be a developmental variant, is most likely to have a genetic basis because it was observed in healthy first-degree relatives. In addition, comparing relatives of probands with sporadic TLE with relatives of probands with a family history of epilepsy showed that the latter had even smaller and more asymmetric hippocampi (figure), implying a “dose” effect, adding further support to the hypothesis that these imaging features have a genetic basis. Recently, genetic factors have been associated with hippocampal size in normal individuals, although other shared environmental factors may also contribute.^{24,25} Atypical distribution of hippocampal volume has also been reported in a population-based study of new-onset epilepsy, being

more common in those cases that had a “temporal” flavor to the clinical presentation.²⁶ This inherited imaging marker could be used to help identify susceptibility alleles for HS.

These observations need to be considered in the context of 2 other previous important studies.^{8,27} A study of 23 individuals from 2 German families with TLE probands showed that many members had FS.⁸ All members with FS had left hippocampal atrophy as did 6 of 10 asymptomatic individuals. None of the subjects had qualitative signal change on T2-weighted imaging. The authors suggested that these hippocampi were malformed because of a hippocampal neuronal migration disturbance, rather than HS.⁸ Our study is largely compatible with their observations. Moreover, we found that this inherited developmental difference not only exists in selected families enriched for FS, but also in families of sporadic TLE probands with HS. We did not confirm the observation of exclusively left-sided occurrence of the change.

A Brazilian group studied 52 asymptomatic relatives from 11 kindreds with familial TLE with 2 or more subjects with TLE.²⁷ They reported 18 relatives (34%) had hippocampal atrophy, of which 14 were regarded as having abnormal T2 signal on visual analysis, but T2 relaxometry was not used and mesial temporal artifacts can influence visual assessment.²⁷ They postulate that relatives in their study had HS. In our study, no relatives had increased T2 relaxation time using quantitative T2 relaxometry, which is more sensitive and unlikely to be contaminated by mesial temporal artifacts such as flow than visual analysis of T2-weighted MRI.²⁸ It is also possible

that the asymptomatic relatives in their study have a different or more severe change as they were selected from familial TLE kindreds. However, in the 5 families in our study in which 2 subjects had seizures, none of the asymptomatic relatives had increased T2 relaxation time or visually increased T2 signal.

The current study has limitations. The sample size was relatively small because of the difficulty in recruiting asymptomatic relatives in a genetic study. Second, it was a clinic-based “convenience” sample and may not be truly representative of the population. Third, those TLE probands who were drug responsive had the diagnosis of HS by MRI alone, without histopathologic confirmation. Fourth, manual segmentation of the hippocampus could have potential operator bias, although all measurements were performed by the same operator. However, our experience showed that it is still superior to automatic segmentation.²⁹

Our study is consistent with the view that HS is a multifactorial complex trait, with both environmental and genetic contributions. Prolonged FS have long been hypothesized as an important cause of HS and subsequent TLE because early studies showed that a history of an initial precipitating injury, such as a prolonged FS, was present in 60% to 80% of patients who had TLE with HS.^{20,30,31} Furthermore, MRI studies of children with a prolonged FS showed subsequent hippocampal volume loss in a proportion of cases.^{32,33}

Our familial imaging study shows that the inherited small hippocampus is likely to also be a risk factor for formation of TLE with HS. It may be that prolonged FS, among other factors, act through this preexisting vulnerability to develop frank HS. The underlying histopathology of these small hippocampi remains unknown. It may be a potential imaging marker for further molecular genetic study into this common but complex epilepsy. The environmental and genetic factors interacting in the complex triangular relationship among FS, HS, and TLE are still waiting to be fully untangled.

AUTHOR CONTRIBUTIONS

Dr. Tsai contributed to the design and conceptualization of the study, analysis and interpretation of the data, and drafting the manuscript for intellectual content. Dr. Pardoe contributed to the design of the study, analysis of the data, and revising the manuscript for intellectual content. Dr. Perchyonok and Dr. Fitt contributed to the analysis and interpretation of the data. Dr. Scheffer contributed to the design of the study and revising the manuscript for intellectual content. Dr. Jackson and Dr. Berkovic contributed to the design and conceptualization of the study, interpretation of the data, and revising the manuscript for intellectual content.

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