Hippocampal Sclerosis Is a Progressive Disorder: A Longitudinal Volumetric MRI Study

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Twelve patients with refractory temporal lobe epilepsy and unilateral hippocampal sclerosis had repeat volumetric magnetic resonance imaging scans after a mean of 3.4 years to determine whether progressive hippocampal volume loss occurred. Seizure-free patients showed no change in hippocampal volume. Patients with continuing seizures had a decline in ipsilateral hippocampal volume that correlated with seizure frequency. Patients with medically refractory temporal lobe epilepsy and unilateral hippocampal sclerosis have progressive hippocampal atrophy.

Ann Neurol 2003;53:413–416

Hippocampal sclerosis (HS) is the most common lesion associated with temporal lobe epilepsy (TLE) in adults and is verified in 60 to 75% of patients treated surgically for medically intractable TLE.[1] HS is characterized by neuronal cell loss and gliosis involving hippocampal sectors cornu ammonis 1 (CA1) and CA3/CA4 region of the hippocampus with relative sparing of CA2, the subiculum, and the dentate gyrus, although in severe cases pathological findings may be widespread.[1–4]

The two principal magnetic resonance imaging (MRI) findings of HS are hippocampal atrophy and MRI signal changes indicative of increased tissue free water.[2] Although HS may be detected visually on routine MRI, the accuracy with which it is identified is in large part dependent on the skill of the analyst and on whether appropriate MR sequences are acquired. Thus, quantitative methods for detecting HS using MRI have been extensively researched. Volumetric measurements of the hippocampus have proved to be both sensitive and specific for HS in TLE, and volume loss on MRI has a close correlation with histologically determined cell loss.[2–4]

Recent studies, using a variety of experimental and clinical methods,[4–14] suggest that persistent temporal lobe seizures over time may result in progressive changes in hippocampal structure and function, including a decline in neuropsychological functioning.[4] Unfortunately, to date, studies with human patients with TLE have utilized heterogeneous samples not limited to patients with unilateral HS and have been either cross-sectional designs[4,6–11] or case studies.[12–14] This limits the robustness and generalizability of the results and conclusions.[5]

In this study, we followed up patients with intractable unilateral TLE and HS over a period of years to determine if there is progression of HS using volumetric MRI.

Patients and Methods

Patients

Of 65 consecutive patients with medically refractory TLE and volumetric MRI evidence of unilateral HS, 47 underwent anterior temporal lobectomy, 5 were lost to follow-up, 1 died during a seizure, 3 became seizure free taking medication within 6 months after their initial MRI scan, and 9 were recommended to have surgery by our epilepsy team but refused. Of the 12 patients (6 men) who did not have surgery, evaluation (seizure semiology, electroencephalogram with zygomatic electrodes, video electroencephalogram monitoring, ^{18}F-fluorodeoxyglucose positron emission tomography scanning) demonstrated unilateral temporal lobe seizure onset (8 left onset) in all. Volumetric MRI evidence of unilateral HS was concordant with side of seizure onset for all patients. Patients underwent a repeat MRI scan with volumetric measurements after 2.5 to 5.2 years (mean [M] = 3.4; standard deviation [SD] = 0.71).

Magnetic Resonance Imaging Methods

MRI studies were performed on a GE 1.5T, Signa 5.4 unit (GE Medical Systems, Milwaukee, WI). MRI-based volumetric measurements of the hippocampus were performed using a three-dimensional spoiled gradient-echo sequence following a method described previously.[2,3,15] The absolute volumes of the two hippocampi were compared with our normal control population after "normalization" by total intracranial volume.[2] We also analyzed the degree of hippocampal asymmetry between sides by calculating a ratio of the abnormal (ie, the epileptogenic) side to the normal (nonepileptogenic) side. Patients with TLE were considered to meet volumetric MRI criteria for HS if their absolute volumes were greater than 2 *SD*s below the mean of the control group and/or the hippocampal ratios were less than 0.92. All 12 patients also had increased T2 signal in the atrophic hippocampus on coronal FLAIR and/or T2-weighted images.

Data Analysis

Measures of principal interest in this study were the interval between the two MRI scans, absolute hippocampal volumes ipsilateral (IHV) and contralateral (CHV) to the side of seizure onset, and number of partial (NPSZ) and generalized (NGSZ) seizures between scans (Table 1). For some analyses, patients were classified according to seizure status during the interval (seizure free vs continuing seizures). Changes in mean

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Received Aug 5, 2002, and in revised form Nov 12. Accepted for publication Dec 4, 2002.

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hippocampal volumes were analyzed using repeated-measures *t* tests and mixed-model analysis of variance as appropriate. Because precise seizure counts are difficult to obtain, correlations of NPSZ and NGSZ with IHV and CHV were analyzed using Kendall's tau (τ), treating the measures as ordinal data.

Because analysis of group data can obscure potentially informative individual change, we also calculated a reliable change index (RCI) for hippocampal volume (HV).[16] The RCI allows identification of significant changes that exceed random fluctuations attributable to the unreliability of a measure. CHV test–retest correlation was used as the basis for the standard error of measurement of HV measures, because these volumes were expected to remain stable with fluctuations reflecting error variance. The relationship between patients showing a significant HV change and seizure status was tested using likelihood ratio χ^2.

Results

Mean age at second scan, age at onset, and duration of epilepsy were not different for seizure-free patients versus patients with continuing seizures. Mean interval between scans was slightly longer for seizure-free patients (4.2 vs 3.2 years, $F[1,10] = 7.35$, $p < 0.05$; see Table 1).

Mean CHV (Table 2) did not change between the first and second scans. However, mean IHV declined ($t[11] = 2.87$, $p < 0.01$; Fig). NPSZ correlated with IHV decline ($t = 0.69$; $p < 0.01$). This held with Patient 12, a potential outlier with 1,500 reported seizures, removed ($t = 0.62$, $p < 0.01$). NPSZ did not correlate with CHV change, and NGSZ did not correlate with IHV or CHV change.

There was an interaction between mean IHV change and seizure status ($F[1,10] = 17.4$; $p < 0.01$), with seizure-free patients showing no IHV change, and patients with continuing seizures showing a decline ($F[1,8] = 54.89$; $p < 0.01$). Patients with continuing seizures did not show CHV decline ($F[1,8] = 1.07$, not significant).

The test–retest correlation for CHV was 0.986, with $SD = 452$, resulting in a 95% confidence interval RCI for HV of 143.28. All patients with continuing seizures showed IHV declines greater than the RCI. All seizure-free patients showed no IHV change (ie, changes were within the range expected because of measurement error alone). The relationship between seizure status and IHV change in excess of the RCI was significant (χ^2lr[1] = 13.5, $p < 0.01$). Only one patient, with continuing seizures, showed significant CHV decline. For the nine patients who did show significant IHV decline, IHV change was not correlated with the interval between MRI scans ($r = -0.21$, not significant).

Discussion

In patients with intractable unilateral TLE and HS, there is progressive volume loss in the hippocampus ipsilateral to the side of seizure onset. This result is consistent with cross-sectional and case studies that have found longer duration of epilepsy,[7,10–12] earlier age of onset,[8,9] or both[4,6] to be related to diminished hippocampal volumes, reduced NAA/Cr, prolonged T2 relaxation times, or increased severity of HS on pathological evaluation. Recent longitudinal studies[17,18] of patients with new onset, mild TLE reported only rare progression to HS, although those patients with more frequent generalized tonic-clonic seizures (GTCSs) exhibited a modest decline in IHV.[18] However, case reports[13,14,19] indicate that, on occasion, hippocampal atrophy can develop fairly rapidly and is not always

Table 1. Sample Characteristics

Patient No.	Age[a] (yr)	Gender	Age at Onset (yr)	Duration (yr)	Interval[b] (yr)	Hippocampal Volume Change (mm^3)		No. of Seizures between Scans		
						Ipsilateral	Contralateral	Partial	Generalized	Total
Seizure-free patients										
1	28.5	F	18	10	3.7	0	14	0	0	0
2	35.3	M	10	25	5.2	−62	2	1	0	1
3	73.1	M	67	6	3.6	26	40	2	0	2
Patients with continuing seizures										
4	30.8	F	23	8	3.1	145	3	26	1	27
5	31	F	6	25	4.1	222	−9	36	18	54
6	26.7	F	6	21	3.5	181	4	66	0	66
7	44.3	F	2	43	3	331	27	75	5	80
8	53.3	M	4	50	3.1	409	−29	105	0	105
9	47.6	M	15	33	2.5	236	485	75	75	150
10	20.7	M	3	18	3.1	273	17	160	0	160
11	34.2	F	29	5	3	175	−18	175	0	175
12	49.8	M	42	8	3	462	23	1,500	0	1,500

[a]At time of second scan.
[b]Between the first and second scans.

associated with frequent GTCSs.[13,19] Our results show a strong correlation between frequency of partial seizures and IHV loss, but no correlation with GTCSs. These differences may be because of the different patient populations being studied. Our patients had long-standing refractory TLE due to HS, whereas those studied by Briellmann and colleagues[18] had more recent onset, mild TLE with evidence of HS in only one patient.

There was no interval change in mean CHV, and CHV declined for one patient (Patient 9) only. This case was somewhat unusual, with seizure semiology concordant with the side of hippocampal atrophy, but electrographic and positron emission tomography data suggestive of the development of a new independent seizure focus in the contralateral temporal lobe. This patient also had very frequent (2.5 per month) GTCSs, suggesting that frequent bilateral seizure activity results in bilateral hippocampal volume loss. Overall, however, the results suggest that contralateral hippocampal volumes do not change in unilateral TLE across the interval sampled by this study.

None of the three patients in our study who became seizure free in the interval between MRI scans showed hippocampal volume loss. There may be an association between cessation of seizures and arrest of hippocampal atrophy. However, given the low number of patients, this finding should be treated with caution until replicated with a larger sample.

For patients who showed progression, there was no correlation between IHV loss and the duration between MRI scans. In this regard, our current findings appear to contradict cross-sectional data showing a linear relationship between hippocampal volume loss and duration of seizure disorder. However, our failure to find a duration/loss relationship in this study may reflect (1) a nonlinear relationship between duration/loss over the relatively short time span between scans used in this study, (2) a statistical artifact, that is, attenuation of correlation due to the restricted range of time between scans in this study, or 3) that seizure frequency, not duration, is the critical effect.

There is evidence that surgery is significantly more effective than antiepileptic drug therapy in controlling seizures in patients with intractable TLE, and that timely evaluation for temporal lobectomy is preferable to prolonged attempts at medical management.[20] Our results support this position. Patients with uncontrolled TLE due to HS suffer progressive hippocampal damage and should be managed aggressively.

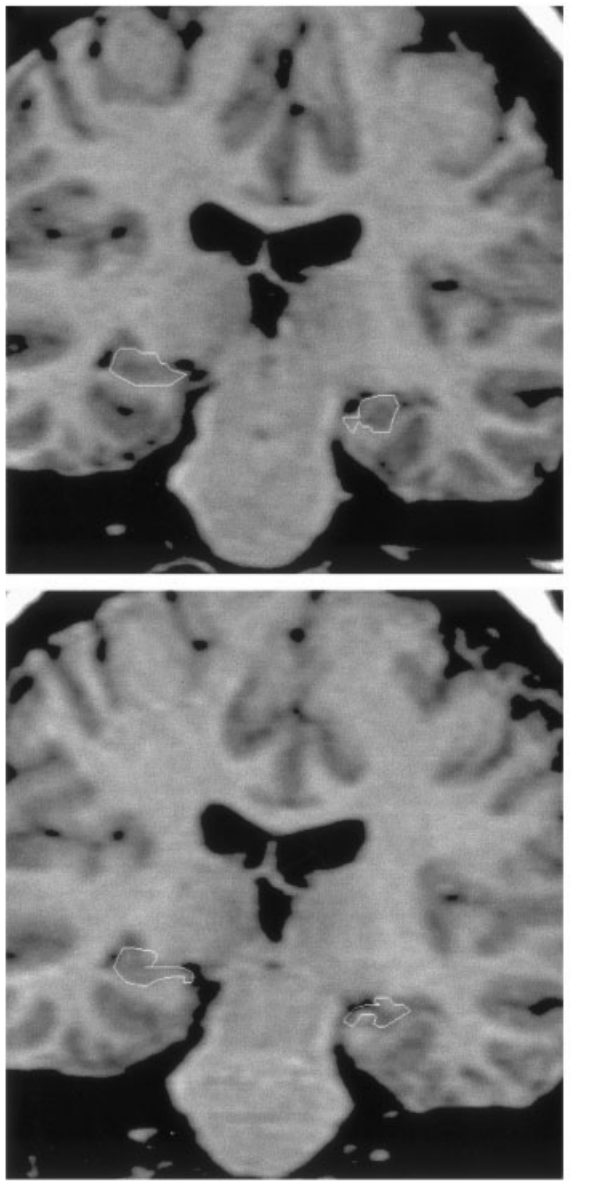

Fig. Coronal spoiled gradient-echo images of the initial scan (top) and the second scan (bottom) of Patient 7 showing a decrease in volume of the left hippocampus.

Table 2. Mean (SD) *IHV and CHV (mm^3) at Initial and Repeat Scans for the Entire Sample (n = 12), Seizure-free Patients (n = 3), and Patients with Continuing Seizures (n = 9)*

	Time 1	Time 2
IHV		
Overall	2676.58 (564.49)	2476.75 (609.54)
Seizure free	2720.67 (290.80)	2732.67 (320.00)
Continuing seizures	2661.89 (645.00)	2391.44 (672.69)
CHV		
Overall	3711.92 (452.01)	3665.33 (452.67)
Seizure free	3697.00 (295.68)	3678.33 (276.77)
Continuing seizures	3716.89 (508.88)	3661.00 (512.36)

SD = standard deviation; IHV = ipsilateral hippocampal volume; CHV = contralateral hippocampal volume.

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