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Pathological Grading System for Hippocampal Sclerosis: Correlation with Magnetic Resonance Imaging-Based Volume Measurements of the Hippocampus

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We studied 20 consecutive patients with medically intractable temporal lobe epilepsy (TLE) using volumetric magnetic resonance imaging (MRI) measurements of the hippocampus. We calculate a "preoperative hippocampal ratio" to determine the degree of hippocampal atrophy on the epileptogenic side as compared with that on the nonepileptogenic or normal side. We then correlated the degree of hippocampal atrophy with the severity of hippocampal sclerosis as determined by a practical, semiquantitative grading system adapted from the schema proposed by Wyler et al. (6). The study confirmed the usefulness of our six-tiered grading system in detecting and characterizing the severity of hippocampal sclerosis. Eighteen of our patients had identifiable hippocampal sclerosis, ranging from minimal (grade I) to severe (grade V). The degree of hippocampal atrophy as measured with preoperative volumetric MRI correlated well with the severity of hippocampal sclerosis as determined by the pathological grading system. These two techniques should aid in the diagnosis, treatment, and research assessment of patients with intractable TLE.
Key Words: Volumetric magnetic resonance imaging—Hippocampal sclerosis—Pathology—Temporal lobe epilepsy—Temporal lobectomy.

Received July 14, 1995; accepted July 18, 1995.
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Approximately 60–75% of patients with temporal lobe epilepsy (TLE) have hippocampal sclerosis, which is characterized by neuronal cell loss and gliosis usually affecting hippocampal sectors CA1 and CA3/CA4 with relative sparing of CA2, the subiculum, and the dentate gyrus, although occasionally pathology is more widespread (1–4). Without question, the best method of detecting, characterizing, and quantifying hippocampal sclerosis is use of the technique of neuronal cell counting to

J. Epilepsy 1996;9:56–64

655 Avenue of the Americas, New York, NY 10010

0896-6974/96/$15.00
SSDI 0896-6974(95)00060-7

quantify the degree of neuronal cell loss (3,5). However, as Wyler et al. note (6), this technique is extremely labor intensive and requires special equipment and personnel not available in most neuropathology laboratories. Nevertheless, there remains a need for a practical, standardized method of describing the degree of hippocampal pathology so that surgical technique and patient populations can be compared in research reports from different epilepsy centers.

For these reasons, in 1992, we began to use the five-tiered, semiquantitative grading system described by Wyler et al. to grade our anterior temporal lobectomy (ATL) specimens for the presence and severity of hippocampal sclerosis. After using the system for some time, we considered that a slight modification of the system made it somewhat more useful. This modification involved the insertion of an additional grade between the moderate (II) and moderate to marked (III) grades.

The development of high-resolution magnetic resonance imaging (MRI)-based volumetric measurement of the hippocampal formation has proven useful in the preoperative evaluation of patients with TLE caused by unilateral hippocampal sclerosis. Studies have shown that significantly reduced hippocampal volumes corroborate neurophysiologic studies and allow lateralization of the epileptogenic region, correlate with neuropathologic and neuropsychologic abnormalities, and correlate with outcome after temporal lobectomy (7–17). We wished to correlate the results of our volumetric MRI studies with those obtained from the pathological grading system for hippocampal sclerosis. We report our findings in 20 consecutive patients who underwent ATL for medically intractable TLE.

Method

Patients

Twenty consecutive patients with medically intractable TLE were studied. The mean age of the patients was 33 years (SD 12, range 6–52). Mean age of seizure onset was 12 years (SD 7, range 0.5–23), and mean duration of epilepsy was 22 years (SD 11, range 2–38). Ten patients experienced febrile seizures during childhood, and 3 patients had other early risk factors (trauma, meningitis). All patients underwent a comprehensive presurgical evaluation including electroencephalographic (EEG)-video monitoring (6 with intracranial electrodes), quantitative volumetric MRI analysis, fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning, neuropsychological testing, and intracarotid amytal (Wada) testing.

MRI Methods

MRI Scan Acquisition

MRI studies were performed on a GE 1.5-T Signa unit (GE Medical Systems, Milwaukee, WI, U.S.A.). A series of sagittal spin-echo images were obtained with 7-mm contiguous (no skip) sections and a 700/17/0.75 (TR ms/TE ms/number of excitations) pulse sequence. The plane of the left lateral sulcus was located on the sagittal images, and angled coronal images were obtained perpendicular to this plane. Volumetric imaging in this patient group was performed with two image sequences. From May 1991 to January 1993, an inversion recovery sequence was used for volumetric measurements. Since January 1993, a spoiled gradient echo (SPGR) sequence has been used for volumetric measurements. The inversion recovery sequence consisted of 26 angled coronal images obtained perpendicular to the plane of the left lateral sulcus with 2.3–3 mm contiguous sections, a 2,000/13/1,000/2 (TR/TE/TI/NEX) pulse sequence, 256 × 192 matrix, and 200-mm field of view (FOV). The three-dimensional SPGR generated 124 contiguous 1.5-mm sections of the entire head, with a 35/5/1 (TR/TE/NEX) pulse sequence, flip angle of 35°, 256 × 128 matrix size, and 240-mm FOV. These images were performed in the coronal plane, and the imaging time for the sequence was 9.5 min.

MRI Scan Analysis

The images were transferred to an IBM PC-based workstation, and volumetric measurements were performed with an interactive semiautomated software package developed at our institution. In this study, the contours of the hippocampus were performed entirely with a manual contouring function due to the complexity of the structures involved. Once the outline of the hippocampus had been defined, a slice volume was calculated by multiplying the area outlined by slice thickness. The total volume of the structure was then calculated by adding the slice volumes. Once the total volumes of the two hippocampi were obtained, we calculated a "preoperative hippocampal ratio" by dividing the volume of the abnormal side (i.e., the epileptogenic or operated side) by the volume of the normal (nonepileptogenic or nonoperated) side. In our normal

Table 1. *Hippocampal sclerosis: Pathologic grading schema*

Grade	Description
0	Normal
I	Gliosis with slight (<10%) or no neuronal cell loss in CA1, CA3, and/or CA4
II	Gliosis with 10–50% neuronal cell loss in CA1 and/or CA3/CA4
III	Gliosis with >50% neuronal cell loss in CA1 and 10–50% cell loss in CA3/CA4, with sparing of CA2
IV	Gliosis with >50% neuronal cell loss in CA1 and CA3/CA4, with sparing of CA2
V	Gliosis with >50% neuronal cell loss in CA1–CA4; DG, subiculum, and PHG may be involved

DG, dentate gyrus; PHG, parahippocampal gyrus.

control population of 30 males and 31 females, the mean value of the hippocampal ratio (smaller side/larger side) was 0.97, with SD 0.02, indicating a high degree of symmetry between the two sides (18).

Volumetric Analysis

Anatomic guidelines for outlining the amygdala and hippocampal formation followed a specific protocol described previously (10,19). Reliability studies to detect the extent of intrarater consistency and interrater variation were also reported previously (13,14,19–21).

Surgical Methods

Hippocampal specimens were obtained by techniques similar to those described by Wyler et al. (6). The additional use of stereotaxis to delineate the location of the anterior end of the inferior horn of the lateral ventricle, the superomedial aspect of the amygdala, and the posterior extent of the hippocampal resection was reported previously (22).

Neuropathological Methods

The fresh temporal lobe tissue blocks were received in the operating room, oriented, and allowed to fix by immersion in 10% buffered formalin for 24–48 h. In most cases, three separate blocks of tissue were obtained and examined: a lateral temporal block, an anterior hippocampal/amygdaloid block, and a posterior hippocampal block. After fixation, the hippocampal segments were sectioned at 3-mm intervals in serial fashion progressing from anterior to posterior. After the sections were photographed, they were dehydrated in the usual manner and embedded in paraffin. Four- to six-micron sections were stained routinely with hematoxylin and eosin (H & E). Sections from selected blocks were stained with cresyl violet (CV), Luxol fast-blue/H & E,

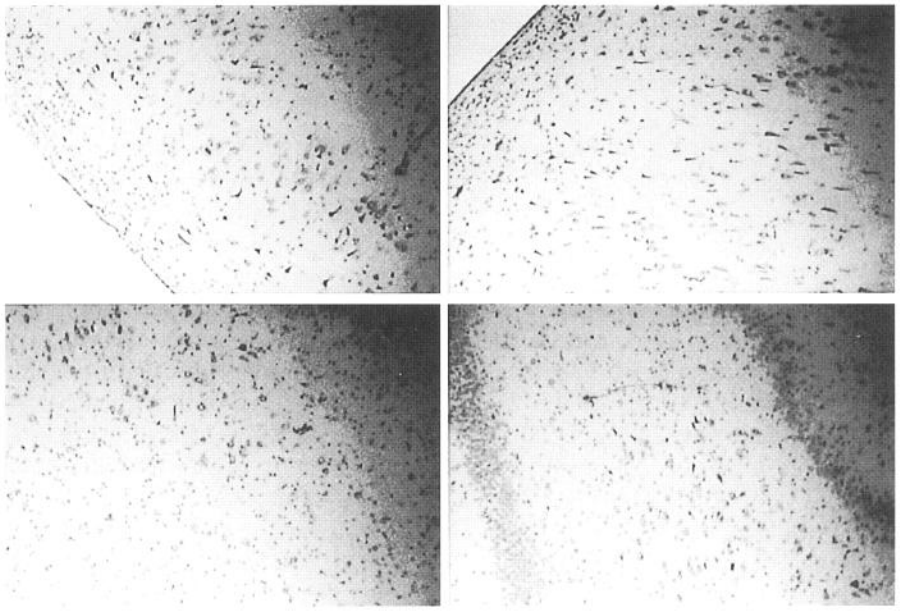

Figure 1. *Normal hippocampus, grade 0 (Patient 2). High-power views of all four hippocampal sectors showing no cell loss or gliosis. CA1* ***(upper left)****, CA2* ***(upper right)****, CA3* ***(lower left)****, CA4* ***(lower right)*** *(H & E ×40).*

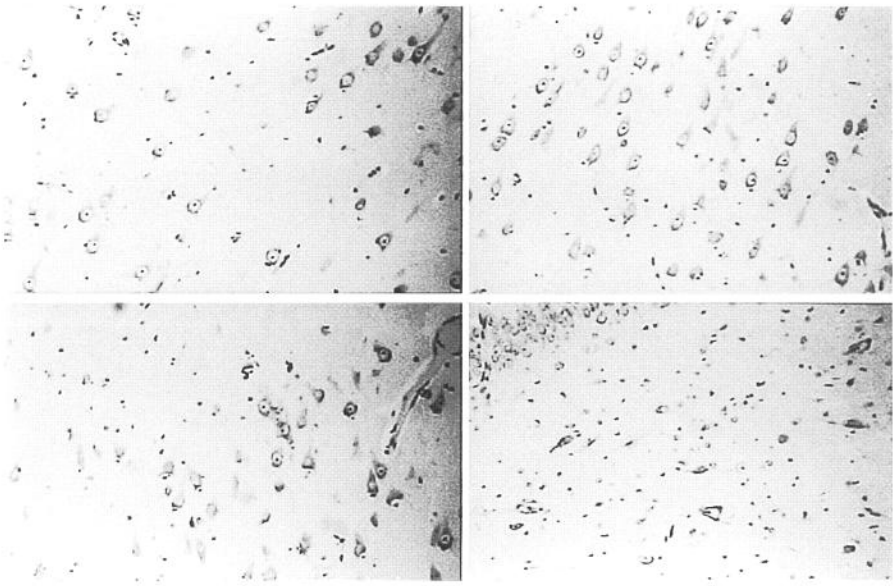

Figure 2. *Hippocampal sclerosis, grade I (Patient 4). High-power views showing no appreciable cell loss in any hippocampal sector, except possibly minimal loss (<10%) in CA4. Glial fibrillary acidic protein (GFAP) stain showed gliosis in CA4. (This section is stained with H & E ×100).*

and/or Luxol fast-blue/CV. Astrocytosis was detected by the immunohistochemical method for detection of glial fibrillary acidic protein (GFAP) antigen. Microscopic grading was accomplished by 1 of the authors (S.L.N.) without knowledge of the volumetric MRI data. The assigned grades were then correlated with the imaging assessment.

Grading System

The grading system was adopted from the schema described by Wyler et al. (6). As in that system, the hippocampal sections showing the most severe involvement were used to grade the degree of hippocampal sclerosis. We modified the system of Wyler et al. (6) slightly by inserting an additional grade between their grades II and III, so that our schema has a six-tiered system (Table 1). Grades are shown in Figs. 1–6.

Results

The distribution of pathological diagnoses is shown in Table 2. Hippocampal sclerosis was evi-

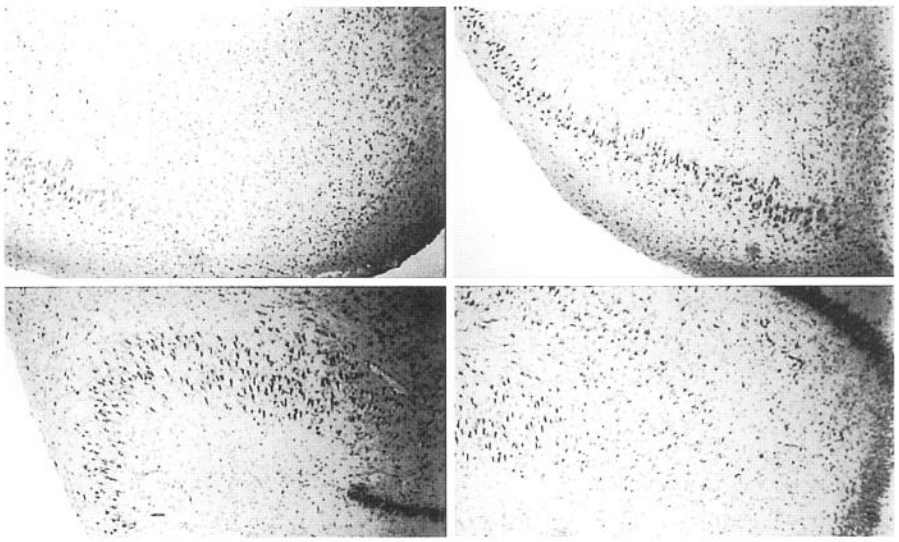

Figure 3. *Hippocampal sclerosis, grade II (Patient 5). High-power views showing 10–50% cell loss in CA1 with sparing of the other sectors (H & E ×40).*

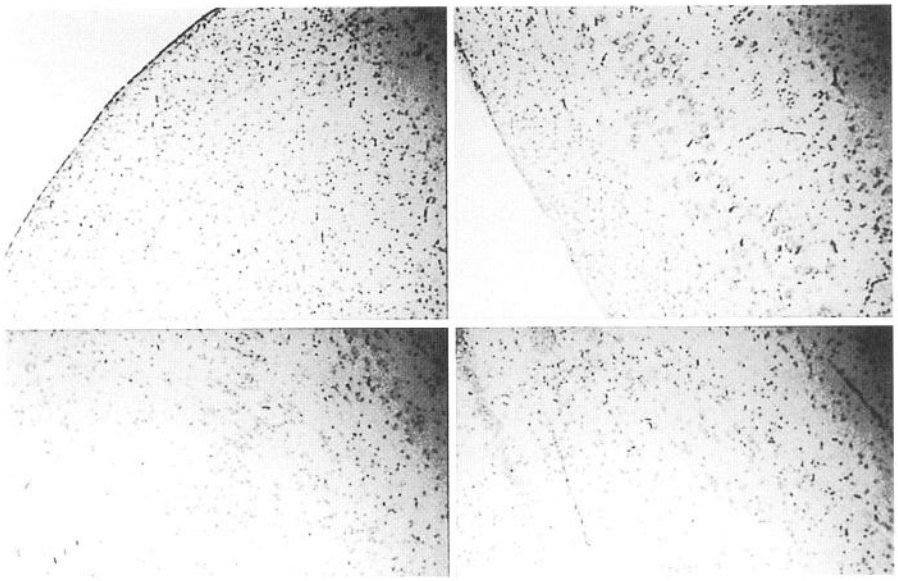

Figure 4. *Hippocampal sclerosis, grade III (Patient 7). High-power views showing >50% cell loss in CA1, 10–50% cell loss in CA4, and sparing of CA2 and CA3 (H & E, ×40).*

dent in 18 patients (90%) and was most commonly moderate to severe (grades III, IV, and V). The 2 patients without hippocampal sclerosis and 1 patient with minimal hippocampal sclerosis had structural lesions involving the medial temporal lobe. In addition, 5 patients (25%) exhibited "dual pathology" in that they had hippocampal sclerosis plus a structural lesion. In these patients, the structural lesions were "developmental" (e.g., cortical dysplasia, heterotopia) or of perinatal onset (e.g., hemispheric hemiatrophy due to birth trauma).

The correlation of the volumetric MRI data with the hippocampal pathology data is shown in Table 3. The correlation of the severity of hippocampal sclerosis with the degree of hippocampal atrophy on MRI was quite good. Normal hippocampal ratios were associated with the absence of hippocampal sclerosis. Mild degrees of hippocampal atrophy (ratios 0.85–0.92) were associated with minimal or mild hippocampal sclerosis (grades I and II) (Fig. 7). Moderate and marked degrees of hippocampal atrophy (ratios 0.60–0.80) were associated with mod-

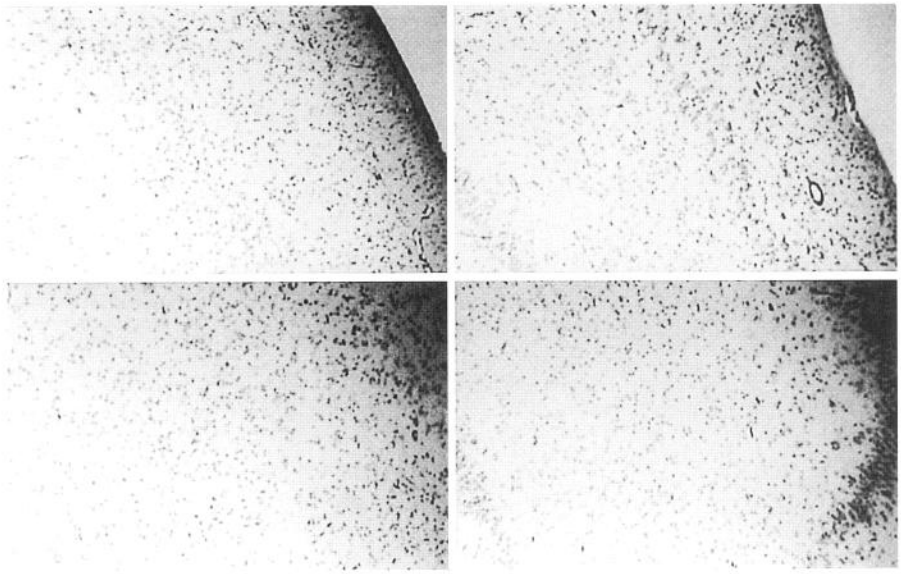

Figure 5. *Hippocampal sclerosis, grade IV (Patient 13). High-power views showing >50% cell loss in CA1, CA3, and CA4 with sparing of CA2 (H & E ×40).*

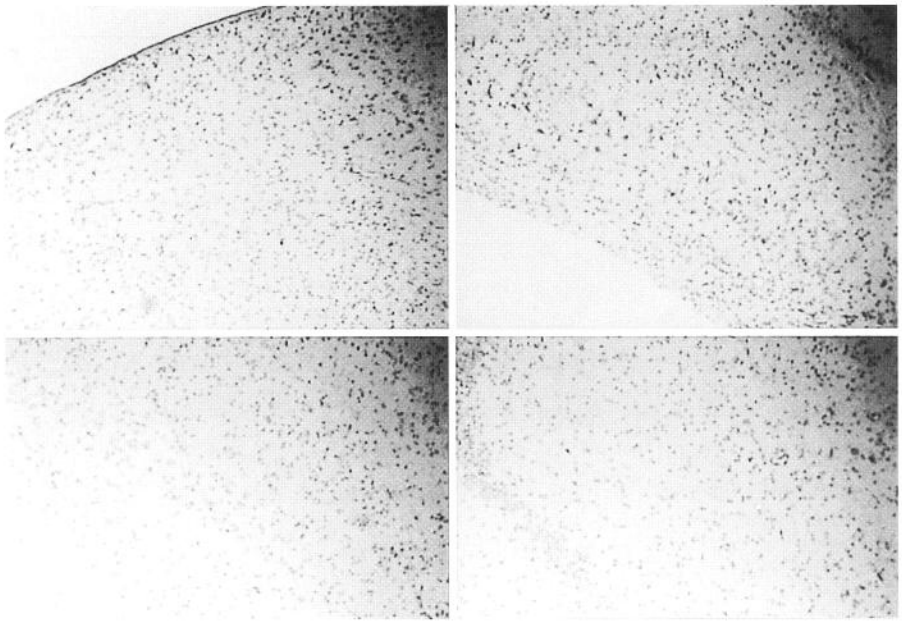

Figure 6. *Hippocampal sclerosis, grade V (Patient 18). High-power views showing >50% cell loss in CA1–CA4 plus some cell loss in the dentate gyrus (H & E ×40).*

erate to marked hippocampal sclerosis (grades III and IV) (Figs. 8 and 9). Severe degrees of hippocampal atrophy (ratios <0.60) were evident in patients with severe hippocampal sclerosis (grade V) (Fig. 10). Therefore, although there was some overlap of hippocampal ratios in patients with grades III and IV hippocampal sclerosis, the degree of hippocampal atrophy on volumetric MRI correlated quite well with the severity of hippocampal sclerosis.

Discussion

Our results confirm the utility of a practical, semiquantitative pathological grading system in assessing the severity of hippocampal sclerosis, the most common cause of medically intractable TLE. The six-tiered system we propose is derived from the system described by Wyler et al. (6) and is meant merely to modify that schema, possibly to become more useful in comparing research results, surgical technique, and outcome assessments. We initially used the five-tiered schema described by Wyler et al. (6). However, we noted that some of our hippocampal specimens showed pathological changes falling between their grades II and III; e.g., Patients 6–9 showed >50% neuronal cell loss in CA1 but <50% cell loss in CA3/CA4 and therefore did not fit into either Wyler grade II or III. Furthermore, we sought to determine whether these patients also had hippocampal volume ratios intermediate to those who would be classified as Wyler grades II and III (our grades II and IV). If so, a slightly more precise correlation would be offered between preoperative hippocampal volumes and ratios and the severity of hippocampal sclerosis. Indeed, this was so, except for some overlap with Patients 10 and 11, indicating that there is a continuum of pathological changes in hippocampal sclerosis.

Our results also indicate that the degree of hippocampal atrophy as measured with preoperative volumetric MRI correlates well with the severity of hippocampal sclerosis as determined by the guide-

Table 2. *Distribution of pathological diagnosis*

Diagnosis	n
HS	18
Grade I	2
Grade II	1
Grade II	4
Grade IV	8
Grade V	3
Dual pathology	5
Heterotopia + HS	1
Cortical dysplasia + HS	1
Heterotopia + cortical dysplasia + HS	1
Heterotopia + gangliocytoma + HS	1
Hemispheric hemiatrophy + HS	1
Heterotopia	1
Epidermoid cyst	1

HS, hippocampal sclerosis.

Table 3. *Temporal lobectomy pathology: HS grade versus MRI hippocampal ratio*

Patient	Hippocampal sector (neuronal cell loss) %				HS grade (0–V)	Preoperative hippocampal ratio (operated/nonoperated)
	CA1	CA2	CA3	CA4		
1	0	0	0	0	0	1.12
2	0	0	0	0	0	0.98
3	0	0	0	<10; Gliosis	I	0.92
4	0	0	0	<10; Gliosis	I	0.87
5	50	0	0	0	II	0.85
6	>50	0	10–50	10–50	III	0.81
7	>50	0	0	10–50	III	0.77
8	>50	0	10–50	10–50	III	0.75
9	>50	0	20	20	III	0.75
10	>50	0	10–50	>50	IV	0.80
11	>50	0	>50	>50	IV	0.77
12	>50	0	>50	>50	IV	0.74
13	>50	0	50	>50	IV	0.69
14	>50	0	>50	10–50	IV	0.69
15	>50	0	50	>50	IV	0.67
16	>50	0	>50	>50	IV	0.64
17	>50	0	?	?	III or IV	0.63
18	>50	>50	>50	>50	V	0.59
19	>50	>50	>50	>50	V	0.59
20	>50	>50	>50	>50	V	0.54

HS, hippocampal sclerosis, MRI, magnetic resonance imaging.

lines of the pathological grading system described herein. These findings agree with the results of previous studies in which both qualitative (8) and quantitative (12) techniques were used. We can now predict the severity of hippocampal sclerosis preoperatively with the use of MRI-based hippocampal volumes and hippocampal ratios. This affords us a powerful tool in the clinical diagnosis and treatment of patients with hippocampal sclerosis and in research into this common cause of medi-

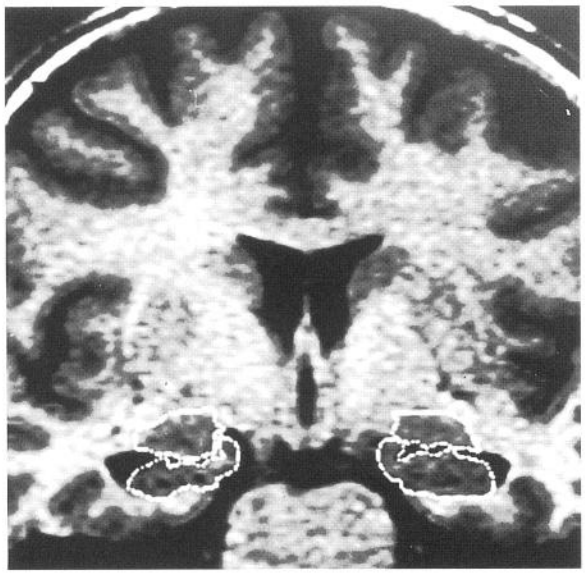

Figure 7. *Coronal magnetic resonance imaging scan (Patient 5) passing through the heads of the hippocampi (lower structures outlined) showing mild right hippocampal atrophy (ratio = 0.85). Upper structures outlined are the amygdalas.*

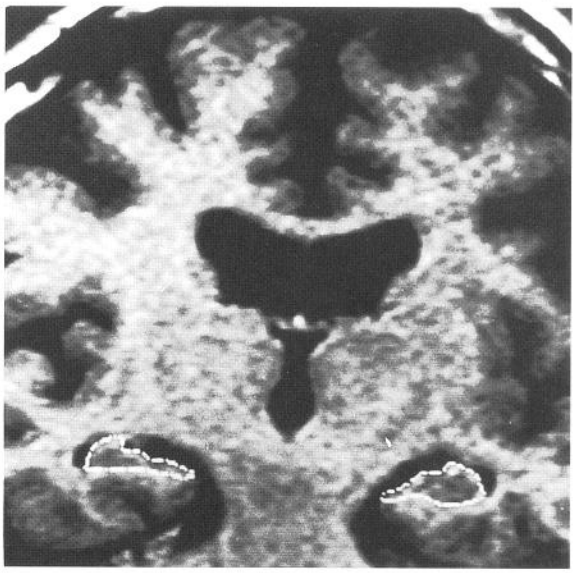

Figure 8. *Coronal magnetic resonance imaging scan (Patient 6) passing through the hippocampal bodies showing moderate right hippocampal atrophy (ratio = 0.81).*

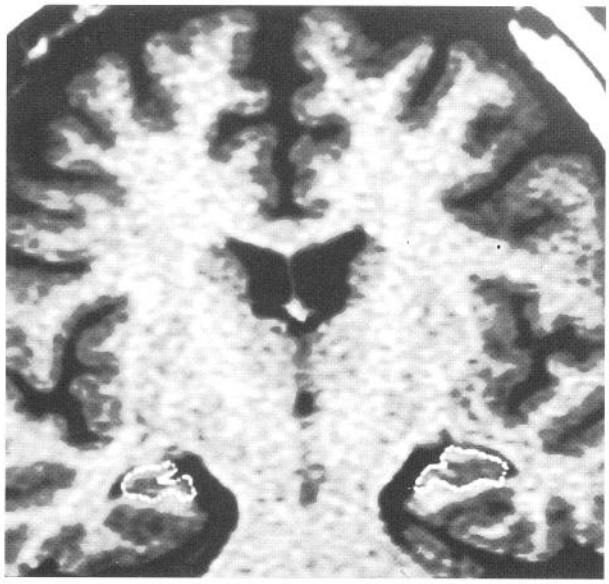

Figure 9. *Coronal magnetic resonance imaging scan (Patient 14) passing through the hippocampal bodies showing marked right hippocampal atrophy (ratio = 0.69).*

cally intractable TLE. We hope that with the accumulation of greater numbers of patients, this relationship will become even more precise and meaningful.

Acknowledgment: This work was supported in part by a grant from the Sutter Institute for Medical Research.

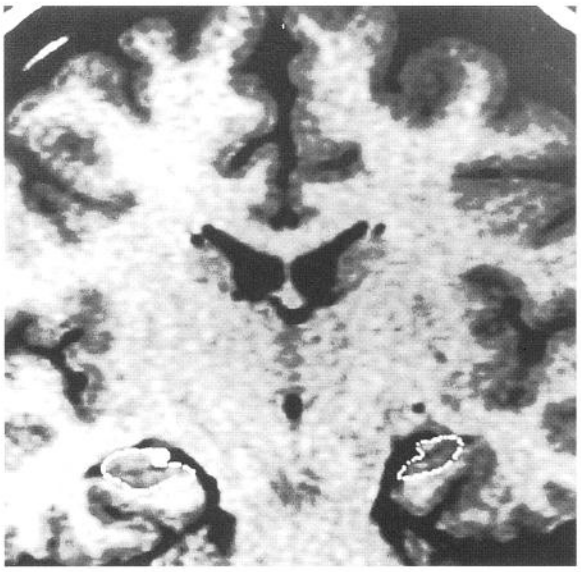

Figure 10. *Coronal magnetic resonance imaging scan (Patient 18) passing through the hippocampal bodies showing severe left hippocampal atrophy (ratio = 0.59).*

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