Specificity of Volumetric Magnetic Resonance Imaging in Detecting Hippocampal Sclerosis

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Background: Magnetic resonance imaging (MRI)–based volumetric measurements of the hippocampal formation are useful in detecting unilateral hippocampal sclerosis (HS) in patients with temporal lobe epilepsy. In this pathologic entity, volumetric MRI analysis shows the epileptogenic structure to be atrophic when compared with the normal, nonepileptogenic side. Some authors have suggested that the radiological features of atrophy of medial temporal lobe structures are common in patients with complex partial seizures, but also are seen frequently in other seizure types and can occur even in patients without epilepsy.

Objective: To determine if seizures originating in extrahippocampal sites cause gliosis, cell loss, and atrophy of medial temporal lobe structures (ie, HS).

Methods: We studied 110 patients with chronic epilepsy using volumetric MRI measurements of the hippocampal formation. Seventeen patients had pathologically proven HS, 27 patients had seizures due to extratemporal structural lesions, 15 patients had seizures caused by extrahippocampal temporal lobe lesions, 29 patients had primary generalized epilepsy, and 22 patients had secondary generalized epilepsy.

Results: All 17 patients with HS showed significantly reduced absolute hippocampal formation volumes of greater than 2 SDs below the mean of the control groups. The preoperative hippocampal formation volume measurements correlated well with the severity of HS on pathological examination. Hippocampal volumes were within the normal range in all patients with primary generalized epilepsy, secondary generalized epilepsy, extratemporal structural lesions, and extrahippocampal temporal lobe lesions.

Conclusions: Seizures originating at extrahippocampal sites do not cause gliosis, cell loss, or atrophy of medial temporal structures. Significant reduction in hippocampal volumes is a specific marker for HS.

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HIPPOCAMPAL sclerosis (HS) is the most common pathologic finding in patients with medically intractable temporal lobe epilepsy. Approximately 60% to 75% of patients undergoing surgical treatment for temporal lobe epilepsy are found to have this pathologic entity. Hippocampal sclerosis is characterized by neuronal cell loss and gliosis involving sectors CA1, CA3, and CA4 of the hippocampus with relative sparing of CA2, the subiculum, and the dentate gyrus. In severe cases of HS all hippocampal sectors, the dentate gyrus, and extrahippocampal structures, such as the amygdala and parahippocampal gyrus, may be involved.[1-4] Since HS is such a common finding in temporal lobe epilepsy, it would be desirable to be able to detect and characterize the condition before surgery.

In recent years, high-resolution magnetic resonance imaging (MRI)-based volumetric measurement of the hippocampal formation has been used in the preoperative evaluation of patients with unilateral temporal lobe epilepsy. Since the initial article by Jack et al,[5] many studies[5-12] have shown the positive correlation between the electroencephalographic (EEG) lateralization of the epileptogenic zone in temporal lobe epilepsy and the presence of significantly reduced hippocampal volumes. Additional studies have found that the volumetric MRI findings of reduced hippocampal volumes correlate with

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PATIENTS AND METHODS

PATIENTS AND CONTROLS

Sixty-one neurologically normal subjects were examined as the control group at Wayne State University School of Medicine, Detroit, Mich (WSU).[33] The mean age of the 30 male subjects was 32 years (SD, 15 years; range, 9-77 years). The mean age of the 31 female subjects was 36 years (SD, 14 years; range, 14-68 years). At the Montreal Neurological Institute and Hospital, Quebec (MNI), the mean age of the 30 control subjects was 32 years (SD, 15 years). Informed consent was obtained for all subjects.

One hundred ten consecutive patients who met criteria for inclusion in 1 of 5 groups were studied prospectively from January 1992 to December 1995. These groups consisted of patients with epilepsy caused by ET lesions (n=27; mean age, 41 years; SD, 15 years), patients with epilepsy caused by EHT lesions (n=15; mean age, 48 years; SD, 18 years), patients with PGE (n=29; mean age, 30 years; SD, 12 years), patients with SGE (n=22; mean age, 26 years; SD, 10 years), and patients with temporal lobe epilepsy caused by pathologically proven HS (n=17; mean age, 34 years; SD, 12 years). Mean age of seizure onset and duration of epilepsy, respectively, for each of the 5 groups were as follows: ET, 27 and 13 years; EHT, 33 and 15 years; PGE, 13 and 16 years; SGE, 5 and 21 years; and HS, 10 and 23 years.

Criteria for inclusion in 1 of the 5 groups were based on clinical features such as seizure history, including early risk factors, family history, physical examination, and seizure semiologic findings; interictal and ictal EEG findings; qualitative MRI findings; and in some cases fludeoxyglucose F 18–positron emission tomographic scan findings. As the number of patients in some of the groups (ET, PGE, and SGE) accumulated, we reported our findings in separate publications,[29,31,32] and additional information concerning inclusion criteria can be found in those sources. Additionally, some patients met criteria for more than 1 group (eg, ET and SGE), but for the purposes of this analysis they were included in only 1 category as described herein.

ET GROUP

Five patients from our original group[29] were removed from this group for this analysis. Two patients had large multilobar structural lesions involving the temporal lobe as well as extratemporal regions. They were therefore included in the EHT group for this analysis. Three others had large and/or multifocal extratemporal lesions but were felt to be more appropriately included in the SGE group. Two additional patients with extratemporal lesional epilepsy were added to this group after the publication of our initial study.[29] Fifteen of the 27 patients underwent surgical procedures with excellent outcome (Engel grade I or II) unless the structural lesion could not be completely removed. Twelve patients did not undergo surgical procedures, either because the lesion could not be resected safely or because the patient refused surgery, and all but 1 of these patients continued to have intractable seizures.

EHT GROUP

Nine of the 15 patients in this group underwent surgical procedures with 6 patients experiencing an excellent outcome. The 3 patients with poor outcomes had incomplete excision of their lesions. Only 2 of the 6 patients not undergoing surgical procedures were able to have their seizures controlled with medications.

PGE GROUP

One of the original patients included in this group[31] was later felt to be more appropriately included in the SGE group.[32] Nine additional patients were added to this group after the publication of our initial study.[31] Of course, none of these patients underwent surgical procedures.

SGE GROUP

None of these patients received surgical treatment for their refractory epilepsy. All 22 of these patients were included in our initial study.[32]

HS GROUP

All 17 of these patients underwent temporal lobectomy and all experienced an excellent outcome (Engel grade I or II). Four of the patients in the HS group also had dual pathology (3 with developmental lesions and 1 with cerebral hemiatrophy caused by birth trauma).

MRI ACQUISITION

Magnetic resonance imaging studies were performed at 1.5 T using thin (1.5- to 3-mm-thick) coronal inversion recovery or spoiled gradient echo sequences following protocols described previously.[9,29]

MRI ANALYSIS

The MRI images were transferred to a computer workstation and volumetric measurements were performed with an interactive semiautomated software package developed at our institutions. In this study the contours of the hippocampus and amygdala were performed entirely with a manual contouring function because of the complexity of the structures involved. Once the outline of the hippocampus or amygdala had been defined, a slice volume was calculated by multiplying the area outlined by slice thickness. The total volume of the structure (amygdala or hippocampus) was then calculated by adding the slice volumes. At WSU the absolute volumes were compared with those of a large control group of the same gender. At MNI the absolute volumes were normalized as described previously[9] so that patients with different brain sizes could be compared directly with one another.

VOLUMETRIC ANALYSIS

Anatomical guidelines for outlining the amygdala and hippocampal formation followed a specific protocol described

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previously.[9,34] Reliability studies to detect the extent of intrarater consistency and interrater variation have also been reported previously.[9,34-36] The absolute volumes of the 2 amygdalae and the 2 hippocampi were compared with our normal control populations. We also analyzed the degree of asymmetry between sides by calculating a ratio of the smaller to the larger volume for both the amygdalae and the hippocampi. Absolute volumes greater than 2 SDs below the mean of the control groups and amygdaloid and hippocampal ratios less than 0.90 were considered abnormal.

STATISTICAL ANALYSIS

Before the data could be analyzed, 2 issues related to the validity of pooling volumetric measurements from the MNI patients, the WSU male patients, and the WSU female patients had to be addressed. First, across sites (WSU vs MNI) the possibility of systematic differences in measurements caused by differences in equipment, imaging parameters, volumetric analysis software, raters, and other factors beyond our control had to be accounted for. Second, as absolute hippocampal and amygdaloid volumes are known to vary with brain size, and brain size is known to vary with gender, for the WSU patients a method was needed to equate these measurements for males and females (this was not required for the MNI data, which were already corrected for total brain volume).

Similar issues commonly arise in psychometrics and neuropsychologic research, where it is often necessary to equate raw scores from patients who differ in sex, age, and other factors that are known to systematically influence performance on neuropsychologic measures. In such instances, 1 solution is to transform raw scores into standardized scores that express a subject's performance relative to an appropriate control or normative sample. In research, the most commonly used standardized score, the z score, expresses the original raw score (x) as a deviation from the mean of an appropriate control or comparison group (x-$\bar{x}$) in SD units ($z=[x-\bar{x}]/s$, where $\bar{x}$ and s are taken from the control group). For example, a z score of -2.5 corresponds to a raw score that is 2.5 SDs below the mean of the control group, a z score of 3.0 corresponds to a raw score that is 3 SDs above the mean of the control group, and so on. In this manner, provided that measurements taken across samples do, in fact, measure the same thing (eg, hippocampal volume) and provided that the measurements are transformed using the means and SDs of an appropriate control group, the resulting z scores will form an equivalent scale of measurement across samples that also takes into account systematic differences in measurement across those scales or groups.

Four measures were of interest in this study and were calculated for each patient: total amygdaloid volume (left plus right), total hippocampal volume (left plus right), ratio of the smaller amygdala to the larger amygdala, and ratio of the smaller hippocampus to the larger hippocampus. The raw volumetric measurements for the MNI patients, the WSU male patients, and the WSU female patients were transformed to z scores using means and SDs of volumetric measurements from the MNI control subjects, the WSU male control subjects, and the WSU female control subjects, respectively. Note that to maintain a common scale (z scores) across measures, total amygdaloid and total hippocampal volumes were calculated and analyzed and are reported in this article as the average of the z scores for the left and right volumes (ie, [left $\pm$ right volume]/2). For statistical purposes, use of the total volume or a constant transformation of the total (in this case the total divided by 2, or average volume) has no effect on the results of inferential tests. In the interests of brevity, these averages are referred to as total volumes hereafter.

Each of the 4 measures was used as the dependent variable in 1-way analysis of variance (ANOVA) tests with the diagnostic group (PGE, SGE, ET, EHT, or HS) forming the independent variable. Where a significant omnibus F ratio was found, post hoc pairwise comparisons of means using the Tukey Honestly Significant Difference method were used to identify significant differences between groups.

neuropathologic findings,[13-16] neuropsychologic abnormalities,[14,17-20] and outcome after temporal lobectomy.[21-23] Our prior study[9] showed that hippocampal volumes alone agreed with the extracranial and/or intracranial EEG lateralization of the epileptogenic region in 87% of cases and that combined hippocampal and amygdaloid volumes agreed with EEG lateralization in 93% of cases. Therefore, MRI-based volumetric measurements of the hippocampal formation and amygdala appear to be sensitive in lateralizing the epileptogenic region.

A second question concerns the specificity of hippocampal volume measurements. Some studies[24-26] have suggested that the volumetric MRI features of atrophy of medial temporal lobe structures are common in patients with complex partial seizures but also are seen frequently in other seizure types, in patients with lesional epilepsy, and even in patients without epilepsy. Others have measured the specificity of volumetric MRI studies and obtained different values.[5,27] A central question is whether frequent seizures originating at sites other than the hippocampus and amygdala cause cell loss and subsequent atrophy of those structures, thereby resulting in significantly reduced hippocampal and amygdaloid volumes. If that were the case, significant reduction of hippocampal and amygdaloid volumes would be much less specific to the pathologic entities of HS and amygdaloid sclerosis. Under those circumstances the ability of volumetric MRI to aid in the differentiation between seizures arising from medial temporal, lateral temporal, and extratemporal sites would be limited. Recently, we and others have begun to study this question by investigating groups of patients with seizures originating in extrahippocampal sites.[7,28-32] In this article we present an analysis of our cumulative findings in 110 consecutive patients, studied prospectively, with epilepsy caused by extratemporal (ET) lesions, extrahippocampal temporal lobe (EHT) lesions, primary generalized epilepsy (PGE), secondary generalized epilepsy (SGE), and pathologically proven HS.

Volumetric Measurements for the MNI, WSU Male, and WSU Female Control Groups*

Control Group	Amygdala			Hippocampus		
	Right, mm³	Left, mm³	Ratio	Right, mm³	Left, mm³	Ratio
MNI	2844 (261)	2812 (251)	0.97 (0.02)	4671 (271)	4564 (254)	0.97 (0.02)
WSU males	2777 (329)	2763 (320)	0.97 (0.02)	4273 (412)	4225 (417)	0.98 (0.02)
WSU females	2365 (291)	2359 (298)	0.97 (0.02)	3663 (352)	3603 (345)	0.97 (0.02)

*Data are expressed as mean (SD). MNI indicates Montreal Neurological Institute and Hospital; WSU, Wayne State University.

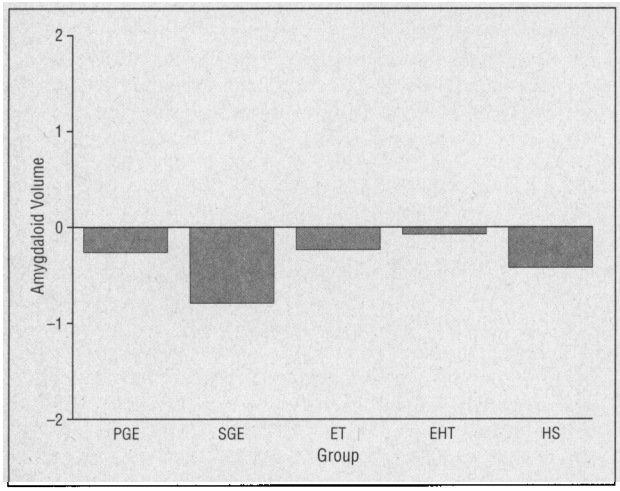

Figure 1. *Mean amygdaloid volumes for the groups expressed as z scores (SDs from the mean volumes of control subjects). PGE indicates primary generalized epilepsy; SGE, secondary generalized epilepsy; ET, extratemporal structural lesion; EHT, extrahippocampal temporal lesion; and HS, hippocampal sclerosis.*

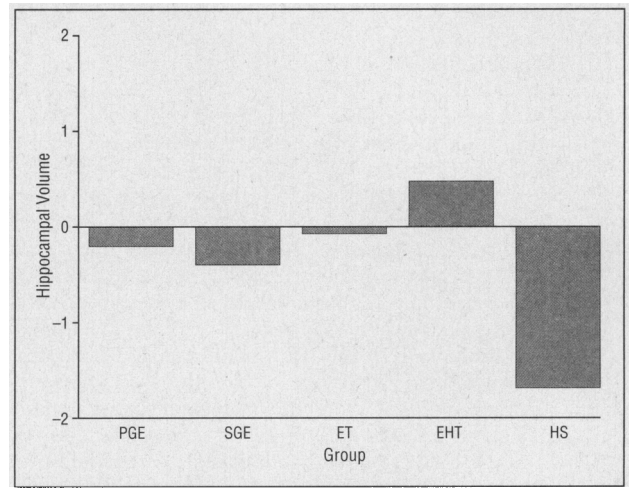

Figure 2. *Mean hippocampal volumes for the groups expressed as z scores. For an explanation of abbreviations, see Figure 1.*

RESULTS

The means and SDs for right amygdaloid volume, left amygdaloid volume, ratio of the smaller to the larger amygdala, right hippocampal volume, left hippocampal volume, and ratio of the smaller to the larger hippocampus for the MNI, WSU male, and WSU female control groups are summarized in the **Table**. These values were used to standardize the patient amygdaloid and hippocampal total volumes and ratios to *z* scores as described herein.

The mean standardized amygdaloid and hippocampal volumes and ratios for each of the patient groups are presented in **Figure 1** through **Figure 4**. Visual inspection of Figure 1 suggested that there were no significant differences between the groups with regard to total amygdaloid volume. One-way ANOVA confirmed this impression ($F_{(4,97)}=1.68$; $P>.01$).

As shown in Figure 2, visual inspection of the group means for total hippocampal volume suggested that this value was lowest in the HS group. This impression was confirmed by 1-way ANOVA ($F_{(4,105)}=7.66$; $P<.01$). Post hoc tests using the Tukey method ($\alpha=.05$) revealed that the HS group had significantly lower total hippocampal volume than all other groups and that none of the other groups were significantly different from each other. Indeed, contrast (L) of the presence vs absence of HS accounted for about 20% ($L=-1.650$; $F_{(1,105)}=27.02$; $P<.01$; $R^2=0.199$) of the total variability in hippocampal volume.

With regard to amygdaloid volume ratios (smaller: larger, Figure 3), 1-way ANOVA indicated significant differences between the groups ($F_{(4,97)}=4.90$; $P<.01$). Post hoc tests using the Tukey method ($\alpha=.05$) indicated that the HS group showed a significantly smaller ratio (ie, greater asymmetry) than did the PGE and ET groups. However, the difference between the HS group and the SGE and EHT groups did not reach statistical significance (although the trend was in the same direction, with the ratio of HS smaller than SGE and EHT).

The mean hippocampal volume ratios (smaller: larger) for the groups are shown in Figure 4. This figure shows a striking difference in the mean ratio for the HS group vs all others, with this group falling some 12 SDs below the mean for control subjects. One-way ANOVA confirmed this impression ($F_{(4,105)}=114.13$; $P<.01$). Post hoc Tukey tests ($\alpha=.05$) demonstrated that the mean hippocampal ratio of the HS group was significantly lower than that of all other groups and that none of the other groups were significantly different from each other. The presence vs absence of HS accounted for almost 80% of the variability in hippocampal volume ratios ($L=-12.054$; $F_{(1,105)}=451.58$; $P<.01$; $R^2=0.804$), which is a robust effect.

We also sought to determine if age of seizure onset and duration of seizures were related to reduction in hip-

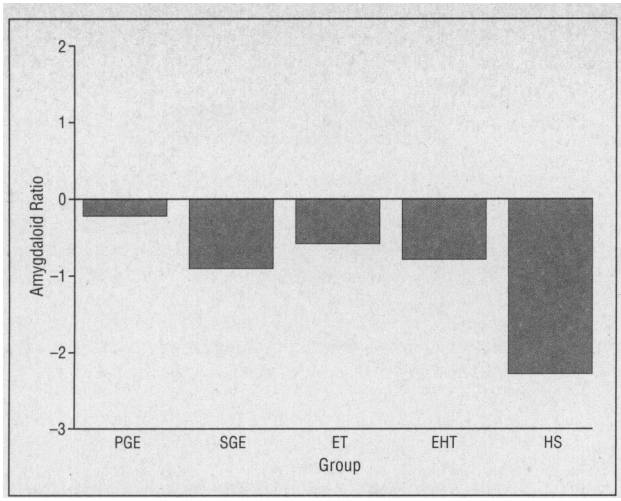

Figure 3. *Mean amygdaloid (smaller-larger) ratios for the groups expressed as z scores. For an explanation of abbreviations, see Figure 1.*

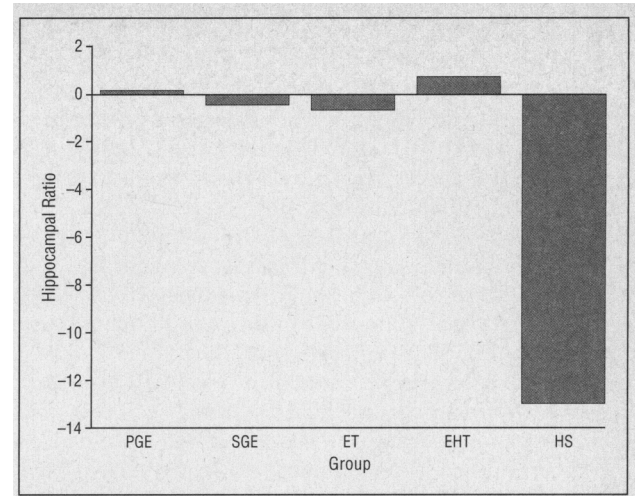

Figure 4. *Mean hippocampal (smaller-larger) ratios for the groups expressed as z scores. For an explanation of abbreviations, see Figure 1.*

pocampal and amygdaloid volumes. This was tested using analysis of covariance (ANCOVA) to partial out the contribution of age of seizure onset and duration of seizures prior to retesting the effect of diagnostic group on the 4 volumetric variables. In none of the 4 analyses did age of seizure onset or seizure duration make a statistically significant contribution to the ANCOVA model. The relationship between diagnostic group and total amygdaloid volumes controlling for age of onset and duration of seizures remained nonsignificant ($F_{(4,95)}=0.53$; $P>.01$). Statistically significant relationships between diagnostic group and total hippocampal volume ($F_{(4,103)}=5.10$; $P<.01$), amygdaloid volume ratios ($F_{(4,95)}=4.08$; $P<.01$), and hippocampal volume ratios ($F_{(4,103)}=107.20$; $P<.01$), with effect sizes comparable to those found using simple ANOVA, were still found. Thus, age of seizure onset and seizure duration cannot account for the results of the analyses described herein.

COMMENT

This study demonstrates that this consecutive series of patients with epilepsy caused by ET lesions, EHT lobe lesions, PGE, and SGE do not have significant reductions in their amygdaloid and hippocampal volumes. Most of our patients suffered from epilepsy for many years without apparent damage to hippocampal and amygdaloid structures.

Our data agree with most prior investigations that found either no reduction in hippocampal volumes in patients with ET lesions[7,29] or a relatively low incidence of "dual pathology," a condition in which the patient has both HS and a potentially epileptogenic structural lesion.[28,30] Cook et al[7] found that none of their patients with frontal lobe epilepsy showed decreased hippocampal volumes. Ten of their 20 patients had frontal lobe structural lesions. None of the patients in our initial study with epilepsy caused by ET lesions had reduced hippocampal or amygdaloid volumes.[29] Cascino et al[28] found 1 patient (6%) in their series of 18 patients with ET lesional epilepsy who had reduced hippocampal volumes. In a multicenter study recently reported,[30] we studied 167 patients with EHT and ET lesions and found only 25 patients (15%) with dual pathology. Gilmore et al[37] have also recently reported that volumetric MRI was exceedingly helpful in distinguishing temporal from extratemporal epilepsy. Likewise, our previous reports of patients with long-standing PGE[31] and SGE[32] failed to show reduction of hippocampal or amygdaloid volumes in any of the patients.

Our findings support an incidence of dual pathology in the range of 10% to 15% of cases of lesional epilepsy. However, certain types of structural lesions, such as developmental abnormalities, may exhibit a higher incidence of coexisting HS.[30] Of our patients, 24% in the HS group exhibited dual pathology, and 3 of those 4 patients had neuronal migration disorders. This may account for some of the differences found in other studies.[24,25] The best approach to the treatment of patients with dual pathology is presently unknown. Further studies involving larger numbers of patients are needed to define the best surgical approach in this group of patients.

Our study also demonstrates that patients with pathologically proven HS have significantly reduced hippocampal volumes. This confirms prior studies[13-16] that showed a strong relationship between the degree of hippocampal volume loss and the severity of HS on pathological examination. These findings have been consistent in studies that used qualitative,[13] semiquantitative,[16] and quantitative[14,15] neuropathologic techniques. On the basis of these studies, it appears that the severity of HS can be predicted preoperatively with the use of MRI-based hippocampal volumes and hippocampal ratios. Therefore, significant reduction in hippocampal volumes appears to be a specific marker for HS.

The findings concerning the amygdala are similar although less statistically powerful. Seven (41%) of our patients with HS had amygdaloid ratios of less than 0.90, but of those 7 only 1 patient's smaller amygdaloid volume was greater than 2 SDs below the mean of the control group. Thus, the amygdaloid ratio is much more sensitive in detecting the abnormal condition than absolute amygdaloid volumes, as can be seen by comparing Figures 1 and 3.

These findings agree with our previous study[9] that showed amygdaloid volumes to be less sensitive than hippocampal volumes (67% vs 87%) in lateralizing the epileptogenic region. We have also reported[38] a subgroup of patients with temporal lobe epilepsy who experience a fear reaction accompanied by a rising epigastric sensation as the initial manifestation of their seizures. This group of patients exhibits significantly smaller amygdaloid volumes than patients without these symptoms and therefore represents a subgroup of patients in which analyses of amygdaloid volumes are more helpful. In our present group of patients with HS, none exhibited isolated amygdaloid sclerosis without HS, as has been described recently by Hudson et al.[39] Our hypothesis is that this group of patients would show isolated amygdaloid atrophy when studied with volumetric MRI, but this will need to be proven with future studies involving large numbers of patients.

On the other hand, some qualifying statements are in order. A few cases of pathologically proven HS have been reported in patients with normal volumetric MRI study results,[40] and therefore one cannot rely solely on volumetric MRI in the evaluation of patients with intractable temporal lobe epilepsy.

Patients who have seizures originating from each temporal lobe independently are a particularly difficult group of patients to deal with in a surgical epilepsy program. Preliminary studies seem to indicate that volumetric MRI may be useful in helping to make those surgical decisions.[41-47] Even though bilateral hippocampal atrophy may be present on volumetric MRI studies, if the more profoundly atrophic side coincides with the side of more frequent seizure onsets, as determined by scalp or intracranial video EEG recording, temporal lobectomy may prove helpful in controlling the patient's seizures.[21,42,44,46,47] However, the use of intracranial EEG is usually critical to establish localization and lateralization of the epileptogenic region in patients with bilateral independent temporal ictal onsets.[48-51]

Obviously, when dealing with bilateral hippocampal atrophy, one must use the absolute hippocampal volumes and their relationship to the normal control group rather than the ratio of one side to the other. If one uses the hippocampal ratio only, no asymmetry or abnormality may be detected.

Finally, it should be emphasized that volumetric MRI is neither a sensitive nor specific tool for the lateralization or localization of temporal lobe seizures of nonhippocampal or neocortical origin, unless dual pathology is present. Other neuroimaging modalities, such as positron emission tomography, ictal single photon emission computed tomography, or magnetic resonance spectroscopy, are likely to be superior to volumetric MRI in this clinical setting.

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