

Normal magnetic resonance imaging and medial temporal lobe epilepsy: the clinical syndrome of paradoxical temporal lobe epilepsy

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Object. The syndrome of medial temporal lobe epilepsy (MTLE) may occur in patients in whom magnetic resonance (MR) images demonstrate normal findings. In these patients, there is no evidence of hippocampal sclerosis on neuroimaging, and histopathological examination of the resected hippocampus does not reveal significant neuron loss. In this paper the authors describe the distinct clinical features of this MTLE subtype, referred to as paradoxical temporal lobe epilepsy (PTLE).

Methods. The authors selected 12 consecutive patients with preoperative findings consistent with MTLE in whom MR imaging did not demonstrate any hippocampal abnormality. Onset of hippocampal seizure was confirmed by long-term intracranial monitoring. There were six female and six male patients with a mean age of 32 ± 11 years (mean \pm standard deviation [SD]) at presentation. These patients' seizure histories, available hippocampal volumetric measurements, and hippocampal cell densities in different subfields were reviewed. Sharp electrode recordings from dentate granule cells that had been maintained in hippocampal slices provided a measure of excitation and inhibition in the tissue. We compared these data with those of a cohort of 50 randomly selected patients who underwent anteromedial temporal resection for medial temporal sclerosis (MTS) during the same time period (1987–1999). The durations of follow up (means \pm SDs) for the PTLE and MTS groups were 51 ± 59 months and 88 ± 44 months, respectively.

A history of febrile seizure was present less frequently in the PTLE group (8%) than in the MTS group (34%). Other risk factors for epilepsy such as trauma, meningoencephalitis, or perinatal injuries were present more frequently in the PTLE group (50%) than in the MTS cohort (36%). In patients in the PTLE group the first seizure occurred later in life (mean age at seizure onset 14 years in the PTLE group compared with 9 years in the MTS group, $p = 0.09$). Ten patients (83%) in the PTLE cohort and 23 patients (46%) in the MTS cohort had secondary generalization of their seizures. Among patients with PTLE, volumetric measurements (five patients) and randomized blinded visual inspection (seven patients) of the bilateral hippocampi revealed no atrophy and no increased T_2 signal change on preoperative MR images. All patients with PTLE underwent anteromedial temporal resection (amygdalohippocampectomy, in five patients on the left side and in seven on the right side). Electrophysiological studies of hippocampal slices demonstrated that dentate granule cells from patients with PTLE were significantly less excitable than those from patients with MTS. The mean pyramidal cell loss in the CA1 subfield in patients in the PTLE group was 20% (range 0–59%) and that in patients in the MTS group was 75% (range 41–90%) ($p < 0.001$). Maximal neuron loss (mean loss 38%) occurred in the CA4 region in six patients with PTLE (end folium sclerosis). At the last follow-up examination, six patients (50%) in the PTLE group were seizure free compared with 38 patients (76%) in the MTS group.

Conclusions. Clinical PTLE is a distinct syndrome with clinical features and surgical outcomes different from those of MTS.

KEY WORDS • temporal lobe epilepsy • hippocampal sclerosis • paradoxical temporal lobe epilepsy • epilepsy surgery • outcome

MEDIAL temporal sclerosis is the most common substrate responsible for epileptogenesis among patients with TLE.^{15,16,55} The characteristic features of MTS on MR imaging include an atrophic hippocampus with a hyperintense signal on long repetition time sequences.^{4,6,21,22,24,25} The degree of hippocampal atrophy correlates directly with the severity of pyramidal cell loss in the cornu

ammonis subfields, especially in CA1.⁸ Patients with MTS who are refractory to medical therapy have a 70 to 90% chance of achieving freedom from seizure after they have undergone anteromedial temporal lobe resection.^{24,31}

The pathogenesis of hippocampal sclerosis may involve an injury acquired during early life (when the patient is younger than 5 years of age) combined with primary or secondary hippocampal atrophy associated with chronic epilepsy.³⁸ Previous reports, however, have suggested that up to 15% of patients with the diagnosis of MTLE may have normal hippocampal volumes on MR imaging.²⁶ This subgroup of patients presents with clinical and scalp EEG findings consistent with MTLE but, paradoxically, no appreciable hippocampal atrophy or signal changes on T_2 -weighted MR

Abbreviations used in this paper: EEG = electroencephalography; EPSP = excitatory postsynaptic potential; FSIQ = full-scale intelligence quotient; IPSP = inhibitory postsynaptic potential; MR = magnetic resonance; MTLE = medial temporal lobe epilepsy; MTS = medial temporal sclerosis; PTLE = paradoxical temporal lobe epilepsy; SD = standard deviation.

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images, even though the hippocampus is considered the most likely electrographic seizure generator observed during long-term intracranial electrode monitoring. We have designated this subgroup of MTLT as PTLE. We have previously reported immunohistopathological changes in a similar group of patients.¹³ In this report, we attempt to define clinical, electrophysiological, and additional pathological characteristics of patients with PTLE and provide an analysis of surgical outcomes in these patients.

Clinical Material and Methods

Patient Population

The epilepsy surgery database at the Yale–New Haven Medical Center was searched to find all patients who underwent temporal lobectomy between 1987 and 2002. Among the 350 patients yielded by this search, we found 12 patients whose preoperative MR images lacked evidence of hippocampal atrophy or signal changes on T₂-weighted and fluid-attenuated inversion recovery sequences, despite the occurrence of a medial temporal lobe seizure confirmed by long-term intracranial monitoring. Two of the 12 patients had other lesions distinguishable on MR imaging (one had a frontal abnormality due to trauma and another had a contralateral nonspecific temporal lesion later diagnosed on biopsy to be gliosis). There were six female and six male patients with a mean age of 32 ± 11 years (mean \pm SD) at presentation. Eleven patients were right handed and one was left handed. These 12 patients were compared with a cohort of 50 randomly selected patients who underwent anteromedial temporal lobe resection for MTS during the same time period. Among the PTLE group, the duration of epilepsy was 20 ± 12 years and the seizure frequency was 9 ± 12 (means \pm SDs) per month. Among the MTS group the duration of epilepsy and the seizure frequency was 21 ± 8 years and 9 ± 16 per month (means \pm SDs), respectively. The duration of follow up for the PTLE group was 51 ± 59 months and that for the MTS cohort was 88 ± 44 months (means \pm SDs).

Preoperative Evaluation

We specifically inquired about each patient's epilepsy risk factors including a family history of seizures or history of head trauma associated with a loss of consciousness, febrile seizures before the age of 4 years, perinatal difficulties, and meningoencephalitis. A comprehensive preoperative epilepsy assessment included continuous video-EEG recordings, high-resolution MR imaging designed for patients with epilepsy,³² neuropsychometric studies, and intracarotid amyltal evaluation (Wada testing). Patients treated recently also underwent positron emission tomography imaging and single-photon computerized tomography scanning. No hippocampal atrophy was observed in the PTLE cohort: in five patients this negative finding was based on hippocampal volumetry performed according to a previously described method⁴⁸ and in seven patients it was based on detailed visual inspection by a reviewer blinded to the study. All these patients underwent an intracranial EEG evaluation in which grids, strips, and depth electrodes were used. Based on extraoperative video-EEG monitoring, the amygdala and hippocampus were considered the only epileptogenic regions.

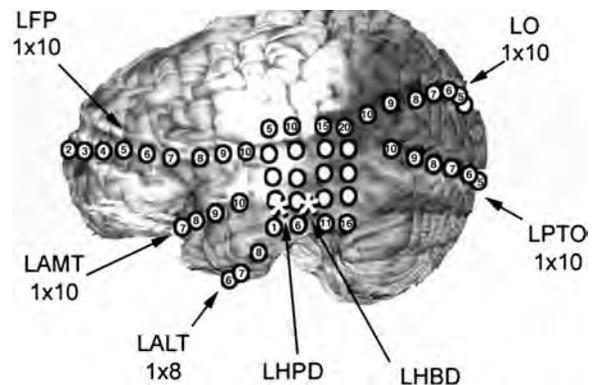


FIG. 1. Schematic representation of the brain showing the locations of intracranial electrodes for patients with presumed TLE and no localizing imaging findings. The asterisks marked in the lateral temporal neocortex represent two hippocampal depth electrodes placed in the hippocampal pes and body. LALT = left anterolateral temporal strip; LAMT = left anteromedial temporal strip; LFP = left frontoparietal strip; LHBD = left hippocampal body depth electrode; LHPD = left hippocampal pes depth electrode; LO = left occipital strip. Numbers underneath labels indicate number of rows \times number of electrodes.

Language and verbal memory assessments were performed preoperatively and 1 year after surgery when possible by using Wechsler Memory Scales and the verbal selective reminding test. Standard scoring of verbal selective reminding test results provide measures of total recall, long-term memory storage, and long- and short-term memory retrieval.^{32,35,41–44,52}

Intracranial Study

The results of preoperative studies, including EEG localization studies, were reviewed. If preoperative EEG reports were unclear, we reviewed the original EEG tracings and operative mapping results. Data obtained in patients were evaluated with the knowledge their imaging findings were consistent with PTLE, but without an a priori knowledge of their final seizure outcomes.

In all patients depth electrodes were placed within the suspected epileptogenic hippocampus. Of these 12 patients, nine underwent bilateral and three underwent unilateral hippocampal depth electrode placement. We implanted subdural grid or strip electrodes unilaterally in the three patients with unilateral depth electrodes, bilaterally in five of the nine patients with bilateral depth electrodes, and unilaterally in two of the nine patients with bilateral depth electrodes. The first two patients admitted to this study did not undergo subdural electrode monitoring. Subdural electrode implantation involved the placement of a small grid over the lateral temporal neocortex followed by placement of one or two basotemporal strips and one anteromedial strip along the long axis of the parahippocampal gyrus (Fig. 1).¹² Hippocampal depth electrodes were implanted parallel or perpendicular to the long axis of the hippocampus.

The additional trauma-induced frontal abnormality in one patient and the contralateral nonspecific temporal lesion in another patient were covered by intracranial electrodes. We determined that these lesions did not contribute electrically to seizure generation in these two patients.

TABLE 1
Clinical features of 12 patients with PTLE*

Case No.	Age (yrs), Sex	Febrile Seizure	Predisposing Factor	Seizure		Video-EEG Localization	Seizure Origin Based on Intracranial EEG	Follow Up (mos)	Outcome
				Age at Onset	Duration (yrs)				
1	30, M	no	trauma	20	12	lt temporal	3 lt HC, 1 contralat temporal neocortex	69	3
2	35, F	no	none	2	31	rt temporal	7 rt mid HC & 1 ipsilat temporal neocortex	39	2
3	44, F	—	none	1	43	rt temporal	5 rt HC, 2 inf temporal gyrus	25	2
4	23, M	yes	none	4	23	rt temporal	rt ant & mid HC	11	1
5	16, M	no	trauma	5	11	lt temporal	3 lt anterior HC, 1? lt mid HC	37	1
6	17, F	no	trauma	10	7	lt hemisphere	3 lt anterior HC, 1? rt HC	175	3
7	50, F	no	none	34	16	rt mid tem- poral	rt mid HC & PH gyrus	99	1
8	24, F	no	none	18	4	lt temporal	lt HC & PH	14	1
9	27, M	no	trauma	8	30	rt mid tem- poral	rt ant HC	90	4
10	40, M	no	trauma	34	4	rt temporal	rt HC	18	1
11	36, F	—	none	8	28	rt temporal	rt HC	2	1
12	44, M	no	trauma	21	26	lt temporal	lt HC/amygdala	35	4

* HC = hippocampus; mid = middle; PH = parahippocampus; ? = questionable electrographic changes in the assigned electrode; — = unknown.

† Based on the modified Engel Scale.

Resection Procedures

All patients underwent a standard anteromedial temporal lobe resection as described previously.⁴⁷ Briefly, a fronto-temporal craniotomy was performed in the standard fashion and the lateral temporal neocortex was exposed. The superior temporal gyrus was spared and 3 to 3.5 cm of the middle and inferior temporal gyri, as measured from the temporal pole, were resected to expose the temporal horn of the lateral ventricle. The exposure of the hippocampus was then extended by dissection of the occipitotemporal fasciculus and gentle lateral retraction of the temporal neocortex. The amygdala was sampled but primarily resected using ultrasonic aspiration; the hippocampus and parahippocampal gyrus were removed en bloc. The resection of the hippocampus was extended to the point at which the tail of this structure curved around the brainstem.

Histopathological and Electrophysiological Studies

We used a coronal section of the midbody of the hippocampus for histopathological morphometry. The tissue was fixed in formalin overnight at room temperature. The tissue was then dehydrated using graded alcohol, washed with xylene, and embedded in paraffin. The extent of pyramidal neuron loss in every hippocampal subfield (CA1–4 and the dentate gyrus) was determined using a previously described method.²⁸ These data were compared with those obtained from autopsy controls.

A midbody slice of resected hippocampus was also selected for electrophysiological studies. For these experiments, we used standard physiological techniques to record synaptic events from dentate granule cells.⁵³ Briefly, we examined the following physiological criteria used to assess the synaptic excitability of these cells:⁵⁴ 1) the ability of cells to fire multiple spikes in response to molecular layer (orthodromic) stimulation; 2) the ability to evoke an

IPSP; 3) the number of presumed polysynaptically mediated events associated with synaptic stimulation; and 4) the frequency of spontaneous excitatory events. Values obtained in these analyses were added to generate an excitability index. With the exception of the IPSP data, larger values are associated with a more severe hippocampus pathological condition. For the analyses, data from both PTLE and MTS tissues were normalized using values obtained from the control hippocampi. These control hippocampi were obtained from patients with extrahippocampal tumors in whom the hippocampus had been resected to assure freedom from seizure. These hippocampi therefore were our best “normal” comparison tissue based on anatomical data.

Statistical Analysis

Data are presented as means \pm SDs. The Student t-test and chi-square statistical methods were used to compare continuous and categorical variables, respectively. We performed an analysis of variance to compare electrophysiological parameters in the hippocampal slice recordings.

Results

Patient Characteristics

A history of febrile seizure was less frequent in the PTLE group (8%) than in the MTS group (34%). Trauma, meningoenitis, and perinatal injuries were more frequent risk factors for epilepsy in the PTLE group (50%) than in the MTS cohort (36%). Patients in the PTLE group tended to present with their first seizure later in life (mean age at seizure onset 14 years in the PTLE group and 9 years in the MTS group, $p = 0.09$). Ten patients (83%) in the PTLE cohort and 23 (46%) patients in the MTS cohort had secondary generalization of their seizures. The clinical features of patients in the PTLE cohort are summarized in Table 1.

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Preresection Studies

Scalp video-EEG studies disclosed the onset of left temporal seizure in five patients and the onset of right temporal seizure in seven patients. Neuropsychological test results were available for 10 of the 12 patients in the PTLE group. The FSIQ of patients with PTLE (mean 96.3) was slightly higher than the FSIQ of patients with MTS (mean 90.4). There were also fewer patients in the PTLE group with FSIQ less than 80 (9% compared with 20% in the MTS group). We observed a similar trend for verbal but not visual memory. Patients in the PTLE group tended to have a better immediate recall of stories than those in the MTS group; however, there was no significant difference in the immediate recall of pictures (visual memory).

Intracranial Study

The final analysis of data in all 12 patients with PTLE demonstrated electrographic seizures that were most consistent with onset in the medial temporal lobe. The mean number of seizures recorded intracranially was 4.58 (range 2–9) per patient. The majority of recorded seizures for 11 of 12 patients demonstrated a classic hippocampal electrographic waveform, whereas in one of 12 patients there was an early ictal onset in the amygdala with a rapid spread to the ipsilateral hippocampus. The EEG waveform of the hippocampal ictal events consisted of a buildup of spikes (typically at 3 Hz) followed by a fast low-voltage discharge. Amplified interictal spikes were seen before the hippocampal–entorhinal discharges in seven of the 12 patients, whereas in the other five no increased hippocampal spiking was observed before seizure onset. Subsequent to the fast (18–20 Hz) hippocampal discharge and the attenuation in amplitude, EEG changes in the ipsilateral cortex and contralateral hippocampus were apparent. The pattern of spread for all patients was from the ipsilateral hippocampus to the ipsilateral cortex and then to the contralateral hippocampus.

Even though the vast majority of seizures in patients with PTLE began in the medial temporal lobe, there were five patients with isolated seizures not originating from this region. For these five patients, the location of seizure onset was unclear in two patients (one fourth of the seizures recorded in each), ipsilateral temporal neocortical (one eighth of the recorded seizures), contralateral temporal neocortical (one fourth of the recorded seizures), and inferior temporal neocortical (two sevenths of recorded seizures). Despite these variances, the clinical consensus indicated a hippocampal or amygdaloid seizure onset for these patients with PTLE.

Histopathological Studies and Patient Outcomes

All patients underwent anteromedial temporal lobectomy and amygdalohippocampectomy (in five patients on the left and in seven patients on the right side). The numbers of neurons in different CA sectors of the resected hippocampi demonstrated that the maximal extent of neuron loss occurred most frequently in the CA4 sector among six patients in the PTLE group (mean cell loss 38%; range 21–51%). The mean extent of CA1 subfield neuron loss for the PTLE group was 20% (range 0–59%) and that for the MTS group was 75% (range 41–90%) ($p < 0.001$). At the last follow-

up examination, six patients (50%) in the PTLE group were seizure free compared with 38 (76%) in the MTS group.

Preoperative and postoperative language evaluations for three of the five patients who underwent left temporal lobectomy were available. One of these three patients experienced a significant language deficit after surgery; none of the patients who underwent a right temporal lobectomy suffered from a similar decline. Among the three patients with left-sided PTLE in whom there were available pre- and postoperative verbal memory data, memory scores declined in two patients. None of the patients who underwent right temporal lobectomy suffered from a decrease in their verbal memory scores after surgery.

Electrophysiological Studies

We were able to obtain intracellular recordings from a total of 16 dentate granule cells from hippocampal sections excised from seven of the 12 patients who met the clinical definition of PTLE. Examples of the synaptic responses are shown in Fig. 2A and B and electrophysiological data useful in comparing patients with MTS and those with PTLE are shown in Fig. 2C. The MTS data were obtained from a total of 48 cells from 22 consecutive patients with that diagnosis. Cells from the hippocampi of patients with PTLE were significantly less excitable than those from the hippocampi of patients with MTS. There were significantly different bursting and polysynaptic EPSP variables between the MTS and PTLE groups ($p < 0.005$ and $p < 0.05$, respectively). Both of these EPSP variables were greater for tissue from the MTS group than for tissue from the PTLE group. Synaptic inhibition was not significantly different between these two groups; however, there was a trend toward more prominent IPSPs in the PTLE group. There was a correlation between the presence of periictal spikes on intracranial EEG and a loss of IPSP among patients with PTLE. Similarly, there was a trend toward a greater frequency of spontaneous synaptic events in MTS tissue than in PTLE tissue, but this did not reach statistical significance.

These group differences were preserved when we added data for each variable to create an excitability index. The normalized data for the combined data are shown in Fig. 2D. In this analysis, cells from the PTLE group were significantly less excitable than those from the MTS group ($p < 0.05$).

Discussion

Medial temporal lobe epilepsy is the most common epileptic syndrome in adults. The presence of hippocampal atrophy and a signal change on MR images associated with other concordant preoperative MTLE findings is consistent with the pathological finding of MTS. In the syndrome of MTLE, the medial temporal structures (hippocampus, amygdala, and perihippocampal/entorhinal cortex) represent the epileptogenic region.³⁹ In the absence of any imaging abnormality but the presence of other clinical manifestations of MTLE, intracranial monitoring involving long-term implanted electrodes may be used to identify patients with medial temporal lobe seizures. We have referred to this syndrome as PTLE (nine of the present patients' histopathological findings previously have been discussed¹³). Although in three previous studies investigators have ex-

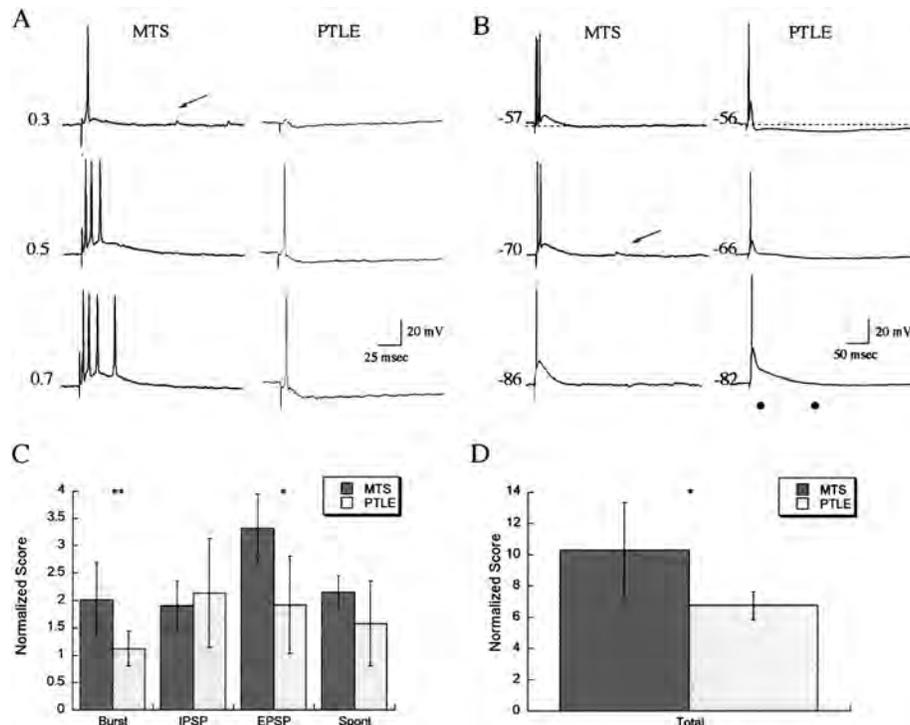


FIG. 2. Results of electrophysiological studies of MTS and PTLE dentate granule cells. A: Representative tracings showing responses to increasing stimulus intensity (in milliamperes). Note that the cell from the MTS dentate fired multiple spikes in response to molecular layer stimulation, whereas only a single action potential was generated in the hippocampal cell in the patient with PTLE. B: Tracings showing that synaptic inhibition appears to be reduced in the MTS hippocampi. The membrane potential was held at different membrane potentials as indicated. Note that a robust biphasic IPSP was seen in the PTLE sample (for example, -56 mV), but not in the MTS tissue. Dots indicate peaks of the IPSPs. Arrows indicate examples of polysynaptic activity. C: Bar graph depicting the group data for four physiological variables. The data were normalized to our comparison population to allow for an easier interpretation. With the exception of IPSPs, larger values indicate a more severe pathological condition. D: Bar graph showing a combined "excitation index." The MTS tissue is significantly more excitable than the PTLE tissue. * $p < 0.05$; ** $p < 0.01$.

explored the clinical features of patients with MTLE who have normal hippocampal volumes, these studies included patients with increased signal changes in the hippocampus on T_2 -weighted MR imaging^{26,29} or included patients who did not consistently undergo long-term intracranial monitoring.¹⁹ The goal of the present study was to define clinical, electrophysiological, histopathological, and surgical outcomes in patients with the syndrome of PTLE.

Febrile seizures are uncommon in patients with PTLE. This is consistent with previous reports in which a correlation between hippocampal signal changes and a history of febrile seizures has been demonstrated.^{30,38} The 8% incidence of febrile seizures among our patients with PTLE is similar to the incidence reported among the general population.¹⁸ Patients with PTLE had risk factors for epilepsy including trauma, meningoencephalitis, and perinatal injuries. Furthermore, they presented with their first seizures slightly later in life than patients with MTS. Even though the small number of patients in the PTLE group precludes a meaningful statistical comparison for many clinical variables, these differences may highlight the underlying pathophysiological disparities between patients with PTLE and those with MTS. The higher incidence of seizure generalization among patients with PTLE compared with those with MTS may underscore the more extensive involvement of the neocortex in the generation of the seizure network.

Preoperative Studies

Magnetic resonance imaging volumetric studies of the hippocampus were available for five patients with PTLE and a blinded reviewer confirmed normal hippocampal volume and signal intensity in the other seven patients. The sensitivity of visual inspection in the detection of these imaging parameters has not differed significantly from that of quantitative volumetric measurements.²³ Furthermore, we did not find any histopathological evidence for hippocampal sclerosis in our seven patients with PTLE who did not undergo formal hippocampal volumetric measurements. The improvement in the sensitivity of imaging modalities during the period of our study may limit an accurate comparison of patients with normal findings on MR imaging in the study.

More detailed imaging modalities may detect mild hippocampal cell loss. If conventional MR imaging protocols do not reveal hippocampal atrophy or a signal change, high-resolution MR T_2 relaxometry of the hippocampus may detect subtle hippocampal abnormalities and assist in a non-invasive lateralization of the seizure focus.⁵ Proton MR spectroscopy of the hippocampus involving *N*-acetylaspartate measurements has been used to predict surgical outcomes in patients with TLE and normal findings on MR images; this may be used as an adjuvant localizing tool.⁴⁹

Patients with MTS and refractory seizures have well-

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described cognitive deficits, including a low average overall IQ and a poor temporal lobe–specific memory. The neuropsychological status of our small PTLE sample appears closer to that of the general population than to the typical patient with MTS. Therefore, patients with PTLE may be at an increased risk for cognitive impairment following amygdalohippocampectomy compared with their MTS counterparts. Previous reports have demonstrated that among patients with MTLE, those without MTS may suffer from a significant decline in verbal memory, confrontation naming, and verbal conceptual ability after a left amygdalohippocampectomy.⁴⁶ Verbal memory is most vulnerable independent of seizure outcome.⁴⁶

Intracranial EEG

In patients in the PTLE group, an intracranial electrophysiological study was needed to identify the epileptogenic zone. Patients with PTLE uniformly presented with an ictal onset from either the hippocampus or amygdala. A report by Holmes and colleagues¹⁹ showed improved surgical outcomes in patients with TLE with normal findings on MR images if the ictal onset was localized to basal temporal regions. In comparison, none of their patients with lateral midposterior temporal seizure onset attained freedom from seizure after surgery. Holmes, et al., also reported an overall 48% rate of operative seizure freedom. Their intracranial study electrodes were composed of subdural strips without a hippocampal depth electrode and, therefore, a comparison with our group may not be justified.

We previously reported on the background EEG activity of four of our patients with PTLE.⁵⁶ Group differences were demonstrated in the spectral energy of background hippocampal signals between patients with PTLE and those with MTS. These dissimilarities may further define functional differences in cellular composition and connectivity in these two patient groups.

Histopathological Findings

Histopathologically, hippocampal sclerosis is defined as astroglial proliferation in different hippocampal cornu ammonis sectors associated with significant neuron loss (> 60%) especially in the end folium (CA4), CA3, dentate, and CA1 sectors, with relative sparing of the CA2 sector.^{27,37} In patients with PTLE, the most frequent sector with maximal cell loss was the CA4 sector (end folium sclerosis) with a relative preservation of the CA1 and CA2 subfields. Anatomically, the end folium or hilar region approximates the CA4 territory and contains the polymorphic cell layer of the dentate gyrus and large pyramidal cells that synapse with mossy fibers.² End folium sclerosis has been found among 4% of patients with normal hippocampi who undergo amygdalohippocampectomy.^{3,7} End folium sclerosis has been proposed to be a consequence rather than a cause of TLE.^{1,50}

Isolated amygdaloid sclerosis has been reported in a subgroup of patients with normal hippocampi and MTLE.^{20,51} The amygdala was not removed en bloc in our series to allow analysis of its neuron loss and gliosis. Satisfactory short-term seizure freedom has been achieved in patients with amygdaloid sclerosis who underwent selective amygdalotomy.¹⁷ Amygdaloid sclerosis may represent a distinct

subtype of MTLE syndrome with specific pathophysiological features.

Electrophysiological Findings

Patients with PTLE appear to form a distinct group based on their cellular electrophysiology. Given the anatomical differences among hippocampi in patients with PTLE, MTS, and autopsy controls, the data indicate that different physiological processes may be involved in seizure generation among patients with PTLE.

One possible difference is synaptic inhibition: there were significant disparities between the PTLE and MTS groups for both the burst and polysynaptic EPSP scores, but no difference in the IPSP scores. Given the complex changes in synaptic inhibition reported in the human hippocampus,¹¹ the PTLE group may demonstrate some but not all changes that characterize MTS. An absence of IPSPs was associated with the presence of periodic spikes at seizure onset in our earlier studies of patients with MTS who were examined using depth electrodes.⁵⁴ Similarly, we found a correlation between the presence of periictal spikes and a loss of IPSP among the patients with PTLE.

Spontaneous activity was the same in patients in both the PTLE and MTS groups. In our previous work, this variable was associated with mossy fiber sprouting.¹⁴ Therefore, we speculate that the PTLE group may have some of the synaptic reorganization that is prominent in the MTS group, but that this synaptic reorganization is below the levels of detection provided by immunohistochemical methods currently in use. It is plausible, however, that mossy fiber sprouting is not associated with generation of spontaneous activity.

Considerations for Surgery

In patients with PTLE, the lack of imaging abnormalities prompted an intracranial study to define the epileptogenic zone. Despite the generous coverage of candidate cerebral epileptogenic regions afforded by electrodes and confirmation of seizure onset in the medial temporal lobe, 50% of patients with PTLE attained freedom from seizure after surgery, compared with 76% of those with MTS. This difference could be due to bilateral hippocampal disease or the presence of dual pathology. Even though intracranial studies excluded contralateral temporal epileptogenicity in some of our patients, the spatial sampling of the intracranial study was incomplete because all cerebral regions could not be covered with electrodes. A sampling error may account for suboptimal localization of the seizure focus.^{36,45}

In the present study, the five patients with isolated seizures not localized to the medial temporal lobe on intracranial monitoring tended to have a worse seizure outcome after surgery. In one patient, a repeated intracranial study revealed occipital lobe seizures; however, additional resection in the occipital region did not provide this patient with more long-term freedom from seizures. Four other patients underwent additional evaluation postoperatively for their recurrent seizures; none of these studies was conclusive regarding an isolated seizure focus dismissed on the initial preoperative evaluation.

Dual Pathology

The less satisfactory surgical outcome of patients with

PTLE syndrome could be explained by the presence of more than one epileptogenic zone. The coexistence of MTL with extrahippocampal lesions has been referred to as “dual pathology” and may occur in up to 30% of patients with refractory partial epilepsy.^{9,10,33,34,40} Dual pathology may more commonly be associated with extrahippocampal developmental cortical malformations or gliotic lesions.^{10,33,34,40} These malformations represent a subtle cortical dysgenesis that may escape detection by current high-resolution MR imaging methods.⁴⁰ Resection of both the extrahippocampal lesion and the atrophic hippocampus provides the most satisfactory seizure outcome.³⁴

The PTLE syndrome may represent kindling or secondary epileptogenesis. Because of its low threshold for hyperexcitability, the hippocampus may become “the corridor of least resistance” to propagate and broadcast the electrical activity of a complex and more widespread extrahippocampal epileptic network. We may hypothesize that this epileptic network may originate from a functionally “silent” part of the cortex. This network may manifest itself electroclinically through the hippocampus, producing stereotypical limbic seizures. This “silent” cortex may be associated with subtle developmental malformations. On the other hand, predisposing factors such as injury early in life may be implicated in the generation of a primary epileptic hippocampal circuitry associated with hippocampal sclerosis; this pathophysiological mechanism is distinct from that involved in the syndrome of PTLE. When compared with primary hippocampal epilepsy, the extent of hippocampal neuron loss among patients with PTLE may be mild, mainly reflecting the extent of neuronal injury secondary to repetitive seizures.

Multicenter studies exploring the clinical and electrophysiological features of a large group of patients with PTLE may be needed to determine whether PTLE is a distinct syndrome or merely a subset of the pathological MTS condition. The extent of hippocampal sclerosis among the patients with PTLE may escape detection due to the resolution of current imaging modalities. Histopathological findings may therefore remain a more accurate measure of pathological conditions of the hippocampus in these patients, indicating that PTLE may represent a subset of patients with MTS disease. Improved patient selection may enhance surgical outcome.

Conclusions

At least two distinct syndromes, MTS and PTLE, may cause electrically identified “nonlesional” seizures originating in the hippocampus. In patients with MTS, the damaged hippocampus will participate in primary hippocampal epilepsy. This substrate favorably responds to focal resection of medial temporal structures. In patients with PTLE, limbic seizures may be the manifestation of a complex epileptic system composed of extrahippocampal components secondarily involving the hippocampus. This PTLE substrate does not respond as favorably to anteromedial temporal lobe resection because the epileptogenic disease state may have been left behind. If the hypothesis regarding the presence of dual disease states is accurate, correct identification of the epileptogenic focus is essential in improving the efficacy of surgical treatment. Different pathogenic mecha-

nisms may be involved in the PTLE and MTS substrates. A better understanding of network processes operating in the generation of medial temporal seizures may facilitate the development of more suitable diagnostic tools and therapies.

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