Surgical treatment of limbic epilepsy associated with extrahippocampal lesions: the problem of dual pathology

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The authors present their review of 178 patients who underwent en bloc temporal lobectomies as surgical treatment for intractable epilepsy. Hippocampal cell density was quantitatively analyzed and the histology of the anterior temporal lobe was reviewed. Fifty-four patients (30.3%) had evidence of extrahippocampal lesions in addition to neuronal cell loss within the hippocampus (the dual pathology group). The pattern of cell loss was analyzed in the remaining 124 cases (69.7%) with no extrahippocampal pathology, and compared with that of the dual pathology group and a control group of four nonepileptic patients.

Hippocampal cell loss was found in almost all epileptic patients compared to the control group. Severe cell loss greater than 30% of control values was found in 88.7% of patients without extrahippocampal lesions, but in only 51.8% of patients with dual pathology. The difference between these two groups was statistically significant (p < 0.001). In the dual pathology group, lesions of different pathology had a significant relationship with the degree of hippocampal cell loss: all 12 patients with glioma had mild cell loss, whereas all 13 patients with heterotopia were associated with severe cell loss. Severity of hippocampal cell loss was also analyzed in relation to seizure history: a prior severe head injury was associated with severe cell loss. Other factors such as seizure duration, secondary generalization, or family history of seizures were not associated with hippocampal damage. Dual pathology may produce a combination of neocortical and temporal limbic epilepsies that warrants a precise definition of the true epileptogenic area prior to surgical treatment.

KEY WORDS - epilepsy surgery • hippocampal sclerosis • dysplasia • glioma • morphological study • seizure

HIPPOCAMPAL sclerosis has been identified as the most frequent pathological substrate of partial limbic epilepsy. 3,21,22,31,45 In some cases, however, the presence of an additional lesion confounds the definition of both the epileptogenic focus and its pathological substrate. 20,39,52 The effects of both repetitive partial seizures and the presence of an additional lesion in relation to the development of hippocampal sclerosis are still a subject of controversy. 11,19,38,40,44 This relationship may influence the surgical decision since resection of sclerotic hippocampus is correlated with a good surgical outcome. 16,29,30 On the other hand, resecting a single extrahippocampal lesion and preserving normal hippocampus and afferent pathways may decrease some neuropsychological deficits associated with anterior temporal lobectomy. 45

Dual pathology is defined when an extrahippocampal structural lesion is found in association with hippocampal damage during surgery for partial limbic epilepsy. This association was noted incidentally in earlier papers, 3,9,10,15,20,26 but the clinical features were not analyzed. In the present report, we analyze the degree of hippocampal cell loss in relation to the type of extrahippocampal lesions and the patients’ seizure history.

Clinical Material and Methods

We retrospectively reviewed 178 patients selected from a larger patient population who underwent presurgical evaluation and surgical treatment for intractable seizure disorders at the University of California, Los Angeles. Age at seizure onset, duration of seizures, seizure type and frequency, total number of generalized seizures, family history of seizures, and history of head injury or febrile illness were obtained from the patients’ medical charts. A complex partial seizure index was
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**FIG. 1.** Bar graph showing the distribution of average hippocampal cell loss (all subfields) compared to four nonepileptic control specimens (standard deviation 13%). In this study, 30% (arrow) is used as the borderline between mild and severe cell loss. The 54 cases with dual pathology are shown as filled blocks, and the 124 cases with hippocampal lesion only as open blocks. N = number of cases.

created to evaluate their frequency by multiplying the average number of complex partial seizures prior to surgery by the duration of the seizure disorder. The number of generalized seizures was estimated from the patients' medical charts. Localization of the epileptogenic focus was obtained by means of various noninvasive and invasive techniques. Patients who had presented with additional signs or symptoms of increased intracranial pressure caused by an expansile brain lesion were excluded from this analysis.

Surgical Procedures

All epileptic temporal lobes were removed by an en bloc resection. Some patients also underwent extratemporal resection of structural lesions at other centers and then required additional temporal lobe resection for seizure control after invasive diagnostic procedures had localized the seizure onset within the temporal lobes. One patient had prior temporal resection followed by extratemporal resection for seizure control.

Pathological Studies

Approximately 5 cm of temporal lobe and 3 cm of the hippocampal formation were sampled. The specimens were fixed and processed for histological examination by light microscopy after fixation in 10% neutral buffered formalin. The light microscopic evaluations were performed and the extrahippocampal lesions diagnosed and categorized according to the criteria of Willis. A qualitative estimate of hippocampal sclerosis was assigned according to neuropathological criteria. Several coronal blocks were embedded in paraffin and sections 10 μm thick were obtained along the anterior to posterior extent of the resected temporal lobe. The location of extrahippocampal lesions was plotted on a coronal plane of the temporal lobe. Quantitative cell counts were made of all hippocampal regions, subicular cortex, and temporal neocortex. Hippocampal cell loss was calculated as an average value of the percentage of cell loss within the presubiculum, CA1, CA2, CA3, and CA4.

Significant hippocampal sclerosis was defined by a cell loss of at least 30% relative to the control hippocampus. Mild or minimal cell loss was defined as less than 30% cell loss compared to the control group. We used this value because the standard deviation (SD) for nonepileptic control tissue was 13%, so 2 SDs was 26%. This measure also corresponds to the approximate level of conventional visual detection of hippocampal sclerosis by light microscopy.

**Statistical Analysis**

The Student t-test and chi-squared test were used for statistical analysis. The level of significance was designated as 95%.

**Results**

Almost all surgical cases (178 patients) had some degree of hippocampal cell loss compared to the nonepileptic control group (Fig. 1). Among the 124 patients (69.7%) without extrahippocampal lesions, significant hippocampal cell loss (> 30% more than nonepileptic controls) was found in 88.7%. In 54 patients (30.3%) with dual pathology, only 51.8% showed significant hippocampal cell loss. Only two patients with low-grade gliomas had no hippocampal pyramidal cell loss, but both had significant granule cell loss in the upper fascia dentata (of 29% and 57%).

The 54 cases of dual pathology were further divided into severe (> 30%) and mild (<30%) hippocampal cell loss groups (Table 1). The most important finding

<table>
<thead>
<tr>
<th>Pathology†</th>
<th>Severe</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>dual pathology</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>glioma only</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>hamartoma only</td>
<td>6</td>
<td>8</td>
</tr>
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<td>heterotopia only</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>heterotopia with</td>
<td></td>
<td></td>
</tr>
<tr>
<td>glioma</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>hamartoma</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>others</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>others</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>hippocampal lesion only</td>
<td>110</td>
<td>14</td>
</tr>
</tbody>
</table>

* Hippocampal cell loss: severe > 30% and mild < 30% cell loss.
† "Glioma" includes ganglioglioma, mixed glioma, low-grade astrocytoma, and high-grade glioma; "hamartoma" includes vascular malformation, glial hamartoma, calcified mass, and tuberous sclerosis; "heterotopia" indicates neuronal heterotopia; and "others" includes cicatrix, arachnoid cyst, porencephaly, Rasmussen's disease, and meningioma.
was that severe hippocampal cell loss did not occur with gliomas, but was always present with heterotopias. Furthermore, the severity of hippocampal damage had no relationship to the site of the additional lesions (Fig. 2), age at seizure onset, age at surgery, average monthly number of complex partial seizures, total number of generalized seizures, previous febrile convulsions, or a family history of seizures. However, all seven patients with a history of anoxia or severe head trauma with transient loss of consciousness were found to have severe hippocampal damage (Table 2).

Both the severity of hippocampal cell loss and its distribution within the hippocampal subfields had a clear relationship to the extrahippocampal pathology (Fig. 3). The heterotopia subgroup was similar to the group with hippocampal lesion only, as judged by the severity of cell loss in each hippocampal subfield. The glioma and hamartoma subgroup had the least hippocampal damage, but CA1, CA2, and CA3 subfields had statistically significant cell loss compared to control specimens (Fig. 4). Differences between the glioma and hamartoma groups were also significant.

Discussion

The surgical treatment of limbic epilepsy must take into consideration the spatial extent of the electrophysiological focus and its pathological substrate. Electroclinically, we use the term “limbic epilepsy,” as opposed to “neocortical epilepsy,” when the stereotypical seizure originates focally within the limbic system and propagates initially, by preferential pathways, to several of its components. This would be manifested by a loss of awareness and amnesia of events during this episode — by definition, a complex partial seizure. In the case of complex partial seizures of temporal lobe origin, hippocampal sclerosis has been found to be the most frequent pathological lesion and some authors have interchangeably used the term “hippocampal epilepsy.” However, approximately 35% of cases have an additional extrahippocampal pathology.
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This study was directed to analyze the relationship between these two lesions in order to determine which was likely to be epileptogenic, coincidental, or nonepileptogenic.

**Hippocampal Cell Loss and Hippocampal Sclerosis**

The degree of hippocampal cell loss varies significantly in epileptic patients and is classically described in the CA1 to CA4 areas and the fascia dentata. For quantitative analysis, we used a 30% cell loss compared to control specimens as the lowest limit of pathological detection and significance. The exact mechanisms responsible for the neuronal loss and reactive gliosis remain unknown. This selective damage is different from that seen in anoxia or hypoglycemia and is not produced by vascular spasm or occlusion, as previously hypothesized.

In our study, almost all epileptic patients had some degree of hippocampal cell loss by quantitative analysis compared to the control group, with or without extrahippocampal lesions (Figs. 1 and 4). The hippocampal cell loss may reflect early longstanding damage or a progressive cell loss following propagation of partial seizures into the hippocampus.

Repeated seizures from electrical kindling have been demonstrated as sufficient to produce cell loss in the rat hippocampus. The presence of cell loss in almost all of our epileptic cases might suggest that mild cell loss is secondary to repetitive seizures; however, the severity of hippocampal damage was not proportional to the number, frequency, or severity of seizures according to the present results (Fig. 2) and in previous experimental findings.

**TABLE 2
Seizure history and degree of hippocampal cell loss with extrahippocampal structural lesion**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Severe</th>
<th>Mild</th>
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<tbody>
<tr>
<td>no. of cases</td>
<td>28</td>
<td>26</td>
</tr>
<tr>
<td>age at seizure onset (yrs)</td>
<td>13.8 ± 11.1</td>
<td>15.1 ± 10.0</td>
</tr>
<tr>
<td>age at surgery (yrs)</td>
<td>29.7 ± 8.6</td>
<td>27.4 ± 11.0</td>
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<tr>
<td>seizure duration (yrs)</td>
<td>15.9 ± 9.7</td>
<td>12.4 ± 8.2</td>
</tr>
<tr>
<td>CPS index &gt; 10/life</td>
<td>15/27</td>
<td>6/21</td>
</tr>
<tr>
<td>generalized seizure &gt; 10/life</td>
<td>4/23</td>
<td>4/22</td>
</tr>
<tr>
<td>febrile seizure</td>
<td>5/27</td>
<td>4/21</td>
</tr>
<tr>
<td>severe head trauma</td>
<td>7/27</td>
<td>0/25</td>
</tr>
<tr>
<td>family history of seizure</td>
<td>3/26</td>
<td>5/25</td>
</tr>
</tbody>
</table>

* Hippocampal cell loss: severe > 30% and mild < 30% cell loss. Values are either means ± standard error of the means or corresponding cases/number of cases with available information. CPS index: (frequency of complex partial seizure before surgery) x seizure duration in years.

† The seven cases included: four with severe head injury and loss of consciousness (three heterotopia and one hamartoma); one post-traumatic intracerebral hematoma (heterotopia with hamartoma); one anoxia at birth (cicatrix); and one perinatal injury after breech delivery (heterotopia).

‡ Significance of difference: p < 0.02.
Previous reports have demonstrated that the presence of hippocampal sclerosis in the surgical specimens from patients with complex partial seizures was correlated with a good surgical outcome. This relationship was further substantiated by demonstrating a definite relationship between the localized damage to the hippocampus and the localized epileptogenicity. The most frequent changes noted were in the anterior hippocampus where the seizures originated. A characteristic pattern of cell loss within the hippocampus was found; that is, severe cell loss in the CA1 subfield, severe to moderate cell loss in the CA3 and CA2 areas, and less damage to the CA4 subfield and the fascia dentata. This was considered to be pathognomonic of hippocampal epilepsy. At the circuitry level it was shown that aberrant synaptic re-innervation may contribute to the hyperexcitability of epileptic tissue despite cell depletion. By feedback and feedforward excitatory circuits, a decreased number of cells could synchronize both local and distal target cell populations.

**Dual Pathology**

A detailed analysis of the semiology and the etiological factors in our dual pathology group demonstrated no causal relationship with the degree of hippocampal cell loss (Table 2). Contrary to some reports, the duration, severity, and type of seizures in our series did not affect the severity of hippocampal damage. This would argue against the theory of cumulative excitotoxicity as the primary mechanism of hippocampal sclerosis. Rather, our findings support the experimental study of Bertram, et al., who demonstrated that intermittent seizures do not cause progressive neuronal loss. Hippocampal sclerosis could be secondary to a previous insult, causing a critical level of cellular loss. This initial injury would induce neuronal reorganization reaching a sufficient “plateau” to generate abnormal synchronized discharges and would then be followed by intermittent seizures.

The presence of circumscribed “indolent” or slowly progressive structural lesions in some cases suggests different pathophysiological mechanisms causing limbic epilepsy. The extratemporal lesion may cause local “irritative” epileptiform phenomena which then spread to the hippocampal circuitry and produce stereotypical complex partial seizures. This lesion could be the parallel in humans of experimental “kindling” models. The hippocampus would undergo only mild changes in the same hippocampal subfields as in the more severe primary hippocampal epilepsy, as shown by our analysis. This mild neuronal cell loss and synaptic reorganization may or may not be followed by a more severe neuronal loss, amplifying the initial responses. The result of such mild to severe hippocampal cell losses may induce synaptic reorganization. The type of extrahippocampal lesion can be predictive of the presence or absence of associated severe hippocampal damage. Our study shows that gliomas and hamartomas are much less likely to be found with hippocampal sclerosis. Such an association was noted in five patients with gliomas described in a previous report. Conversely, the heterotopias are almost always associated with severe hippocampal cell loss and may be coincidental to the epileptogenicity within the hippocampus. The location of the extrahippocampal lesion has no relationship with the presence of hippocampal sclerosis. Lesions were found anywhere within the medial or lateral temporal cortex and even remotely in two cases, one within the ipsilateral cingulate gyrus and another in the contralateral parietal lobe. Thus, in patients with complex partial seizures, an incidental lesion detected outside the temporal lobe does not rule out the hippocampus as the site of seizure origin. This may become a more important factor with the high anatomical resolution of magnetic resonance imaging, since small lesions can be detected preoperatively.

**Conclusions**

Our analysis supports the overall concept of at least two types of pathophysiological mechanisms causing limbic seizures of temporal origin. The first mechanism involves seizures arising from a damaged hippocampus and hippocampal sclerosis being an almost pathognomonic substrate of hippocampal epilepsy. Its focal nature could support a more limited resection such as a selective hippocampectomy or posterior medial temporal resection in affected patients. The second mechanism is that of complex partial seizures caused by an extrahippocampal pathology. The seizure would secondarily spread to the hippocampus, which would amplify and propagate abnormal epileptiform discharges. Gliomas and hamartomas are such lesions, resection of which could produce a good surgical outcome without additional resection. An intermediate type would be heterotopias associated with severe hippocampal sclerosis where a “standard” temporal lobectomy, sufficient to remove a “critical” mass of epileptogenic tissue, would be indicated. Dual pathology may thus produce a combination of neocortical and temporo-limbic epilepsies that warrants a precise definition of the true epileptogenic area prior to surgical treatment. To further substantiate alternative surgical approaches, additional analyses of possible dual epileptogenicity and surgical outcome are currently under way.

**Acknowledgments**

We are grateful to Jim Pretorius and Bill Kupfer for their technical skills in the morphometric analyses.

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Manuscript received October 8, 1990.
Accepted in final form February 25, 1991.
This study was supported in part by an Academic Senate Grant to Dr. Lévesque from the University of California, Los Angeles (UCLA), by the UCLA Epilepsy Surgery Program, and by National Institutes of Health Grant NS 02808.
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