

## THE VARIOUS NEUROPATHOLOGICAL “FACES” OF TEMPORAL LOBE EPILEPSY

### A Retrospective Analysis of Hippocampal Pathology in Human Temporal Lobe Epilepsy: Evidence for Distinctive Patient Subcategories

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**PURPOSE:** This study is a retrospective analysis of the pathology of the hippocampus from patients with medically intractable temporal lobe epilepsy. We attempted to relate neuronal density, immunohistochemistry, electrophysiologic data, and surgical outcome.

**METHODS:** Immunostaining patterns for neuropeptide Y, somatostatin, substance P, and dynorphin defined the immunohistochemical characteristics of the hippocampi. Neuronal densities were determined by microscopic cell counts. Sharp electrode recordings from dentate granule cells determined measures of inhibition and excitation.

**RESULTS:** Patient hippocampi without evidence of sclerosis generally resembled autopsy controls on the basis of neuronal densities of hippocampal subfields and patterns of immunostaining. The nonsclerotic hippocampi were divisible into two subgroups on the basis of neuronal-density correlations between hippocampal subfields, the excitability of dentate granule cells, etiology, and surgical outcome. Hippocampi with sclerosis were divisible into those with significant neuronal loss confined to area CA1 and those with neuronal loss throughout the hippocampus and dentate gyrus. In the former, the dentate gyrus resembled in morphology the nonsclerotic hippocampi but with slightly increased excitability of the dentate granule cells. The hippocampi with more extensive neuronal loss had changes in immunostaining patterns associated with the dentate gyrus, correlated with significant hyperexcitability of dentate granule cells. The surgical outcome, with the exception of one group, was good in approximately 70% to 90%.

**CONCLUSIONS:** Hippocampi from patients with intractable temporal lobe epilepsy can be assigned to several groups on the basis of pathophysiology. Different pathologies may represent differing causative mechanisms of intractable temporal lobe epilepsy and be predictive of surgical outcome.

### COMMENTARY

In temporal lobe epilepsy (TLE), seizures may result from mesial temporal sclerosis (MTS); from an extrahippocampal structural lesion (e.g., tumor, cavernous angioma, or focal dysplasia), with or without involvement of hippocampal structures (known as dual pathology); or, in individuals with completely normal brain magnetic resonance imaging (MRI) studies, seizures may originate from temporal–lateral neocortex. In patients with normal MRI, however, seizures may at times originate in “noneloquent” extratemporal cortex and propagate to anterotemporal structures where they may mimic TLE, both clinically and electrographically.

The classic neuropathologic findings of MTS include (a) gliosis and cell loss most prominently in the dentate hilus, CA1, CA3, a relative sparing of cells in CA2, and the granule cells of the dentate gyrus and the subiculum; (b) loss of hilar inhibitory interneurons containing somatostatin, substance P, and neuropeptide Y; and (c) sprouting of mossy fibers and inhibitory interneurons, resulting in reorganization of the dentate gyrus (1–3). However, as shown in this elegant study by de Lanerolle and colleagues, MTS has more than one neuropathologic and electrophysiologic presentation. In their neuropathologic analyses of 151 hippocampi from patients with intractable TLE, the authors demonstrated three “forms” of MTS. The first and most frequently encountered type (72 of the 151 cases) included all the neuropathologic features cited earlier. From a neurophysiologic standpoint, there was a significant loss of neuronal cell inhibition and greater hyperexcitability of the dentate granule cells. In addition, these findings were more likely to be identified in patients with a first seizure at a younger age and an excellent postsurgical outcome (85% were seizure free at 1 year).

A second presentation of MTS, found in only 10 cases, differed from the first type by the absence of immunoreactivity

to the opiate dynorphin in the inner molecular layer of the dentate gyrus and was associated with a comparatively lower cell loss in CA3 and CA4 (about 20% to 30% vs. 60% to 70%). These differences, however, did not translate into differences in the level of granule cell hyperexcitability or loss of neuronal inhibition. Furthermore, patients did not differ with respect to age at first seizure, duration of seizure disorder, or postsurgical outcome.

A third type of MTS, identified in nine of the 151 hippocampi, revealed an 80% neuronal cell loss primarily in CA1 (similar to the other two types of MTS); a 20% granule cell loss; and a 20% to 30% cell loss in CA2, CA3, and CA4. These changes were associated with a lesser degree both of loss of neuronal inhibition and of hyperexcitability in granule cells, compared with the other two types of MTS. Patients with these findings were older at the time of their first seizure but had a comparable postsurgical outcome to the other two patient groups.

Hippocampi from 21 patients did not reveal any neuropathologic findings consistent with MTS. Nine belonged to patients with a normal MRI study and 12 to patients with a temporal extrahippocampal structural lesion. Five other specimens obtained from patients with a structural lesion met criteria (i.e., more than 60% neuronal cell loss) of dual pathology. In each of these five cases, the lesion was immediately adjacent to or invaded the hippocampus. The other 21 non-MTS hippocampi failed to differ from a group of 26 "normal" hippocampi, with the exception of a 20% to 25% neuronal cell loss that was found across all hippocampal areas. The hyperexcitability of granule cells and loss of neuronal inhibition was significantly less in the "normal" slices than in the hippocampi with MTS. Hip-

pocampi of patients with a normal MRI had a greater degree of neuronal hyperexcitability than did those of patients with a structural lesion, but both had intact neuronal inhibition. From a clinical standpoint, patients from these two groups were older at the time of first seizure than were those with MTS. Patients with a structural lesion had as good a postsurgical outcome as did those with MTS, whereas patients with a normal MRI had the worst outcome, with only 44% becoming seizure free.

The similar neuropathologic findings of the non-MTS hippocampi raises the question of whether the 20% to 25% neuronal cell loss is the result of an "hippocampal bombardment" by epileptic activity from an extrahippocampal (or possibly an extratemporal) source. It is unfortunate that the authors did not analyze separately the neuropathologic, immunohistochemical, and neurophysiologic data of the hippocampi belonging to the patients with a normal MRI who became seizure free. Had they compared these data with those of patients with normal MRI and persistent seizures, significant differences might have been identified. One wonders whether such analyses would have demonstrated the neuronal cell count "threshold" below which hippocampal seizures are likely to occur and with which a favorable postsurgical outcome may be associated.

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## References

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