

# HIPPOCAMPAL CELL LOSS IN POSTTRAUMATIC HUMAN EPILEPSY

**Hippocampal Cell Loss in Posttraumatic Human Epilepsy.** Swartz BE, Houser CR, Tomiyasu U, Walsh GO, DeSalles A, Rich JR, Delgado-Escueta A. *Epilepsia* 2006;47(8): 1373–1382. *Purpose:* We performed this study to determine whether significant head trauma in human adults can result in hippocampal cell loss, particularly in hilar (polymorph) and CA3 neurons, similar to that observed in animal models of traumatic brain injury. We examined the incidence of hippocampal pathology and its relation to temporal neocortical pathology, neuronal reorganization, and other variables. *Methods:* Twenty-one of 200 sequential temporal lobectomies had only trauma as a risk factor for epilepsy. Tissue specimens from temporal neocortex and hippocampus were stained with glial fibrillary acidic protein (GFAP) and hematoxylin and eosin (H&E). Eleven hippocampal specimens had additional analysis of neuronal distributions by using cresyl violet and immunolabeling of a neuron-specific nuclear protein. *Results:* The median age at onset of trauma was 19 years, the median time between trauma and onset of seizures was 2 years, and the median epilepsy duration was 16 years. The length of the latent period was inversely related to the age at the time of trauma ( $r = 0.75$ ; Spearman). The neocortex showed gliosis in all specimens, with hemosiderosis ( $n = 8$ ) or heterotopias ( $n = 6$ ) in some, a distribution differing from chance ( $p = 0.02$ ; Fisher). Hippocampal neuronal loss was found in 94% of specimens, and all of these had cell loss in the polymorph (hilar) region of the dentate gyrus. Hilar cell loss ranged from mild, when cell loss was confined to the hilus, to severe, when cell loss extended into CA3 and CA1. Some degree of mossy fiber sprouting was found in the dentate gyrus of all 10 specimens in which it was evaluated. Granule cell dispersion ( $n = 4$ ) was seen only in specimens with moderate to severe neuronal loss. *Conclusions:* Neocortical pathology was universally present after trauma. Neuronal loss in the hilar region was the most consistent finding in the hippocampal formation, similar to that found in the fluid-percussion model of traumatic head injury. These findings support the idea that head trauma can induce hippocampal epilepsy in humans in the absence of other known risk factors.

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## COMMENTARY

Epilepsy Currents, Vol. 7, No. 3 2007 pp. 156–158  
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**A**mong patients with temporal lobe epilepsy and mesial temporal sclerosis (MTS), early studies found that any

initial precipitating injury, including trauma, most commonly had occurred at or before age 5 years (1,2). Subsequently, Diaz-Arrastia et al. reported MTS-compatible MRI abnormalities in 8 of 23 patients (35%) whose trauma occurred after age 10 years; neuropathological studies confirmed MTS in the two patients who underwent temporal lobectomy (3). Meticulously employing sophisticated techniques, Swartz et al. in this article, document hippocampal neuronal loss in 14 of 15 specimens among patients whose trauma occurred principally in adolescence or adulthood (median age of trauma 19 years; range 1 week–38 years).

The mechanisms underlying posttraumatic seizures and neuronal loss are not completely understood. Previously, Babb and Brown found dual pathology in 13% of temporal lobe epilepsy patients, defined as a macroscopic lesion and severe hippocampal neuronal loss (4). Yeh and Privitera postulated that frequent, chronic activation of a primary focus could produce such hippocampal neuronal loss (5). In adult rats, a single fluid percussion injury evoked ipsilateral frontoparietal seizures that evolved to increasing hippocampal seizures over 7 months and were associated with CA1 and CA3 hippocampal atrophy (6). Importantly, a minor percussion to rat dura also may evoke hilar cell loss and an increase in hippocampal excitability (7). Posttraumatic seizure evolution in humans can parallel that of the rat model: early (<1 posttraumatic week) seizures are focal motor and secondarily generalized, while temporal lobe seizures predominate thereafter, with occasional secondary generalization (8). Thus, trauma either leads directly to mesial temporal neuronal loss or to a focal trauma-induced lesion elsewhere in the cortex, which in some currently unknown manner, leads to hippocampal neuronal loss and provokes temporal lobe seizures. One or both of these sequences could account for the described findings.

Several trauma-related processes may produce mesial temporal neuronal loss and gliosis, including hypoxia, if an injury to the respiratory system has occurred; ischemia from hypotension (systolic pressure < 30 mm/Hg for  $\geq$  15 minutes); increased intracranial pressure that decreases cerebral perfusion; and carotid or vertebral artery dissection from sudden neck extension (9). One or more such factors may have produced or contributed to MTS in the patients studied here, as all patients (according to the inclusion criteria) suffered moderate trauma. Status epilepticus occurs in 10–20% of early seizures (8), and trauma is an etiology in about 4% of child and of adult status epilepticus series (10). Hippocampal neuronal loss is one consequence of human status epilepticus (10) and occurs in kainic acid-, pilocarpine-, and electrical-stimulation-induced status epilepticus experimental models (11). Enquiry into components of the immediate posttrauma period may clarify longer-term pathophysiological mechanisms.

In humans with temporal lobe epilepsy, Mathern et al. found that hippocampal CA4 neuron densities decrease with longer seizure durations but that this inverse correlation became apparent only after 30 years (12). Although recurrent seizures may have contributed to neuronal loss, Mathern concluded that the initial precipitating injury was the principal culprit. However, this late occurring (>30 years) negative correlation suggests that recurrent limbic seizures may further damage the hippocampus. Mouritzen Dam also documented progressive hippocampal loss, particularly in CA3, that correlated with the duration of the seizure disorder, the number of generalized convulsive seizures, and head injury prior to seizure onset; but not with seizure type, history of status epilepticus, or age at first seizure (13). Additionally, rat hippocampal cell loss from electrical stimulation-induced status epilepticus correlated better with duration to sacrifice than with number of spontaneous seizures (14). Clinical and experimental data suggest that one or more of several trauma-related factors may cause hippocampal neuron loss and other MTS components, launching a process that may spontaneously evolve, augmented by any subsequent recurrent seizures.

In 1899, Bratz, in a detailed and accurate description of MTS, indicated involvement of not only the hippocampus but also of the parahippocampal gyrus and adjacent temporal convolutions (15). The importance of this seminal description increases with recent pathophysiological data that suggest a pivotal role for the subiculum and the parahippocampal region in temporal lobe epilepsy (16). In a human study, microelectrode recordings have disclosed epileptiform activity to propagate from the subiculum to the hippocampus (17) and from the entorhinal cortex to the hippocampus in rat slices (18). Hopefully, future physiopathological studies by Swartz and colleagues as well as by other investigators will determine: (a) the extent and distribution of any lesions in patients with posttraumatic epilepsy and (b) the influence of the lesions on propagation pathways of ictal and inter-ictal epileptiform phenomena.

by Warren T. Blume, MD

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