Hippocampal Atrophy: Another Common Pathogenic Mechanism of Depressive Disorders and Epilepsy?

Bilateral Hippocampal Atrophy in Temporal Lobe Epilepsy: Effect of Depressive Symptoms and Febrile Seizures.

PURPOSE: Neuroimaging studies suggest a history of febrile seizures, and depression, are associated with hippocampal volume reductions in patients with temporal lobe epilepsy (TLE). METHODS: We used radial atrophy mapping (RAM), a three-dimensional (3D) surface modeling tool, to measure hippocampal atrophy in 40 patients with unilateral TLE, with or without a history of febrile seizures and symptoms of depression. Multiple linear regression was used to single out the effects of covariates on local atrophy. KEY FINDINGS: Subjects with a history of febrile seizures (n = 15) had atrophy in regions corresponding to the CA1 and CA3 subfields of the hippocampus contralateral to seizure focus (CHC) compared to those without a history of febrile seizures (n = 25). Subjects with Beck Depression Inventory II (BDI-II) score ≥14 (n = 11) had atrophy in the superoanterior portion of the CHC compared to subjects with BDI-II <14 (n = 29). SIGNIFICANCE: Contralateral hippocampal atrophy in TLE may be related to febrile seizures or depression.

Commentary
Since the arrival of MRI of the brain, hippocampal atrophy (HA) has been recognized as the most frequent neuroradiologic abnormality in temporal lobe epilepsy (TLE). The use of volumetric measurements of temporal lobe structures on MRI facilitated the recognition of subtle HA, not identified by visual exam, including HA contralateral to the seizure focus in patients with unilateral TLE. In psychiatry, the use of volumetric measurements has revolutionized our understanding of the pathogenic role played by temporal and frontal lobes in mood disorders. In fact, bilateral HA has become one of the most frequent neuroradiologic findings in major depressive disorders (MDD), but volumetric measurements are necessary to detect the 10 to 20 percent volume loss in this condition (1).

Sheline et al. were the first to report bilateral HA in a group of women with recurrent MDD (1). The magnitude of the decrease in hippocampal volume was correlated with the duration of the depressive episode, and in particular with the duration of “untreated” depression (2). Hippocampal atrophy in MDD can be detected after recurrent MDDs (1, 3); it is a trait of this disease, as patients with a remitted depressive episode, off antidepressant medication, continue to have smaller posterior hippocampal volumes (3).

In addition to measuring the volume of mesial temporal structures, investigators have examined changes in the shape of the hippocampal formation with high–dimension brain mapping. This method revealed surface deformations at the level of the subiculum (4) and in CA1–CA3 cell fields (5). As in the case of mesial temporal sclerosis in TLE, the presence of HA in MDD has been associated with memory deficits (6). Thus, it is not surprising that in the study selected for this commentary, Finegersh et al. found that depressive symptomatology was associated with bilateral HA in patients with unilateral TLE.

Is it possible that the presence of bilateral HA in depressed patients with epilepsy may account for the worse response of the seizure disorder to pharmacologic, surgical therapy, or both reported in recent years (7, 8)? In one study of 780 patients with new-onset epilepsy, a history of depression preceding the onset of the seizure disorder was associated with a two-fold higher risk to develop treatment-resistant epilepsy (7). Likewise, in a study of 138 patients with new-onset epilepsy, the identification of symptoms of depression, anxiety, or both at the time of diagnosis of epilepsy was associated with a significantly lower probability of seizure-freedom at 12-month follow-up (8). In MDD, HA is also associated with a worse prognosis, as evidenced by the higher risk of recurrence of MDD in these patients (9).

The HA in MDD has been attributed to high cortisol serum concentrations associated with a hyperactive hypothalamic-pituitary-adrenal axis, which has been demonstrated in up to 50% of patients with the dexamethasone suppression test (DST). These high cortisol levels are a trait, as nonsuppression in the DST has been found in patients who have remitted from an MDD.

In experimental studies with rats and monkeys, high concentrations of cortisol were found to be neurotoxic as they were associated with 1) damage of hippocampal neurons, particularly CA3 pyramidal neurons mediated by reduction...
of dendritic branching and loss of dendritic spines that are included in glutamatergic synaptic inputs; 2) decreased levels of brain-derived neurotrophic factor (BDNF) reversed by long-term administration of antidepressants; and 3) interference with neurogenesis of granule cells in the adult hippocampal dentate gyrus (10). Furthermore, pretreatment of rats with corticosteroids accelerated amygdale kindling in rats, as a lower number of stimulations were needed to reach a full-kindled state than rats pretreated with saline or antagonists of corticosteroids (11). Of note, a failed suppression to the DST has also been identified in patients with TLE without depression.

Clearly, these data support our hypothesis that HA may be a common pathogenic mechanism of epilepsy and depressive disorders, even though the neuropathologic findings in HA of mesial temporal sclerosis differ from those of HA in MDD. Yet, HA may be one of the reasons for the high comorbidity of mood disorders in epilepsy. The million dollar question remains… if antidepressant therapy can reverse (at least in part) HA in animal models of hyperactive hypothalamic pituitary adrenal axis (10), can a timely and effective treatment of a depressive disorder prevent the development of bilateral HA in patients with unilateral TLE?

by Andres M. Kanner, MD

References
10. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–935.
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. **Identifying information.**
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

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   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

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<th>Money to Your Institution*</th>
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