

IMAGING DEPRESSION IN EPILEPSY: HINTS AT THE BIOLOGY OF DESPAIR

Major Depression in Temporal Lobe Epilepsy with Hippocampal Sclerosis: Clinical and Imaging Correlates. Briellmann RS, Hopwood MJ, Jackson GD. *J Neurol Neurosurg Psychiatry* 2007 Jan 26; [Epub ahead of print] PURPOSE: Refractory temporal lobe epilepsy (TLE) is often associated with hippocampal sclerosis (HS). Patients with Major Depression (MD) may also show structural abnormalities in the limbic system. Co-occurrence of TLE with HS and MD is not uncommon. We investigate clinical and morphological characteristics of TLE patients in relation to MD. METHODS: Thirty-four TLE patients with HS were assessed at a Comprehensive Epilepsy Program. All relevant clinical data were obtained, including the history of antecedent events to epilepsy. MD was diagnosed based on detailed psychiatric investigation. MRI was used to measure the volume and tissue signal (T2-relaxometry) of the hippocampus and amygdala. The imaging data were expressed as percentage of the values obtained in a series of 55 controls. RESULTS: A history of MD was present in 15 (44%) of the 34 patients. Patients with MD had a longer duration of their epilepsy ($p < 0.05$), and a lower frequency of antecedent events (13% with MD, 58% without MD, $p < 0.05$). Both groups had a similar degree of ipsilateral HS (small hippocampal volume, increased hippocampal T2-relaxation time), and demonstrated bilateral amygdaloid atrophy. However, the contralateral amygdala showed lower signal in presence of MD (97 ± 9 msec; no MD: 103 ± 8 msec, ANCOVA, $p < 0.05$). CONCLUSION: The integrity of the amygdala may influence mood disturbances in TLE patients with HS, as depression was associated with a relative preservation of the contralateral amygdala. In contrast, hippocampal abnormalities were not related to the presence of depression.

Hippocampal 1H-MRSI Correlates with Severity of Depression Symptoms in Temporal Lobe Epilepsy. Gilliam FG, Maton BM, Martin RC, Sawrie SM, Faught RE, Hugg JW, Viikinsalo M, Kuzniecky RI. *Neurology* 2007;68(5):364–368. OBJECTIVE: To investigate the association of an indicator of hippocampal function with severity of depression symptoms in temporal lobe epilepsy. METHODS: We evaluated 31 patients with video/EEG-confirmed temporal lobe epilepsy using creatine/*N*-acetylaspartate ratio maps derived from a previously validated ^1H magnetic resonance spectroscopic imaging (^1H -MRSI) technique at 4.1 T. We also assessed depression symptoms, epilepsy-related factors, and self-perceived social and vocational

disability. We used conservative nonparametric bivariate procedures to determine the correlation of severity of depression symptoms with imaging and clinical variables. RESULTS: The extent of hippocampal ^1H -MRSI abnormalities correlated with severity of depression (Spearman $\rho = 0.65$, p value < 0.001), but other clinical factors did not. CONCLUSION: The extent of hippocampal dysfunction is associated with depression symptoms in temporal lobe epilepsy and may be a more important factor than seizure frequency or degree of disability.

COMMENTARY

Depression is increasingly recognized as an important comorbid condition for patients with epilepsy. It is more common in people who have epilepsy than in either the general population or people who have other chronic medical conditions. While much of the focus of a physician's clinical visits tends to be on seizure control and medication side effects, mood status overwhelmingly drives quality-of-life measures for individuals with epilepsy (1). The mounting interest in epilepsy-associated depression has spawned two recent reports in which investigators attempt to relate functional and structural imaging findings to mood status in patients with temporal lobe epilepsy (TLE).

Prior studies have documented the importance of limbic structures in depression. Patients with major depressive disorder may have reduced hippocampal volumes compared to the general population (2). Since hippocampal volumes are even more profoundly reduced in patients with TLE, Briellmann and colleagues sought to determine whether the hippocampal volume loss might be an important predisposing factor for depression in patients with TLE. They used a 3-T MRI scanner to obtain volume and T2 relaxation measurements of both the epileptogenic and contralateral medial temporal structures. As expected, the structures demonstrated varying degrees of volume loss and prolonged T2-relaxation times, with the most prominent findings on the side of the seizure focus. The only finding that was associated with depression, however, was relative sparing (at least with regard to the T2 signal) of the amygdala contralateral to the seizure focus. They speculate that a preserved amygdala allows for abnormal processing of negative emotions. Patients in this study were classified according to a history of depression—either past or present. In fact, many of these patients were not depressed at the time of the imaging study. Accordingly, the authors acknowledge that an intact amygdala may be a *predisposing factor* for depression, although the person is not depressed much of the time.

Since patients with normal MRI scans were not included in this study, it is not possible to exclude hippocampal sclerosis as a risk factor for major depression. Investigators have found that MRI evidence of mesial temporal sclerosis increases the risk for both moderate depressive symptoms (3) and drug-induced depression (4) in patients with epilepsy. Patients were selected for the current study based on the presence of mesial temporal

sclerosis on clinical MRI examinations. If patients with normal MRI were also included in this study, it is possible that the authors would have found that, as in patients with major depression who do not have epilepsy, the presence of a hippocampal MRI abnormality is a risk factor for depression, although the degree of the abnormality is not important (2).

In contrast to the study by Briellmann et al., Gilliam and colleagues used proton spectroscopy, a functional rather than anatomical measure of hippocampal integrity, to assess the relationship between the integrity of medial temporal structures and the presence of ongoing depressive symptoms. They measured creatine/*N*-acetylaspartate (Cr/NAA) ratios, which increase (as the neuronal marker NAA decreases) and found that the degree of hippocampal dysfunction (as assessed by proton spectroscopy) was strongly associated with depressed mood. At first glance, the strong correlation between mood and hippocampal function seems surprising, if not contradictory, given the finding of Briellmann et al. that hippocampal volume is not related to depression. However, Gilliam and colleagues point out that anatomical (5) and functional (6) hippocampal measures are not always tightly correlated in TLE. In fact, many patients with TLE and normal MRI scans have profoundly reduced NAA measurements (5). The current studies suggest that brain function, rather than structure, determines a person's mood status.

The strong association between hippocampal function and depression reported by Gilliam and colleagues provides powerful support for the involvement of limbic structures in depression in patients with epilepsy. It is surprising, then, that another measure of cerebral function, glucose metabolism, as measured by ^{18}F -fluorodeoxyglucose PET (^{18}F -FDG PET), fails to demonstrate this relationship (7). The authors speculate that glucose metabolism might be affected by the neuron/glia ratio, which is known to be extremely variable in TLE, making NAA synthesis a better measure of hippocampal function. Other PET ligands may more effectively evaluate hippocampal function than ^{18}F -FDG for this purpose, however. Recent studies suggest that hippocampal serotonin receptor binding, as assessed by [^{18}F]FCWAY PET, correlates well with depressive symptoms in patients with and without epilepsy (8).

While these studies do not provide conclusive evidence for the involvement of limbic structures in epilepsy-related depression, they do point to its being a strong possibility. The current body of knowledge suggests that hippocampal

function is likely important in epilepsy-related mood disorders. In addition, other limbic structures probably play a role. These reports represent an initial attempt to understand depression as an important comorbidity in patients with epilepsy. Wisely, neither group makes a strong case for the imaging findings being causally related to depression. Rather than providing a call for changing diagnostic or treatment strategies, each group of investigators illustrate the fact that depression is a complex condition that will require further research to elucidate the mechanisms involved. It is hoped that an understanding of the biological processes will help to develop better ways to address patients' depression. Perhaps more important, these studies are a blunt reminder to screen patients for depression in order to provide the best treatment currently available.

by Paul A. Garcia, MD

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