



PSYCHOPATHOLOGY AND EPILEPSY: IS IT THE CHICKEN OR THE EGG?

Depression and Attempted Suicide as Risk Factors for Incident Unprovoked Seizures and Epilepsy

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Major depression has been shown to increase the risk for development of epilepsy, but prior studies have not evaluated whether this is due to specific symptoms of depression. We conducted a population-based case-control study of all newly diagnosed unprovoked seizures among Icelandic children and adults aged 10 years and older to test the hypothesis that major depression is a risk factor for developing unprovoked seizure and epilepsy, and to address whether specific symptoms of depression account for this increased risk. Cases were matched to the next two same sex births from the population registry. Using standardized interviews, we ascertained symptoms of major depression to make a *Diagnostic and Statistical Man-*

ual, Fourth Edition (DSM-IV) diagnosis. A history of major depression was 1.7-fold more common among cases than among controls (95% confidence interval, 1.1–2.7). A history of attempted suicide was 5.1-fold more common among cases than among controls (95% confidence interval, 2.2–11.5). Attempted suicide increased seizure risk even after adjusting for age, sex, cumulative alcohol intake, and major depression or number of symptoms of depression. Major depression and attempted suicide independently increase the risk for unprovoked seizure. These data suggest that depression and suicide attempt may be due to different underlying neurochemical pathways, each of which is important in the development of epilepsy.

COMMENTARY

It has been recognized for a very long time that depression and epilepsy bear a close relationship. Yet, data from two population-based case-control studies published in the last 15 years (and discussed in *Epilepsy Currents* issue 5.1) suggest the two disorders have a bidirectional relationship: that is, not only are patients with epilepsy at greater risk of developing depression, but patients with depression have a greater risk of developing epilepsy. In the first study, carried out in Sweden, Forsgren and Nystrom found that in patients with newly diagnosed epilepsy, depression preceding the seizure disorder was seven times more common than among age- and sex-matched controls ($p = 0.03$) (1). When analyses were restricted to cases with a localized onset seizure, depression was 17 times more common among subjects than among controls ($p = 0.002$). In a second population-based case-control study performed in Minnesota,

Hesdorffer et al. found that a diagnosis of depression preceding the first seizure occurred 3.7 times more frequently among adults aged 55 years and older than among controls without epilepsy (2). An interesting finding of the Minnesota study was that among people with epileptic seizures, an episode of major depression had taken place closer to the time of the first seizure than for controls. The authors interpreted these data saying: “pathophysiology leading to depression may lower the seizure threshold.”

Now, a third study, reviewed here, also addresses the relationship between epilepsy and depression. In an Icelandic population-based study, Hesdorffer et al. confirm the role of major depression as a predictor of epilepsy and determined that people with a suicidality history have a five-fold risk of developing epilepsy compared to controls, even after controlling for a history of major depression and alcohol abuse. It is a very significant finding because suicidality occurs in psychiatric disorders other than depression, particularly anxiety disorders, drug abuse, and personality disorders. What do depression, suicidality, and epilepsy have in common? The answer is: disturbances of CNS serotonergic activity.

The central serotonergic system is thought to function as a behavioral inhibitory system and is involved in the regulation of food intake, circadian rhythms, mood, anxiety, aggression, and impulsivity (3). The pathogenic role of serotonin (5-hydroxytryptamine, 5-HT) in epilepsy has been identified in various animal models; studies carried out with two strains of the genetically epilepsy-prone rat (GEPR), GEPR-3 and GEPR-9, are worth reviewing (4). The GEPR rats are characterized by a predisposition to sound-induced generalized tonic-clonic seizures. Both strains of rats have innate noradrenergic and serotonergic presynaptic and postsynaptic transmission deficits as well as abnormal serotonergic arborization in brain, which is coupled with deficient postsynaptic 5-HT_{1A} receptor density in the hippocampus. Of note, GEPRs display endocrine abnormalities (e.g., increased corticosterone serum levels, deficient secretion of growth hormone, and hypothyroidism) that are similar to those identified in patients with major depressive disorder (4).

Augmentation of 5-HT transmission prevent seizure occurrence, while reduction will have the opposite effect. Thus, administration of the selective serotonin-reuptake inhibitor (SSRI) sertraline, results in a dose-dependent reduction in seizure frequency in GEPRs, which correlates with an extracellular thalamic serotonin concentration (5). In addition, the 5-HT precursor 5-hydroxytryptophan (5-HTP) has anticonvulsant effects in GEPRs when combined with the SSRI fluoxetine, and both SSRIs and monoamine-oxidase inhibitors exert anticonvulsant effects in other experimental animals, including baboons and nongenetically prone cats, rabbits, and rhesus monkeys (4). The antiepileptic effect of 5-HT_{1A} receptors involves a membrane hyperpolarizing response, associated with increased potassium conductance in models of hippocampal kindled seizures in cats and intrahippocampal kainic-acid-induced seizures in freely moving rats (6). Of note, antiepileptic drugs with established psychotropic effects (e.g., carbamazepine, valproate, lamotrigine) cause an increase in synaptic 5-HT.

Deficits in 5-HT transmission in human depression have been recognized for a long time and have been the target of pharmacotherapy for depression. The deficits are thought to be partially related to a paucity of serotonergic innervation of terminal areas—a theory that is supported by a scarcity of 5-HT levels in brain tissue, plasma, and platelets and by a deficit in serotonin transporter binding sites in postmortem human brain. PET studies designed to measure the binding potential values of the 5-HT_{1A} receptor have been very useful in identifying these abnormalities. In a PET study using the 5-HT_{1A} receptor antagonist [¹¹C]WAY-100635, Drevets et al. compared 5-HT_{1A} binding potential values of 12 patients with familial recurrent major depressive episodes and 8 healthy

controls; they found significantly decreased binding potential values in mesial-temporal structures and the raphe in depressed patients (7). Likewise, a prominent pathogenic role for 5-HT_{1A} has been identified in brains of patients who committed suicide. For example, a deficit in the density or affinity of postsynaptic 5-HT_{1A} receptors has been reported in the hippocampus and amygdala of untreated depressed patients who committed suicide (8).

Similar findings were identified in patients with temporal lobe epilepsy. In a study in which 12 patients with temporal lobe epilepsy and 10 healthy controls underwent PET with the 5-HT_{1A} receptor antagonist [¹⁸F]*trans*-4-fluoro-N-2-[4-(2-methoxyphenyl)piperazin-1-yl]ethyl-N-(2-pyridyl) cyclohexanecarboxamide ([¹⁸F]FCWAY), Toczek et al. found reduced 5-HT_{1A} binding in mesial temporal structures ipsilateral to the seizure focus in patients irrespective of the presence of hippocampal atrophy (9). In addition, a 20% binding reduction in the raphe and a 34% lower binding in the thalamic region ipsilateral to the seizure focus was found (this difference yielded a statistical trend). In a separate PET study, 14 patients with temporal lobe epilepsy had decreased 5-HT_{1A} receptor binding in the epileptogenic hippocampus, amygdala, anterior cingulate, and lateral temporal neocortex ipsilateral to the seizure focus, and to a lesser degree, in the contralateral hippocampus and the raphe nuclei (10). Merlet et al. conducted a study aimed at comparing 5-HT_{1A} receptor density in epileptogenic and nonepileptogenic areas of patients with temporal lobe epilepsy. The epileptogenic zone was established with intracranial electrode recordings; the 5-HT_{1A} receptor density was measured with PET studies using the 5-HT_{1A} tracer, 4-(2'-methoxyphenyl)-1-[2'-[N-2'-pyridinyl]-*p*-(¹⁸F)fluorobenzamido] ethylpiperazine ([¹⁸F]MPPF). Significantly lower 5-HT_{1A} binding potential values were found in the areas of seizure-onset and propagation than in other brain areas. These findings were not affected by the presence or absence of hippocampal atrophy (11). Finally, in a recent study of 46 patients with temporal lobe epilepsy, Theodore et al. demonstrated an inverse correlation between increased severity of symptoms of depression, identified on the Beck Depression Inventory, and 5-HT_{1A} receptor binding at the hippocampus ipsilateral to the seizure focus and, to a lesser degree, at the contralateral hippocampus and midbrain raphe (12).

These studies clearly indicate that comorbid psychopathology in epilepsy can no longer be viewed as “a nuisance” to be ignored. Instead, its presence could be considered a means to help unmask important pathophysiologic processes that may become potential targets for the treatment of both epileptic seizures and comorbid psychiatric disorders.

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References

1. Forsgren L, Nystrom L. An incident case-referent study of epileptic seizures in adults. *Epilepsy Res* 1990;6:66–81.
2. Hesdorffer DC, Hauser WA, Annegers JF, Cascino G. Major depression is a risk factor for seizures in older adults. *Ann Neurol* 2000;47:246–249.
3. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron* 2002;34:13–25.
4. Jobe PC, Dailey JW, Wernicke JF. A noradrenergic and serotonergic hypothesis of the linkage between epilepsy and affective disorders. *Critical Rev Neurobiol* 1999;13:317–356.
5. Dailey JW, Mishra PK, Ko KH, Penny JE, Jobe PC. Serotonergic abnormalities in the central nervous system of seizure-naïve genetically epilepsy-prone rats. *Life Sci* 1992;50:319–326.
6. Beck SG, Choi KC. 5-Hydroxytryptamine hyperpolarizes CA3 hippocampal pyramidal cells through an increase in potassium conductance. *Neurosci Lett*, 1991;133:93–96.
7. Drevets WC, Frank E, Price JC, Kupfer DJ, Holt D, Greer PJN, Huang Y, Gautier C, Mathis C. PET imaging of serotonin 1A receptor binding in depression. *Biol Psychiatry* 1999;46:1375–1387.
8. Cheetham SC, Crompton MR, Katona CL, Horton RW. Brain 5-HT₁ binding sites in depressed suicides. *Psychopharmacology* 1990;102:544–548.
9. Toczek MT, Carson RE, Lang L, Ma Y, Spanaki MV, Der MG, Fazilat S, Kopylev L, Herscovitch P, Eckelman WC, Theodore WH. PET imaging of 5-HT_{1A} receptor binding in patients with temporal lobe epilepsy. *Neurology* 2003;60:749–756.
10. Savic I, Lindstrom P, Gulyas B, Halldin C, Andree B, Farde L. Limbic reductions of 5HT_{1A} receptor binding in human temporal lobe epilepsy. *Neurology*, 2004;62:1343–1351.
11. Merlet I, Ostrowsky K, Costes N, Ryvlin P, Isnard J, Faillenot I, Lavenne F, Dufournel D, Le Bars D, Mauguiere F. 5-HT_{1A} receptor binding and intracerebral activity in temporal lobe epilepsy: an [18F]MPPF-PET study. *Brain* 2004;127:900–913.
12. Theodore W, Giovacchini G, Kelley K, Hassler G, Drevets W, Herscovitch P, Carson R. Reduced hippocampal 5HT_{1A} receptor binding is related to depression in patients with temporal lobe epilepsy. Presented at the 58th annual meeting of the American Academy of Neurology, San Diego, CA, April 2006.