Psychopathology and Seizure Threshold

Epilepsy, Suicidality, and Psychiatric Disorders: A Bidirectional Association

Hesdorffer DC, Ishihara L, Mynepalli L, Webb DJ, Weil J, Hauser WA. *Ann Neurol* 2012;72:184–191.

OBJECTIVE: A study was undertaken to determine whether psychiatric disorders associated with suicide are more common in incident epilepsy than in matched controls without epilepsy, before and after epilepsy diagnosis. METHODS: A matched, longitudinal cohort study was conducted in the UK General Practice Research Database. A total of 3,773 cases diagnosed with epilepsy between the ages of 10 and 60 years were compared to 14,025 controls matched by year of birth, sex, general practice, and years of medical records before the index date. We examined first diagnosis of psychosis, depression, anxiety, and suicidality in each of the 3 years before and after the index date and annual prevalence of suicide. Referent diagnoses were eczema and acute surgery. The incidence rate ratio (IRR) was calculated for each year in the study period; the prevalence ratio (PR) was calculated for suicidality. RESULTS: The IRR of psychosis, depression, and anxiety was significantly increased for all years before epilepsy diagnosis (IRR, 1.5–15.7) and after diagnosis (IRR, 2.2–10.9) and for suicidality before epilepsy diagnosis (IRR, 3.1–4.5) and 1 year after diagnosis (IRR, 5.3). The PR was increased for suicide attempt before epilepsy onset (PR, 2.6–5.2) and after onset (PR, 2.4–5.6). Eczema and acute surgery were both associated with epilepsy in the first and third year after diagnosis. INTERPRETATION: Epilepsy is associated with an increased onset of psychiatric disorders and suicide before and after epilepsy diagnosis. These relations suggest common underlying pathophysiological mechanisms that both lower seizure threshold and increase risk for psychiatric disorders and suicide.

Commentary

This expertly designed, conducted, and analyzed study adds to prior studies that have examined the bidirectional association between psychopathology and epilepsy. Adelöw et al. (1) recently provided robust prospective data in a population-based case-control study using the Stockholm Epilepsy Register that confirmed this relationship in individuals hospitalized for a wide range of psychiatric disorders following an unprovoked seizure. In the Hesdorffer et al. prospective UK General Practice Research Database (GRPD), findings in individuals who were not selected because of psychiatric hospitalization suggest that the bidirectional association is not merely a function of the severity of psychiatric illness. Similar to Adelöw et al., the prevalence and incidence of a wide range of psychiatric diagnoses and suicidality underscore that the association between psychopathology and epilepsy is not a function of the type of psychiatric disorder. Further, it does not appear to be a function of epilepsy syndrome, as most of the subjects in both studies had idiopathic and cryptogenic epilepsy. However, since those in Adelöw et al. had predominantly focal seizures and this information is lacking in Hesdorffer et al., it remains to be determined if type of seizures (i.e., focal seizures) is related to the more severe psychopathology that necessitates psychiatric hospitalization.

Based on the study's prospective findings of incident epilepsy subsequent to psychiatric diagnoses, Hesdorffer and colleagues concluded that psychopathology lowers the seizure threshold rather than increases the propensity for seizures. Animal studies have shown that Genetic Absence Epilepsy Rats from Strasbourg (GAERS) with absence-like seizures demonstrate behaviors thought to represent anxiety before and subsequent to the onset of seizures (2). Jones et al. (2) concluded that these findings suggest that anxiety and absence seizures share common mechanisms. However, the pilocarpine animal model of temporal lobe epilepsy (TLE) manifests behavior equivalents of depression and involves lesions of the hippocampus and amygdala, as well as an increase in corticosterone and activity of the HPA axis (3). In contrast, the kainate model of TLE does not demonstrate depression, has minimal involvement of the amygdala and hippocampus, and is unrelated to an increase in corticosterone (3). Thus, different mechanisms appear to underlie the relationship between type of psychopathology (anxiety and depression) and type of seizures (absence and focal seizures) in animal models of epilepsy.

Therefore, in the absence of specific measures of seizure threshold in Hesdorffer et al., markedly different variables across individuals might contribute to the study's findings of an increased propensity for seizures. These include genetic, neurotransmitter, stress, psychosocial, and other environ-

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mental variables—variables that also play a role in the onset of psychiatric disorders. A lifetime history of psychiatric disorders in almost 50% of the adult population (4) and a one-year prevalence of 4.3–26.4% (IQR of 9.1–16.9%) (5) is much higher than the median lifetime prevalence of 5.8 per 1,000 (5th–95th percentile range 2.7–12.4) of epilepsy in developed countries (6), such as the UK. Thus, psychopathology per se does not appear to reduce the seizure threshold in the majority of patients with psychiatric diagnoses. Psychopathology and epilepsy appear to share common underlying mechanisms, albeit in only some individuals with psychopathology. Similar high rates of a wide range of psychopathology in about one-third of patients with epilepsy, migraine, and chronic headaches (7), as well as in those with traumatic brain injury (8), irrespective of the presence of posttraumatic epilepsy, imply that common CNS pathways that are unrelated to seizure threshold underlie psychopathology in these neurological disorders.

The study by Hesdorffer et al. demonstrated a significantly increased risk for attempted and completed suicide 3 years before and 2 years after the onset of epilepsy. In addition to suicide, Hesdorffer et al. also found an increased risk for anxiety and substance abuse/dependence during this period. The results section does not indicate whether the suicidal individuals also had anxiety (9) and substance abuse/dependence (10), variables associated with suicide. Nevertheless, this finding is particularly important because it challenges the FDA conclusion that AEDs cause suicide in individuals with epilepsy. Interestingly, Adelöw et al. found that the risk of developing unprovoked epileptic seizures was highest less than 2 years before and up to 2 years after a first psychiatric hospitalization for depression and psychosis but not for suicide. Additional studies are needed to determine what features of this 4- to 5-year vulnerable period increase the likelihood of seizures.

Finally, the study's strengths included the 1) completeness of the GRPD database, 2) the population-based nature of the cohort, 3) the representativeness of the UK population, 4) the data analytic techniques, definition of incident epilepsy as a diagnosis of epilepsy, and at least 2 antiepileptic drug prescriptions close in time to entry of the epilepsy code, and 5) a medical contact or prescription in the database for the controls. Study weaknesses are lack of information on type of seizures, how GRPD psychiatric diagnoses were determined, and confirmation of these diagnoses through information on treatment.

by Rochelle Caplan, MD

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