Psychopathology and Epilepsy: A Two-Way Relationship

Hospitalization for Psychiatric Disorders Before and After Onset of Unprovoked Seizures/Epilepsy.

Adelöw C, Andersson T, Ahlbom A, Tomson T. *Neurology* 2012;78:396–401.

OBJECTIVE: To study hospitalization for psychiatric disorders before and after onset of unprovoked epileptic seizures/epilepsy. METHOD: In this population-based case-control study, the cases were 1,885 persons from Stockholm with new onset of unprovoked seizures from September 1, 2000, through August 31, 2008, identified in the Stockholm Epilepsy Register. Controls, in total 15,080, were randomly selected from the register of the Stockholm County population. Odds ratios (ORs) were calculated to assess the risk of developing unprovoked epileptic seizures before and after hospitalization for a psychiatric diagnosis defined as a psychiatric hospital discharge diagnosis using International Classification of Disease codes from the Swedish Hospital Discharge Registry. RESULTS: The age-adjusted OR (95% confidence interval) for unprovoked seizures was 2.5 (1.7-3.7) after a hospital discharge diagnosis for depression, 2.7 (1.4-5.3) for bipolar disorder, 2.3 (1.5-3.5) for psychosis, 2.7 (1.6-4.8) for anxiety disorders, and 2.6 (1.7-4.1) for suicide attempts. The risk of developing unprovoked epileptic seizures was highest less than 2 years before and up to 2 years after a first psychiatric diagnosis. CONCLUSION: The increased rate of psychiatric comorbidity predating and succeeding seizure onset indicates a bidirectional relationship and common underlying mechanisms for psychiatric disorders and epilepsy.

Commentary

Since Slater's description of a schizophrenia-like psychosis in epilepsy in the 1960s, studies have mainly examined the one-way relationship between epilepsy and a schizophrenia-like or interictal psychosis (1, 2). More recently, a U.K. epidemiological study (3) has shown that this is a two-way relationship and that epilepsy is also prevalent among patients with schizophrenia. Prior to the present study by Adelöw et al., however, similar studies had not been conducted on psychiatric patients with nonpsychotic diagnoses commonly found in epilepsy patients.

This population-based study is the first study to provide robust data supporting the two-way relationship. The comparable odds ratios (2.3–2.7) for depression, bipolar disorder, anxiety disorders, psychosis, combined psychiatric disorders, and suicide is a particularly interesting finding. It implies that the propensity for psychopathology, rather than the type of psychopathology and its severity, increase the risk for epilepsy. Similarly, having an unprovoked seizure or self-report of epilepsy increases the likelihood of depression, suicide, and attention deficit hyperactivity disorder (ADHD) (4, 5) and of six neuropsychiatric disorders (anxiety, depression, bipolar disorder, ADHD, sleep disorder/apnea, and movement disorder/tremor), respectively (6). The findings of Adelow et al., are in line with genetic evidence that several large, rare genomic copy number variants substantially increase the risk of schizophrenia, generalized epilepsy, intellectual disability, autism-spectrum disorders, and ADHD (7).

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They also support evidence from epidemiologic studies that a family history of psychosis and a family history of epilepsy are significant risk factors for schizophrenia, schizophrenia-like psychosis associated with epilepsy, and epilepsy (2, 8) and for the association with an unprovoked seizure in a first-degree relative of children with uncomplicated epilepsy who have aggression and behavior problems (9).

The predominance of focal seizures and mainly cryptogenic/idiopathic epilepsy rather than remote symptomatic epilepsy in the subjects with psychiatric diagnoses in Adelow et al. is similar to the higher psychopathology rates in community studies of adult patients with focal epilepsy. Similarly, Berg et al. (10) also demonstrated significantly fewer subjects with internalizing behavior problems, such as sadness, withdrawal, and anxiety, among children with complicated epilepsy (most of whom had symptomatic epilepsy) compared with those with uncomplicated epilepsy. Adelow et al. suggest that the increased likelihood of dermatologic and opthalmologic disorders in their remote symptomatic epilepsy group probably reflects adverse antiepileptic drug effects involving the skin and ophthalmic lesions associated with skull and face fractures. However, increased medical illness, including allergies, asthma, and cardiovascular disorders, in children with psychiatric disorders (11) and in children with epilepsy (12), suggests that both psychopathology and epilepsy are related to increased clinical medical morbidity.

From the methodological perspective, the inclusion of eight control subjects matched on sex and year of diagnosis with each study subject ensured that similar clinical approaches were used for making the psychiatric diagnoses of the study's subjects. This is an important aspect of the study design because of fluctua-

tions in psychiatric diagnostic practices and the collection of the hospital discharge data over a long period (1986–2009). Whereas schizophrenia, schizotypal personality disorder, and borderline personality disorder were common psychiatric diagnoses in the 1960s, during the 1970s to 1990s diagnoses such as depression, ADHD, schizoaffective, and anxiety disorder were frequently made. Over the past 15 years, bipolar disorder, prodromal psychosis, and autism spectrum disorders have become more prominent psychiatric diagnoses.

Additional methodological strengths of this study include the well-defined exclusionary criteria, particularly the need to rule out psychiatric diagnoses due to organic causes. By measuring the time from psychiatric discharge to first seizure and from first seizure to psychiatric discharge diagnosis, these investigators have also avoided a recall bias for determining past seizures in patients with psychiatric diagnoses. In addition, comparison of the relationship between psychiatric diagnoses and the development of seizures in subjects with and without recurrent seizures demonstrated that the two-way relationship between psychopathology and epilepsy is not a function of ongoing seizures.

Despite the wide age range of subjects in this study, the authors did not examine if the risk for seizures varied by age. About one-third of the subjects were 15 years old and younger, an additional third were between the ages of 31 and 65, 15% were 15 to 30 years old, and 20% were over age 65. In light of the increasing prevalence of depression and schizophrenia in older adolescents and young adults, the small sample size of the subjects, aged 15 to 30 (n = 287, 15% of the sample), might have precluded these analyses and is a study limitation. In addition to age, low IQ is related to both higher rates of psychopathology and poor seizure control, and as previously mentioned, to the genetic collocation of a wide range of psychopathology and epilepsy. The lack of information on the intellectual functioning of the study's subjects is an additional study limitation.

Given recent evidence for phobias, particularly social phobia in epilepsy (13), and involvement of the limbic system in this disorder (14), exclusion of patients with phobias from the anxiety disorder category might underestimate the risk for seizures and the time frame for the development of seizures in this study. As previously mentioned, the extended period during which hospital discharge information was collected (1986–2009) and the use of three different psychiatric classification systems (ICD-8, ICD-9, and ICD-10) during this period is a study limitation because of changing diagnostic practices. The authors emphasize that their findings cannot be generalized to individuals with psychiatric diagnoses who are not hospitalized. The two-way relationship between psychopathology and epilepsy, therefore, might reflect the severity of psychopathology.

Finally, the finding by Adelow et al. that patients with depression and psychosis developed seizures within 2 years of their psychiatric admission compared with those with anxiety and bipolar disorder implies similar underlying mechanisms for the development of depression, psychosis, and seizures. Animal models demonstrating involvement of similar neurotransmitters, brain-derived neurotrophic factor, the hypothalamic-pituitary axis, inflammation, and kindling in these disorders might underlie the increased likelihood of a similar time frame during which individuals might be at risk for co-occurrence of these disorders. Identification of biomarkers of risk for seizures and for psychiatric disorders is the first step needed to begin to delineate the mechanisms underlying the two-way relationship between psychopathology and epilepsy. Use of these biomarkers in prospective studies in large samples of newly diagnosed psychiatric patients and individuals with new-onset seizures with psychiatric diagnoses and seizures as outcome measures would then be the next step.

by Rochelle Caplan, MD

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