Psychiatric comorbidity in epilepsy represents not only a matter of intellectual interest but also an important variable that affects prognosis in terms of morbidity and mortality.

For a long time, the correlation between epilepsy, seizures, and emotions has been a matter of debate, fascinating generations of clinicians and neuroscientists. In his famous quotation, Hippocrates reported that “melancholics ordinarily become epileptics, and epileptics, melancholics: what determines the preference is the direction the malady takes; if it bears upon the body, epilepsy, if upon the intelligence, melancholy.”¹ This ancient observation has been recently revitalized by modern epidemiological data that suggest a bidirectional relationship between epilepsy and mood disorders and between epilepsy and suicide.²,³ However, psychiatric comorbidity in epilepsy represents not only a matter of intellectual interest but also an important variable that affects prognosis in terms of morbidity and mortality.

Mood and anxiety disorders are the most frequently reported psychiatric comorbidities with epilepsy, with a prevalence of 20% to 22%; however, in select populations, the prevalence can reach 50%.⁴ Reasons for the association are both biological and psychosocial. Epilepsy is a chronic disorder that brings about a number of social limitations and discriminations that lead to demoralization and poor self-esteem. Moreover, epilepsy and mood disorders seem to share a common neurobiology, with involvement of the limbic structures and the modulation of major neurotransmitter pathways by anticonvulsant medications.

Compared with mood disorders, psychoses seem to be relatively rare in patients with epilepsy but represent serious complications that affect morbidity and mortality. Epidemiological data indicate that the incidence of non-organic, non-affective psychoses, including schizophrenia and related disorders, is generally overrepresented in patients with epilepsy compared with the general population or those with other chronic medical conditions. Higher prevalence has been seen in hospitalized patients.⁵,⁶ The relationship between epilepsy and psychoses has strong neurobiological underpinnings related to the involvement of specific brain areas.

The issue of phenomenology and diagnosis of mood disorders
Mood disorders in epilepsy frequently go unrecognized and untreated because of lack of time, lack of training, and clinicians’ reluctance to refer patients because of psychiatric symptoms. In addition, up to 50% of patients with epilepsy and depression present psychiatric symptoms that are not captured by standardized classificatory systems, such as DSM and ICD-5.⁷,⁸ This is particularly evident in the case of interictal dysphoric disorder (IDD).

The concept of IDD is derived from Kraepelin and Diefendorf⁹ and Bleuler,¹⁰ who observed that in patients with untreated epilepsy, a pleomorphic pattern of depressive symptoms intermixed with euphoric moods, irritability, fear, and anxiety as well as with anergia, pain, and insomnia could develop. This concept has been subsequently rejuvenated by Blumer,¹¹ who coined the term “IDD” and described 8 key symptoms, grouped into 3 categories: labile depressive symptoms (depressive mood, anergia, pain, insomnia); labile affective symptoms (fear, anxiety); and “specific” symptoms (paroxysmal irritability, euphoric moods).

The specific symptoms are a peculiar symptom cluster characterized by periodic mood changes and outbursts of irritability and aggressive behavior. These episodes occur without external triggers and without clouding of consciousness; they begin and end quickly and recur fairly regularly (every few days to every few months and last from a few hours to 2 days). The symptom cluster described in patients with IDD and epilepsy is quite peculiar and is rarely reported in psychiatric practice, even in patients with rapid cycling bipolar disorder or cyclothymia. It is interesting to note that in about 50% of patients, dysphoric symptoms present a clear-cut relationship with epileptic seizures occurring either preictally or postictally.¹² Epileptic seizures are characterized not only by the ictal phase but also by a number of behavioral manifestations that may precede or follow the seizure. Such peri-ictal symptoms may fail to meet temporal DSM criteria when too short-lasting. However, it appears that they are highly responsible
for the atypical presentations of psychiatric disorders in epilepsy.\textsuperscript{13} Alternatively, peri-ictal symptoms may be misleadingly interpreted as psychiatric manifestations when they are long-lasting. In fact, a cross-sectional study of patients shows that a diagnosis of bipolar disorder can be overestimated in epilepsy if peri-ictal mood changes are not correctly identified.\textsuperscript{14} In fact, of the 11.8% of DSM-based diagnoses of bipolar disorder, only 1.4% can be considered as a “pure” psychiatric diagnosis because in all other cases, manic/hypomanic symptoms are temporally related to seizures that occur either postictally or preictally. Thus a careful assessment of seizure-based behavioral manifestations should always be part of a routine assessment, with treatment strategies based on peri-ictal symptoms.

The Interictal Dysphoric Disorder Inventory (IDDI) is used for the evaluation of IDD and the identification of seizure-associated symptoms.\textsuperscript{8} This 38-item, self-report questionnaire looks at a time interval of 12 months and provides a total score in addition to 3 subscale scores that mirror the major symptom categories of IDD. The questionnaire is also used to measure the degree of interference or distress caused by mood symptoms. The IDDI has demonstrated good internal consistency, acceptable sensitivity, and excellent specificity. The Appendix to the questionnaire includes 6 questions that pinpoint the time course and duration of mood symptoms and their associations with seizures or antiepileptic drug therapy.

**Psychoses of epilepsy: an evergreen**

Psychoses of epilepsy have fascinated neuropsychiatrists for decades. Although an important topic of research, psychoses of epilepsy are definitely less prevalent than seizure-based psychotic symptoms. Mood symptoms are conveniently classified according to their temporal relationship with seizures as preictal, ictal, or postictal.

Ictal psychoses usually represent a nonconvulsive epileptic status of temporal lobe origin. Postictal psychoses are probably the most relevant in epidemiological terms, representing approximately 25% of all psychoses of epilepsy. They are usually precipitated by a series of secondary generalized tonic-clonic seizures followed by a period of normal mental state of 24 to 48 hours. Almost all patients have this lucid interval, and failure to recognize it can lead to misdiagnoses. The pathophysiology of postictal psychoses is unknown, but it is a highly stereotyped phenomenon that occurs mainly in patients with mild intellectual disabilities, temporal lobe epilepsy, and extratemporal structural lesions. Findings indicate a correlation between postictal psychoses and déjà vu auras or ictal fear.\textsuperscript{15}

The phenomenology of postictal psychoses is polymorphic, but most patients present with abnormal mood and paranoid delusions with mystic and religious content. Consciousness can be variably impaired (e.g., from overwhelming confusion to totally clear sensorium). High levels of anxiety with a fear of impending death represent another typical symptom that may precipitate in episodes of violence, self-injury, or suicide if command hallucinations are present.

Postictal psychoses are characterized by spontaneous remission within days or weeks; antipsychotic drug treatment is only required to reduce mortality and morbidity. Finally, it has to be kept in mind that in a minority of cases, postictal psychoses may evolve into chronic interictal psychosis. Nowadays, interictal psychoses represent a rare complication, and the general impression is that this is probably because of effective treatment of epileptic syndromes. In fact, interictal psychoses usually develop subtly after 25 years of active lesional temporal lobe epilepsy. Neuropathology studies of patients with interictal psychoses show cerebral malformations, such as hamartomas and gangliogliomas, and gross abnormalities, such as enlarged ventricles and periventricular gliosis. The link between interictal psychoses and mesiotemporal lobe structures is well established and demonstrated by clinical and neuroimaging findings.\textsuperscript{16,17} However, the timing of the lesions and the functional changes in the brain of patients with interictal psychoses are largely different from those described in schizophrenia, which suggests that the pathophysiology of interictal psychoses is largely integrated with that of epilepsy.

The phenomenology of interictal psychoses seems to be slightly different from that of schizophrenia. Slater and Beard\textsuperscript{18} emphasized the preservation of affect in the context of first-rank symptoms of Schneider, with religious mystical content. The paucity of negative symptoms and the absence of formal thought disorders and catatonic states have also been proposed.\textsuperscript{19} The longterm prognosis of interictal psychoses seems to be better than that of schizophrenia, with less reported long-term cognitive deterioration and institutionalization. This is probably because of the preservation of personality and the tendency for psychotic symptoms to attenuate over time.

Landolt phenomenon, also known as “forced normalization” or “paradoxical normalization,” can occasionally be seen.\textsuperscript{20} In the 1950s, Landolt published a series of papers on patients in whom a psychotic state emerged when their epilepsy was controlled.
Tellenbach described the clinical counterpart of this phenomenon: patients who became psychotic on sudden remission of seizure symptoms. Landolt originally associated the forced normalization phenomenon with focal epilepsies, but subsequent studies suggest an association with generalized epilepsies. In any case, what seems to be striking is the association with neurobiological mechanisms underlying seizure control. In fact, Landolt’s phenomenon has been reported not only with antiepileptic drugs but also with vagus nerve stimulation, and it is likely implicated in psychoses following surgery.

It terms of phenomenology, the classic presentation is that of psychosis, but other symptoms may be present, such as manic episodes, depressive episodes, and dissociative states. Generally, forced normalization is a self-limited phenomenon that lasts days or weeks, and drug treatment is only required to reduce mortality and morbidity.

Conclusions
Data on treatment of psychiatric disorders in epilepsy are still limited and based mainly on clinical observations. However, in recent years, international societies (eg, the International League Against Epilepsy and the American Epilepsy Society) have paid increasing attention to the problem. Treatment follows the internationally accepted guidelines for treating psychiatric disorders while keeping in mind pharmacodynamic and pharmacokinetic idiosyncrasies, such as drug interactions and the effects of psychotropic medications on seizure threshold. New generations of antidepressants and antipsychotics can be considered reasonably safe in patients with epilepsy, if they are appropriately prescribed in terms of titration and dosages. The “start low/go slow” recommendation represents a starting point, but bear in mind that low starting doses do not necessarily correspond to low target doses. The primary goal is full symptom remission.

Disclosures:
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