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Review

The interictal dysphoric disorder of epilepsy: Legend or reality?

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ABSTRACT

For a long time, the relationships between epilepsy and mood disorders captured the attention of clinicians and neuroscientists. The existence of a peculiar clinical presentation for mood disorders in epilepsy has been a matter of debate since the early reports of Kraepelin and Bleuler. The interictal dysphoric disorder (IDD) represents the modern reinterpretation of such early observations. This paper reviews current research on this topic discussing clinical implications, phenomenological observations, and directions for future research.

1. Introduction

For a long time, the association between epilepsy and depression has been a matter of debate. 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, suggesting a bidirectional relationship between epilepsy and mood disorders and between epilepsy and suicide [2–4]. Although such a bidirectional link seems to be present in several chronic conditions, for example, Parkinson's disease [5], stroke [6], dementia [7], diabetes [8], and cardiovascular diseases [9], the case of epilepsy is definitely intriguing given the neurobiological underpinning shared by the two conditions [10–12].

If epilepsy and depression share a number of pathophysiological mechanisms, it is also possible that there would be a peculiar syndrome characterized by seizures and mood symptoms. Epilepsy is not a unique entity, with a number of syndromes characterized by recurrent seizures as the main element. However, behavioral symptoms are rarely considered as part of the whole picture. The concept of interictal dysphoric disorder (IDD) derives from original observations of classic German psychiatrists, namely Kraepelin and Bleuler, who observed that patients with untreated epilepsy could develop a pleomorphic pattern of depressive symptoms intermixed with euphoric moods, irritability, fear, and anxiety as well as anergia, pain, and insomnia [13,14]. This concept has been subsequently rejuvenated, in modern times, by Blumer who actually coined the term IDD [15]. Since its introduction, the concept of IDD has been a matter of debate. The aim of this paper is to discuss current research on this affective–somatoform syndrome with special attention to clinical implications. References were identified by searches of Medline/PubMed using the keywords "epilepsy", "depression", and "interictal dysphoric disorder". Only papers written in English have been considered. However, the list of relevant articles was handsearched for additional publications (e.g., book chapters or review papers) if relevant for the discussion.

2. The nonconforming features of mood disorders in epilepsy and the concept of IDD

A number of authors agree that up to 50% of patients with epilepsy and depression present psychiatric symptoms that are not captured by standardized classificatory systems such as DSM or ICD [16–20]. This observation might explain the high variability in epidemiological data on mood disorders in epilepsy. In fact, community-based studies report prevalence rates on the order of 20%–22% [21,22], but in selected populations, such as tertiary referral centers, prevalence rates seem to be as high as 50% [23,24]. Although it is plausible that such differences reflect the severity of the individual seizure disorder [25,26], it is also possible that atypical presentations of depression are not captured by international coding systems or standardized clinical instruments.

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Interictal dysphoric disorder is operatively conceptualized by Blumer in eight key symptoms, grouped in three major categories, namely, labile depressive symptoms (depressive mood, anergia, pain, and insomnia), labile affective symptoms (fear, anxiety), and supposedly "specific" symptoms (paroxysmal irritability and euphoric moods) (Table 1). The latter, in particular, identify a peculiar symptom cluster characterized by periodical mood changes and outbursts of irritability and aggressive behavior. Such episodes are described as occurring without external triggers and without clouding of consciousness, beginning and ending rapidly and recurring fairly regularly in a uniform manner (every few days to every few months and lasting a few hours up to 2 days). Interestingly, the concept of IDD goes beyond the mood disorder per se, encompassing a spectrum of conditions with transient psychotic features or even prolonged psychotic states. In other words, Blumer suggests that interictal psychoses of epilepsy represent severe forms of IDD with prominent psychotic features [15,27].

Although it appears evident that Blumer's description has been highly influenced by the Kraepelinian view of the relationship between mood disorders and schizophrenia, modern studies on the phenomenology of IDD and psychoses of epilepsy partly support this hypothesis. In fact, IDD seems to be closer to bipolar depression rather than to the unipolar one [20,28,29], and psychoses of epilepsy are characterized by a preserved personality and prominent mood symptoms [30], suggesting that psychoses of epilepsy belong to the mood spectrum rather than to the psychotic spectrum. However, the symptom cluster described in patients with IDD and epilepsy is quite peculiar and is rarely reported in psychiatric practice, even in rapid cycling bipolar disorders or cyclothymia [28]. Probably for this reason, Blumer stated that IDD is unique for epilepsy [27].

3. The concept of periictal dysphoric syndrome (PDS)

It seems now established that epileptic seizures are not just characterized by the ictal phase, but a number of behavioral manifestations can occur around the ictus, either preceding or following it [31,32]. Such symptoms may be subtle and difficult to identify if not specifically sought. In addition, they often fail to meet temporal criteria for mood symptoms according to DSM. It is, thus, evident that such manifestations are highly responsible for the atypical presentation of mood disorders in epilepsy.

A cross-sectional study in patients with epilepsy reported that most of the pleomorphic features of IDD are related to periictal symptoms [33]. In fact, among patients with a diagnosis of IDD, about 50% present symptoms with a clearcut relationship with epileptic seizures either presenting preictally or postictally [33]. Premonitory symptoms are reported by one-third of patients with temporal lobe epilepsy, usually preceding secondarily generalized tonic–clonic seizures [34]. Prodromal mood changes may occur hours to days before a seizure and are often relieved by the convulsion [35]. A cross-sectional study in tertiary referral centers in Europe pointed out that around 13% of patients may experience irritability, dysphoria, or depressed mood preceding seizures [33]. As for preictal symptoms, postictal mood changes are rarely recognized by clinicians, but a case series of presurgical patients suggests that up to 18% of patients can report postictally at least five symptoms of depression lasting more than 24 h, and up to 22% present manic symptoms often with associated hallucinations or delusions [36]. Postictal anxiety seems to be even more frequent, being reported by 45% of patients [36]. The median duration of symptoms ranges from 6 to 24 h, but in one-third of cases, postictal anxiety may last 24 h or longer.

All these data taken together have relevant implications in terms of prognosis and treatment, emphasizing the need to dissect out periictal manifestations from interictal ones. It is estimated that around 12% of patients with TLE may present isolated periictal dysphoric symptoms without interictal chronic symptoms [33]. In such patients, a so-called periictal dysphoric syndrome (PDS) can be recognized, but the prognosis and treatment is that of the epileptic syndrome rather than that of a psychiatric disorder.

Table 1
Symptom clusters for interictal dysphoric disorder.

Labile depressive symptoms
Depressed mood
Anergia
Pain
Insomnia
Labile affective symptoms
Fear
Anxiety
Specific symptoms
Mood swings
Paroxysmal irritability
Euphoric moods

4. Diagnosing IDD and PDS

Periictal symptoms are not rare, but clinicians need to specifically inquire [29]. Moreover, periictal symptoms may be almost indistinguishable from interictal ones, apart from duration and the close relation with seizure occurrence. It is, thus, possible, if not recognized, to overestimate psychiatric diagnosis or even misdiagnose behavioral problems in some cases. A cross-sectional study of patients recruited in two epilepsy centers in Europe showed that a diagnosis of bipolar disorder may be overestimated in epilepsy if periictal mood changes are not correctly identified [29]. In fact, out of the 11.8% of DSM-based diagnoses of bipolar disorder, only 1.4% could be considered as a "pure" psychiatric diagnosis because, in all other cases, manic/hypomanic symptoms were temporally related to seizures occurring either postictally or preictally [29]. A careful assessment of seizure-based behavioral manifestations should always be part of a routine assessment of patients with epilepsy and behavioral problems. In fact, the identification of patients with PDS may be relevant in terms of localizing seizure onset and prognostic value. As such, postictal mania seems to be associated with frontal, nondominant involvement [37,38] and is associated with a poor prognosis after surgery identifying temporal lobe "plus" patients [38]. In this regard, a specific clinical instrument for the evaluation of IDD and PDS has been developed, namely, the Interictal Dysphoric Disorder Inventory (IDDI) [20]. The IDDI is a 38-item, self-report questionnaire exploring a time interval of 12 months. It is possible to obtain a total score and three subscale scores that mirror the three major symptom categories described by Blumer. Besides, the IDDI measures the degree of interference or distress caused by IDD symptoms. The instrument shows a good internal consistency, an acceptable sensitivity, and an excellent specificity. Finally, in the appendix to the questionnaire, six questions investigate the time course of the disorder, duration of dysphoric symptoms, and their associations with seizures or antiepileptic drug therapy. A recent study investigated test–retest reliability of the IDDI, showing a 50% agreement [39]. This is something frequently seen in psychological testing as the attribute that is being measured may change between the first test and the retest; because the experience of taking the test itself can change a person's true score (for example, completing an anxiety inventory could serve to increase a person's level of anxiety); and finally, because when retested, people may remember their original answer, which could affect answers on the second administration in order to minimize some symptoms. In the case of PDS, this is further complicated by the seizure itself as it is entirely possible that patients do not remember some symptoms that are part of the postictal state. For all these reasons, a careful clinical evaluation should be part of the assessment apart from the use of clinical rating scales.