Bipolar Disorder and Epilepsy

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Abstract

The comorbidity of epilepsy and mood disorders has been a subject of interest and of many studies for decades. Although the data on the prevalence of bipolar disorder in epilepsy is still limited, there is growing evidence that these disorders are frequently comorbid. Bipolar disorder and epilepsy have a number of clinical, biochemical and pathophysiological features in common.
Mood disorders in epilepsy often have atypical symptomatology and fail to meet DSM-IV-TR criteria. They can be classified according to the temporal relationship between the onset of psychiatric symptoms and seizure occurrence into ictal (as a clinical manifestation of the seizure), peri-ictal (symptoms precede [pre-ictal] and/or follow [postictal] the seizure), and interictal (symptoms occur independently of the seizure occurrence).

A pleomorphic affective syndrome in patients with epilepsy has been named interictal dysphoric disorder (IDD). Recent data suggest that some symptoms of IDD can be related rather to bipolar spectrum disorder than to unipolar depression, which has implications for treatment and prognosis.

Key Words: epilepsy, bipolar disorder, interictal dysphoric disorder, kindling.

Introduction

Epilepsy is a common and diverse set of chronic neurological disorders characterized by seizures (1). It is the most common serious neurological disorder (2). The lifetime prevalence of true epilepsy is 2-5%. Mood disorders represent a frequent psychiatric comorbidity in epilepsy and often go unrecognized, underdiagnosed and untreated with adverse consequences for health-related quality of life, costs and utilization of epilepsy healthcare, and an increased risk of suicide (3, 4). Most studies on mood disorder have focused on major depressive disorder (MDD) as it is the most frequent psychiatric comorbidity in people with epilepsy (PWE), with a lifetime prevalence of 11-62 % (5, 6). The symptomatology of mood disorders in epilepsy is often atypical, intermittent and pleomorphic. Because the clinical picture can be so diverse it is often difficult to classify mood disorders in epilepsy according to DSM-IV-TR (7) categories, with symptoms overlapping, especially between unipolar and bipolar spectrum disorders. Bipolar disorder features include manic and hypomanic episodes as well as major depressive episodes. Combined mixed episodes also exist (7). The lifetime prevalence of bipolar spectrum disorders may be as high as 2.6 % in the general population (8).

Studies and data on prevalence, recognition and clinical features of bipolar disorder in epilepsy remain limited. Nevertheless, there is growing evidence of bipolar disorders and epilepsy being frequent comorbid conditions. There are features that are common to both conditions, suggesting that there might be a shared mechanism of pathogenesis.

DSM-IV-TR criteria and bipolar disorder recognition

Bipolar Disorder until recently has been classified according to Diagnostic and Statistical Manual

of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR). There are two main types of bipolar disorder, depending on the occurrence of manic/mixed (type I) or hypomanic (type II) episodes in addition to major depressive episodes. Bipolar disorder not otherwise specified (NOS), is the category that includes bipolar spectrum disorders that do not fulfil type I or type II criteria. Cyclothymic disorder represents a more chronic and less severe, clinical form of bipolar disorder with periods of hypomanic symptoms alternating with periods of mild or moderate depression. Lifetime prevalence of bipolar disorder type I has generally been estimated at 2% (9). However, including bipolar II type, cyclothymic disorder and sub-threshold diagnostic criteria for BPD, 6.4 % of the general population has been classified as having bipolar spectrum disorder (8). There is evidence that BPD is often not recognized and is misdiagnosed. In an attempt to improve recognition of BPD, self-report instruments such as the Mood Disorder Questionnaire (MDQ) (10) or the Hypomania Checklist (HCL-32) (11) have been developed.

Recognition of bipolar disorder in epilepsy

When reviewing the literature on mood disorders in epilepsy it is important to note that there are significant methodological differences among the studies, including variable, often non-standardized diagnostic instruments, small sample size, lack of control groups, variability in study populations (inpatients, outpatients, neurosurgical patients, refractory epilepsy) (12). There are only limited studies on bipolar disorder in epilepsy and most of the studies are based on clinical examination but without the use of standardized diagnostic criteria such as DSM-IV-TR or ICD-10. This probably explains, at least partially, why bipolar disorder was rarely reported in epilepsy in the older literature (13,14).
Recent studies have pointed out that manic or hypomanic symptoms are not rare in epilepsy. A large U.S. survey revealed that bipolar symptoms occurred in 12.2% of community-based epilepsy patients, screened with MDQ, and were 1.6 to 2.2 times more common in subjects with epilepsy than with migraine, asthma, or diabetes mellitus, and 6.6 times more likely to occur than in the healthy control group. A total of 49.7% of the patients with epilepsy who screened positive for bipolar symptoms were diagnosed with bipolar disorder by a physician (15). In another study a group of consecutive patients with epilepsy (PWE) or migraine (M) have been established using the MINI for DSM-IV Axis I disorders. All subjects were also screened with the MDQ. Patients with epilepsy were more likely than those with migraine to screen positively with the MDQ (PWE = 17% vs. M = 5.3% $p = 0.006$) and to have a diagnosis of bipolar disorder (PWE = 14.5% vs. M = 4.5% $p = 0.013$) (16).

The Kindling model

Bipolar disorder and epilepsy share some similarities, such as a chronic, episodic course, often with increasing disability and drug resistance if not treated, and the fact that some of the antiepileptic drugs are also used as a first-line or second-line treatment in bipolar disorder. Unipolar depression may evolve into bipolar disorder, (17) more mood episodes can lead to a more chronic course of illness whilst in epilepsy it had been suggested (although not subsequently confirmed) that each epileptic event might increase the risk of future seizures. The idea that "seizures beget seizures" is sometimes confused with the experimental model seizure kindling in animals (see later). These observations led to a proposed kindling model as a common mechanism of pathogenesis of both disorders. The kindling phenomenon in epilepsy was discovered in 1967 by Graham Goddard (18) and was previously used as a model for the development of seizures in epilepsy in which the duration and behavioural involvement of induced seizures increases after seizures are induced repeatedly (19). The true model of kindling in epilepsy is somewhat different from what is usually envisaged. The amygdala is a key structure for the development of spontaneous epileptic activity (20). The type of kindling that has been confirmed in epilepsy refers to the experimental observation that repetitive subthreshold stimulation in animals can eventually induce seizures until seizures occur spontaneously without any stimuli. In unipolar and bipolar disorder life events trigger affective episodes, but finally relapse occurs in the absence of any obvious stress factor. It has been also postulated that each new mood episode contributes to the progression of the mood disorder in a similar manner to that of the experimental kindling model in epilepsy (21). These hypotheses were made partly on the observation that antiepileptic drugs (AEDs) such as carbamazepine, valproate and lamotrigine have a high antikindling

effect (20, 22, 23) and are also are broadly used in BPD due to their strong mood-stabilising properties (24, 25).

Treatment with antiepileptic drugs

There is considerable overlap in the pharmacological agents used in epilepsy and BPD. Controlled studies have shown that a number of antiepileptic drugs are effective in bipolar disorder in the treatment of acute mania (carbamazepine, valproate), as well as depression (lamotrigine) and for long-term mood stabilization (24, 25).

There are practically no controlled studies on the efficacy of AEDs on bipolar symptoms in epilepsy. Given the lack of data and guidelines for treatment of BPD in epilepsy, probably the primary strategy would be to optimize AED therapy to improve seizure control, preferably using an AED that also has mood-stabilising properties.

Valproate has similar actions to lithium (used in bipolar disorder) in that it manipulates inositol metabolism and extracellular signal-regulated kinase (ERK) pathways. These may lead to altered synaptic plasticity and anti-apoptotic effects. Lamotrigine can also be useful across these conditions, having inhibitory actions upon sodium channels. Its optimal effect is achieved long-term, as with lithium and valproate; thus these agents may act by a combination of acute actions on neurotransmission (reducing excitability) and longer-term genomic effects (26).

Molecular biology, neurotrophic factors and network remodelling

All major antiepileptic drugs that are also mood stabilisers, are known to inhibit sodium and calcium currents. The efficacy of AEDs in both conditions, suggests the existence of similar changes in neurotransmitters and voltage-dependent ion channels in epilepsy and bipolar disorder (26). Electrolyte regulation is considered important in the pathogenesis of bipolar disorder and epilepsy, given the suggestion that they involve a hyper-excitable state. Calcium is of further interest in that one hypothesis of bipolar disorder features underlying mitochondrial dysfunction (27).
Disturbance of neurotrophic factors may be involved. BDNF levels are reduced in bipolar disorder and can modify cellular excitability, whilst treatment can alter its expression (28). Conversely, levels are sometimes raised in epilepsy. The end result could be aberrant network changes, including microstructural abnormalities and sensitisation - in particular the above described kindling phenomenon (29). Cell death may also be a feature, given observations of larger-scale brain changes. Limbic structures are frequently affected in bipolar disorder and epilepsy. One theory of bipolar disorder postulates loss of function of 'mood-stabilising neurons' (27) regulating affective circuits, in keeping with the idea that the disorders may share altered inhibition.

Epilepsy-specific mood disorders

Mood disorders in epilepsy often have atypical symptomatology and fail to meet DSM-IV-TR criteria. As already stated, they can be classified according to the temporal relationship between the onset of psychiatric symptoms and seizure occurrence into ictal (as a clinical manifestation of the seizure), peri-ictal (symptoms precede [pre-ictal] and/or follow [postictal] the seizure), and interictal (symptoms occur independently of the seizure occurrence).

Ictal psychiatric symptoms are manifestations of the seizure itself. However, since most seizures are brief, with a few exceptions, it might be difficult to establish whether any ongoing psychiatric symptoms were truly ictal. Some of the older publications suggested that depression of sudden onset in people with epilepsy might be precipitated by the mood changes associated with a simple partial seizure, although it should be noted that simple partial seizures are usually very brief. This phenomenon was said to appear to be more common in patients with temporal lobe epilepsy, in whom rates of about 15 % were reported (30,31). The severity of symptoms could range from mild feelings of sadness to profound helplessness and despair, guilty feelings and anhedonia.

Prodrome is a well-recognised epilepsy-associated phenomenon, typically lasting for perhaps half

an hour to two or more days before a seizure. Mood and consequently behaviour can be disturbed during this period. Preictal dysphoria can manifest as prodromal depressive mood or irritability. The prodrome is resolved when the seizure occurs. (30, 31, 32). Preictal unstable mood with euphoria and paroxysmal irritability has also been observed (33). It has also been reported that in children, these dysphoric moods can take the form of irritability, frustration intolerance, and aggressive behaviour (34).

Postictal symptoms typically last up to 48 hours after ictus with median duration from 6 to 24 hours (34, 35). Some studies indicate that postictal depression can last up to 2 weeks after the ictus and may lead to suicide (32, 36, 37). The most frequent symptoms are anhedonia, irritability, frustration, poor tolerance, feelings of hopelessness and helplessness, suicidal ideation, feelings of guilt and self-deprecation, and crying bouts (32). Postictal manic/hypomanic symptoms, usually lasting up to 2 hours, have also been reported. These symptoms could represent a part of postictal psychosis or more often a mixed episode with psychotic features. (38,39,50).

Interictal Dysphoric Disorder

The Interictal recurrent syndrome of periodic dysphoria is the most common form of mood disorder in epilepsy. Frequently, it does not fulfil any of the DSM-IV criteria and has an atypical clinical presentation of depressive symptoms with paroxysmal irritability and also euphoric mood. It is commonly described as a chronic depression or dysthymic disorder but without fulfilling time criteria for these DSM-based diagnoses. However, it can also be a part of the bipolar disorder spectrum. These episodes have symptomatic periods ranging from hours to days interrupted by symptom-free periods of similar duration.

Blumer et al. (51) drew attention to these forms of mood disorder commonly seen in patients with epilepsy and coined the term interictal dysphoric disorder (IDD). A long time before Blumer, similar clinical observations had been made by Kraepelin, who provided a similar clinical description of such a form of mood disturbances in epilepsy (52). IDD is characterized by a constellation of eight symptoms and requires the presence of any three: depressive mood, anergia, pain, paroxysmal irritability, euphoric moods, fear/anxiety and insomnia. Interictal dysphoric disorder is typically of short duration; symptoms occur at various intervals and tend to last from hours to two or three days. In women, these symptoms can become accentuated in the premenstrual period. Blumer et al. considered that almost one-third to one-half of patients with epilepsy suffer from IDD and require pharmacological treatment (51). Unfortunately there are only limited data on comparisons in the literature evaluating this form of mood disorder in epilepsy using standardized DSM-IV based diagnostic techniques with IDD criteria. Recently Mula et al. (16) investigated whether IDD occurs only in patients with epilepsy and validated IDD features against DSM-IV criteria. Consecutive patients with a diagnosis of epilepsy (E) or migraine (M) have been assessed using the BDI, MDQ, and the Interictal Dysphoric Disorder Inventory (IDDI). Diagnosis of current and lifetime DSM-IV Axis I disorders was established using the MINI. Validation of IDD against DSM-IV categories showed current major depression being the foremost diagnostic category correlated with IDD in both epilepsy and migraine. They concluded that IDD was not typical only of epilepsy, occurring also in other central nervous system disorders such as migraine (16). Interestingly, in the study sample PWE were more likely to have a diagnosis of bipolar disorder as compared to migraine patients.

In another study, Mula et al. (53) examined a group of 143 adult outpatients with epilepsy and revealed that 11.8% had the DSM-based diagnosis of bipolar disorder but only 1.4% of whom could be considered as having "pure" bipolar disorder. In all other cases, BPD symptoms were related to symptoms of interictal dysphoric disorder, postictal manic or hypomanic states, and preictal dysphoria.

Based on these observations, it was suggested that perhaps interictal dysphoric disorder with its specific features and labile-angry-irritable states represents a more unstable form of bipolar spectrum disorder (53, 54). IDD could be a form of cyclothymic disorders that sometimes exacerbate and meet criteria of major depression episode. Mula et al. speculated that there is enough evidence suggesting that IDD may be closer to bipolar than unipolar mood disorders (53).

Conclusion

The comorbidity of epilepsy and mood disorders has been a subject of interest of many studies over many decades. Although data on the prevalence of bipolar disorder in epilepsy are still limited, there is growing evidence of bipolar disorder and epilepsy being frequent comorbid conditions. Bipolar disorder and epilepsy have a number of clinical, biochemical and pathophysiological features in common.

Bipolar disorder in epilepsy, excluding the ictal or peri-ictal symptoms, can be categorized using standardized measures. Standardized psychiatric interview procedures based on DSM criteria like SCID-I or MINI provide a comprehensive way to diagnose mood disorders in patients with epilepsy.

Different authors have suggested the occurrence of a pleomorphic affective syndrome in patients with epilepsy named interictal dysphoric disorder (IDD). There are only limited data on comparisons in the literature using standard diagnostic techniques with IDD criteria. Recent data suggest that some symptoms of IDD can be related rather to bipolar spectrum disorder than to a unipolar disorder, which has implications for the treatment and course of the illness. Standardised measures that include these unique aspects of symptomatology in epilepsy need to be developed and more direct comparisons with other populations should be evaluated (34).

GP Comment

What have I learned from this paper?

I found the molecular biology, network remodelling and kindling models made for interesting reading; however, perhaps more relevant to specialist physicians as compared general practitioners. I imagine more research could be directed towards this overlap in diagnoses, so as to obtain larger participant numbers.

Dr Vishal Naidoo, GP.

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