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Review

Depression and epilepsy, pain and psychogenic non-epileptic seizures: Clinical and therapeutic perspectives

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ABSTRACT

The clinical manifestations of depression in people with epilepsy (PWE) are pleomorphic, often associated with anxiety symptoms and anxiety disorders. The ongoing debate of whether the clinical presentation of depression in PWE is unique to this neurologic disorder is reviewed. Comorbid depression can impact the recruitment of PWE for pharmacologic trials with antiepileptic drugs (AEDs). Yet, the impact of depression on the response of the seizure disorder to pharmacotherapy with AEDs and its impact on worse adverse events may bias the interpretation of the trial findings, particularly when depressed patients are included in the AED trials.

PWE have a greater suicidal risk than the general population. This risk is mediated by multiple factors, and recent data from the FDA have imputed a potential pathogenic role to all AEDs. The recognition of patients at risk is reviewed. Yet, the validity of the FDA data has been questioned, and the status of this controversial question is analyzed.

As in the case of epilepsy, depression and pain syndromes have a relatively high comorbidity. The negative impact of depression on pain is reminiscent of that of depression in PWE; furthermore, the high comorbidity may be also associated with the existence of common pathogenic mechanisms.

Neurologists and in particular, epileptologists establish the diagnosis of psychogenic non-epileptic seizures (PNES) in whom a comorbid depressive disorder is very often identified. The role of depression in the course of PNES and its treatment are discussed.

Scarce data are available on the treatment of depression in PWE. Thus, clinicians have had to adopt data from patients with primary depressive disorders. We outline a consensus strategy on the identification and treatment of depressive disorders in adult and pediatric patients with epilepsy.

1. Introduction

Given that one of every three people with epilepsy (PWE) is likely to experience a depressive episode in the course of their life, neurologists and other health professionals that take care of these patients should screen for these disorders. Yet, from a clinical standpoint, depression is a heterogeneous syndrome with several clinical expressions, some of which have been considered to be specific to PWE, in particular the peri-ictal symptomatology. Furthermore, depressive episodes are often associated with anxiety symptoms and/or full anxiety disorders, which also need to be recognized and incorporated into the overall management of the depressive disorder to ensure its complete and enduring remission. These important clinical aspects of depression in PWE were reviewed in an international symposium on Epilepsy and Depressive Disorders that took place in Chicago, Illinois in September 2010 (see also companion paper in this issue).

Suicidality in PWE is another topic that was discussed in some detail, given the complex relation of epilepsy and suicidality and the significant increase in the risk of completed suicide (by 32-fold) in those patients with mood disorders. The highly debated question of a potential pathogenic role of antiepileptic drugs (AEDs) was also discussed. Clearly, identification of depressive and anxiety disorders as well as patients with an increased suicidal risk cannot be expected from non-psychiatrists in busy neurology clinics. Yet, as stated above, the use of screening instruments can overcome these problems and should be incorporated into the evaluation of all PWE.

Despite the relatively high prevalence of depressive disorders in adults and pediatric patients with epilepsy, there are few data on this important issue, both as it pertains to research studies and clinical practice. In pediatric patients, this problem is compounded by the difficulties inherent in the recognition of depressive disorders in this age group. Furthermore, the role of neurologists in the management of depressive disorders in PWE remains to be established, as non-psychiatrists should not be treating patients with bipolar illness,

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psychotic depressive episodes or patients with treatment-resistant epilepsy, as summarized in this review.

Depressive disorders can also impact the tolerability of AEDs, as depressed PWE are significantly more likely to report adverse events, even when the depression presents as a sub-syndromic episode. This problem is poorly recognized despite the significant implications it may have on the interpretation of toxicity data from AED trials. In addition, depression compounds the severity of other medical and psychiatric conditions such as pain syndromes and psychogenic non-epileptic seizures, topics that are further explored here.

2. Clinical aspects

2.1. Are mood disorders in epilepsy unique?

Marco Mula, MD, PhD

The issue of phenomenology of depression has been a matter of debate for a long time, having a number of implications in terms of diagnosis, treatment and prognosis. Numerous authors have pointed out that depression in epilepsy is more often than not characterized by atypical features that are poorly reflected by conventional classificatory systems such as DSM-IV and ICD-10 [1–3]. However, other studies clearly suggest that it is possible to apply standardized criteria of the DSM in a not negligible proportion of patients [4,5]. In general terms, the psychopathological spectrum of depression in epilepsy is likely to be large. On the one hand, it is reasonable to hypothesize that patients with epilepsy experience forms of mood disorders identical to those of patients without epilepsy. However, it is equally reasonable to assume that the underlying brain pathology may influence the expression of mood disorder symptoms making less evident some aspects or emphasizing others. A number of variables may account for such atypical features in epilepsy such as peri-ictal symptoms, the high comorbidity between mood and anxiety disorders (up to 73%), the underlying neurologic condition and the psychotropic effect of AEDs.

Pre-modern psychiatrists, such as Kraepelin and Bleuler, observed that patients with epilepsy may develop a mood disorder characterized by a pleomorphic pattern of symptoms such as depression intermixed with euphoria, irritability, fear and anxiety as well as anergia, pain and insomnia [6,7]. This concept was revitalized during the XXth century by Blumer who coined the term interictal dysphoric disorder (IDD) to refer to this type of somatoform-depressive disorder claimed as typical of patients with epilepsy [8]. Studies of my group pointed out that such a condition is a mood disorder, probably not specific for epilepsy, that is usually diagnosed during the depressive phase, with a significant comorbid anxiety (social phobia and/or generalized anxiety disorder) and a relevant component of mood instability [9]. However, a number of atypical and pleomorphic features of this condition are related to peri-ictal symptoms [10] that, indeed, are typical only of patients with epilepsy. This issue has relevant implications in terms of prognosis and treatment. On the one hand, it emphasizes the need to dissect out peri-ictal manifestations from interictal ones, the former being related to the prognosis and treatment of the epileptic syndrome. On the other hand, the presence of mood instability as an essential element of IDD suggests the need to prescribe mood stabilizing AEDs as preferred treatment and the utility of antipsychotic drugs in selected cases.

The arguments for whether or not clinical presentations of depression in epilepsy are similar to those in the general population have been variably prominent across the authors. However, whatever way one views this, the literature suggests that a sub-group of patients may have an affective syndrome with peculiar features which some have referred to as the IDD. Such a condition seems to overlap with the bipolar spectrum, with possible consequences in terms of prognosis and therapeutic strategies. However, in a proportion of cases, the number of behavioral manifestations that occur around the seizure plays a relevant role in such an atypicality. It is, therefore, essential that clinicians carefully assess the mental state of their patients, taking into account a number of variables that are principally related to the underlying neurological disorder.

2.2. Is it only depression or depression and anxiety disorders? Clinical implications and impact on quality of life

Andres M. Kanner, MD

Depression and anxiety disorders are the two most frequent psychiatric comorbidities in PWE [11]. Yet, the high comorbidity of these two conditions has also been demonstrated in patients with primary mood and anxiety disorders with a mean of 67% (range: 42 to 100%) of patients with depressive disorders also experiencing anxiety disorders concurrently or in their lifetime and 40% of patients with anxiety disorders (range: 17 to 65%) also suffering from depression. Recognition of this comorbidity has important implications on the course and response to therapy of depressive disorders. For example, the National Comorbidity Study has demonstrated that depressed individuals with a history of anxiety disorders are at increased risk for hospitalization, suicide attempt, and greater impairment from the depression [12,13]. In the NIMH Collaborative Depression Study, the presence of panic attacks predicted a lower likelihood of recovery during the first 2 years of the follow-up interval [14]. A worse response of depressive disorders to therapy in the presence of a comorbid anxiety disorder has been reported in several studies. For example, in an 8-month follow-up study of depressed primary care patients treated with nortriptyline or interpersonal therapy, patients with a history of generalized anxiety disorders (GAD) or panic disorder were less likely to have recovered from their depressive episode [15]. In the Medical Outcomes Study, panic or phobic disorder, but not GAD, coexisting with major depressive disorder predicted a lower remission rate of the latter condition one year after the initial evaluation through 2 years after the evaluation; only panic disorder was significantly associated with a lower remission rate [16]. In fact, in recognition of the high comorbid occurrence of the two conditions and their impact on response to treatment, the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) has included a specific diagnostic category for a mixed depression/anxiety disorder.

The co-occurrence of depressive and anxiety disorders is also relatively frequent in PWE. Thus, in one population-based study, a lifetime prevalence rate of anxiety disorders was found in 22.8% of PWE vs. 11% in non-epilepsy subjects while lifetime rates of 34% were found for comorbid anxiety and depressive disorders [11]. Anxiety disorders are also relatively frequently found in PWE attending specialized epilepsy centers. In a study of 188 consecutive PWE from five epilepsy centers in the USA (50% of whom had been seizure- free for the last six months), 83 were found to be experiencing a comorbid psychiatric disorder (established with the Mini International Neuropsychiatric Interview (M.I.N.I.)). Current anxiety disorders were identified in 49 patients (26%). Among these 49 patients, 28 were suffering from comorbid anxiety and depressive disorders; of note, 27 patients (14.4%) had two or more anxiety disorders [17].

Several studies have found a negative impact of comorbid symptoms of depression and anxiety on the quality of life of PWE [18–23]. For example, symptoms of depression and anxiety were independently associated with reduced health-related quality-of-life measures in a study of 87 PWE; psychiatric comorbidity explained more variance in HRQOL than did combined groups of clinical seizure or demographic variables [23].

A recent study has found a comparable negative impact of depressive and anxiety disorders (according to DSM-IV criteria) on the quality of life of 188 outpatients with PWE [17]. Of note, that study also demonstrated that a sub-syndromic form of depression has a comparable negative impact on the quality of life of PWE as major