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Depressive disorders in patients with epilepsy: Why should neurologists care?

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ABSTRACT

Epilepsy is a complex disorder that is commonly associated with brain dysfunction, social isolation, and vocational difficulty. Each of these factors may contribute to the increased prevalence of psychiatric illness in epilepsy, but emerging evidence is providing a more complete and clearer elucidation of the problem. Clinical investigations have consistently demonstrated that depression has a large impact on subjective health status. In patients with recurrent seizures, depression appears to have a stronger association with quality of life than does the seizure rate. In fact, depression is second only to medication toxicity as the clinical factor that explains the greatest variance in quality of life. Only a small number of studies have investigated the plausible neurobiological mechanisms of depression in epilepsy, but preliminary data suggest that underlying brain dysfunction may be a more important predictor than vocational or social disability. Furthermore, specific aspects of hippocampal dysfunction may be a causal factor in the genesis and maintenance of depression in temporal lobe epilepsy. Current treatment recommendations for depression in epilepsy are similar to those for otherwise neurologically normal depressed patients, emphasizing the role of serotonin reuptake inhibitors, but certain antidepressants should be used with caution. Ongoing studies are attempting to define optimal treatment strategies, and more definitive data to guide clinical management are expected to become available in the near future.

Keywords: Depression; Seizures; Temporal Lobe Epilepsy; Quality of Life; Serotonin Reuptake Inhibitors (SSRIs)

1. INTRODUCTION

Epilepsy is a chronic condition that may be associated with several other neurological disorders; stroke, migraine, and psychiatric disorders are the most frequent comorbid disorders in patients with epilepsy (PWE). The term comorbidity is used to describe greater than coincidental association of two or more conditions in the same individual [1].

Epilepsy has been associated with increased risk of psychiatric disorders, although incidence and prevalence rates of psychiatric comorbidities vary widely among studies, from 12% - 41%. This variation is largely due to methodological differences among the studies; selection bias, population under study, diagnostic methods used, antiepileptic drugs (AED) numbers and dosages are some of the confounding factors that could have an effect on the prevalence rates [2-5]. Epilepsy has also been associated with increased risk of suicide, even after adjustments for various factors known to pose a risk for suicide in the general population [6-9].

The most frequent psychiatric diagnoses reported in people with epilepsy include psychoses, neuroses, mood disorders (DSM-IV axis I disorders), personality disorders (DSM-IV axis II disorders), and behavioral problems. Among these, mood disorders are the most frequent psychiatric comorbidity in PWE with a prevalence of depression estimated between 11% and 60% in patients with recurrent seizures [10,11]. Indeed, it is well established that one of every three patients with epilepsy (PWE) will experience a depressive disorder in the course of their life, often associated with anxiety symptoms or a full blown anxiety disorder. In this review article, we will focus on the comorbidity of depression and epilepsy. We will review the available information regarding the etiologies of depression in epilepsy as well as the current recommendations for management. We attempt to offer areas for further research in order to alleviate the burden of depression in persons with epilepsy.

2. PREVALENCE OF DEPRESSION IN EPILEPSY

Based on the available epidemiological studies, the prevalence of depression ranges from 11% to 60% in patients with recurrent seizures and from 3% to 9% in patients with well-controlled seizures. Mendez *et al.* [11] used the Hamilton Depression Rating Scale in 175 consecutive patients in an outpatient epilepsy clinic, finding that 55% met criteria for depression. In a community-based study that used the Hospital Anxiety and Depression Scale, Jacoby *et al.* [12] observed, in a well-designed survey, that 21% of 168 patients with recurrent seizures were depressed; whereas, only 9% of controlled patients had significant symptoms of depression. On the other hand, in a primary care setting, O'Donoghue *et al.* [13] used the same scale to demonstrate that, out of a group of 155 patients in the United Kingdom, 33% with recurrent seizures and 6% of those in remission had probable depression. Finally, a recent study by Seyal *et al.* [14] using the Patient Health Questionnaire nine-item depression scale (PHQ-9) found that 30% of their patients attending a specialized epilepsy clinic have scored in the depressed range. In fact, despite several methodological variability among various studies, depression is consistently found to be up to 10 times more prevalent in association with uncontrolled epilepsy than in the general population. The findings from these studies underscore the importance of depression in epilepsy and the need to effectively screen and treat depressive disorders.

3. IMPACT OF DEPRESSION ON HEALTH RELATED STATUS

Several studies have studied the implication of depression on health related quality of life (QOL) in PWE. Ettinger *et al.* [2] recently utilized the household panel maintained by the National Family Opinion to study depression and QOL in persons with epilepsy, asthma, and healthy controls. The response rate for the survey was approximately 50% in each group, with a total of 1532 responses. PWE were significantly more likely to score in the depressed range on the Center for Epidemiological Studies Depression Scale (CES-D) (37%), than were those with asthma (28%) or healthy subjects (12%). Although nearly half of the group with epilepsy had not had a seizure during the past year, suggesting that the sample represented the less severe aspect of the spectrum of epilepsy, the mean scores on the Short Form—36 scales for role limitations, emotional wellbeing, and social wellbeing were significantly worse than the asthma group. On the other hand, none of the scales was lower for asthma. In another cross sectional study, Beghi *et al.* [15], compared depression severity across disease states in a recent study of epilepsy, type I diabetes mellitus, and community controls. Fifty-five patients with idiopathic or cryptogenic epilepsy were compared with age and sex matched subjects with type I diabetes or persons donating blood in the local medical clinic. Epilepsy subjects with any structural brain abnormality were excluded from the study, and only 37% reported a seizure within the past year, reflecting less form of severe epilepsy similar to the study of Ettinger *et al.* [2]. Thirty-four percent of epilepsy patients scored in the depressed range compared with 27% of type I diabetes patients and 7% of blood donors.

4. THE IMPORTANCE OF IDENTIFYING DEPRESSION IN PWE

The impact of depression on QOL in patients with epilepsy has been well described in five studies involving patients with pharmacoresistant epilepsy. They demonstrated that depression is the most powerful predictor of health related quality of life, even after controlling for seizure frequency, severity, and other psychosocial variables [16-20].

Furthermore, several studies have demonstrated the increased incidence of suicide in patients with depression and epilepsy. In a review of 11 studies, Harris and Barrowclough [21] found the overall suicide rate in people with epilepsy to be five times higher than in the general population and 25 times greater for patients with complex partial seizures of temporal lobe origin. In a review of the literature, Jones *et al*. [6] identified a lifetime average suicide rate of 12% in people with epilepsy compared to 1.1% to 1.2% in the general population.

Moreover, other studies have clearly shown that depression in people with epilepsy has significantly increased the healthcare costs associated with the management of the seizure disorder. Cramer *et al*. [22] found that patients with untreated depression used significantly more health resources of all types, independent of seizure type or latency. Likewise, mild-to-moderate depression was associated with a two-fold increase in medical visits compared with non-depressed controls, while severe depression was associated with a four-fold increase.

Finally, recent data suggest that presence of depression in PWE may predict a failure to respond to pharmacotherapy with AEDs in patients with newly diagnosed epilepsy. Of a cohort of 890 patients with newly diagnosed epilepsy, Hitiris *et al.* [23] found that a prior history of depression is associated with at least 2.5 times risk of not responding to AEDs over 5 years of follow up. On the other hand, the presence of depression prior to epilepsy surgery may also serve as an independent marker for worse postsurgical outcome following anterior temporal lobectomy (ATL), as shown by the study of Kanner *et al*. that included 100 patients with a mean follow up of 4 years [24]. These studies raise the question

of whether depression can be considered as a marker for "difficult to control" epilepsy.

5. ETIOLOGIES OF DEPRESSION IN EPILEPSY

The perception that depression is a "normal" response to havinga chronic condition such as, epilepsy has long been held, by both patients and physicians, but is no longer acceptable or valid. Instead, several emerging data have explored other multifactorial etiologies of depression in epilepsy. These include underlying genetic, neurochemical, anatomical, neurologic, and iatrogenic factors.

5.1. The Role of Genetics

The role of genetics in the etiology of depression in epilepsyis suggested by the fact that a family history of depression is quite common among depressed patients with epilepsy. Morethan half of these patients have been reported to have family histories of psychiatric illness, usually mood disorders [25].

5.2. The Role of Neurotransmitters

It appears that epilepsy and depression may share common pathogenic mechanisms involving decreased serotonergic, noradrenergic, dopaminergic, and GABAergic activity, which has been shown totake part in the kindling process of seizure foci, exacerbatingseizure frequency in some animal models [26]. Studies of neurotransmitter activity in both epilepsy and depression suggest that the occurrence of one disorder may facilitate the development of the other, and vice versa [27]. As a matter of fact, several imaging studies utilizing interictal PET using different ligands, have consistently shown some degree of decreased 5-HT1A binding in the mesial structures, raphe nuclei, thalamus, and cingulate gyrus [28-30]. In a study of 45 patients with TLE, Theodore *et al.* demonstrated an inverse correlation between increased severity of symptoms of depression identified on the Beck Depression Inventory (BDI) and 5HT1A receptor binding at the ipsilateral hippocampus to the seizure focus and to a lesser degree at the contralateral hippocampus and midbrain raphe [31]. These changes in 5 HT1A receptor binding are quite similar to those identified in PET studies of patients with primary major depressive disorders (MDDs). To further support this shared pathogenic mechanisms, three case-control population based studies have shown that a history of depression was associated with several fold increased risk for developing new onset epilepsy among cases than among controls [32-34]. This bidirectional relationship does not necessarily suggest that depression causes epilepsy or vice versa. Rather, it may support the point towards the existence of common pathogenic mechanisms operant in both conditions which facilitate the development of one disorder in the presence of the other. Interestingly enough, many centuries ago, Hippocrates 400 BC had suggested this type of bidirectional relationship when he wrote, "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". Galen at 200 AD had further reconfirmed the organic cause of depression [35].

Neuroanatomical factors: Changes in common brain structures have been identified in patients with primary major depressive and bipolar disorders and in PWE, including atrophy of temporal- and frontal-lobes. These changes have been identified with the use of high-resolution MRI and volumetric measurements of the amygdala, hippocampus, entorhinal cortex, temporal, lateral neocortex, as well as of the prefrontal, orbitofrontal, and mesial-frontal cortex, and to a lesser degree, of the thalamic nuclei and basal ganglia [36]. It is, therefore, not surprising that PWE whose seizure foci are in temporal and frontal lobes have a higher prevalence of depression. Furthermore, hippocampal atrophy/sclerosis (HS) which is a hallmark of mesial temporal lobe epilepsy is a common finding in patients with depression and, according to some studies, correlate with both the severity and duration of the depressive state [37]. Furthermore, Quiske *et al*. [38] examined the association of MRI defined mesial temporal sclerosis (MTS) with BDI scores in 60 patients with temporal lobe epilepsy (TLE). Mean depression scores were significantly higher in patients with MTS, independent of the lateralization of MTS. The investigators described depression as "a good indicator of MTS, but not vice versa". Moreover, a study by Gilliam has shown a correlation of the degree of MR spectroscopic abnormalities in the ipsilateral hippocampus in patients with TLE and the severity of depression as measured by BDI [39]. In addition, some studies suggest that the presence of HS is a risk factor for developing depression in PWE when treatment is initiated with certain AEDs, such as topiramate, and levetiracetam [40,41].

5.3. The Role of Neurological/Seizure Factors

Seizure type has been shown to correlate with depression, which is more common in patients with complex partial seizures, particularly those of temporal lobe origin. Others have looked at the possibility that depression might be associated with laterality of seizure focus. Most studies have found that depression is more common in those with left-sided foci [42]. Furthermore, a recent work by Theodore *et al.* suggest that patients with right

TLE are more likely to have depression and left MTS, compared with left TLE without depression, as measured by BDI sores [43].

5.4. The Role of Iatrogenic Factors

Among the most important factors contributing to the risk for depression in people with epilepsy are those associated with medication. A number of drugs and drug classes have been implicated in the etiology of depression, including some antiepileptic drugs (AEDs), such as barbiturates, levetiracetam, vigabatrin, and topiramate which are clearly associated with behavioral changes and depression [42]. Other investigators have related depression to the rapid withdrawal of an AED with mood stabilizing properties, such as, carbamazepine, oxcarbazepine, and lamotrigine [44]. Another, uncommon, but well documented example is the occurrence of de novo depression following ATL. Interestingly, this risk occurs independently of postsurgical outcome. This paradoxical "iatrogenic" cause of psychopathology among patients with epilepsy includes the phenomenon of "forced normalization." This phenomenon consists of the appearance of psychiatric disorders associated with the cessation of epileptic seizures [45]. On the other hand, a recent study showed significant improvement in depression and anxiety in patients with refractory epilepsy following epilepsy surgery, especially in those who became seizure-free [46].

6. CLINICAL MANIFESTATIONS

Depressive symptoms can present according to the temporal relation to the seizures occurrence into *ictal* (the depressive symptoms are a clinical manifestation of the seizure, a rare form of depression in PWE), *periictal* (symptoms precede and/or follow the seizure occurrence), and *interictal* (symptoms occur independently of the seizure occurrence). Interictal depression is the most frequently "recognized" type of mood disorder and can present differently among PWE. Major depression, bipolar disorder, dysthymic disorder, and minor depression are all well described in PWE. Nevertheless, a significant percentage of patients present an atypical clinical picture that fails to meet any of the DSM Axis I categories, which lead Blumer to coin the term "interictal dysphoric disorder" to refer to this type of depression in epilepsy with its prolonged and interrupted depression free course that is often associated with anhedonia, hopelessness, helplessness, anergia, pain, and insomnia [47]. In a study by kanner *et al.*, symptoms of depression mimicked dysthymic disorders in 69 of 97 consecutive patients (70%); the interrupted nature of these symptoms accounted for the failure to meet DSM-IV criteria of dysthymic disorder [25].

7. SCREENING FOR DEPRESSION

Despite its high frequency and great impact on the QOL and care for PWE, depressive symptoms remain undertreated and unrecognized in a significant number of PWE. Kanner *et al*. determined that 63% of patients with spontaneous depression and 54% of patients with an iatrogenic depression were symptomatic for more than 1 year before treatment was initiated [48]. While the clinical manifestations of depression in people with epilepsy can be atypical, the most frequent cause for the under-recognition is the failure of clinicians to inquire about it and of patients or families to report it. In a survey of neurologists, Gilliam found that 80% do not routinely screen for depression in patients with epilepsy [49]. This suggests that in a busy neurology practice, where the major focus is seizure control, it is likely that symptoms of depression may be missed.

Several tools have been used to screen for depression in PWE; most of which are time consuming in a busy clinic setting. Recently, a 6-item questionnaire has been developed and validated to screen for depression, the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E), NDDI-E; it takes less than 3 minutes to fill out at the office and has a sensitivity and specificity of 90%, 81%, respectively [50]. A score of 14 and higher is suggestive of the possibility of a major depressive disorder and can serve as an alarming sign to carry out a more in-depth evaluation. Clearly, the use of this and other screening instruments for psychiatric research on epilepsy must be followed by structured psychiatric interviews designed to establish a DSM-IV-TR diagnoses, which would permit regular rescreening to yield meaningful data on changes in severity of symptomatology.

8. TREATMENT OPTIONS

A significant percentage of PWE and depression are under-recognized and under-treated. Reasons for this include lack of appreciation of the impact of depression on QOL and the fear that seizures are exacerbated by antidepressants. Despite its relatively high prevalence and significant impact on management, the treatment of depression in PWE remains an, "unexplored territory". The treatment of these patients has been, for all intents and purposes, empiric, based on the untested assumption "that patients with depression and epilepsy should respond to antidepressant drugs in the same manner as depressed nonepileptic patients." In fact, there has only been one double-blind, placebo-controlled study published to date that included 42 patients. It compared the efficacy of mianserin, amitriptyline, and placebo to treat major depression in PWE in three treatment arms. At the end of 6 weeks of treatment, no significant differences in outcome were observed between the groups. Obviously,

the small sample size limits the draw of any meaningful conclusions [51].

Before starting a patient on antidepressant drug therapy, it is important to rule out the following potential causes for a depressive episode: 1) the depressive episode followed the discontinuation of an AED with mood stabilizing properties, such as carbamazepine, valproic acid, or lamotrigine [44]. In such a case, reintroduction of that AED or of another mood-stabilizing agent may be sufficient to reach a euthymic state; and 2) the depressive episode followed the introduction or dose increment of an AED with known negative psychotropic properties, such as Phenobarbital, topiramate, vigabatrin. In such cases, lowering of the dose or discontinuation of the culprit AED should result in symptom remission.

In general, the delay of initiating treatment in PWE, stem from misbelieve that antidepressants worsen or trigger seizures. As a matter of fact, and in contrary to that believe, the actual risk of antidepressant drugs causing or worsening of seizures in PWE is small and should not deter the start of therapy. In a study at the Rush Epilepsy Center, sertraline was found to definitely worsen seizures in only 1 out of 100 patients [52]. In another five patients, a transient increase in seizure frequency was attributed to this antidepressant drug with a probable but not definite causality. On the other hand, bupropion, maprotiline, and amoxapine are the antidepressant drugs with the strongest proconvulsant properties and should be avoided in epileptic patients [53]. Current recommendations for the treatment of depression in persons with epilepsy are SSRI or cognitive therapy [54]. SSRIs are generally considered safe and well tolerated, keeping in mind that all of the currently available SSRIs, except for citalopram and escitalopram, inhibit one or more of the hepatic cytochrome P450 isoenzymes, an enzyme system involved in the metabolism of the "old" AEDs, carbamazepine, phenytoin, and phenobarbital.

In fact, one recent and very reassuring article suggests a possible "protective" effect of SSRIs and serotonin and epinephrine reuptake inhibitors (SNRI) in depressed patients: In that study, Alper *et al*. [55] compared the incidence of seizures between depressed patients randomized to placebo and SSRIs, SNRIs and the $\alpha 2$ antagonist mirtazapine in the course of regulatory studies submitted to the FDA. The seizure frequency among patients randomized to placebo was 1501.5 seizures/100,000 years, while that of patients randomized to the antidepressants was 534.8 seizures/100,000 years. Other options for treatment include cognitive, interpersonal and behavioral therapy, and, in severe cases, electroconvulsive therapy (ECT) can be considered safely in PWE who do not respond to appropriate antidepressant therapy [56].

A randomized trial of an SSRI and cognitive behavior therapy (CBT) in depressed patients without other neurological disorders demonstrated greater efficacy with combined therapy compared to either one alone [57]. A similar trial design for PWE randomizing 140 PWE to either sertaline or CBT for 16 weeks has been recently completed. At the end of the trial, no significant difference in outcome for depressive symptoms remission was observed in the two arms. Moreover, patients whom their depressive symptoms remit had significant improvement in QOL independent of other epilepsy related factors. Similar to the study of Alper *et al.*, no worsening of seizures were observed in patients randomized to sertaline [58].

Finally, in selected cases, one may consider an AED that has an antidepressant and or a mood stabilizing properties to treat both conditions with a single agent. Alternatively, vagal nerve stimulator (VNS), which has a unique mechanism of action that would explain its antiepileptic and antidepressants' properties, can also be considered in selected cases [59].

9. FINAL THOUGHTS

Epidemiological studies should address the unanswered question of the risk factors of depression in epilepsy and its impact on selecting the most optimal treatment strategies. Furthermore, future randomized controlled trials are needed to assess the effect of immediate vs delayed treatment on seizure response, compliance rate, and overall QOL. A positive result of such a trial is expected to improve the willingness of physicians to systematically screen patients for depression early on. On the other hand, effective and early treatment of depression is expected to increase the patients' compliance with AEDs. Consequently, this could result in a better seizure control and an overall better QOL.

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