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Review

Anxiety disorders in people with epilepsy

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ABSTRACT

Anxiety disorders are frequent, though probably underdiagnosed, comorbidities in epilepsy. Epilepsy and anxiety may share common neurobiological correlates as shown in animal models and suggested by studies demonstrating anxiety disorders before the manifestation of epilepsy. Comorbid anxiety disorders have a major impact on the affected patients' quality of life and may increase the risk for suicidality. Successful treatment of the epilepsy may alleviate anxiety symptoms. Treatment of anxiety is based on selective serotonin reuptake inhibitors, benzodiazepines (although only as second-line choices), and psychotherapy. Specific AEDs (especially pregabalin) have been shown to have anxiolytic properties. This paper is aimed at reviewing anxiety disorders in patients with epilepsy discussing current scientific evidence about pathophysiology, clinical aspects, and treatment strategies.

1. Introduction

Psychiatric diseases constitute important comorbidities of epilepsy. This is not only because of their high prevalence, but also because of the impact they have on the affected individual's life. They also merit attention because of special implications for treatment and specific pathophysiological considerations. While psychoses and depressive disorders have found attention over the past several years, it is only in recent years that anxiety disorders have received the attention they deserve [1]. Anxiety disorders are even called the "forgotten comorbidity" [2]. The importance of this topic has also recently been underlined by the fact that a workgroup of the International League of Epilepsy has worked on a consensus paper concerning neuropsychiatric conditions in epilepsy, which also included anxiety [3]. The current review is aimed at giving an overview of relevant aspects of anxiety disorders in epilepsy with a special focus on prevalence, the impact of an anxiety disorder on the affected individual's daily living, and aspects of treatment.

2. Prevalence

Symptoms of anxiety and anxiety disorders are more frequent in patients with epilepsy than in the general population. A reference study concerning the prevalence of anxiety disorders in people with epilepsy (PWE) is the frequently cited study by Tellez-Zenteno et al. [4]. According to this study, people without epilepsy reported a lifetime incidence of 11.2% for any anxiety disorder compared with 22.8% in the group with epilepsy. With regard to the last 12 months, there was a prevalence of 4.6% in the group without epilepsy compared with 12.8% in the group with epilepsy. That study has strengths and weaknesses. A major strength is that it is a population-based study with a huge number of included subjects. A potential weakness of the study is how the diagnosis of epilepsy was asserted. This may have led to over- or underreporting. A study from England [5], using a similar approach, also reported an elevated prevalence of depressive and anxiety disorders in people with epilepsy (30.6%, corresponding to an adjusted odds ratio (OR) of 1.9). The OR for social phobia was 5.2, for agoraphobia 3.2, and for generalized anxiety disorder (GAD) 2.6.

One might assume that the prevalence of anxiety disorders was higher in people with refractory epilepsy than in those with well-controlled epilepsy. Brandt et al., however, found a prevalence of 19.6% in patients with refractory epilepsy, a figure that is well within the range reported for epilepsy in general [6]. See Table 1 for prevalence rates for the subtypes of anxiety disorder. A trend for people with shorter epilepsy duration ($P = 0.084$) and younger age ($P = 0.078$) being more likely to have a diagnosis of anxiety disorder was revealed. This could mean that people with epilepsy might develop coping strategies with increasing age or with increasing duration of the disease. Gandy et al. directly compared people with refractory epilepsy and with well-controlled epilepsy with respect to mood and anxiety disorders and suicidality [7]. They did not find any significant difference between the groups. For all patients, they found a rate of 29% for an anxiety disorder.

Prevalence rates of obsessive–compulsive disorder (OCD) in patients with epilepsy (PWE) or obsessive–compulsive symptoms (OCS) vary [6,8–10]. Such a discrepancy may be related to OCS in epilepsy representing a spectrum rather than an Axis I disorder.

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Table 1
Prevalence rates for subtypes of anxiety disorder according to [6].

Subtype of anxiety disorder	Prevalence (%)
Social phobia	7.2
Specific phobia	6.2
Panic disorder	5.1
Generalized anxiety disorder	3.1
Anxiety disorder not further specified	2.1
Obsessive–compulsive disorder	2.1
Posttraumatic stress disorder	1.0

A current history of depression, perceived side effects, lower educational attainment, chronic ill health, female gender, and unemployment have been identified as risk factors associated with comorbid anxiety disorders in epilepsy [11]. In contrast to other studies, there was no association with the duration of epilepsy in this study. State anxiety was significantly associated with symptomatic focal epilepsy, and trait anxiety with high seizure frequency, symptomatic focal epilepsy, and female gender in a study from Greece [12]. The coexistence of another chronic disorder does not seem to have an influence on the presence of anxiety symptoms in PWE [13] although poorer general health has been found as a contributing factor to anxiety [14]. Good social support is, however, protective [14]. A recent review analyzed studies assessing risk factors for depression and anxiety in PWE [15]. All six studies assessing anxiety found one or more risk factors for the development of that comorbidity. A problem is, however, that the findings of these studies were not consistent with each other and that the identified risk factors generally only explained a certain amount of the variance. A statistically significant relationship has been found between anxiety and higher scores relating to powerful others health locus of control (HLOC; see also below: Impact/Quality of life) [13]. The presence of anxiety (and also depressive) disorders worsened adverse events to antiepileptic drugs [16]. Increased levels of neuroticism have also been found to be a risk factor [17]. Stigma [18], higher escape-avoidance and decreased distancing [19], and increased use of wish-fulfilling fantasy [20] predicted higher levels of anxiety. Generally, those studies have been criticized for their quality by the authors of the review [15].

A study from Hong Kong found a higher prevalence of anxiety in patients with frontal lobe epilepsy than in those with generalized epilepsy [21]. This would highlight pathophysiological considerations, as psychosocial factors should be similar in both groups of epilepsy syndromes. A limitation of that study might be that the authors combined idiopathic, cryptogenic, and symptomatic forms of generalized epilepsies (GE). They included, for instance, patients who were diagnosed as having GE after stroke, infection, or trauma. There was also a high proportion of cryptogenic GE. It would be of interest to see the results for idiopathic GE, which might form a more homogeneous group.

Anxiety disorders not only are important comorbidities of epilepsy, but may also precede the onset of epilepsy. According to a large register study, the incidence rate ratio for an anxiety disorder was significantly increased in the three years before epilepsy onset and in the first two years after [22]. See the "Neurobiological correlates" section for implications of these epidemiological findings.

It is of importance to differentiate anxiety symptoms from the diagnosis of an anxiety disorder. Postictal cognitive and psychiatric symptoms have been studied thoroughly using a questionnaire of 42 items answered by 114 patients with respect to their occurrence during the 72 h after a seizure [23]. Anxiety was the most frequent postictal emotional symptom, experienced by 45 out of the 114 patients. This means that some patients deserve special attention during the first three days following a seizure because of emotional disturbances.

3. Anxiety in childhood and adolescence

Anxiety not only affects adult patients with epilepsy but also children and adolescents, and it exerts an impact on their quality of life [24]. In children, the rate of self-reported anxiety is higher than parent-reported anxiety, showing the importance of relying on the children's self-assessment wherever possible [25]. Persons in the general population (not restricted to PWE) with a diagnosis of anxiety disorder at age 26 years have had an anxiety disorder during adolescence in many cases [26]. The importance of anxiety disorders in younger years has led the American Academy of Child and Adolescent Psychiatry to recommend that children and adolescents should be routinely screened for symptoms of anxiety [27]. Data in children with epilepsy are still limited, and evidence is sparse. Further studies are urgently needed in order to understand whether specific pediatric epilepsy syndromes are associated with an increased risk of anxiety disorders.

4. Neurobiological correlates

Although numerous brain regions are likely to be involved, the amygdala and the hippocampus play a key role in the neurobiology of both epilepsy and anxiety. This strict association seems to be further supported by the existence of a bidirectional relationship between epilepsy and anxiety meaning that anxiety not only follows epilepsy, but it may also precede the onset of epilepsy by years [28], which is, by the way, also true for psychosis, depression, and suicidality. One explanation for the bidirectional relationship between anxiety disorders and epilepsy may be in the role that serotonin plays for both diseases [29]. These findings are paralleled in a couple of animal studies listed below.

The amygdala is determinant in the experience of fear and its autonomic and endocrine response (through the output to the hypothalamus), while the amygdala output to the periaqueductal gray is mainly implicated in avoidance behavior, also typical of fear responses [30]. Furthermore, the hippocampus is important in the reexperiencing of fear. Activation of fear circuits is a major hypothesis for explaining symptoms in anxiety disorders, and the reduction of an excessive output from these neurons may theoretically improve the clinical picture [30,31]. Such a mechanism has a number of similarities with the excessive outburst typical of epileptic neurons, explaining the effects of antiepileptic agents (such as benzodiazepines, BDZs) in the treatment of anxiety [32]. In fact, the potentiation of GABA-ergic inhibition and the modulation of calcium channels represent valuable antianxiety mechanisms [30,32].

Animal models of epilepsy also suggest a correlation with anxiety. Genetic absence epilepsy rats of Strasbourg (GAERS), a genetic model of human generalized epilepsy, were tested using the elevated plus maze (EPM) and the open-field (OF) arena tests. When compared with healthy controls, the GAERS showed increased levels of anxiety. An important finding is that the development of anxiety was already detectable before the onset of epilepsy. This is an especially important paper as it suggests a common pathophysiological basis of epilepsy and anxiety rather than explaining anxiety as a secondary (neurodegenerative or psychosocial) consequence of epilepsy and seizures [33].

Anxiety-like behavior has been observed during the maturation phase in male Wistar rats in the pilocarpine model [34]. This finding supports the hypothesis that anxiety and epilepsy are associated on a pathophysiological level. Status epilepticus in early life caused an increase in anxiety-like behavior in male Wistar rats. Behavioral change could be prevented by administration of ketamine during the status [35].

Long–Evans rats with spontaneous spike–wave-discharges and normal (healthy) Wistar rats as controls were examined with two animal models of anxiety disorders: the open-field (OF) and the elevated plus maze (EPM) tests. Long–Evans rats interestingly showed a less anxious behavior, i.e., longer duration on the open arms of the EPM and in the center zone of the OF [36]. Their level of anxiousness was associated with spike–wave frequency and could be ameliorated by administration of ethosuximide.