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Anxiety Disorders in Epilepsy

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1. Introduction

Epilepsy is a heterogeneous entity with enormous variation in etiology and clinical features and is defined as two unprovoked seizures of any type (Waaler et al., 2000). Epilepsy is one of the most common neurological disorders in pediatric and adult population (Moshé et al., 2011). Research in the past 20 years showed that the patients with epilepsy commonly have coexisting psychiatric conditions including mood disorders, anxiety disorders, psychotic disorders and attention deficit hyperactivity disorder (Garcia Morales et al., 2008; Waaler et al., 2000; Ekinci et al., 2009). Historically, psychiatric disorders in epilepsy have been considered a consequence of psychosocial disturbance due to poor adaptation to a chronic disease with stigma (Thome Souza et al., 2004). However, recent studies indicates that there is a bidirectional relationship between epilepsy and psychiatric disorders. This relationship may be conceptualized as an epiphenomena rather than cause–consequence factors (Kanner, 2011; Thome Souza et al 2004).

2. Anxiety disorders in epilepsy

Among the psychiatric comorbidites in epilepsy, anxiety disorders are highly frequent and have a profound influence on the quality of life of epilepsy patients (Kanner et al., 2010; Beyenburg et al., 2005; Choi-Kwon et al., 2003; Johnson et al., 2004; Tellez-Zenteno et al., 2007). Several studies have reported elevated rates of panic attacks, panic disorder, obsessive compulsive disorder (OCD), social anxiety disorder and generalized anxiety disorder (GAD) in adult patients with epilepsy as compared with the general population (Piazzini et al., 2001; Issacs, 2004; Baker at al., 2005; Marsh & Rao 2002; Vazquez & Devinsky 2003).

2.1 DSM-IV anxiety disorders

The DSM-IV defines 11 different types of anxiety disorders. Generalized anxiety disorder presents with (GAD) a disabling and persistent worry that is free-floating and present much of the time for at least 6 months. Somatic or vegetative symptoms such as increased fatigue, insomnia, difficulty with concentration, and sleep problems are commonly seen in GAD. Panic attacks are defined by sudden and severe paroxysmal episodes of anxiety of typically sudden onset and short duration. A frequency of more than one attack per week for a period of at least 1 month is in the diagnostic criteria of panic disorder. Obsessive–compulsive disorder (OCD) is characterized by recurrent unwanted, intrusive and stressing thoughts or images often allied with compulsive actions (American Psychiatric Association, 1994).

2.2 The prevalence and the phenomenology of anxiety disorders in epilepsy

The differences in the methodology of the studies have affected the consistency of prevalence rates of anxiety disorders in epilepsy (Williams et al., 2002; Ekinci et al., 2009). The avaliable data indicates a prevalence somewhere between 14% and 78% (Wittchen et al., 2002; Vasquez & Devinsky, 2003; Kanner et al., 2001) in adults and somewhere between 16% and 48% in children and adolescents (Ettinger et al., 1998; Williams et al., 2003; Caplan et al., 2004; Alwash et al., 2000).

It is important to note that the special features of anxiety disorders in epilepsy have not been studied sufficiently in clinical and community studies. Therefore, it's largely unknown if the current diagnostic instruments for anxiety disorders perform adequately in this special population. Because of the complex nature of epilepsy, the phenomenology of anxiety disorders may be different than in the general population, which can make it difficult to isolate symptoms to a single DSM-IV-TR diagnosis. For example, the fear of unexpected seizures in special places may lead to a variant of agoraphobia. In children, the fear of having a seizure can be associated with anxiety about separation from the parents or home. The fear of embarrassment about having a seizure in public may also lead to a variant of social phobia and result in isolation of the patient from social activites (Ekinci et al., 2009; Beyenburg et al., 2005). It is also important to highlight that DSM-IV-TR criteria require the absence of a physiological condition when considering symptoms in anxiety disorders (DSM IV, 1994). However, experimental studies suggest that kindling mechanisms and the recurrent epileptic stimulation of the amygdala may predispose patients with epilepsy to interictal anxiety (Depaulis et al., 1997). Because of this, it would be reasonable to consider an alternative classification system for epilepsy-related anxiety that accounts for the different manifestations of anxiety in individuals with epilepsy. For instance, some individuals experience anxiety in response to the stress of the condition (i.e., reactive) or whereas others because of a preexisting propensity for anxiety (i.e., endogenous) (Ekinci et al 2009). Beyenburg et al. in his comprehensive review offer phenomenologic suggestions about the types of anxiety disorders in epilepsy (Beyenburg et al., 2005).

3. Associated factors of anxiety disorders in epilepsy

Multiple factors have been found to be associated with anxiety symptoms and/or DSM IV anxiety disorders in patients with epilepsy. In this chapter, the factors associated with anxiety disorders in epilepsy are grouped in five categories including: Neurobiological factors, psycholocial factors, epilepsy related factors, age of the patients and the medication related factors.

3.1 Neurobiological factors

There is neurobiological evidence for the possible common pathophysiological mechanisms of anxiety symptoms and epileptic seizures. This theory is mainly based on the observation that epileptic activity in certain areas of the brain directly causes paroxysmal anxiety, usually in the form of panic (Chapouthier & Venault, 2001; Trimble & Van Elst, 2003). The amygdala seems to be a particularly important structure for the production of anxiety symptoms and epileptic discharges in temporal lobe epilepsy (Beyenburg et al., 2005). In correlation with this hypothesis, patients with temporal lobe epilepsy and ictal anxiety symptoms have been found to have a reduced amygdala volume (Cendes et al., 1994). Neurotransmitter systems are also suggested be related with the link of anxiety disorders

and epilepsy. The role of GABA receptors and neurotransmitters including serotonin, dopamine and noradrenaline in both epilepsy and anxiety disorders indicate another pathophysiological similarity between the two disorders (Beyenburg et al., 2005; Lydiard, 2003; Charney, 2003).

3.2 Psychological factors

Psychological factors, such as the unpredictability of seizures, the fear of death, feeling of poor control over seizures, and perceived stigma likely predispose some epilepsy patients to anxiety (Pellock, 2004; Jacoby et al., 2005; Beyenburg et al., 2005). Misinformation or insufficient information about the disorder also seems to be related to increased anxiety (Ekinci et al., 2009; Couldridge et al., 2001). Lower levels of epilepsy knowledge were found to be significantly related to higher levels of social anxiety, higher levels of depression, and lower levels of self-esteem (Baker et al., 2005).

3.3 Epilepsy related factors

Previous studies linked some epilepsy related factors with anxiety symptoms. Higher seizure frequency has been found to be associated with anxiety disorders in some adult studies (Jacoby et al., 1996). In the case of children and adolescents, most of the literature supports a direct relationship between increased seizure frequency and anxiety disorders (Williams et al., 2003; Ettinger et al., 1998; Kessler et al 2001; Oguz et al 2002; Alwash et al., 2000; Adeewuya et al., 2005). In adults, the risk of anxiety disorders appears to be higher in focal (especially temporal lobe) than in generalized epilepsies (Garcia Morales et al., 2008; Goldstein & Harden, 2000; Vasquez & Devinsky 2003; Marsh & Rao, 2002, Piazzini et al., 2001). Anxiety disorders were found to be linked with the seizures originated from left temporal lobe but this is not entirely consistent in the literature (Andelman et al., 2001). In children and adolescents, the contribution of seizure type to anxiety disorders appears to be much less clear. Most of the studies have failed to demonstrate a relationship between seizure type and risk of anxiety [Williams et al., 2003; Ettinger et al., 1998; Oguz et al., 2002; Pianta & Lothman, 1994). Epilepsy surgery is also reported to be related with the development of anxiety symptoms. Transient anxiety symptoms have been reported after following temporal lobe surgery for epilepsy (Ring et al., 1998).

3.4 Age as a factor

The age of the patient and the age of seizure onset were examined as associated factors for anxiety disorders in epilepsy. In adult patients, first-onset epilepsy in late life is shown to be linked with higher levels of anxiety (Baker et al., 2001). However, in children and adolescents, most of the studies do not support a relationship between age at seizure onset and increased risk of anxiety (Williams et al., 2003; Ettinger et al., 1998; Pianta et al., 1994; Oguz et al., 2002). In pediatric population, older age has been found to be a significant risk factor for anxiety. Adolescents with epilepsy are considered to be at higher risk for anxiety than younger children (Oguz et al., 2002; Williams et al., 2003). There are several possible explanations for this relation. Adolescents have a greater cognitive capacity than children to understand and question the unpredictable and poorly controlled nature of the seizure disorder. This can, in turn, potentiate anxiety and contribute to negative emotional responses. Morever, with the significant social demands and challenges, adolescence is

unique among the other phases of development. Peer relationships are central to the teenage experience and the risk of having a seizure at school or in a social activity with friends is a severe threat to an adolescent's ability to successfully achieve the developmental milestones for this age. This can result in significant problems with self-esteem and potential social isolation, thus increasing the likelihood of anxiety in various forms (Ekinci et al., 2009).

3.5 The possible role of antiepileptic drugs

Most of the previous studies have demonstrated that antiepileptic drug (AED) polytherapy is associated with increased risk of anxiety disorders (Mula & Sanders 2007; Williams et al., 2003; Ettinger et al., 1998; Oguz et al., 2002; Adeewuya et al., 2005). This increased risk can occur as a side effect of the AEDs or as a function of complications related to AED withdrawal. However, it is unclear whether there is a direct causal relationship between AED polytherapy and anxiety. It is also possible that the need of using AED polytherapy may reflect the the intractability of the seizure disorder.

4. Treatment of anxiety disorders in epilepsy

4.1 Psychosocial interventions

For the optimal management of anxiety disorders in epilepsy, an essential component is the adequate explanation of the condition (Couldrigde et al., 2001; Kendal et al., 2004). The degree of information requested may vary relatively between patients and families in different socioculturel levels. A comprehensive psychoeducation can be best achieved with the availability of professional specialists including nurses (Beyenburg et al., 2005).

Regular psychiatric and/or psychological consultation that involves developmentally appropriate methods of approach is important. Among the psychosocial approaches, cognitive behavioural therapy (CBT) may potentially serve as a treatment option both for anxiety symptoms and also for the optimal seizure control (Ekinci et al., 2009; Goldstein et., al 2003; Spector et al., 1999; Engelberts et al., 2002). CBT has been found to be effective in adult patients with epilepsy who have agoraphobia and OCD (Newsom-Davis et al., 1998). A more recent study showed CBT as an acceptable and promising treatment option for the patients with epilepsy and comorbid anxiety symptoms (Macrodimitri et al., 2011).

4.2 Medical treatment

A limited number of studies have focused on the pharmacotherapy of anxiety disorders in epilepsy to date. The available research have revealed that the SSRI group antidepressants appear to be safe and effective treatment options (Scicutella & Ettinger, 2002; Schmitz, 2002; Kanner et al., 2000; Jobe & Browning, 2005). The possible psychiatric and/or therapeutic effects of AED also deserve attention. Some AED including valproate, gabapentin, tiagabine and vigabatrine have been reported to anxiolytic effects and have been used with varying success in the treatment of anxiety disorders in adult studies (Johannessen Landmark, 2008; Kinrys et al., 2003; Blanco et al., 2003, Pande et al., 2000,2003; Rosenthal, 2003). Several hypotheses and suggestions have been made for why some AEDs have anti-anxiety effects (Ketter et al., 1999). There is some evidence that the past history and family history of psychiatric disorders may increase the risk of psychiatric side effects with AEDs (Mula &

Monaco, 2007; Marsh & Rao, 2002). It is suggested that the AEDs that attenuate glutamate excitatory neurotransmission (e.g., lamotrigine) may cause neurotransmitter activation that leads to an increase in anxiety and GABAergic AEDs may serve to decrease anxiety (e.g., barbiturates, benzodiazepines, valporate, tiagabine, gabapentin and vigabatrin) (Ketter et al., 1999; Mula & Monaco, 2007). Beyond this theoretical explanation, there are no placebo-controlled studies on the anxiolytic effects of AEDs in adults or pediatric patients with epilepsy. Nevertheless, based on the extant literature thus far, it is reasonable to consider choosing an AED with anxiolytic potential in a patient with epilepsy who also has a comorbid anxiety disorder. (Scicutella & Ettinger, 2002; Beyenburg et al., 2005; Mula & Monaco 2007).

5. The differential diagnosis of seizures and anxiety disorders

It is important to note that this chapter mainly discusses the anxiety disorders in patients with epilepsy which are unrelated with seizure events. This type of anxiety is defined as interictal anxiety. However, patients with epilepsy can also experience increased levels of anxiety at different stages of the seizure events, such as preictally, ictally, or postictally. Ictal anxiety is defined as anxiety symptoms during the seizure event. Ictal anxiety is known to be associated with focal seizures of temporal origin, particularly when there is amygdalar involvement (Marsh & Rao 2002; Vasquez & Devinsky 2003). Anxiety as a postictal phenomenon refers to the anxiety symptoms shortly after a seizure or a cluster of seizures (Kanner et al., 2004). This type of anxiety may be associated with dysphoria or depressive symptoms (Kanner & Palac, 2000). Postictal anxiety symptoms similar to those in panic attacks can be observed in temporal lobe epilepsy and less frequently in extratemporal lobe epilepsies (Beyenburg et al., 2005). The differential diagnosis of seizure-related events is sometimes problematic for the clinicians since such events may be misled by panic attacks that present like complex partial seizures (Bernik et al., 2002). Differentiating symptoms that are more suggestive of a seizure include motor automatisms, alterations in consciousness, the possible presence of an aura and postictal confusion (Vasquez & Devinsky 2003; Scicutella & Ettinger, 2002). In addition, panic attacks usually last several minutes whereas seizures are usually more brief. The exception to this, of course, is seizures that secondarily generalize or progress to status epilepticus (Ekinci et al., 2009). Complicated cases may warrant further investigation with EEG, Video EEG monitoring, and/or brain imaging studies (Handal et al., 1995).

6. Suggestions and future research

When compared with depression, less attention has been focused on anxiety disorders in epilepsy. The factors that have been suggested for the increased risk of anxiety disorders in epilepsy are reviewed in Figure 1. For the management of this disabling comorbidity, different strategies including psychosocial, behavioral and medicational interventions are found to be helpful. However, for an effective management, gaining optimal seizure control must be the first step. Without total seizure control, complete treatment of anxiety symptoms is considered unlikely (Ekinci et al., 2009; Beyenburg et al., 2005). Further research is needed to better examine the specific phenomenology of anxiety disorders in patients with epilepsy in order to guide clinicians about when psychiatric referrals are needed.

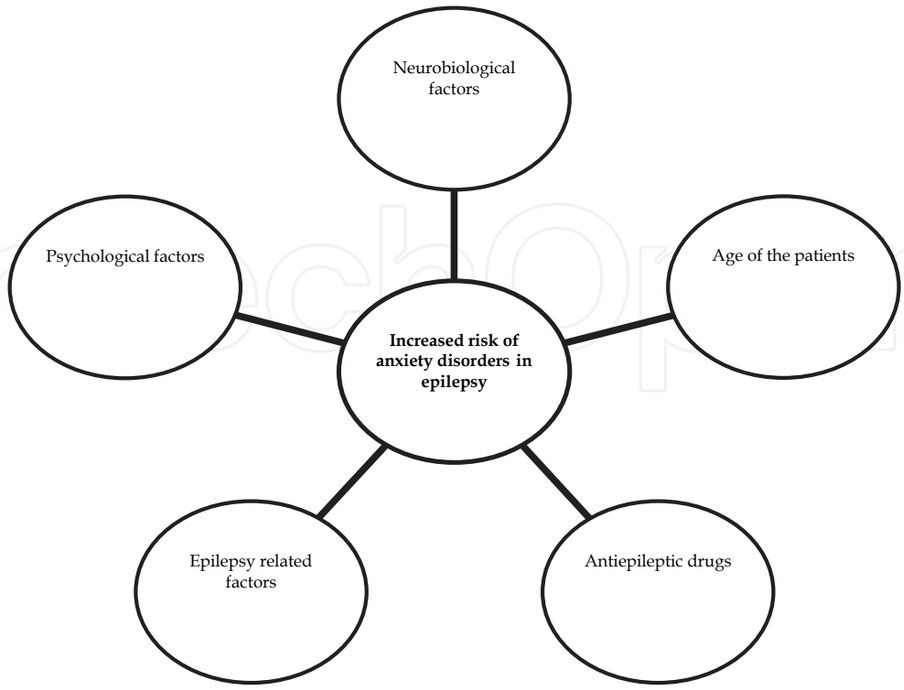

Fig. 1. Overview of the factors associated with increased risk of anxiety disorders in patients with epilepsy

Neurobiological factors: The role of of amygdala and GABA receptors
Unpredictability of seizures, the fear of death, feeling of poor control over seizures and the perceived stigma
Epilepsy related factors: Higher seizure frequency, focal epilepsy types (especially temporal lobe epilepsy) and epilepsy surgery (especially after temporal lobe surgery)
Age of the patients: In adults, later onset of epilepsy. In pediatric population, older age
Role of antiepileptic drugs (AED): AED polytherapy and the effects of spesific AED on anxiety symptoms

7. Conclusion

Anxiety symptoms, either in the form of the DSM- IV diagnoses or single symptoms, are frequenty experienced in patients with epilepsy. Morever, anxiety in epilepsy is not simply a reactive emotional response to epilepsy or just a feature of the seizures. The current literature indicates that anxiety disorders are frequent comorbid conditions of epilepsy in children, adolescents and adults. The worries of the patients about having accidents, losing control and social embarrassment may be associated with an underdiagnosed or untreated anxiety disorder. Comprehensive and effective management of anxiety symptoms can be accomplished by a psychiatrist and/or psychologist, particularly when a the patients' condition is more severe and/or refractory. The collaboration between different disciplines, including the psychiatry and neurology specialists, offers the best hope for early identification and treatment of anxiety disorders in epilepsy. Because of the potentially

severe impact of anxiety disorders on the quality of life in patients with epilepsy, anxiety symptoms should be screened and treated early in this special population.

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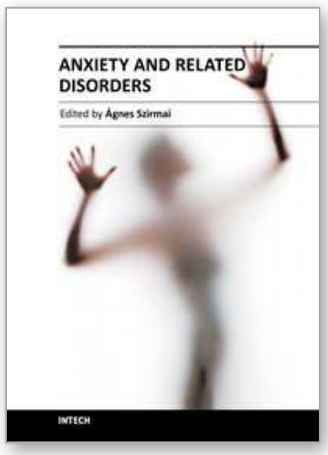

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Anxiety disorders are one of the most common psychiatric disorders worldwide and many aspects of anxiety can be observed. Anxious patients often consult primary care physicians for their treatment, but in most cases they do not accept the diagnosis of anxiety disorder. Anxiety is a symptom that could be seen in many organic disorders and can accompany almost any psychiatric disorder. Anxiety disorders are frequent and are associated with significant distress and dysfunction. Stigmatization is an important factor in insufficient diagnosis. The problems of anxiety cover all fields of life. This book intends to describe the epidemiological aspects and the main co-morbidities and consecutive diseases of the anxiety disorders.

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