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Epilepsy and anxiety

CLINICAL REVIEW

MIA TUFT

E-mail: miatuft@neuropsychology.no
Neuropsychology Centre
Oslo
Mia Tuft is a specialist in neuropsychology and works daily with rare epilepsy-related diseases at Oslo University Hospital.
The author has completed the ICMJE form and reports no conflicts of interest.

OLIVER HENNING

National Centre for Epilepsy
Division of Clinical Neuroscience
Oslo University Hospital
Oliver Henning is a specialist in neurology and psychiatry with particular expertise in epileptology. He is a senior consultant.
The author has completed the ICMJE form and reports no conflicts of interest.

KARL O. NAKKEN

National Centre for Epilepsy
Division of Clinical Neuroscience
Oslo University Hospital
Karl O. Nakken is a retired neurologist. He served for many years as medical director of the National Centre for Epilepsy in Sandvika.
The author has completed the ICMJE form and reports the following conflicts of interest: He has received lecture fees from the pharmaceutical company Eisai.

Up to one-quarter of people with epilepsy have mental health disorders in addition to seizures. Depression has received the most attention although anxiety disorders

occur just as frequently, if not more so. Even though psychiatric symptoms can reduce quality of life more than epileptic seizures, they continue to go unnoticed and untreated.

Mental disorders, most often in the form of anxiety and/or depression, are found 2–3 times more frequently in people with epilepsy than among the general population (1). Those with focal epilepsy have the greatest predisposition, and as a general rule the causes are both biological and psychosocial. Compared with depression, there are strikingly few studies of anxiety in patients with epilepsy. In recent years, however, we have gained more insight into the underlying causal mechanisms as well as the clinical significance of such comorbidity.

This article is based on PubMed searches on the phrases 'epilepsy and anxiety' and 'epilepsy and psychiatric comorbidity', as well as on our own clinical experience.

Epidemiology

The precise incidence of anxiety disorders in people with epilepsy is unknown. Results from epidemiological studies deviate widely, primarily due to differences between the patient groups studied and the use of different diagnostic criteria and instruments. Prevalence rates of 11 % to almost 50 % have been reported (2–7). A Canadian population-based study showed a lifetime prevalence of up to 22.8 %, which was 2.4 times higher than among the general population (6).

The incidence of anxiety disorders increases with the severity of the epilepsy and is seen most often in those with pharmacoresistant medial temporal lobe epilepsy (4, 8, 9), especially among those with right-sided focus (10). Stigma experienced by the patient and limited knowledge about the disease have also been related to the risk of anxiety (5).

The incidence of the various types of anxiety in the patient group has not been studied more closely, but our impression is that generalised anxiety disorder is the most common type (see figure 1 and box 1). A combination of anxiety and depression is seen quite often (11).

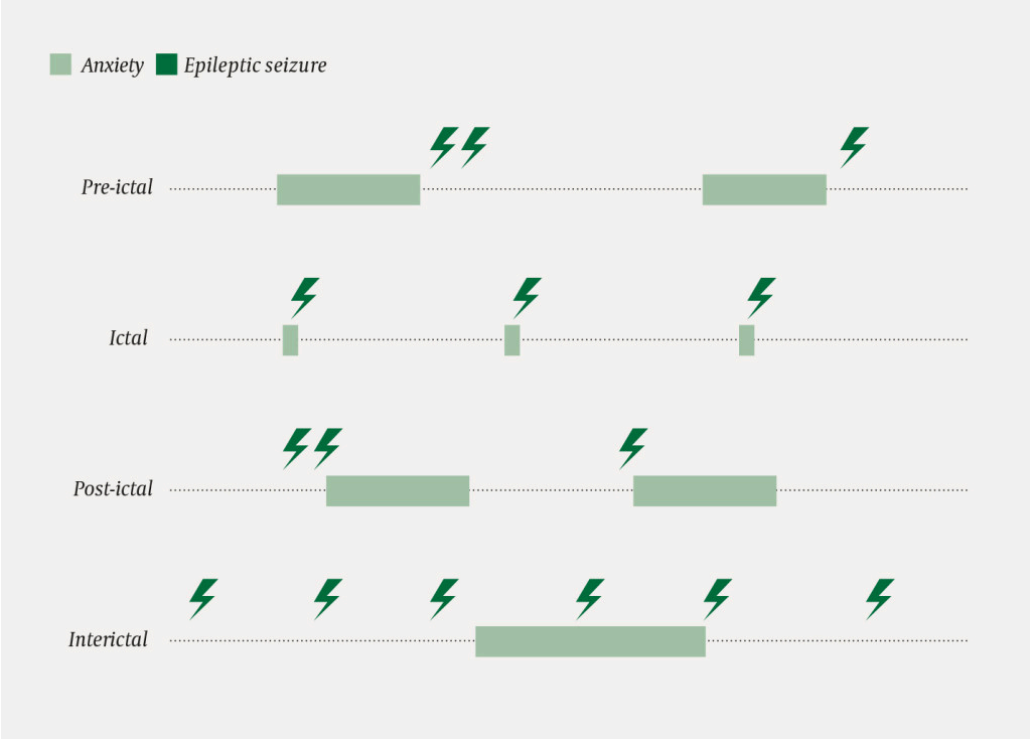

Figure 1 Temporal relationship between epileptic seizures and anxiety symptoms.

Box 1 Types of anxiety in connection with epilepsy

Peri-ictal

- pre-ictal anxiety (seizure prodromes)
- ictal anxiety
- post-ictal anxiety

Interictal anxiety

- generalised anxiety
- phobic anxiety
- social phobia (social anxiety disorders)
- specific phobia
- panic disorder, with or without agoraphobia
- obsessive compulsive disorder
- post-traumatic stress disorder

Interictal anxiety related specifically to epilepsy

- anxiety related to the diagnosis
- anxiety about having a seizure
- anxiety about side effects of antiepileptic drugs

Anxiety related to seizures

It has been usual practice to classify anxiety disorders in people with epilepsy according to the temporal relationship between the anxiety symptoms and the epileptic seizures (figure 1).

Peri-ictal anxiety

Some patients experience nervousness, irritability and anxiety in the prodromal phase, i.e. hours or days prior to a seizure. This is known as *pre-ictal anxiety*. In these cases, the seizure often comes as a relief; the anxiety then subsides.

Ictal anxiety, i.e. anxiety as a symptom of the seizure, occurs especially in patients with temporolimbic epilepsy. This is a focal type of seizure, and awareness may be maintained or reduced. Patients suddenly experience intense anxiety or panic, sometimes combined with other known temporal lobe phenomena such as déjà vu or autonomic symptoms (4). Distinguishing ictal anxiety from a non-epileptic panic attack can present a diagnostic challenge. Typical features of an ictal anxiety attack are a sudden onset of anxiety that appears 'out of the blue', shortness of duration (0.5–2 minutes), automatism (especially when the seizure spreads to other parts of the temporal lobe) and often, but not always, pathological MRI or EEG findings. Non-epileptic panic attacks usually last longer (5–10 minutes), are often stress-related, and the MRI and EEG are usually normal (4). Ictal anxiety is reported to occur in up to 15–20 % of patients with medial temporal lobe epilepsy (12).

We believe it is important to explain to patients and their close family members that the anxiety experienced by the patient is caused by epileptic disorders. This is likely to improve compliance with treatment.

Post-ictal anxiety occurs hours and sometimes days after a prolonged seizure or series of seizures, and is often combined with confusion and dysphoria (4). About one-third of patients with post-ictal anxiety have also experienced anxiety prior to the onset of epilepsy (11).

Interictal anxiety

Anxiety that arises independently of the seizures is most common, and is often of a generalised type. Also in this case, patients with temporolimbic epilepsy have the greatest predisposition (13).

Aetiology and pathophysiology

As a rule, the causes of mental disorders in patients with epilepsy are complex. In addition to neurobiological causes, psychosocial problems and pharmaceutical side effects are often present.

There is solid evidence that ictal anxiety in patients with temporolimbic epilepsy is generated mainly from the amygdala. However, ictal anxiety is also seen in patients with epileptic disorders in the orbitofrontal cortex and anterior cingulate gyrus (14). The cingulate gyrus regulates functions in the amygdala, and it is believed that anxiety is caused by a disruption of this regulatory function (15). A disruption in the amygdala-orbitofrontal network has been found in patients with social anxiety (4).

Anxiety and epilepsy have some underlying neurochemical features that involve GABA and serotonin in particular. GABAergic drugs such as valproate, phenobarbital and benzodiazepine have both seizure- and anxiety-reducing properties (16). A negative correlation between the GABA level in the frontal cortex and neuroticism was found in healthy research subjects (17). Reduced serotonin receptor binding has been shown both in patients with panic anxiety and in patients with epilepsy (18).

Genetic mechanisms probably play a part as well (2). A study of patients with temporal lobe epilepsy found that a specific allele of the 5-HT_{1A} receptor gene (C1019G polymorphism) was an independent risk factor for anxiety (2). A major heredity analysis also indicates a genetic correlation between epilepsy and anxiety (19).

The unpredictability of epileptic seizures distinguishes epilepsy from most other chronic diseases. This creates anxiety and insecurity in many patients even if the seizures are well controlled. Anxiety about having a seizure in a shop, at the theatre or on a train – with the consequences this may entail – can easily result in avoidance behaviour (20). It has been shown that psychiatric comorbidity has a greater effect on the quality of life of people with epilepsy than seizure control (21).

Anxiety about pharmaceutical side effects is not uncommon, nor is worry about loss of cognitive faculties, as a result of either side effects or a seizure (2).

According to one study, people who had been hospitalised because of an anxiety disorder were more than twice as likely to develop epilepsy as people in the control group (2). Therefore, it appears that anxiety is a predisposing factor for epilepsy and that epilepsy is a predisposing factor for anxiety.

How can anxiety disorder be identified in epilepsy patients?

A thorough case history is essential for identifying anxiety disorders. All patients with epilepsy should be asked about anxiety. Key questions are how does the anxiety manifest itself, how long does it last, under what circumstances does it arise, how disabling is it, and what is the relationship between the anxiety and the seizures or treatment. A survey instrument in the form of questionnaires can help to obtain answers to the most relevant questions. However, it has been shown that questionnaires alone, such as the subscale for anxiety on the Hospital Anxiety and Depression Scale (HADS-A), do not reliably identify anxiety symptoms in this patient group (22). This is also consistent with our experience. Another questionnaire, the Generalised Anxiety Disorder 7 (GAD-7), is a screening tool that is quick to administer and has norms for classifying anxiety into mild, moderate and severe (23).

Treatment

Prior to any treatment, health professionals should consult with the patient and any close family members and agree that the patient's anxiety is so disabling that treatment is indicated. The type of anxiety experienced by the patient and the relationship between the anxiety and the seizures should be documented. Cooperation between the neurologist or paediatric neurologist and other health professionals, e.g. the district psychiatric centre or a psychologist or psychiatrist in private practice, is often necessary.

In cases of peri-ictal anxiety, the most important measure is improvement of seizure control. There may also be a need to teach the patient specific coping strategies, which must be adapted to the individual.

The International League Against Epilepsy has established guidelines for the treatment of interictal anxiety and depression (24). Cognitive behaviour therapy is the preferred form of treatment for anxiety disorder among the general population. Medication to reduce anxiety should preferably be avoided. Many GPs are skilled in cognitive therapy and/or exposure therapy. However, if there is no choice but to use medication, often in combination with other treatment, selective serotonin reuptake inhibitors (SSRIs) or selective serotonin and norepinephrine reuptake inhibitors (SNRIs), such as sertraline or paroxetine, should be chosen. There has long been widespread fear that SSRI or SNRI drugs may reduce the seizure threshold in epilepsy patients. This fear has been shown to be unfounded as long as doses are maintained at therapeutic levels (25, 26). Higher doses, however, may intensify seizures. One study showed that prolonged use of SSRI drugs can increase epileptogenesis in a kindling model in rats (27). It is unknown whether this has transfer value to humans. Nor is it known whether these drugs have the same anti-depressive and anxiety-reducing effect in epilepsy patients as in psychiatric patients. Unfortunately, no control studies have been conducted in this area. Moreover, in recent years the question has been raised as to whether such drugs increase the risk of suicide, regardless of whether or not the patient had depression prior to treatment with medication. It also appears that a sub-group of patients are disposed to developing serious psychological side effects from antiepileptic drugs. People with epilepsy have a heightened risk of suicide. There are probably multiple, complex reasons for this (28, 29).

Epilepsy patients with anxiety should avoid taking antiepileptic drugs that may have negative psychotropic properties, for example levetiracetam, topiramate, zonisamide and felbamate. In such cases, we recommend the use of medications that can have mood-stabilising and anxiety-reducing properties, such as lamotrigine, carbamazepine, valproate and pregabalin.

Benzodiazepine, lacosamide and pregabalin have particularly anxiety-reducing properties (30, 31), but it is important to recognise that long-term use of benzodiazepine *may* increase anxiety and that there is the potential for misuse of pregabalin.

In psychopharmacological treatment of epilepsy patients, it is important to be aware that enzyme-inducing antiepileptic drugs (e.g. carbamazepine, phenytoin, phenobarbital) interact with psychopharmacological drugs, thereby reducing the serum concentration of the psychopharmacological drugs. Consequently, it is easier to combine psychopharmacological drugs with newer, non-enzyme-inducing antiepileptic drugs (4).

Epilepsy patients with anxiety have been found to experience pharmacological side effects more often than those without anxiety (32) and to benefit less from both antiepileptic drugs (33) and epilepsy surgery (22).

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