

TOPICAL REVIEW

Comorbidity psychiatric disorders in epilepsy: a review of literature

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Abstract: While reviewing the available literature, we noticed comorbidity of epilepsy and psychiatric disorders. Psychiatric disorders were observed more frequently in patients with high seizure frequency. There is significant prevalence of epilepsy comorbidity with depression, anxiety disorders, and to a lesser extent with bipolar disorders and other forms of psychosis. Suicidal risk factors, ideation and attempts in these patients as correlates of depression or as psychopathological features were associated to epileptic disease. This is confirmed by additional burden of epilepsy patients with psychic disorders (*Ref. 70*). Full Text (Free, PDF) www.bmj.sk.
Key words: comorbidity, epilepsy, psychiatric disorders, depression, anxiety, psychosis, bipolar symptoms.

Comorbidity is a condition in clinical practice where several diseases coexist with the same patient at the same time (1). Clinicians often rise the question whether comorbidity is an accidental or a consequential disease occurrence. This issue has been dealt with by numerous studies. Case-control studies in the community have reported higher risk for various somatic disorders in epilepsy (2–4).

Patients with epilepsy have a high prevalence of psychiatric comorbid disorders. Many comorbidities have a significant impact on the medical management and quality of life of these patients. The most common psychiatric conditions in epilepsy in adults were depression, anxiety, and psychoses (5).

We tried establishing the prevalence of particular forms of psychiatric disorders in patients with epilepsy by reviewing the available literature. We studied the forms of psychiatric disorders, their prevalence, as well as their occurrence related to epileptic seizures.

Materials and methods

By reviewing literature in the MEDLINE/Pub med database, as well as the medical evidence base, we tried establishing the comorbidity of epilepsy and psychiatric disorders. In doing this we searched for depression, epilepsy and psychiatric disorders. We also searched for depression, anxiety, psychosis, schizophrenia, etc. In our literature research, we were interested in epidemiological information and pathophysiological explanations of epilepsy and psychiatric disorders comorbidity.

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Results

Patients with epilepsy have a high prevalence of psychiatric comorbid disorders. Depression in epilepsy is very common, especially in patients with partial seizures of temporal lobe origin (6). According to some researches, the prevalence of depression in epilepsy ranges between 13–18 % (7, 8). Other authors think the prevalence of depression in epilepsy is higher than in a matched population of healthy controls, and ranges from 3–9 % in patients with controlled epilepsy to 20–55 % in patients with recurrent seizures (9–12). The prevalence of depression is much higher in patients with epilepsy than in the general population (2 % to 9 % for women; 1 % to 3 % for men) (13, 14). Community-based studies of epilepsy populations report rates of depression from 9 % to 22 % (15–17). Hospital-based samples generally report higher rates of depression (27 % to 58 %) for patients with epilepsy or medically refractory epilepsy (18–20).

The mortality of depression is manifested in suicide, which accounted for over 31 000 cases in the United States in 2003 (21). The suicide rate in depressed patients with epilepsy is five times higher than predicted in the overall population (22, 23). Compared to the general population, the suicide rate in epilepsy is 5-fold increased. In particular, patients with temporal lobe epilepsy have a 25-fold increased risk of suicide, and surgically treated patients present an extremely high risk for suicide (24, 25).

The anxiety prevalence is 19–25 %, whereas Currie and colleagues documented a 19 % point prevalence of anxiety disorder in patients with temporal lobe epilepsy (26, 27). In one large study based on diagnoses in primary care records, the rate of anxiety disorders was 11 % in people who had epilepsy, compared with 5.6 % in people without epilepsy (5). The 1-year prevalence of anxiety disorders was 25 %, and that of mood disorders, 19 % (26).

45 % of patients are postictally anxious, which is very often joined with postictal dysphoria and depression. Postictal symp-

tomatology is most often joined with refractory and extended discharges. 20–30 % of patients have specific fears of epileptic seizures.

By their characteristics, anxiety disorders are divided to generalised anxiety disorders, panic attacks and panic disorders, phobias, obsessive-compulsive disorders (26).

The cardinal symptom of generalized anxiety disorder is disability and persistent worry that is free floating and present much of time for at least 6 months. Associated somatic or vegetative symptoms such as increased fatigue, insomnia, difficulty with concentration, and sleep problems are common (26).

Panic attacks are defined by sudden and severe paroxysmal episodes of anxiety of typically sudden onset and short duration, often with no clear external precipitant. A frequency of more than one attack per week for a period of at least 1 month is sufficient for the diagnosis of panic disorder (26). The prevalence of panic attacks in general population is 3.5 %. Epileptic patients have panic attacks 6 times more often than the general population. Authors found a 5–21 % prevalence of panic disorders in patients with epilepsy. 66 % of patients have panic attacks accompanying depression (28, 29).

Phobias are characterized by fear of specific situations or confinement of the anxiety to the feared domain. Phobias in epilepsy are fear of seizure or accidents occurring out of the house, leading to a variant of agoraphobia, or fear of social embarrassment, leading to a variant of social phobia (30).

Obsessive-compulsive disorders are recurrent intrusive and unpleasant thoughts often allied with compulsive actions. The prevalence of obsessive symptoms using two self-reported measures in patients with temporal lobe epilepsy obtained scores in the clinical range in 22 % of the patient group and 2.5 % of healthy controls (31).

Postictal psychosis is sometimes comorbid with epilepsy. Bipolar disorders are found in 12.2 % with epilepsy (32). Schizophrenia and epileptic psychosis showed different symptom profiles. Epilepsy patients with interictal psychoses achieved high remission rates with lower doses of antipsychotic drugs as compared to patients with schizophrenia (33).

The epilepsy prevalence in patients with intellectual damages is high as compared to the general population (34). The subject matter of research is the possible comorbidity of attention-deficit hyperactivity disorder (ADHD) and epilepsy that is often accompanied with other diseases, wherefore it is hard to make valid conclusions (35). Wendorff et al established no difference in general IQ among children with rolandic epilepsy and control group, there are some cognitive deficits in this epilepsy particularly concerning auditory memory and logical thinking. The children with atypical changes in EEG are the risk group of lower full and nonverbal score analytic synthetic thinking based on concrete material and hyperactivity (36). Guye et al researched intellectual capacities of patients with absence epilepsy and concluded that intellectual capacities were “borderline” in each case, with visible social and learning handicaps. Ring et al found that depression and psychoses were more common in those with no seizures in the preceding 3 months, but that which of these psy-

chiatric states was manifest was related to the severity of learning (intellectual) disability. Psychosis rates were higher in those with mild learning disability, whereas depression rates were higher in those with severe learning disability (37).

Discussion

Patients with epilepsy have a high prevalence of psychic disorder comorbidity. Most psychiatric disturbances are predominant in people with drug-resistant epilepsy and temporal lobe epilepsy, with/without associated neurological or mental abnormalities and psychosocial problems (38–42). Comorbidity of epilepsy may be due to a shared pathophysiological mechanism, however, coincidence or selection bias cannot always be excluded. In addition, genetic, psychosocial and iatrogenic factors may also contribute to the comorbidity (6). Comorbidity of epilepsy and psychiatric disorders are often, yet the most common are depression, nervousness and anxiety, less common being psychosis and schizophrenia (5).

The cause of depression in patients with epilepsy are probably multifactorial, including clinical (seizure frequency, seizure type or foci, epilepsy duration, age at onset) and psychosocial factors (quality of life, life stressors, employment, marital status) (43, 44, 10). Clinical or psychosocial factors cannot fully account for the high prevalence of depression in patients with epilepsy because the biological characteristics of epilepsy also affect the manifestation of depression (45, 46). Most studies report no association between depression and the age of onset of epilepsy or duration of epilepsy (19, 47). Mendez et al reported that patients with epilepsy and depression had fewer generalized tonic-clonic seizures than epilepsy patients without depression (48).

Depression is reported more frequently in patients with complex partial seizures and temporal lobe foci than in patients with generalized epilepsy or extratemporal foci (40). An explanation for these inconsistencies may be that frontal lobe dysfunction is a necessary component for the development of depression in temporal lobe epilepsy patients, as suggested by the findings of a bilateral reduction in inferior frontal lobe glucose metabolism on PET scans in patients with depression and temporal lobe epilepsy (49). Dysfunction in the temporal lobe due to an epileptic focus may result in hypometabolism of extratemporal regions, increasing the vulnerability to depression (50). Authors reported that the combination of interictal left temporal lobe hypometabolism and “high-degree” hypometabolism was significantly associated with major depression (20). Reduced activity measured with SPECT in bilateral frontal and right temporal regions was associated with higher scores on the BECK Depression Index in patients with left side temporal lobe epilepsy (51). The hypoperfusion (hypometabolism) observed in the limbic frontal regions in patients with temporal lobe epilepsy may be related to interictal inhibitory activity, postictal depletion of substrates (decreased levels of neurotransmitters), or functional deafferentation (49, 52). Hippocampal dysfunction is associated with depression symptoms in temporal lobe epilepsy and may be a more important factor than seizure frequency or degree of disability (53).

Preclinical and clinical studies suggest that 5-HT_{1A} receptors play a role in the pathophysiology of both temporal lobe epilepsy and depressive disorder. The study compared 5-HT_{1A} receptor binding between temporal lobe epilepsy with and without depressive disorder. Authors conclude, reductions in 5-HT_{1A} receptor binding might help elucidate the neurobiological mechanisms underlying the temporal lobe epilepsy-depressive disorder comorbidity (54).

Iatrogenic mechanisms such as type of AED (phenytoin, topiramate, vigabatrin, tiagabine), secondary effects of AEDs, or polypharmacy are associated with increased risk for depressive symptoms (52).

Decreased serotonergic, noradrenergic, and GABAergic functions have been identified as pivotal pathogenic mechanisms of depression and have been the basis for antidepressant pharmacologic treatments (9). Some anticonvulsant treatments (vagus nerve stimulation therapy, valproate, carbamazepine, lamotrigine, and gabapentin) have demonstrated mood improvement in epilepsy patients and may have therapeutic potential for this patient population (52).

Depression and epileptogenic seizures decrease the patient's life quality compared to the general population. Similarly, the depression and epilepsy comorbidity decrease the patient's life quality as related to patients with epilepsy only and no depression (55). Authors reviewed 17 studies pertaining to mortality in epilepsy and established that suicide occurred ten times more frequently than in the general population (56, 57).

Anxiety in epilepsy, symptoms may result or be exacerbated by psychological reactions, including responses to the unpredictability of seizures and restrictions on normal activities, resulting in low self-esteem, stigmatization, and social rejection (42, 58). In Anxiety, depending on the time of seizures, can be ictal, postictal and interictal. Ictal anxiety symptoms manifest as fear or panics, sometimes with other characteristics of temporal discharges, such as depersonalisation and *déjà vu*, as well as other psychological and psychopathological and autonomous phenomena, resulting from structural changes in the right-side temporal lobe (26). Interictal anxiety significantly influences the life quality since patients with anxiety disorder comorbid with epileptic seizures have a permanent fear of new discharges (26).

The risk of anxiety disorders appears to be higher in focal (especially temporal lobe) than in generalized epilepsies, but they are also seen in patients with frontal lobe epilepsy as well as primary or generalized seizures. The highest rates of psychiatric comorbidity (including anxiety) are reported in patients with chronic refractory seizure disorders (26, 58, 59).

The correlation of anxiety and epilepsy may be explained by the role of the amygdale as well as the GABA theory. The theory of common pathophysiological mechanism of anxiety attacks and epilepsy is based on the observation that epileptic activity in certain areas of the brain directly causes paroxysmal anxiety, usually in the form of panic. The amygdale seems to be a particularly important structure for the production of anxiety symptoms and epileptic discharges in temporal lobe epilepsy. The amygdale is responsible for processing and relaying emotional stimuli from

multiple sources to limbic and other cortical structures, basal ganglia, hypothalamus, and brainstem. The amygdale is therefore central to the generation of affective, autonomic, cognitive, and endocrine components of the clinical symptom "anxiety" (60–65).

Gamma-aminobutyric acid (GABA) is the most important inhibitory transmitter in the central nervous system. Recent evidence suggests that the abnormal functioning of GABA receptors could be of great importance in the pathophysiology of epilepsy and anxiety disorders (60, 66).

The evaluation of behavioural disturbances in epilepsy is an area fraught with complexity. There are no instruments that have been developed specifically for the assessment of behavioural disturbances in epilepsy. But, the phenomenology and pathophysiology of behavioural disturbances in epilepsy are unique and defy conventional descriptions in the psychiatric literature. Instruments that have a basis in psychiatric criteria as opposed to symptomatology have inherent pitfalls at the interface between epilepsy and behavior.

The paleocerebrum, limbic system and their connections have been considered to be the center of emotions, feelings, attention, motivation and autonomic functions. The hippocampus has a key role in regulating memory, learning, emotion and motivation.

Neurogenesis persists throughout life in the adult mammalian dentate gyrus. Adult-born dentate granule cells integrate into existing hippocampal circuitry and may provide network plasticity necessary for certain forms of hippocampus-dependent learning and memory. Neural stem cells and neurogenesis in the adult dentate gyrus are regulated by a variety of environmental, physiological, and molecular factors. These include aging, stress, exercise, neurovascular components of the stem cell niche, growth factors, neurotransmitters, and hormones. Similar findings of granule cell layer dispersion and ectopic granule neurons in human temporal lobe epilepsy suggest that aberrant neurogenesis contributes to epileptogenesis or learning and memory disturbances in this epilepsy syndrome (67). Based on the developmentally regulated psychosis/epilepsy-related thalamocortical circuitry, it is proposed that antiepileptic drugs that promote GABAergic mechanisms may decrease the probability of episodic psychosis from any cause (68). But other study introduce the hypothesis that epilepsy-related psychoses may partially result from excessive hippocampal dynorphin release and kappa opioid receptor overstimulation aimed at seizure control (69). The neurotransmitter with a key role is GABA, although ionic currents, catecholamines, opiates, adenosine, glutamate, and nitric oxide play a role. Brief postictal and alternating psychoses provide an opportunity to understand the complex relationships between epilepsy and schizophrenia-like brief psychotic episodes, and this understanding can assist in their management (70).

Conclusion

Patients with epilepsy are uniquely at risk for high physical-psychiatric comorbidity profiles, with concomitant losses in perceived health status.

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