REVIEW ARTICLE

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Co-existence of mental disorders in patients with epilepsy – literature review

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Abstract

Introduction and Objective. Epilepsy has a significant impact on patients' psychiatric condition. Epidemiological studies have shown that comorbid psychiatric disorders can occur in about 20–40% of patients with epilepsy. The aim of th study is to raise awareness of how much neuropsychiatric comorbidity exists, and to expand knowledge about this problem.

Review Methods. The review was based on articles from the PubMed and Google Scholar databases, by searching terms: epilepsy; epilepsy comorbidity; epileptic syndromes, seizures, mental disorders, depression, suicide, neuro-developmental disorders, suicide attempt, self-injurious behaviour, quality of life.

Brief description of the state of knowledge. Numerous studies conducted over the past years show an increase in the prevalence of mental disorders occurring in patients with epilepsy, compared to healthy people. Mental disorders can be part of an epileptic seizure, have a temporal relationship with them, or occur independently. Problems in the adult population mainly involve depression and anxiety. Along with epilepsy, psychotic and personality disorders can co-occur. In the paediatric population, one of the most common problems reported by parents is attention deficit disorder, especially with ADHD. Furthermore, anxiety disorders and depression are at the forefront in adolescents. The correlation with suicide in epilepsy patients, both adults and minors, is significant, as suicide risk is up to 10 times higher, compared to the general population.

Summary. Comorbidity of mental disorders in the course of epilepsy poses significant difficulties for both patients and clinicians. Thus, in the proper manage of those patients, it is important to possess a comprehensive knowledge about the prevalence of such phenomenon, as well as about the different complications and risks associated with it, including the possibility of suicide.

Key words

depression, anxiety, suicide, seizures, epilepsy, mental disorders, epilepsy comorbidity, neurodevelopmental disorders, quality of life

INTRODUCTION

Numerous studies conducted over the past years dedicated to mental disorders occurring in patients with epilepsy, unanimously show an increased prevalence compared to healthy people [1–4]. The increased rate of psychiatric illness in patients with epilepsy is determined by converging pathogenetic pathways, including abnormalities in brain bioelectrical activity, CNS availability of neurotransmitters (monoamines) or activity of ubiquitin proteins (polyamines) [1, 3, 4]. In addition, comorbidities are influenced by the location of the epileptic foci located in the centres of the limbic system, which is directly related to emotions, urge behaviour and memory [1, 2, 4]. According to studies, it is in cases of temporal lobe epilepsy (TLE), in which the amygdala may be the seizure focus, that the highest percentage of psychiatric disorders is observed [1, 2, 4]. This was about 37.3% of patients, compared to 14.85% of subjects with 'extratemporal lobe epilepsy' (ETLE) [4]. Social withdrawal, dependence on the environment, stigma, and insecurity of the patient, which increase with the frequency of seizures, are also important factors promoting the occurrence of psychiatric disorders in epilepsy patients [1, 4].

The pharmacological control of epilepsy is therefore crucial for reducing the risk of mental illness, although simultaneously, some antiepileptic drugs, due to their mechanism of action (e.g., levetiracetam, tiagabine, topiramate, clonazepam) or metabolism (e.g., cytochrome P450-inducing phenytoin, which degrades antidepressants), have the opposite effect [1]. A special situation is drug-resistant epilepsy in which psychiatric disorders, due to the inability to effectively treat epilepsy, occur about four times more often than in the drug-sensitive variant [4]. The co-occurrence of epilepsy and psychiatric disorders significantly affects the quality of life of patients and also increases the risk of the suicide [5]. On the other hand, for clinicians it poses a considerable diagnostic and therapeutic problem, and may therefore require interdisciplinary care from both neurologists and psychiatrists, as well as the involvement of the patient and family or caregivers in the treatment process.

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OBJECTIVE

The aim of the review is to provide a comprehensive overview of the current state of knowledge on the comorbidity of psychiatric disorders and epilepsy in different patient groups, and to raise awareness of this frequently occurring phenomenon among both clinicians and patients.

MATERIALS AND METHOD

The review was based on articles from the PubMed and Google Scholar databases. Key search terms included: epilepsy; epilepsy comorbidity, epileptic syndromes, seizures, mental disorders, depression, suicide, neurodevelopmental disorders, suicide attempt, self-injurious behaviour, and quality of life.

STATE OF KNOWLEDGE

Psychiatric comorbidity in adults with epilepsy. In the adult population, a person with epilepsy is more likely to have a mental illness compared to a healthy person. Common mental illnesses include anxiety disorders, depression, addiction, psychosis and schizophrenia. In addition, people with epilepsy have a higher risk of suicide [6]. The prevalence of various psychiatric disorders and suicide attempts in adults with epilepsy is presented in Table 1.

A *Lancet* cohort study of nearly 70,000 people in Sweden showed that about 9% of the group died prematurely, on average, around the age of 35. Some of the main causes of the deaths were external, such as non-vehicle accidents (95%) and suicide (4.2%), while others (72.5%) also had a mental illness. It is interesting to note that epilepsy patients are more likely to have alcohol and other substance addictions (4.7%), compared to a control sample (1.9%) [7].

Depression in the epilepsy population is experienced by 12%-62% of patients, with the likelihood of depression in epilepsy patients being increased by poor control of seizure onset. A study by Dias et al. shows that patients who experienced an uncontrolled seizure had twice the incidence of major depression, compared to patients without seizures [8, 9]. A recent study showed that people with epilepsy and depression have higher cortisol levels compared to those with only depression or epilepsy. In addition, the study found elevated levels of cortisol, ACTH and TNF-a, indicating an inflammatory basis for both diseases [10].

Anxiety disorders are one of the main psychiatric disorders that occur in patients with epilepsy, and can be divided into pre-seizure, during seizure, post-seizure and inter-seizure. Symptoms that fall under pre-seizure anxiety include stress and hyperventilation seizures. It is interesting to note that in people suffering from psychogenic seizures, a hyperventilation seizure associated with the disease can trigger a true epileptic seizure. We can compare a panic attack to the anxiety experienced by patients during a panic attack Symptoms of post-epileptic anxiety include panic, agoraphobia, which is experienced by about 40% of patients, and depression. Interictal anxiety disorder includes: anxiety due to fear of having another epileptic seizure, too great a fear of seizures, is characterized by perfectionism, careful guarding of certain behaviours (such as monitoring the quality of sleep, doses of medication), and avoidance of behaviours that the patient believes may trigger a seizure. The patient also fears that bystanders will see him during a seizure. Anxiety occurring with agoraphobia, characterized by fear of a seizure occurring, and doing everything to prevent a seizure for more than a month [11, 12]. Psychosis during an epileptic seizure occurs in about 4–6% of patients, whereas psychosis after an epileptic seizure occurs, on average, in about 2%. In temporal epilepsies, about 7% of patients experience psychosis. Patients who have previously experienced paranoid disorders are seven times more likely to develop an epileptic seizure. According to Braatz et al. predisposing factors for psychosis in patients with epilepsy are male gender, the presence of psychosis in the family history, seizures with aura, and clustering seizures. Seizures of psychosis last about a month. Patients are more likely to experience psychosis when taking levetiracetam and lamotrigine, while carbamazepine has a protective effect. Atypical neuroleptics that do not lower the seizure threshold, such as risperidone and aripiprazole, are used to treat epileptic patients with psychosis [13–15].

Mental disorders in people with epilepsy can be triggered by medications. Sudden discontinuation of medications such as carbamazepine, benzodiazepines and lamotrigine can be associated with increased anxiety in patients. It is important to remember that side-effects of medications can overlap, and include ataxia, behavioural hyperactivity, behavioural changes, depression and insomnia. Some medications, e.g. benzodiazepines, are addictive; therfore, before administering them to a patient, special consideration should be given to whether the proposed therapy is appropriate for the patient and its inclusion will not have more psychiatric side-effects than beneficial effects [11, 16].

Psychiatric comorbidity in children with epilepsy. Most children with epilepsy experience psychiatric comorbidity [6]. The prevalence of co-occurring psychiatric disorders and suicide attempts in children with epilepsy is demonstrated in Table 2. Children with epilepsy have lower IQs compared to their healthy peers, which results in poorer academic performance and social problems [19]. It is interesting to note that the IQ of parents of children with epilepsy, compared to parents of healthy children, does not differ. Therefore, it can be concluded that a parent's IQ value is not a significant predictor of the occurrence of epilepsy in children [20, 21].

About 76% of children with epilepsy are observed to have behavioural difficulties. Attention deficit/hyperactivity disorders (ADHD) are observed in 40% of children with epilepsy. Autism spectrum disorders are frequently seen in about 6.3–17% of children with epilepsy [22, 23].

Factors that increase the likelihood of comorbidity of autism spectrum symptoms in children with epilepsy are: IQ<70, first epileptic seizure at less than two years of age, focal seizures with a dyscognitive component, neural/genetic condition, family history – having more (>1) family member on the autism spectrum increases the risk of autism spectrum in children with epilepsy [23, 24]. In contrast, in children with ADHD, factors in the development of epilepsy include IQ <85, neurodevelopmental vulnerability, and the presence of ADHD symptoms at age 0–6 years [25].

Among the drugs used in the treatment of ADHD, methylphenidate is likely to cause sleeping problems, which can affect the prognosis of epilepsy in the patient. Moreover, in some studies, the use of methylphenidate occurred to

Table 1. Prevalence of various psychiatric disorders and suicide attempts in adults with epilepsy

Name of authors	Depression	Anxiety disorders	Psychosis	ASD**/ Autism	ADHD*	Suicide ideation	Suicide attempt	Suicide
Jezowska-Jurczyk K, et al. [1]	10%–46%	10%–45%	2%–40%	-	-	-	0,2%–0,4%	-
Mesraoua B, et al. [5]	23.1%	-	-	-	-	23.2%	7.4%	0.5%
Verrotti A, et al. [6]	20%	22.8%	-	-	-	-	-	2.32%
Fazel S, et al. [7]	-	-	-	-	-	-	-	-
Błaszczyk B, et al. [8]	11%–62%	-	-	-	-	-	-	-
Hingray C, et al. [11]	-	11%–50%	-	-	-	-	-	-
Ertan D, et al. [12]	-	53%	-	-	-	-	-	-
Clancy MJ, et al. [13]	-	-	10%–19%	-	-	-	-	-
Kanner AM et al. [14]	-	-	7%–10%	-	-	-	-	-
Abraham N, et al. [17]	-	-	-	-	-	23.2%	7.4%	0.5%
Kim SJ, et al. [18]	22.2%	-	-	-	-	31.6%		

* Attention deficit hyperactivity disorder ** Autism spectrum disorder/ autism

lower the seizure threshold, especially in poorly-controlled epilepsy [22, 26–28]. Of interest is a cohort study by Reilly et al. on a group of children with epilepsy and a control group of children with neurodisability. It was found that the presence of epileptic seizures did not significantly increase the likelihood of a child having a behavioural disorder [23].

Children with epilepsy are often affected not only by behavioural disorders but also with problems at school. The percentage of children with this problem is higher than that of healthy children. This is related to the frequency of seizures, the amount of antiepileptic drugs taken, and age – the older the child, the more the perception of epilepsy changes. Children with epilepsy mostly have problems with internalization – problems characterized by social withdrawal, somatic complaints and anxiety/depression. These problems lead to increased parental stress, therefore it is important that the entire families of children with epilepsy receive psychological support [23, 29].

Anxiety and depressive disorders are very common psychiatric disorders, with a probability of occurrence of 21%-60%, and appear especially in children with newly-diagnosed epilepsy. Before the onset of a seizure, symptoms such as anxiety, irritability and psychomotor agitation are particularly common in children. In addition, drugs used to reduce seizures can cause as their side-effect the buildup of depressive disorders in children. Drugs such as phenobarbital and carbamazepine can exacerbate depression and suicidal thoughts [30]; levetiracetam increases nervousness and aggression [28]; while vigabatrin exacerbates depression and can lead to psychosis [31].

Sleep disorders are one of the factors that reduce the seizure threshold. Children with epilepsy often have seizures during sleep, resulting in a decrease in sleep quality, which leads to sleeplessness, behavioural problems and decreased academic performance. Another problem is insomnia, which is more common in children with epilepsy and autism spectrum disorders [28, 32].

Most children with epilepsy experience problems in the learning and psychological spheres, as well as in the medical sphere, such as side-effects of medications; therefore, it is important to identify problems early and correct them, and thus improve the quality of life.

Risk of suicide in patients with epilepsy. The scientific studies analyzed and available medical data, clearly indicate the co-occurrence of suicidal behaviour in patients with epilepsy. Patients affected by epilepsy make suicide attempts three times more often than the healthy population [5, 17]. The epidemiology, pathomechanism and symptoms of the disease itself, its impact on quality of life, the presence of comorbidities and its treatment methods are responsible for this [5, 17, 33, 34]. On the other hand, people with a history of suicidal behaviour were five times more likely to develop epilepsy [5]. The link between the above disorders is confirmed by the fact that the symptoms of epilepsy developing in patients, may have been preceded by a suicide attempt [5]. In addition, suicidal episodes are more likely to recur in patients with a history of epilepsy [33]. A key factor inducing an increased incidence of suicide in epilepsy patients, is the co-occurrence of psychiatric disorders with

Table 2. Prevalence of various psychiatric disorders and suicide attempts in children with epilepsy

Name of authors	Depression	Anxiety disorders	Psychosis	ASD**/ Autism	ADHD*	Suicide ideation	Suicide attempt	Suicide
Jezowska-Jurczyk K, et al. [1]	10%–46%	10%–45%	2%–40%	-	-	-	0.2%–0.4%	-
Mesraoua B, et al. [5]	23.1%	-	-	-	-	23.2%	7.4%	0.5%
Verrotti A, et al. [6]	20%	22,8%	-	-	-	-	-	2.32%
Ono KE et al. [22]	-	-	-		30%–40%	-	-	-
Reilly C et al. [23]	-	-	-	18%	40%	-	-	-
Strasser L, et al. [24]	-	-	-	6.3%	-	-	-	-
Downs J et al. [27]	-	-	-	-	33%	-	-	-

* Attention deficit hyperactivity disorder ** Autism spectrum disorder/ autism

epilepsy, most commonly depressive disorders, particularly exacerbated in TLE [1, 3, 5, 17, 33, 35]. Correlations have also been demonstrated between increased seizures and a higher incidence of self-destructive behaviour, compounded by a sense of dependence on the environment, stigma, and insecurity of the patient, and social withdrawal accompanying the whole situation [17, 34, 36]. This directly correlates with the undeniable impact of appropriate treatment of epilepsy and mental illness as a prevention of suicide.

With the introduction of new anticonvulsants, such as eslicarbazepine, perampanel, brivacetam, and cenobamate (new ASMs), into the pharmaceutical market, newer studies on their possible effects not only on mental disorders, but also on suicidal tendencies, are needed, although they have not shown an increased risk of suicide in subjects taking them [34]. Among the better-studied older-generation drugs, the incidence of suicidal behaviour may be more frequent only when taking agents that cause depressive disorders due to their mechanism of action (e.g., levetiracetam, tiagabine, topiramate, clonazepam), or metabolism (e.g., phenytoin, which induces cytochrome P450, which breaks down antidepressants) [1]. In general, taking antiepileptic drugs has a statistically favourable effect on decreasing suicide rates from the first month of therapy. It has also been proven that the month of diagnosis of epilepsy was the most frequent moment when patients attempted suicide, that is, when pharmacotherapy had not yet had a significant effect on the patient's condition [18, 33, 37].

A significant factor that can elevate the prevalence of suicide among individuals diagnosed with epilepsy is the absence of profound history-taking and physical examination of patients by neurologists during routine follow-up appointments. This may indicate a degree of unawareness on the part of clinicians who, while focusing on effective and accurate treatment of epilepsy, do not analyze the risk of suicidal behaviour [36]. Despite the availability of a number of scales for the early detection of those with an increased risk of suicide, such as the Suicide Ideation Scale (SSI), the Mini Neuropsychiatric Interview (MINI), and the Columbia-Suicide Severity Rating Scale (C-SSRS), they are not used often enough. Only 5% of doctors undertook the above diagnostics at the first visit, less than half used them within the first year of treatment, and 6% made no attempt to identify risk at all [34].

CONCLUSIONS

The co-occurrence of mental illnesses in epilepsy patients is widespread, with reported prevalence ranging from 5%-40%, depending on factors such as age, gender, and type of epilepsy. Regardless of etiological footnotes to psychiatric comorbidities, it is clear today that the treatment of epilepsy must target psychiatric illnesses. Treating patients with epilepsy can cause multiple difficulties. Patients experience side-effects of treatment and fear of seizures; they struggle with problems in daily functioning, such as the inability to drive a car or work in their dream job because of the occurrence of seizures, leading to a decrease in their quality of life [16].

Mental disorders significantly affect the quality of life and functioning of epilepsy patients. Consequently, they may require appropriate therapeutic approaches and the cooperation of multidisciplinary teams. Based on the findings of this review, it is recommended that future studies systematically include demographic factors, such as age and gender, when analyzing psychiatric comorbidities in epilepsy, and that clinical practice considers these differences in screening and support planning.

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