

Epilepsy on the Border of Psychiatry and Neurology

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Introduction

Epilepsy represents a global health problem, because according to reports from the World Health Organization (WHO), an estimated 50 to 69 million people suffer from it [1-3].

It is considered as old as humanity itself and one of the most frequent disorders of the Central Nervous System (CNS) [4]. Of significance should be mentioned the involvement in the psychological and social sphere of patients who suffer from it, because they are among the most vulnerable in any society, related to the particular stigma that this disease carries, which has been transmitted for generations until our days [5]. People who suffer from epilepsy, experience a discriminatory behavior in many areas of life, with an associated psychiatric comorbidity, all of which implies that it is considered a complex pathology, with social, psychobiological and economic consequences [6,7].

This disease, in turn, can significantly compromise the quality of life of those who suffer from it, since in many cases it affects, albeit in a variable way; emotional state, behavior, social and cognitive functioning [8].

Since ancient times, in the first descriptions of epileptic disease it is related to alterations in behavior, thought and humor [9] and was considered a mental illness for millennium, with a religious magical etiological concept.

The International League Against Epilepsy (ILAE) and the World Health Organization (WHO) in 1973 defined Epilepsy as a chronic and recurrent condition of paroxysmal crisis, triggered by abnormal electrical discharges that have varied clinical manifestations of multifactorial origin and associated with paraclinical disorders that occur in an unprovoked manner.

Thirty years later, the conceptual definition of epilepsy, according to the report of the working group of the International League Against Epilepsy (ILAE) of 2005, states the following [10]:

Brain disorder characterized by a continuous predisposition to the onset of epileptic seizures and the neurobiological, cognitive, psychological and social consequences of this disease. The definition of epilepsy requires the presence of at least one epileptic seizure.

Recently (2014) has been published by a group of experts from the ILAE, the operational (practical) clinical definition of this disease [11]:

It is considered that epilepsy is a brain disease that is defined by any of the following circumstances:

1. At least two unprovoked (or reflex) crises with >24 hours of separation.
2. An unprovoked (or reflected) crisis and a probability of presenting new crises during the next 10 years similar to the general risk of recurrence (at least 60%) after the appearance of two unprovoked crisis.
3. Diagnosis of an epilepsy syndrome.

According to these criteria, a patient who has suffered a crisis presents epilepsy and whose brain, for whatever reason, shows a pathological and continuous tendency to suffer recurrent crises with biological, cognitive, psychological and social consequences.

In fact, there is a consensus that the incidence of neurobehavioral disorders is higher in patients with epilepsy than in the general population and many authors establish a relationship between these disorders and complex partial epilepsy of the temporal lobe [12].

The objective of this article is to specify in this disease if there is a border between Psychiatry and Neurology. Bearing in mind, moreover, that psychiatric comorbidity in patients suffering from epilepsy is frequent and of multifactorial cause, it becomes of significant interest for the physician to be able to identify early the risk factors that are related to the neurobehavioral symptoms, in order to minimize their effects and improve their quality of life.

Related Factors Between Epilepsy and Behavior Disorders

Multiple biological and psychosocial factors interacting, determine the risk for the development of schizophreniform psychosis, major depression and behavioral disorders in patients with epilepsy [7].

Despite being frequent and important, mental disorders are underdiagnosed in patients with this disease, whose causes are usually: tendency to minimize symptoms; difficulty in recognizing unusual, atypical symptoms in the population with epilepsy; tendency on the part of patients to minimize complaints for fear of being discriminated against and fear that psychotropic drugs will lower the seizure threshold [13].

The association between epilepsy and psychiatry has a long history. The traditional approach to the care of epilepsy has been directed to the crisis and its treatment. However, this only occupies a small proportion in the affectation of the patient with epilepsy and their quality of life. Sackellares and Berent considered that an adequate care of the patient with epilepsy requires “attention to the psychological and social consequences as well as to the control of the crises” [14].

Frequency of Psychiatric Disorders in Patients with Epilepsy

The psychiatric symptoms characteristic of the neurobehavioral syndrome in epilepsy tend to be distinguished by being atypical, episodic and pleomorphic.

It is estimated that between 20-30% of patients with epilepsy have psychiatric disorders [9,15].

Of patients with intractable complex focal seizures, 70% may have 1 or more diagnoses of mental disorders; 58% of these patients have a history of depressive episodes, 32% have agoraphobia without panic or other anxiety disorders and 13% have psychosis.

The risk of psychosis in patients with epilepsy can be 6-12 times more than the general population, with a prevalence of around 7-8%; In patients with temporal lobe epilepsy refractory to treatment, prevalence has been reported in a range of 0-16%.

The most common psychiatric conditions in epilepsy are depression, anxiety and psychosis.

Psychotic Disorders

Psychotic disorders are severe mental disorders that cause abnormal perception and thinking. Psychotic individuals lose their relation to reality [16-18].

Vuilleumier and Jallon found that 2-9% of patients with epilepsy have psychotic disorders [19]. These are more common in patients with epilepsy than in the general population.

However, many questions hover around this issue [20].

They can be classified according to their relationship with the occurrence of epileptic seizures in periictal (preictal, ictal or postictal) and interictal [21-23].

Perez and Trimble reported that about half of patients with epilepsy and psychosis could be diagnosed with schizophrenia [24].

The etiology and pathogenesis of psychosis in epilepsy is still poorly understood, however, neuroanatomical changes have been observed in patients with psychosis and include the following:

- Asymmetry of the amygdala and the anterior segment of the hippocampus.
- Reduction of the volume of the amygdalo-hippocampal complex in the pathogenesis of schizophrenia.
- Reduction of the volume of gray matter in the left temporal and left upper temporal gyrus.
- Reduction of the volume of the bilateral middle frontal gyrus (prefrontal cortex) in psychosis concomitant with schizophrenia.
- Dysfunction of discharges in the upper temporal cortex in auditory hallucinations [25].

In general, patients with temporal lobe epilepsy and psychosis have a significantly smaller brain volume than patients with temporal lobe epilepsy only.

Psychosis in the patient with epilepsy is a nosological entity that differs from schizophrenia.

Factors in the Development of Psychosis in the Patient with Epilepsy

- Family history of psychosis. Patients with a family history, or with an early age of onset of psychosis, tend to have longer interictal episodes [24].
- Age of onset of epilepsy. Patients with interictal psychosis showed a significantly early onset of epilepsy.
- Type of epileptic seizure. The existence of complex focal seizures (more than the temporal lobe) may be closely related to interictal psychosis.
- Intelligence - patients with borderline functioning tend to develop relatively frequent psychotic symptoms.
- Complex focal crisis, especially in focus of the temporal lobe, frontal lobe epilepsy, the presence of “foreign tissue” (example, small tumors, hamartomas, gangliomas of the mesial temporal lobe).

Despite these considerations, Trimble and Schmitz estimate that the conclusions presented in the literature in relation to risk factors are controversial [26].

Studies in small samples have reported reductions in regional cerebral flow in the left superior temporal gyrus with tasks of verbal fluency or mesial temporal region and lower regional oxygen extraction in fronto-temporal regions in patients with psychosis.

Schizophrenia

In a review of patients with epilepsy who developed psychosis, the researchers found that patients with psychosis were generally a form of schizophrenia, most commonly the paranoid.

Stagno reported that the persistent interictal psychosis of epilepsy and the psychosis of epilepsy with schizophrenia like are distinguishable from schizophrenia [27].

Forced Normalization

In the treatment of any patient with psychosis and epilepsy, the phenomenon called forced normalization (alternative psychosis or antagonism between seizures and behavioral abnormalities) must be taken into consideration, which was a concept described by Landolt in 1950. When the electroencephalogram (EEG) in psychotic patients it is normalized, frequently with antiepileptic medication, psychiatric disorders worsen (worsening of the behavior with improvement of the control of the crisis).

Forced normalization is frequently described in patients treated with Ethosuximide; however, it has been reported in the treatment with other antiepileptic drugs, including the most novel ones. The mechanism of action of this interesting phenomenon is still unknown and controversial.

Bipolar Affective Disorders

A number of studies have shown that affective disorders in epilepsy represent a common psychiatric comorbidity [28]; however, the neuropsychiatric literature focuses on depression, which is predominant [29]. Our knowledge about the relationship between epilepsy and these disorders is limited, which, in turn, is presented with an episodic course that can be chronic [30].

The incidence of bipolar affective disorders in epilepsy is 1.69 cases per 1000 persons/year, compared with 0.07 in the general population.

Bipolar symptoms were 1.6-2.2 times more common in subjects with epilepsy than with migraine, asthma or diabetes mellitus and they occur 6.6 times more than in healthy subjects.

A total of 49.7% of patients with epilepsy who were selected with positive symptoms of bipolar disorders by a physician, had about twice the rates seen in other disorders.

Other authors, such as Lau, demonstrated in their series that only 12% of epileptic patients had symptoms of bipolar disorder [31].

Depression

Depression is the most frequent psychiatric comorbidity seen in patients with epilepsy, with a prevalence between 10 and 20% in patients with controlled seizures and between 20 and 60% in those with refractory epilepsy [32].

It occurs more frequently in patients with focal frontal and temporal lobe seizures. It is also more frequent in patients with poor control of seizures.

Two etiological possibilities exist: depression as a reaction to epilepsy or depression as part of epilepsy.

Méndez and colleagues found that while 55% of patients with epilepsy reported depression, only 30% of the control group reported it.

In patients with refractory epilepsy, the presence of depression is one of the most important variables to have an impact on their quality of life, even more than the frequency and severity of the crisis.

Some studies have documented that quality of life improves significantly in patients with epilepsy who are crisis-free. However, Boylan *et al* have found that quality of life is related to depression, but not to the degree of crisis control [33].

Mania

In a careful and selected series of patients with epilepsy, Williams found that only 165 of 2000 patients had complex ictal experiences, including emotional ones [34].

Of these 165 patients, only 3 were described as rejoicing. Mania and hypomania are rare in association with epilepsy.

Manic depressive illness is also rare and was not commonly associated with epilepsy even before the modern use of antiepileptic drugs.

Suicidal Behavior

Suicide is significantly more frequent among patients with epilepsy than in the general population [35].

Depression is one of the psychiatric disorders that increases the risk of suicide. This in depressed patients is considered around 15%.

On average, the risk of suicide in patients with epilepsy is around 13% (prevalence rates of 5-10 times that of the general population).

However, some authors question the methodology and selection techniques of these studies and mention the Barraclough meta-analysis, which revealed that the risk of suicide in patients with temporal lobe epilepsy increases as much as 25 times the general population.

Even so, the relationship between epilepsy and suicide is complex and multifactorial.

Adverse psychiatric events, including symptoms of depression and anxiety, have been reported with the use of some antiepileptic drugs, particularly barbiturates (Phenobarbital and Primidone), Topiramate, Tiagabine, Zonisamide, Vigabatrin and Leviteracetam [36].

However, the incidence of suicide phenomena related to antiepileptic drugs has not been systematically well studied.

Frequent Risk Factors Associated with Suicide Include

Current or past anxiety and mood disorders, psychiatric family history or mood disorders, particularly suicidal behaviors and previous suicide attempt.

In the study published by Nilsson *et al* in 2002 [37], conducted in Sweden, it was found that the early onset of epilepsy, the presence of an associated mental illness and the use of antipsychotic drugs were factors associated with suicidal behavior.

The factors associated with suicidal tendencies in patients with Temporal Lobe epilepsy are: left epileptogenic zone, presence of a family history of psychiatric illness, presence of a current depressive episode, low cholesterol levels, executive dysfunction, long data of epilepsy, Interictal and post-chronic psychosis, phenomenon of forced normalization, use of antipsychotics, the loss of family, the loss of work, divorce and legal problems.

In January 2008, the US Food and Drug Administration (FDA) warned about the association between suicide and antiepileptic drug. This was based on the results of a meta-analysis that included data from 199 trials of 11 drug antiepileptics. The meta-analysis included 43,892 patients treated for epilepsy, psychiatric disorders and other disorders, with pain predominating.

In the study, suicide occurred in 4.3 of 1,000 patients treated with DAE. The result of this study should be considered with great caution and other studies are necessary [36,38].

Anxiety Disorders

Anxiety is common in patients with epilepsy and may also be related to non-epileptic seizures. Anxious symptoms, especially if they are noticeable, can have significant implications for the quality of life of patients with epilepsy [39,40].

The consequences can be disabling, provoking evasive behaviors and isolation [41,42].

GABA is the most important inhibitory transmitter in the central nervous system.

Evidence suggests that the abnormal functioning of GABA receptors could be of great importance in the pathophysiology of epilepsy and anxiety disorders.

Anxiety in Association with Types of Epilepsy and Frequency of Seizures

The highest rates of psychiatric comorbidities, including anxiety, are reported in patients with chronic refractory crisis [43].

The risk of anxiety is higher in focal epilepsies (more frequent in the temporal lobe) than generalized epilepsy. In patients with temporal lobe epilepsy, Trimble *et al* reported that 19% of patients were diagnosed with anxiety and 11% with depression.

Edeh and Toone found that patients with temporal and frontal lobe epilepsy had higher anxiety scores than extratemporal ones [44].

Personality Disorders

Personality disorders in epileptic patients can cause abnormal behaviors, which can have a direct impact on the control of seizures and quality of life [45,46].

This relationship has a long history and remains controversial. In 1975, Woxman and Geschwind described the term they coined as a syndrome of interictal behavior consisting of circumstantiality (excessive verbal expression, hyperviscosity, and hypergraphia), altered sexuality, and animosity in a patient with temporal lobe epilepsy (TLE). This was called Geschwind syndrome [47].

Benson and Herman reported that the data are insufficient to establish a pattern of behavioral changes in patients with Temporal Lobe Epilepsy. Complex focal epilepsy should not be diagnosed on the basis of the presence of Geschwind syndrome without any paroxysmal episode that may induce epilepsy [48].

The relationship of personality disorders with epilepsy was not only seen in Temporal lobe epilepsy. Trinka *et al* found that personality disorders were present in 23% of patients with Juvenile Myoclonic Epilepsy.

Trimble has summarized that the personality profile of a patient with epilepsy can be explained by a complex combination of effects of the relationship with chronic diseases, the effects of antiepileptic drugs and the pathology of the temporal lobe.

He asserted that certain personality alterations in epilepsy should be seen as associated with brain abnormalities that are also crisis-inducing [36].

Hyperactivity Disorders and Attention Deficit

Hyperactivity disorder and attention deficit disorder is another psychiatric comorbidity in patients with epilepsy and more common in children. The occurrence may result from the inclusion of altered neurobiological mechanisms in the early development of the brain.

The incidence is around 7.76 cases per 1000 persons/year in patients with epilepsy and 3.22 in patients without epilepsy. In turn, the incidence of epilepsy is 3.24 cases per 1000 person-years in patients with the disorder studied and 0.78 in those without it [38].

Many antiepileptic drugs can cause symptoms that mimic these disorders and the most common are GABAergic drugs such as Barbiturates, Benzodiazepines and Vigabatrin.

Methylphenidate can cause an increase in epileptic seizures in patients with hyperactivity disorder and attentional deficit, however, it is considered safe in those who are crisis-free [49].

Psychotropic Effects of Antiepileptic Drugs

Knowledge about the psychotropic effects of antiepileptic drugs is crucial and still very limited in the epileptic population. Evidence suggests that Lamotrigine and the vagal stimulator may have antidepressant properties that could be used in common comorbid depression [50].

Carbamazepine, Valproate, Lamotrigine, and possibly Oxcarbazepine may have mood stabilizing properties. Gabapentin, Pregabalin, and Tiagabine may have anxiolytic benefits.

There is a risk of depression related to Barbiturates and Topiramate and possibly Phenytoin.

The underlying symptoms of depression and anxiety may be exacerbated by Leviteracetam, while psychotic symptoms, although rare, have been reported with Topiramate, Leviteracetam, and Zonisamide [51].

Psychiatric Disorders in Surgery in Epilepsy

Generally, psychiatric symptoms improve with surgery in epilepsy. A history of psychiatric disorders before surgery is associated with poor postsurgical remission of epileptic seizures. After resective surgery, only patients with good or excellent seizure control had a substantial improvement over long periods of time in mood [52].

Post-surgical patients had high suicide mortality rates compared to the general population and people who continue to have seizures after surgery had a high mortality rate due to suicide, in contrast to those who were crisis-free after surgery (4-5 times) [53].

In a series of 26 patients, with Gamma Knife Radiosurgery in patients with mesial temporal lobe epilepsy (LTM), they did not show significant psychiatric changes between the preoperative period and the following 24 months [54].

Risk factors for depression after surgery in epilepsy include preoperative history of mood disorders and Lobe Temporal Mesial surgery [55,56].

Behavioral disorders can interfere with the preoperative evaluation and the patient may not be willing to provide informed consent in the research and surgery.

Stimulation of the vagus nerve showed better responses in patients with major chronic depressive disorders in the 12 months of the study [57,58].

Elger and colleagues in small studies showed that treatment with vagal stimulation improves depression in patients with epilepsy, independent of the effects of the frequency of seizures. Vagal stimulation is a useful therapy in the treatment of resistant depression.

The postoperative decline in memory depends on the volume of tissue that is removed during surgery, the functional reserve of the remaining structures, the age at the time of surgery, the gender and the previous intellectual quotient. Patients who can reduce or stop antiepileptic drugs after surgery may experience significant improvement in memory, processing speed, and language, particularly if they were taking multiple antiepileptic drugs at high doses, as is typical of refractory epilepsy [54].

Conclusions

Conclusively, it is highlighted that psychiatric comorbidity in patients suffering from epilepsy is frequent and multifactorial. It is of significant importance for the physician to be able to recognize the elements that are related to the neurobehavioral symptoms in them, in order to adopt the necessary measures to minimize their effects and improve their quality of life. In addition, it is considered that there is no border between Psychiatry and Epilepsy, since there is a common anatomical substrate and a close symptomatic relationship, which implies the need to manage these patients comprehensively. Of significant interest it is considered that the patient with epilepsy, must be managed integrally by the specialties of Neurology, Psychiatry and Psychology.

Summary

Epilepsy represents a global health problem and is considered as old as humanity itself and one of the most frequent disorders of the Central Nervous System. Patients suffering from this disease have an associated psychiatric comorbidity and, in turn, social, psychobiological and economic consequences, which is why it is necessary for health professionals to know these alterations for their comprehensive management. The objective of this article is to specify in this disease if there is a border between Psychiatry and Neurology. We realized a deep analysis of the relationship of epilepsy, with the psychiatric alterations that occur in these patients and, at the same time, with the neuroanatomical alterations. Mention is made of the most frequent psychiatric disorders that occur in patients with epilepsy, such as psychotic and affective bipolar disorders, depression, mania, suicidal behaviors, anxiety and personality disorders, hyperactivity and attention deficit, psychotropic effects of drugs antiepileptic drugs and psychiatric disorders in epilepsy surgery. At the same time, some significant aspects of depression and psychosis, which are considered necessary, are detailed. Conclusively, it is highlighted that psychiatric comorbidity in patients suffering from epilepsy is frequent and multifactorial. It is of significant importance for the physician to be able to recognize the elements that are related to the neurobehavioral symptoms in them, in order to adopt the necessary measures to minimize their effects and improve their quality of life. In addition, it is considered that there is no border between Psychiatry and Epilepsy, since there is a common anatomical substrate and a close symptomatic relationship, which implies the need to manage these patients comprehensively. Of significant interest it is considered that the patient with epilepsy must be managed integrally by the specialties of Neurology, Psychiatry and Psychology.

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