Psychiatric Comorbidities of Epilepsy: A Review
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Abstract

People with epilepsy (PWE) have an increased risk for cognitive, behavioral, and psychosocial disorders. The presence of comorbidities may directly affect quality of life of PWE. For example, there is an increased risk for suicide in PWE, compared to the general population. Association between epilepsy and mental disorders is a condition known since Antiquity, and its ranges from 20 to 50%, reaching 80% in selected populations, like individuals with temporal lobe epilepsy (TLE), and medicinally intractable patients, candidates to surgical treatment, and these indices are far superior to those found in general population (10-20%). Risk factors for the main psychiatric comorbidities in PWE (depression, anxiety and psychosis) are classified in (1) neurobiological, (2) psychosocial, and (3) pharmacological factors. There is a bidirectional relationship between epilepsy and mental disorders, namely, not only epilepsy can antedate settlement of psychiatric symptoms in a given patient, but also the diagnosis of mood and behavioral disorders may be made before a first epileptic seizure. This bidirectionality suggests that structural and functional modifications of one disease increase the risk for the development of the other. In this review, we included the most recent articles concerning the terms “mental disorders”, “epilepsy”, and “risk factors” in PubMed. Book chapters were also referred for this work. We gave preference for population-based studies, especially those with more than 100 patients studied.

Keywords: Epilepsy; Comorbidity; Mental disorders; Risk factors; Physiopathology

Introduction

Ian Curtis, the famous Joy Division band’s vocalist and song writer had a transient personality. He could show different behaviors at different times and with different people. Sometimes he was angry and spiteful, but more often was compliant and kind. He was diagnosed as epileptic when he was 23 years old. His fits varied in frequency and intensity, and anticonvulsant medication, which he took regularly, seemed to make his mood swings more radically. His frenetic style on stage simulated his own real epileptic seizures. Ian Curtis killed himself at his home in Macclesfield, England. He was 24 years old. The history of his life was recently portrayed in the movies “Control”, launched in 2007 [1].

This case exemplifies how an epileptic disorder can transform people’s lives in true tragedies, harming their quality of life, changing personality traits and eventually increasing malady and causing death. Epilepsy is quite common also in “anonymous” individuals, and comprehension of its comorbidities, especially those pertaining to the psychiatric sphere, is a basic element for its management.

Epilepsy is a frequent neurological disorder with a worldwide distribution, although most people with epilepsy (PWE) live in underdeveloped countries. The term Epilepsy comprises many conditions typified by a tendency to spontaneous recurrence of epileptic seizures. Epilepsy occurs in all ages and can be associated to several cognitive, social and psychiatric troubles [2].

Epileptic seizures are clinical expressions (symptoms) that begin abruptly and have a great variability in presentation form. A seizure can present with motor, sensorial, autonomic and/or state of consciousness changes [3]. The common physiopathological substrate for all types of epileptic seizures is disequilibrium between excitatory and inhibitory influences on unsettled neuronal pathways. In summary, there is a state of hyperexcitability supplied by predominant excitatory strengths. Epilepsies and epileptic seizures are divided in generalized (when neuronal hyperexcitability originates in both cerebral hemispheres simultaneously) and focal (localized unilateral neuronal hyperexcitability) [4,5].

The most common epileptic disorder is the Temporal Lobe Epilepsy (TLE) that affects 40% of adult PWE [6]. Temporal lobe seizures belong to three distinct types: simple partial (aura only), complex partial (most commonly absences with automatisms), and secondarily generalized. TLE is divided in mesial (onset on hippocampus and amygdala) and lateral (onset on temporal neocortex). Mesial TLE has high indices of association with psychiatric disorders, because it involves the Lymbic System, the main integrator of emotional processes [7,8]. The most common pathology causing mesial TLE is hippocampal sclerosis [3].

The epileptic seizure temporally subdivides the clinical state of the PWE into two distinct periods of time: ictal (or peri-ictal) and interictal (when there isn’t any sustained-release excessive rhythmic neuronal discharge). The essential focus of pharmacologic treatment of epilepsy is the hamper of ictal phenomenon. In general, this is achieved in about two thirds of cases [2]. Nevertheless, study of the interictal condition of PWE is also very important, and has improved the comprehension of epileptic phenomenon as a whole.

One of the most important issues not linked to the pharmacological control of seizures is the assessment of comorbidities in PWE. These patients have an increased risk for cognitive, behavioral, and psychosocial disorders. [8,9] By the way, not only a poor control of...
seizures, but also the presence of comorbidities may directly affect quality of life of PWE. There is an increased risk for suicide in PWE, compared to the general population, and this risk is even greater in patients with a history of a psychiatric disorder, especially with the association between depression and anxiety [10].

Epilepsy associated with mental disorders is a condition already known since Antiquity. Most part of stigma that follows PWE is descendent from the assignment of supernatural entities, like gods, witches, and devils, to the epileptic disorder [11].

Prevalence of the association of epilepsy and psychiatric disorders ranges from 20 to 50%, reaching 80% in selected populations like individuals with TLE, and medically intractable patients, candidates to surgical treatment. These indices are far superior to those found in general population (10-20%). Differences in methods of investigation and in populations studied are the main contributory factors for variable results. Also distinct epidemiological definitions (punctual prevalence, cumulative prevalence, lifelong prevalence), with their proper meanings, may contribute equally to variability of results [12,13].

Risk factors for the main psychiatric comorbidities in PWE (depression, anxiety and psychosis) are classified in (1) neurobiological, (2) psychosocial, and (3) pharmacological factors. Major neurobiological factors are: type, frequency, duration, age of onset, and lateralization of epileptic seizure, genetic predisposition, gender, and presence of structural lesion. Issues concerning surgical treatment of epilepsy, like lateralization, type of resection, histopathological diagnosis, and surgical prognosis have been studied also. Other factors like hippocampal volume loss, temporal and frontal lobe glucose hypometabolism, and neurotransmitter and hormonal substances changes, may also be highlighted. As psychosocial factors we could name the “learned despair”, restraints to normal daily living activities, low self-esteem, educational and Professional difficulties, stigmatization, and social rejection. Among pharmacological factors, adverse effects of central nervous system (CNS) depressor antiepileptic drugs (DAEs), withdrawal of a mood stabilizer drug, polytherapy, starting a new DAE, and dose adjusting have been cited [14,15].

There is a heterogeneous association between epilepsy subgroups and psychiatric disorders. In most patients, several chronic and acute risk factors can be identified. These factors are difficult to study retrospectively, and establishment of a cause and effect relationship may not always be possible. Literature data is highly controversial, and there is a huge difficulty to compare studies, because of the great variability in definition of essential terms like “epilepsy”, “psychiatric disorder”, and the proper explored risk factors.

It is important to highlight that there isn’t a unidirectional relationship between epilepsy and mental disorders, namely, not only the epileptic disorder can antedate settlement of psychiatric symptoms in a given patient, but also the diagnosis of mood and behavioral disorders may be made before a first epileptic seizure. This bidirectionality suggests that structural and functional modifications of one disease increase the risk for the development of the other [16].

There is increasing evidence that both in epilepsy and in mental disorders, changes in interaction between serotonergic and noradrenergic neurons with glutamatergic systems are associated to abnormal neuronal circuits and hyperexcitability. This hyperexcitability could evoke both seizure activity and emotional dysfunctions [15]. Furthermore, decrease in synaptic levels of neurotransmitters, as well as elevation in glucocorticoid levels could influence intracellular signaling pathways, like cyclic Adenosine Monophosphate (cAMP), and originating disorders of neurotrophic factors, like Brain-Derived neurotrophic Factor (BDNF) [17,18].

Therefore, the association between TLE and psychiatric disorders seems to be highly prevalent. This comorbidity affects directly clinical prognosis of the epileptic seizures, and also the quality of life of the patients with this type of epilepsy. It appears that there are common physiopathological mechanisms in both TLE and mental disorders, in general affecting neuronal circuitries of Lymbic System. Genetic disorders, like polymorphisms of receptor genes of many neurotransmitters, and also of neurotrophins, like BDNF, might be involved in this association.

In this review, we included the most recent articles concerning the terms “mental disorders”, “epilepsy”, and “risk factors” in PubMed. Book chapters were also referred for this work. We gave preference for population-based studies, especially those with more than 100 patients studied.

Concepts in Epilepsy

The term Epilepsy comprises several syndromes which the main characteristic is an enduring redisposition to recurrent non-provoked epileptic seizures [2]. Epileptic seizures are sudden and brief attacks of altered consciousness, motor, sensitive, psychic, cognitive or autonomic dysfunctions, or an inappropriate behavior, caused by excessive or synchronic abnormal neuronal activity in the brain [3].

The epilepsies and epileptic seizures are classified in focal and generalized [4,5]. Regarding focal epilepsies, the seizure clinical expression is determined by the topographical localization of the neuronal discharge, as well as its extent of spread in the brain. For the sake of conceptualization and pre-surgical neurophysiologic assessment of epilepsies, the region that yields the neuronal discharge is named Ictal Onset Zone, and the regions that generate the seizure’s clinical features are named Symptomatogenic Zones. This is an important distinction, because the region where the discharge starts is not always able to produce clinical manifestations (“silent cortex”). In this case, surgical removal of the symptomatogenic zone would not be curative, because the real source of the epileptic disorder would not be included in the removed tissue [19]. The physiopathology of generalized seizures is diverse, depending on a genetically-determined thalamocortical circuitry dysfunction [20].

Regarding etiology, epilepsies are divided in idiopathic (without structural brain lesion), symptomatic (with a structural lesion seen in neuroimaging exams) and cryptogenic (with a presumable etiology, not diagnosed at all) [5]. Estimated incidence of epilepsy in developed countries is about 50/100,000/year [21], and these numbers may double in poor countries [22]. In general, we find a bimodal distribution, with peaks of incidence in the first year of life and after 60 years of age. Prevalence of active epilepsy in most regions of the world is in turn of 5-10/1,000, although it may be even greater in some localized areas [23,24]. General prognosis for complete seizure control is good, since 70% of patients acquire remission after five years of diagnosis [25,26]. Nevertheless, both adults and children with epilepsy an increased risk for death, when compared with normal individuals [27,28].

Temporal Lobe Epilepsy

Temporal lobe epilepsy represents most patients with symptomatic or cryptogenic focal epilepsies. Types of seizures in TLE include simple
partially, complex partial and secondarily generalized seizures. Seizures most often originate in amygdalo-hippocampal region, in the medial and basal portion of temporal lobe. Hence, mesial temporal epilepsy (MTE) is the most frequent focal epilepsy [29-32].

In MTE, seizure begins in more than 90% of the cases with an unnatural rising epileptic sensation. Other autonomic, psychic (i.e.: fear) and sensitive (i.e.: olfactory sensation) symptoms could occur also. Complex partial seizures of MTE almost always implicate motor arrest or automatisms (oroalimentary or gestural), early in the course of seizure. Ictal features with lateralizingatory value include: dystonic posture of one superior limb (contralateral to the epileptic focus), early shift of the head (ipsilateral), late version of head, on transition to secondary generalization (contralateral). Intelligible vocalizations suggest onset of seizure in the non-dominant hemisphere. Most often, temporal lobe seizures last about two minutes, and are followed by a post-ictal confusional state. Post-ictal aphasia suggests seizure activity in the dominant hemisphere. MTE is the most common medically refractory focal epilepsy, and also one of the most surgically treatable [33].

Lateral (neocortical) TLE is less frequent, and generally is characterized by an auditory aura [34]. Most often, seizures yielded in the lateral portion of temporal lobe are shorter in duration. Vertiginous hallucinations were described with temporo-parietal discharges.

Most frequently structural lesions associated with TLE are: hippocampal sclerosis, benign tumors (i.e.: ganglioglioma, neuroepithelial dyssembrioplasic tumors), vascular malformations (i.e.: cavernoma), and malformations of cortical development (i.e.: focal cortical dysplasia). Hippocampal sclerosis coexisting with an extratemporal lesion is called dual pathology, a condition that carries a greater degree of difficulty for diagnosis, and worst prognosis [35].

Considering the importance of limbic circuitries for the neuropsychiatric diseases, it is not a surprise the observation that many patients with TLE present concomitant psychiatric disorders, like depression and anxiety [36].

Comorbidities in Epilepsy

The term comorbidity refers to a more than occasional concomitant presence of two medical conditions in the same individual [37]. Comorbidity does not implies directionality or a cause-and-effect relationship, and diseases may coexist randomly, or also share common genetic and/or environmental mechanisms [9]. Epilepsy is frequently associated to cognitive, psychiatric or social troubles [38].

Psychiatric Comorbidities in Epilepsy

Historical

Association between epilepsy and psychiatric disorders has been described since the beginnings of Neurology and Psychiatry practices, and there are many examples found in literature. Hippocrates, about 400 b.c., observed a dichotomy between epilepsy and melancholia, and purposed that these two entities could be linked by a probable common physiopathological mechanism [11].

The history of the epilepsy-psychiatry interface had its beginning imprinted by the empirical association of these conditions with gods, witches, devils, and supernatural phenomena. The Greeks referred to epilepsy as the “sacred disease”. In those years, Hippocrates that rush of fury that led Hercules to kill his children had an epileptic nature. The Romans referred to epilepsy as “morbidus lunaticus”, related to the different phases of the moon. In the Arabic world, the epilepsy-mental disorders-devils association persisted, and prophets, like Mohammed and Saint Paul, that periodically heard voices and fell on the floor, supposedly had epilepsy [39].

In the XIXth century and in the beginning of the XXth century, epilepsy was a common diagnosis in asylums housing patients with mental disorders. The most sicker individuals were treated by psychiatrists, whereas those with less severe pictures stayed in the community, where they were treated by general physicians or neurologists [40].

In the 1920’s decade, Emil Kraepelin made observations that are considered the basis for the modern psychiatric diagnostic classification. Kraepelin described precisely the affective changes of PWE, years before the age of electroconvulsive therapy. Dysphoric events, characterized by irritability, with or without bursts of fury, were considered by him the most frequent psychiatric disorder in PWE. Depression, anxiety, headache, and insomnia were very frequent complementary symptoms, although euphoric mood was less common [41].

Heinrich Landolt identified different types of psychotic episodes and their correlations with epileptic seizures and the electroencephalogram (EEG), introducing the concept of “Alternant Psychosis or Forced Normalization” [42]. His work was later complemented by Slater and Beard, with the article “Schizophrenia-Like Psychosis of Epilepsy”, where it was purposed an agonic relation between epileptic seizures and psychotic states [43].

More recently, the introduction of advanced techniques of neuroimaging, like Positron Emission Tomography (PET), Magnetic Resonance Imaging (MRI), and the spectroscopy, combined with animal models and refined behavioral tests, made it possible the identification of common physiopathological mechanisms to both the epilepsies (especially TLE) and psychiatric disorders (especially major depression).

Epidemiology

There are few community-based studies on prevalence of psychiatric conditions in PWE. Most of these studies involve specific epileptic populations, in tertiary centers for attention to PWE. Community-based epidemiologic studies suggest a lifelong prevalence of psychiatric disorders in PWE, both adults and children, between 20 and 50% [13,44-52]. Recently, Tellez-Zenteno et al. [9] using data from the Canadian Community Health Survey, with administration of the World Mental Health Composite International Diagnostic Interview (CIDI), found a lifelong psychiatric disorder diagnosis in 35% of PWE, compared with 20% of non-epileptic individuals.

The great variability of results obtained has been ascribed to differences in the methodology applied and in populations studied. It is well known that psychiatric pathologies could be overrated in selected populations, like TLE or refractory patients [53], in whose prevalence of mental disorders may reach 80% [54].

Methods of psychiatric assessment

Psychiatric assessment can be made basically by two types of interviews: structured interviews and self-applicable questionnaires (non-structured) [12]. Non-structured interviews have been progressively replaced by structured interviews in the last years, to obtain a greater diagnostic accuracy. Structured interviews are composed by a
set of key questions intending the fulfillment of well-defined diagnostic criteria included in the Diagnostic and Statistical Manual, Fourth Edition (DSM-IV). Main representatives are the Structured Clinical Interview for DSM Disorders (SCID) [55] and the Mini-International euro psychiatric Interview (MINI) [56]. Self-applicable questionnaires, like the Beck Depression Inventory (BDI) [57], and the Center for Epidemiologic Studies Depression Scale (CES-D) [58], in general are less extensive and are based upon subjective criteria. Results obtained by self-applicable tests tend to be overrated regarding prevalence of psychiatric disorders.

Nevertheless, studies of lifelong prevalence of psychiatric disorders in PWE point to upper indices, compared to those found in general population [59]. For a comparison between several studies, see Tables 1 and 2. In community-based studies (Table 1), prevalences varied between 5.9% e 54.5%. Only one study (Davies et al.) used structured interview for psychiatric diagnosis. This study found a superior number (37%), compared with other older population-based studies that used unstructured interviews. Regarding studies of selected populations (performed in tertiary centers, in general as part of a pre-surgical evaluation), prevalence varied between 6.7% and 80%. Clearly, patients with difficult-to-control seizures, and especially those studied in presurgical evaluation (clinical interview for psychiatric diagnosis), prevalence varied between 6.7% and 80%. Clearly, patients with difficult-to-control seizures, and especially those studied in presurgical evaluations, showed increased frequencies of psychiatric comorbidities.

### Risk factors

Many papers have been demonstrated that patients with TLE have an increased risk for psychiatric disorders, when compared to patients with other non-neurological chronic diseases [7,38,54,60]. Notwithstanding, it is still controversial if patients with TLE have increased risk for development of a mental disorder when compared with patients with other types of epilepsy. Two important studies didn’t find any differences in the risk of patients with TLE, focal extratemporal, and idiopathic generalized epilepsies [61,62]. It is possible that greater prevalence of psychiatric disorders in patients with TLE could depict just the dominant prevalence of TLE related to other epilepsies [63].

Despite this conjecture, it is plausible to believe that the same neuronal circuitry involved in the physiopathogenic mechanisms of TLE are also responsible for the production of psychiatric symptoms [15]. Purposed mechanisms for this frequent association could be arbitrarily divided in clinical, biological and environmental causes. Regarding clinical factors, it has been enrolled: number of epileptic seizures since onset of disease, effects of antiepileptic drugs, social stigma, financial and legal restraints (i.e.: driving license) [64]. In a prospective study achieved in the New York University, Devinsky et al. assessed the impact of several clinical variables on the quality of life of patients with intractable epilepsy, in pre-surgical evaluation. Presence of depression, assessed by the BDI, was the only predictive factor for

<table>
<thead>
<tr>
<th>AUTHORS</th>
<th>N</th>
<th>INSTRUMENT</th>
<th>POPULATION</th>
<th>PSYCHIATRIC DISORDERS</th>
<th>MOOD DISORDERS</th>
<th>ANXIETY DISORDERS</th>
<th>PSYCHOSIS</th>
<th>SUBSTANCE ABUSE</th>
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<tr>
<td>Pond and Bidwell, 1960 UK</td>
<td>245</td>
<td>Unstructured psychiatric interview</td>
<td>Children with epilepsy – community-based</td>
<td>29%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Gudmundsson, 1966 Iceland</td>
<td>654</td>
<td>Clinical interview (unstructured)</td>
<td>Epilepsy (community-based)</td>
<td>54.5%</td>
<td>-</td>
<td>-</td>
<td>9%</td>
<td>-</td>
</tr>
<tr>
<td>Graham and Rutter, 1970 UK</td>
<td>63</td>
<td>Unstructured psychiatric interview</td>
<td>Children with epilepsy – community-based</td>
<td>28.6%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Forsgren, 1992 Sweden</td>
<td>713</td>
<td>Chart review (unstructured)</td>
<td>Epilepsy – community-based</td>
<td>5.9%</td>
<td>-</td>
<td>-</td>
<td>0.7%</td>
<td>-</td>
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<td>Bredtjær et al., 1998 Denmark</td>
<td>67</td>
<td>ICD-8</td>
<td>Epilepsy – community-based</td>
<td>16.8%</td>
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<td>Hackett et al., 1998 India</td>
<td>26</td>
<td>ICD-10</td>
<td>Epilepsy – community-based</td>
<td>23.1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Davies et al., 2003 UK</td>
<td>67</td>
<td>SCID</td>
<td>Epilepsy – community-based</td>
<td>37%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Ettinger et al., 2004 USA</td>
<td>775</td>
<td>CES-D</td>
<td>Epilepsy – community-based</td>
<td>-</td>
<td>36.5%</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Strine et al., 2005 USA</td>
<td>427</td>
<td>Kessler 6 scale</td>
<td>Epilepsy – community-based</td>
<td>-</td>
<td>32.6%</td>
<td>14.4%</td>
<td>-</td>
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<tr>
<td>Kobau et al., 2006 USA</td>
<td>131</td>
<td>Health Style Survey (self-reported depression and anxiety)</td>
<td>Epilepsy – community-based</td>
<td>-</td>
<td>39%</td>
<td>39%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Tellez-Zenteno et al., 2007 Canada</td>
<td>253</td>
<td>CIDI</td>
<td>Epilepsy – community-based</td>
<td>23.5%</td>
<td>17.4%</td>
<td>12.8%</td>
<td>-</td>
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</table>

Table 1: Prevalence of psychiatric comorbidities in PWE. Population-based studies.
achievement of low indices of quality of life, assessed by the Quality of Life in Epilepsy (QOLIE-31) survey. Neither other factor (frequency of seizures, localization, age, gender, marital status, duration and type of seizure, or number of DAE) was predictor for quality of life [65].

PWE have a significantly increased risk for suicide related to general population. Two big studies, made in Canada [9] and Denmark [10], showed that PWE has 2 to 3 times more risk of suicide than control individuals. Danish study found a risk of suicide even greater between epileptic patients with a specific comorbidity: mood disorder plus anxiety.

**Specific Psychiatric Disorders**

**Mood disorders**

Main neurobiological risk factors for depression in PWE that has been studied are: lateralization of epileptic focus, frontal lobe hypometabolism, and hippocampal volume.

Regarding lateralization, Hurwitz et al. [66] found association between left-sided epileptic focus and depressive mood. In this study, seizures yielded by the right hemisphere were followed by laughter and seductive behavior. As a seizure activity localized in one hemisphere probably “releases” the opposite hemisphere, the authors postulated that the dominant hemisphere could be responsible for negative emotional states, and the non-dominant hemisphere could yield the opposite effect. Other theory hypothesizes that a seizure activity in the non-dominant hemisphere could result in neglect of negative emotions [63]. Many controlled studies comparing seizure focus with degrees of depression found increased frequencies of depression with a focus in the left hemisphere, independent of seizure type [67-70], although other studies didn’t ratify this correlation [71]. A complex interaction between several factors would be employed in this association.

Recent works using PET and SPECT have shown an association between epilepsy and frontal lobe dysfunction with hypo metabolism. Bromfield et al. [72] studied 23 patients with complex partial seizures, candidates for surgery, regarding depressive features (BDI > 11), compared to normal controls. Patients with a left-sided temporal focus presented more depressive symptoms as well as a bilateral inferior frontal lobe hypo metabolism. Victor off et al. [70] studying 53 epileptic patients candidates for surgical treatment, observed that an ictal onset on the left was associated to an increased frequency of depression (79% x 50%, non-significant). It has not been found any correlation between current affective state and metabolism in the frontal lobes, but it was interesting to observe that a history of depressive episodes (identified by SCID) significantly correlated with a left frontal lobe hypo metabolism. Hermann et al. [73] didn’t find any correlation between humor and laterality, but a left-sided focus was significantly associated to the severity of frontal dysfunction (measured by Wisconsin Card Sort Test) and dysphoria. Contrarily, a right-sided focus was inversely associated to frontal dysfunction and dysphoria (non-significant results).

Our group studied 97 patients with TLE regarding risk factors for affective disorders [74]. A positive family history of psychiatric disorders (O.R. = 3.8; p = 0.003) and interictal EEG epileptiform discharges involving the left temporal lobe (O.R. = 2.9; p = 0.041) were significantly associated with an increased risk for an affective disorder in population studied. This article reinforced the importance

<table>
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<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Sample Size</th>
<th>Sample Description</th>
<th>Cases</th>
<th>Controls</th>
<th>Note</th>
<th>Risk Factor</th>
<th>Reference</th>
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<td>Edel and Toone, 1987 UK</td>
<td>88</td>
<td>CIS</td>
<td>5834</td>
<td>Epilepsy – selected from a database generated by GP</td>
<td>41%</td>
<td>18.2%</td>
<td>11.1%</td>
<td>9%</td>
<td>[74]</td>
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<td>Mensah et al., 2006 UK</td>
<td>499</td>
<td>HADS</td>
<td>38</td>
<td>JME and TLE (selected) patients</td>
<td>80%</td>
<td>55%</td>
<td>15%</td>
<td>-</td>
<td>[75]</td>
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<td>Swinkels et al., 2001 Netherlands</td>
<td>209</td>
<td>EDI</td>
<td>225</td>
<td>Epilepsy – tertiary epilepsy center</td>
<td>-</td>
<td>24.9%</td>
<td>29.7%</td>
<td>0.5%</td>
<td>[76]</td>
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<td>Havlová, 1990 Czech Republic</td>
<td>241</td>
<td>ICD-9</td>
<td>94</td>
<td>Cohort of epileptic children</td>
<td>6.7%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[77]</td>
</tr>
<tr>
<td>Stefansson et al., 1998-99 Iceland</td>
<td></td>
<td>ICD-9</td>
<td>204</td>
<td>Epilepsy – tertiary epilepsy center</td>
<td>37%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>[78]</td>
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<tr>
<td>Jalava and Sellanpaa, 1999 Finland</td>
<td></td>
<td>ICD-9</td>
<td>270</td>
<td>Refractory TLE and JME (selected)</td>
<td>50%</td>
<td>55%</td>
<td>15%</td>
<td>-</td>
<td>[79]</td>
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<td>Araújo Filho et al., 2006 Brazil</td>
<td></td>
<td>SCID</td>
<td>98</td>
<td>TLE – selected from a tertiary epilepsy center</td>
<td>54.1%</td>
<td>42.9%</td>
<td>18.4%</td>
<td>6.1%</td>
<td>[80]</td>
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Table 2: Prevalence psychiatric comorbidities in PWE. Studies in selected populations.
of biological factors, specifically genetic and anatomical substrates, for the development of humor disorders in PWE.

Few studies evaluated the association between hippocampal volume loss, depression and epilepsy. Quiske et al. [75] found higher BDI scores in patients with TLE and hippocampal sclerosis, when compared to patients with normal MRI. Another study also identified an association between higher scores for depression and increased volume of left hippocampus, in patients with right hippocampal sclerosis [76]. Also studies with PET showed an association between higher scores for depression in PWE with metabolic alterations in temporal lobes, compared to PWE with normal PET [77].

**Anxiety disorders**

The main types of anxiety disorders described in DSM-IV are: generalized anxiety disorder, panic disorder, phobia, and obsessive-compulsive disorder. The risk factors pointed for the association between epilepsy and anxiety are: frequency of seizures, surgical treatment for epilepsy, age, type of seizure, and perception of stigma [78,79].

Frequency of seizures was associated to anxiety in some works [80,81], but this is not an unanimity [82]. Studies combining PET with electrophysiological data indicate the right temporal lobe as the main structure responsible for pathogenesis of anxiety in epilepsy [83]. Probably, more than the frequency of seizures, fear of falling down or to die is the real critical factor for the development of anxiety in PWE. Surgical treatment for epilepsy may increase the frequency of anxiety disorders in these patients, especially those that experience a greater than 75% reduction in their seizures after surgery [84].

Regarding age, minimal effects were observed, although a late onset of epilepsy could be associated with higher degrees of anxiety [85]. Risk for anxiety seems to be greater in focal epilepsies (especially TLE) than in generalized epilepsies [86]. Higher indices of anxiety were found in patients with poor pharmacological control of their seizures [87,88]. An important factor linked to anxiety in PWE is the stigma perception [89,90], and this factor is heavier in young patients [83,91].

**Psychotic disorders**

Literature regarding risk factors for psychotic disorders in epilepsy is highly controversial, and most studies are restricted to interictal psychosis [92].

Regarding duration of epilepsy, in most series, time for the first psychotic manifestation from the onset of epilepsy is about 11 to 15 years, raising an etiological meaning to the epileptic disorder, through a mechanism “kindling-like” [40]. TLE is the epilepsy most associated with psychosis in almost all case series. In a non-systematic revision of 10 studies, 76% patients suffering from psychosis had TLE [40]. Major criticism to these studies is that their results may reflect just the higher prevalence of TLE in the community. Severity of epilepsy is one of the most important risk factors for psychosis, and it could be measured by duration and multiplicity of seizures, history of status epilepticus, and poor clinical response to treatment [40]. Flor-Henry [93] originally suggested that left temporal lobe dysfunction was a risk factor for schizophrenia-type psychosis. Trimbble’s analysis of 14 studies with 341 patients with TLE found that 43% had a left-sided epileptic focus, 23% on the right, and 34% had bilateral changes [40]. This data regarding laterality were supported by neuroimaging studies, especially SPECT and MRI. Mellers et al. [94], using a verbal fluency activation paradigm and SPECT, compared patients with schizophrenia-like psychosis (n = 12), schizophrenia (n = 11), and non-psychotic epileptic patients (n = 16). Psychotic epileptic patients showed and increased blood flow in the superior temporal gyrus, during activation, related to the other groups. Maier et al. [95] compared the amygdalo-hippocampal volumes and hippocampal N-Acetyl Aspartate (NAA) (by spectroscopy) of patients with TLE, with (n = 12) and without schizophreniform psychosis (n = 12), non-epileptic schizophrenics (n = 26), and normal individuals (n = 38). Psychotic patients showed significant reduction of NAA in the left temporal lobe, with a more accentuated phenomenon observed in epileptic patients. PWE showed bilateral volume reduction, whereas psychotic patients had a more prominent atrophy of the left amygdalo-hippocampal complex.

Interictal psychosis seems to be different from schizophrenia, especially because interictal psychosis courses with more affective symptoms and has a better prognosis. Although hippocampal alterations could be related to both disorders, bilateral increase of amygdalae (with less volumetric changes in hippocampi) is typical of interictal psychosis, suggesting a great difference between both conditions. This hypothesis was supported by a recent study, with 26 patients with epileptic psychosis, 24 non-psychotic patients with TLE, and 20 normal controls. Psychotic patients had significant bilateral increases of amygdalae, in comparison with the other groups. These findings were not correlated with lateralization of the focus, and neither with the duration of epilepsy [96].

**Phsyiopathology**

**Bidirectional relation**

It is demonstrated that some specific humor and behavioral disorders may show a bidirectional relation with the onset of epileptic seizures, namely, a psychiatric diagnosis may precede onset of seizures, especially in three situations: major depression, suicidal ideation, and Attention Deficit Disorder with Hyperactivity (ADDH).

Case-control studies [97,98] as well as longitudinal studies [99], in children, showed an increased risk of 2.5 fold for patients with a diagnosis of ADDH suffer a first epileptic seizure.

Three controlled studies assessed the temporal relation between depression and epilepsy. One population-based case-control study found a 7-fold increased risk for and adult with depression to develop epileptic seizures, compared to normal individuals. The risk increased to 17-fold with focal epilepsies [49]. Hesdorffer et al. [100] observed the same temporal relation between depression and a first seizure, with a 6-fold increased risk. Data from these two studies were confirmed in a population-based controlled study, proceeded in Island, with 324 patients above 10 years of age, with a first non-provoked seizure or newly diagnosed epilepsy, and 647 controls: major depression, diagnosed after DSM-IV criteria, increased the risk for epilepsy in 1.7-fold. This same study showed that a suicide temptation is associated with a 3.5-fold increased risk for epilepsy [16].

**Common physiopathologic mechanisms**

This bidirectionality suggests a common underlying susceptibility to epilepsy and humor disorders. Literature is plentiful of studies on molecular and cellular biology and anatomy of the brain in both diseases [101]. Those mechanisms are strongly interconnected, and functional and structural alterations in one disease may give rise to the other.

**Animal models**: One of the best studied models in TLE uses...
Moreover, studies with PET suggest a glucose hypometabolism in binding, involving non-lymbic areas, distant from the epileptic focus. Patients with major depression exhibited a more extensive reduction in beyond a decreased binding to 5-HT1A receptors in the epileptic focus, receptor binding to a specific antagonist, in 37 patients with TLE, feature found in studies with PET, in patients with TLE [109,110]. In serotonin reuptake inhibitor, provoked a dose-dependent reduction in [105]. One classic study showed that fluoxetine, a selector synaptic prevent seizures, whereas diminished levels have the opposite effect of noradrenergic and serotonergic circuitries were observed in those patients: increased corticosteroid plasmatic levels, decreased secretion of growth hormone, and hypothyroidism [105]. Defective arborizations of sweet taste, compared to controls. The authors concluded that the alterations in neuronal plasticity caused by kindling would be followed by a depressive behavior. The role of neurotransmitters in the physiopathologic mechanisms of humor disorders is recognized since some decades ago [104].

The roles of gama-aminobutyric acid (GABA) and glutamate in epileptogenesis were already demonstrated in several studies in animals and humans. The Genetically Epilepsy-Prone Rat (GEPR) provides an experimental model for both epilepsy and depression. In this model, mutated animals are highly sensible to auditory stimuli, to which they answer with generalized tonic-clonic seizures. Moreover, GEPRs show endocrinologic changes similar to those identified in depressive patients: increased corticosteroid plasmatic levels, decreased secretion of growth hormone, and hypothyroidism [105]. Defective arborizations of noradrenergic and serotonergic circuitries were observed in those animals. An increase in the levels of these neurotransmitters could prevent seizures, whereas diminished levels have the opposite effect [105]. One classic study showed that fluoxetine, a selector synaptic serotonin reuptake inhibitor, provoked a dose-dependent reduction in the frequency of seizures in GEPRs, which correlated with extracellular thalamic serotonin concentrations [106].

Studies in humans: Animal serotonergic transmission was demonstrated in the brain of depressed patients [107,108], the same feature found in studies with PET, in patients with TLE [109,110]. In a more recent study, Hasler et al. [111] compared the level of 5-HT1A receptor binding to a specific antagonist, in 37 patients with TLE, with and without major depression (diagnosis by SCID), using PET. Beyond a decreased binding to 5-HT1A receptors in the epileptic focus, patients with major depression exhibited a more extensive reduction in binding, involving non-lymbic areas, distant from the epileptic focus.

One of the most important proteins involved in the functioning of Lymbic System is the BDNF. This element may influence both neuronal electrical activity and memory and behavior functions, which are directly related to hippocampus in its connections. Changes in BDNF are associated to hippocampus atrophy, alterations in memory, and temporary amygdalar hypertrophy, with alteration in fear process. Moreover, studies with PET suggest a glucose hypometabolism in temporal and frontal lobes in the TLE-depression association [112].

A functional polymorphism of BDNF gene, the Val66Met, has been studied as a predisposition factor for many neurological and psychiatric disorders, with variable results. Regarding epilepsy, it seems that there isn’t any direct relation with the polymorphism [113]. Notwithstanding, depression, anxiety, psychosis and eating disorders have been often associated to the presence of Val66Met polymorphism in the BDNF gene [112]. A recent meta-analysis affirmed the association of Val66Met to substance-related disorders, eating disorders, and schizophrenia [114].

Our group also studied the association between 5HTTLPR and 5HTTVNTR allele variants in serotonin transporter gene and epileptogenesis in TLE. We compared 175 patients with TLE and 155 healthy control individuals, and observed an association between the presence of 5HTTLPR and 5-HTTVNTR less transcriptional efficient combined genotypes and TLE. Our results agreed with several other studies showing that low transcriptional activity 5-HTT genotypes are associated with neuropsychiatric disorders, such as depression, suicidal behavior, attention deficit hyperactivity disorder, and personality disorder [115].

Discussion

There is a growing evidence for psychiatric comorbidities in epilepsy. Studies on prevalence have demonstrated advances in methodological issues, improving reliability of results. Future research need to focus on physiopathologic mechanisms, especially regarding functional and structural alterations involving human neuronal circuitries in the Lymbic System. Although many studies on a possible association between epilepsy and the polymorphism of the BDNF gene, Val66Met, did not find any positive result, strong evidence exists linking this polymorphism to psychiatric disorders. Likely, serotonin allelic variants may also influence the modulation of serotoninergic system, and eventually epileptogenesis in TLE. For those reasons, it remains plausible to continue researching genetic variants in this field.

References

1. http://www.joydiv.org/lancurtis.html#blog


the genetically epilepsy prone-rat (GEPR). Depression and Brain Dysfunction. London, Taylor & Francis, UK.


