Depression and epilepsy

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Abstract

Depression is the most common psychiatric comorbidity in epilepsy with a lifetime prevalence of between 30 - 35%. Depression has a greater negative impact on quality of life (QOL) in people with epilepsy (PWE) than seizure frequency, but remains under-recognized and under-treated. A lifetime history of depression has a negative influence both on response to antiseizure medication and response to resective surgery. Depression may also be associated with decreased adherence to antiseizure medication. Comorbid depression increases the risk of suicidal ideation and behaviour; it is associated with premature mortality, including death from suicide. There is a bidirectional relationship between epilepsy and depression, suggesting that there might be underlying mechanisms predisposing to both conditions. This implies that having epilepsy increases the risk of developing depression and having depression increases the risk of developing epilepsy.

1. Introduction

Depression is said to be the most prevalent DSM (Diagnostic and Statistical Manual of Mental Disorders) disorder in people with epilepsy (PWE). The causes of depression in PWE can be the same as those in people without epilepsy but there are additional factors that may cause depression in PWE. Furthermore, in more than 50% of PWE depressive disorders may present with atypical clinical features which do not meet the DSM-IV criteria for depression. Kanner et al. (1) found that symptoms in 69% of 100 consecutive patients with epilepsy referred for psychiatric treatment failed to meet any DSM-IV classification. There is substantial evidence that the relationship between depression and epilepsy is bidirectional, suggesting a common underlying mechanism that may precipitate both conditions, or that having either condition predisposes to the development of the other (2-5). Features of depression often precede the onset of seizures, and patients with primary depressive disorders are more likely to develop epilepsy than non-depressed individuals. Depression cannot only be attributed to the secondary effects of seizures, nor can it be solely as a consequence of the psychosocial limitations resulting from the epilepsy. PWE with an existing psychiatric disorder at time of initial diagnosis have a decreased chance of achieving seizure control with antiseizure drugs (ASDs) (6, 7) or with resective surgery (8, 9). Mood disorders in patients with intellectual disabilities are often atypical, rapidly-cycling and chronic, and present additional challenges to diagnosis and treatment. Depression in these patients may often take the form of somatisation (fatigue or regression), dysphoria or sudden sadness (10).

2. Prevalence

2.1 How frequent is depression in epilepsy?

Major depression is consistently reported as being the most common comorbid DSM-IV disorder in PWE (11). The quoted prevalence of depression in PWE ranges between 20% and 55% in refractory epilepsy and between 3% and 9% in well-controlled epilepsy (12). However, several studies have illustrated that the majority of cases in PWE go unrecognised (13-15). A review of the literature between 1806 and 2012 by Fiest et al. (16) found a mean prevalence of active (current or past year) depression in PWE of 23.1% (95% CI 20.6%-28.31%) in 9 studies. Five studies showed an overall odds ratio (OR) of active depression of 2.77 (95% CI 2.09-3.67). The mean prevalence of lifetime depression reported in four studies was 13.0% (95% CI 5.1-33.1) and an overall OR of 2.20 (95% CI 1.07-4.51) was reported in 3 studies. In children

with epilepsy, depression has been reported in 8 - 35% of cases (17). Gaus et al. (18) found a significant (p=0.009) gender disparity in rates of depression between male and female patients, with female patients being more affected. A 2007 Canadian cross-sectional study by Tellez-Zenteno et al. (19) found a lifetime prevalence of psychiatric disorder in PWE of between 30% and 35%. Major depressive disorders were found in 17.4% of patients (95% CI 10.0 - 24.9) and 10.7% of controls (95% CI 10.2 - 11.2). Lifetime prevalence of any mood disorder, including major depressive disorder (MDD), bipolar disorder, dysthymia and cyclothymia was 34.2% (95% CI 25.0 - 43.3) in PWE and 19.6% (95% CI 19.0 - 20.2) in controls (20).

2.2 How frequent is epilepsy in depression?

There is evidence that mood disorders, including depression, may in some cases predate the onset of epilepsy. Studies have demonstrated an increased risk for the later development of epilepsy in children and adults with past or pre-existing major depression, bipolar disorder and attempted suicide (2-5). Similarly, data from epidemiological studies show a higher prevalence of primary psychiatric disorders in PWE preceding the onset of the seizure disorder than in the general population, and a greater risk of comorbid psychiatric disorders in PWE than neurologically normal controls (21). A Swedish study by Forsgren and Nystrom (22) found a 7-fold increased risk of pre-existing depressive symptoms in patients with new-onset epilepsy than in age and gender matched controls. In a study in the US by Hesdorffer et al. (3) in patients > 55 years old at the time of epilepsy onset, a pre-existing diagnosis of depression was 3.7 times more likely than among controls. A study in Iceland found a 1.7 times greater risk of epilepsy in patients with an existing diagnosis of a major depressive episode and a 5.5 times greater risk of epilepsy in individuals with a history of attempted suicide (5). Similar findings were reported in further studies in the UK (23) and Sweden (24). In the latter study, the odds ratio for idiopathic or cryptogenic seizure disorders among depressed patients was greater (3.9; 95% CI 2.4 - 6.1) than for symptomatic seizures (1.5; 95% CI 0.8 - 2.6) (21).

2.3 Screening

Gilliam et al. (25) recognised that, although depression is very common in people with epilepsy, most individuals will be seen in a busy neurology clinic, where there will seldom be time to screen for depression unless this can be achieved quickly and reliably. They created a rapid, accurate screening instrument for this purpose. Starting with a set of 46 symptoms of depression that did not overlap with common comorbid cognitive deficits or adverse effects of antiseizure drugs, they used discriminant function analysis to identify six items that fulfilled the requirements of such a screening instrument, the neurological disorders depression inventory for epilepsy (NDDI-E). Each item is scored on a LIkert-like scale, from 4 (statement applies always or often) to 1 (statement applies never). In the original validation study, a cut-off score of 15 had a specificity of 90%, sensitivity of 81%, and positive predictive value of 0.62 for the diagnosis of major depression. It is recommended that this rapid and brief screening instrument should be used in epilepsy clinics to allow the identification and subsequent proper management of those with major depression. The six items of the NDDI-E appear below.

Table 1: the six-item NDDI-E

	Always or often	Sometimes	Rarely	Never
Everything is a struggle	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
I'd be better off dead	4	3	2	1
Frustrated	4	3	2	1
Difficulty in finding pleasure	4	3	2	1
For the statements in the table, patients are asked to circle the number that best describes them over the past 2 weeks, including the day of the assessment				

3. Treatment

The complex relationship between epilepsy and depression has implications for treatment. The interactions between antidepressant medication and ASDs need to be taken into account. Some ASDs are associated with an increased risk of depression. These ASDs should be avoided in PWE that have a current or past history of depression. Extensive data on the treatment of psychiatric comorbidities in PWE, based on sound methodological research, is not available. However, failure to treat depressive disorders has serious implications for the QOL of affected individuals (26).

3.1 How should depression be treated in people with epilepsy?

Several studies have found that people with epilepsy with co-occurring depressive symptoms were frequently not receiving treatment for depression at the time of evaluation (27). This may have been due to a number of factors, including lack of recognition by neurologists of depressive symptoms as a separate and treatable comorbidity of the epileptic disorder. Insufficient clinical resources, lack of appropriate referrals for assessment, the reliability of screening instruments, disagreement on optimal treatment, the unknown effectiveness of antidepressant drug treatment in epilepsy (28), patient-experienced stigma, and geographical distance may also, in some cases, contribute to this deficit (29). Treatment choices should be made with an understanding of the relationship between emergent psychiatric symptoms and the epilepsy itself as this may have implications for the appropriate clinical approach and for treatment efficacy. Psychiatric symptoms may be temporally related to seizures; depression may be pre-ictal, post-ictal, interictal or a para-ictal phenomenon (forced normalisation). Depression can also be the result of pharmacological or surgical treatment.

There is a lack of evidence for response of post-ictal depression to antidepressant medication (30). In the circumstances, the focus in treating post-ictal depressive symptoms should be on achieving good seizure control which removes the context for the mood disorder.

Forced normalisation implies that when the seizure control improves the psychiatric symptoms are worse and when the seizure control is worse, the psychiatric symptoms are better (31). In strict terms, forced normalisation refers to the situation of 'EEG better, psychiatric symptoms worse and EEG worse, psychiatric symptoms better'; in practice, however, the term is often used to imply 'seizures better, psychiatric symptoms worse and seizures worse, psychiatric symptoms better'. "Forced normalisation" appears particularly to be associated with certain ASDs, including vigabatrin, clobazam and ethosuximide (31).

In general, the guidelines for treatment of comorbid depression in people with epilepsy are the same as those recommended for depression in otherwise neurologically normal patients. Cognitive behavioural therapy (CBT) and selective serotonin reuptake inhibitors (SSRIs) have both achieved a degree of clinical success in treating comorbid depressive symptoms (see below). The effectiveness of antidepressants in PWE is poorly established in randomised-controlled trials. However, there is only limited research in this area. A small number of open trials have suggested that SSRIs (sertraline and citalopram) are effective in PWE (1, 32). Generally, depression in epilepsy is thought to be mild to moderate in severity and anecdotal evidence suggests a positive response to treatment (10).

A perceived proconvulsant effect of some psychotropic drugs has resulted in reluctance by some clinicians to prescribe antidepressant medication. However, the evidence for an increased risk of seizures with antidepressant medication is confined to relatively few drugs. Higher doses of maprotiline have reportedly resulted in increased seizure risk in patients with no history of epilepsy, with an incidence rate of 15.6% (26). There is similar evidence from older studies that imipramine, particularly at higher doses, precipitates seizures (33). The belief that this might apply to other tricyclic antidepressants may have led to the misconception that antidepressant medication necessarily increases seizure risk. Newer psychotropic drugs are generally better tolerated, with fewer adverse effects and a lower risk of interaction with ASDs. The evidence relating to SSRIs suggests they tend to decrease rather than increase the likelihood of seizures; a study by Alper et al. (34) found no evidence for proconvulsant effects in an analysis of research reporting on the incidence of seizures in patients participating in randomised-controlled drug trials. The incidence of seizures in patients receiving SSRIs was significantly lower than in controls (standardised incidence ratio = 0.48; 95% CI = 0.36 - 0.61) while a 19-fold higher incidence of seizures was recorded in patients in placebo groups compared with the general population. The authors also noted that the base-

line incidence of seizures was greater in patients assigned to either antidepressants or placebo than in the general population, supporting the view that depression may predispose affected individuals to the development of epilepsy. Gilliam et al. (12) reviewed the literature on the possible exacerbation of seizures with tricyclic and SSRI antidepressants. They noted numerous reported cases of isolated seizures following initiation of antidepressant treatment but found only one prospective randomised controlled trial measuring the adverse effect on seizure frequency of tricyclic agents (35). This study found no difference in seizure rates compared with placebo, although the small number of patients implied that only larger effects might have been detected. A retrospective study of the effects of doxepin by Ojemann et al. (36) found only 2 cases of increased seizure frequency following introduction of treatment in 19 patients with epilepsy. Fifteen patients had a reduction in seizure rate after doxepin was commenced.

The possibility of bipolar disorder must be excluded when starting patients on antidepressants to avoid the risk of manic or hypomanic episodes or the development of rapid-cycling (37). Bipolar disorder may initially manifest as a depressive episode, with a period of up to several years before the first manic or hypomanic episode. A family history of manic or hypomanic episodes is a strong predictor of bipolar disorder and should always be the subject of inquiry by clinicians (38).

CBT may be preferred as first-line treatment, particularly in children. CBT may either be used on its own or with adjunctive antidepressant medication. CBT has demonstrated a similar degree of effectiveness to antidepressants in PWE. A double-blind study by Gilliam et al. (39) compared the relative efficacy in PWE of SSRIs (sertraline) and CBT over a 16-week trial. 60% of patients in each treatment arm achieved full remission with no recurrences within 52 weeks. There is additional evidence that a combination of CBT and antidepressants is more effective than medication alone (40). Where in-person clinical care provision is unavailable or inadequate, alternative or supplementary home-based behavioural therapies have been successfully trialled. An evaluation of the long-term effectiveness of the PEARLS program, a home-based, collaborative care intervention, in people with epilepsy and depression resulted in lower depression severity, lower suicidal ideation and better emotional wellbeing over 18 months compared with controls (41). Dworetzky et al. (29) examined the feasibility of an internet-delivered cognitive-behavioural therapy (CBT) program, the Chronic Conditions Course, with the aim of treating symptoms of anxiety, depression and disability, in 27 adults with epilepsy. Significant patient-assessed improvements were reported in depression (within-group Cohen's $d \geq 1.24$; avg. reduction $\geq 54\%$) and epilepsy-specific depression ($d \geq 0.95$; avg. reduction $\geq 35\%$). Similar studies, for example project UPLIFT, have demonstrated the feasibility and, in some cases, a similar degree of benefit of this approach (42, 43).

If antidepressant medication is prescribed it is important to take account of potential interactions with ASDs. Fluoxetine and fluvoxamine are powerful enzyme inhibitors and increase the blood levels of some ASDs. Enzyme-inducing ASDs, including carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine and topiramate, can decrease the blood levels of psychotropic medication.

In summary, both CBT and antidepressant therapy have demonstrated effectiveness in treating depression in PWE in clinical settings, although extensive evidence from randomised controlled trials is unavailable. There is little evidence of a proconvulsant effect of antidepressants, with the exception of a small number of drugs, namely imipramine and maprotiline, at high doses. SSRIs are considered safe, have a favourable adverse effect profile and are not expected to exacerbate seizures in PWE.

3.2 How should epilepsy be treated in people with depression?

Under certain conditions, antiseizure medication may influence the emergence or re-emergence of depressive symptoms. Some ASDs, for example barbiturates, benzodiazepines, ezogabine, gabapentin, levetiracetam, perampanel, phenobarbital, primidone, tiagabine, topiramate, vigabatrin and zonasamide, can have negative psychiatric adverse effects, particularly in patients with a personal or family history of psychiatric disorders (44-48). The occurrence of symptoms is often dose-related or associated with rapid titration schedules. Depressive symptoms may emerge or re-emerge after the withdrawal of a mood-stabilizing ASD such as valproic acid, carbamazepine, oxcarbazepine or lamotrigine. Additionally, as already stated, ASDs with enzyme-inducing actions can lower serum levels of certain antidepressants with a resultant loss of efficacy. These factors should be considered in the choice of individual ASD therapy, particularly where a family or personal psychiatric history has been identified.

4. Why do epilepsy and depression frequently occur together?

Evidence suggests a complex association between epilepsy and depression, with indications of a bidirectional relationship. The prevalence of comorbid depression in people with epilepsy is well-established with evidence of multiple neurobiological, psychosocial and iatrogenic aetiologies. Furthermore, studies have revealed evidence of an increased risk of developing epilepsy in patients with primary depressive disorders. Functional neuroimaging studies have indicated that the presence and severity of depressive symptoms in epilepsy strongly correlate with cerebral abnormalities (12, 49). Epilepsy-related stress and psychosocial variables contribute to depression in many patients. A review of studies of the psychosocial predictors of depression in PWE by Gandy et al. (50) found likely support for the role of stress in the development of depression in PWE; the development of coping strategies and the presence of perceived social support appear to have a positive effect on the depression. The stigma experienced by PWE together with the demoralisation and poor self-esteem that often result, are likely to be factors in the emergence of mood disorders in many individuals with epilepsy.

4.1 Genetics

Genetic factors are evident in all primary psychotic disorders (51, 52). As already stated, a personal or family history of psychiatric disorders in PWE can predispose individuals to a recurrence of psychiatric symptoms or a *de novo* presentation after epilepsy onset (20). Hesdorffer et al. (53) researched the possibility of a common genetic predisposition in the development of epilepsy and psychiatric disorders. Behavioural disorders in children with uncomplicated and complicated epilepsy were assessed using the Child Behavior Checklist (CBCL) and the DSM-oriented scales for affective disorder, anxiety disorder, attention-deficit hyperactivity disorder, conduct disorder and oppositional defiant disorder. First-degree family history of unprovoked seizures and febrile seizures was assessed in parents and siblings of probands and associated with each of the clinical cut-offs and DSM-oriented scales after a nine-year follow-up assessment. The authors found a statistically significant association between first-degree family history of unprovoked seizure and the clinical cut-off for CBCL withdrawn/depressed (prevalence ratio (PR) 3.5; 95% CI 1.2 - 10.5) and DSM-oriented scales for affective disorder (PR 2.8; 95% CI 1.1 - 7.1) and anxiety disorder (PR 2.6; 95% CI 1.1 - 6.6) in probands. The results support the hypothesis of a common genetic predisposition for epilepsy and depressive disorders in uncomplicated epilepsy. This would further support the concept that epilepsy belongs to a spectrum of disorders, the underlying pathophysiology of which may manifest as a psychiatric disorder, epilepsy or a combination of both.

4.2 Environment

Several environmental factors, including familial circumstances, as well as variables associated with epilepsy therapy, have been identified as potential influences on the development of depression in epilepsy patients. A study of 391 adult PWE recruited from Korean hospitals explored the interactions between epilepsy and family factors as determinants of Beck-Depression-Inventory (BDI)-measured depression in patients. BDI assessment of patients and caregivers revealed depressive symptoms (BDI ≥ 10) in 68.3% of patients and 57% of caregivers. Multivariate analysis revealed that only caregiver BDI scores were an independent factor associated with patient BDI and concluded that caregiver depression is the most important contributor to depression in adults with epilepsy (54).

4.2.1 ASD effects

Iatrogenic effects associated with some ASDs may result in *de novo* or worsened depressive symptoms. As already stated, a personal or family history of psychiatric disorders appears to be a predisposing factor in the development of psychiatric adverse effects, in particular with certain ASDs (see section 3.2). On the other hand, some ASDs with mood-stabilizing or antidepressant properties (valproic acid, carbamazepine, oxcarbazepine, lamotrigine) may be effective in treating both the epilepsy and psychiatric conditions. Withdrawal of these ASDs can result in the emergence or re-emergence of psychiatric symptoms

4.2.2 Surgery

Episodes of postsurgical depression or anxiety occurring 3 - 6 months after surgery are observed in 20 - 40% of patients who undergo anterior temporal lobectomy. Symptoms may be an exacerbation or recurrence of a pre-existing psychiatric comorbidity or represent a *de novo* condition. In 10 - 15% of cases, symptoms may result in suicidal ideation and behaviour. Lifetime psychiatric history is strongly predictive of post-surgical depression and should be identified in surgery candidates as a potential risk factor for the re-emergence of symptoms post-surgery (20). Alternatively, pre-surgical depressive symptoms associated with seizures may be ameliorated or remit with successful surgical outcomes for the epilepsy (31).

4.3 Acquired brain disease

Acquired brain disease, for example resulting from traumatic brain injury (TBI), may disturb neural networks and give rise to cognitive deficits or neuropsychiatric symptoms, including depression (55). In more severe cases, neurological conditions, including post-traumatic epilepsy (56), may result. The abnormalities in functional networks that can result from cortical insults display a high degree of heterogeneity, dependent on the exact nature of the injury. For this reason, identifying the underlying disrupted mechanisms responsible for specific emergent symptoms following brain injury can be challenging (57). However, particular abnormalities in temporal lobe structures and the functional network connectivity originating in the temporal regions have been identified as common factors in depressive disorders and temporal lobe epilepsy. Some of these abnormalities are discussed in the following sections.

4.4 Common underlying networks and structural determinants

There is evidence of shared pathogenic mechanisms underlying some forms of epilepsy and depression. A higher incidence of depression has been observed in frontal and mesial temporal lobe epilepsies (58), a finding which could be indicative of specific abnormalities in the temporal lobe structures involved in regulating mood and emotional responses (i.e. the hippocampus and amygdala), that may be implicated independently in the development of both disorders. Neurobiological pathogenic mechanisms associated with psychiatric disorders may facilitate or influence epileptogenesis. These mechanisms include abnormalities in neurotransmitter function (serotonin, GABA, glutamate), a hyperactive hypothalamic-pituitary-adrenal axis resulting in high serum cortisol levels, abnormal CNS opioid production and inflammatory mechanisms (21) (see below).

4.4.1 Structural networks

Doucet et al. (59) investigated functional connectivity (FC) emerging from the amygdala in patients with mesial temporal lobe epilepsy (MTLE) and its relation to depression and anxiety. The amygdala has been identified as a brain region affected by MTLE, and structural abnormalities in the amygdala have previously been implicated in both comorbid depression and anxiety. Focusing on resting-state BOLD (blood oxygen level dependent) activity, the authors discovered significant differences in FC originating in the limbic system between patients with MTLE and healthy controls, with abnormal FC observed in patients with both left and right MTLE laterality. Correlations were found between the functionally impaired networks and the presence of psychiatric symptoms in both MTLE groups. However, the precise effect differed with respect to lateralisation of MTLE focus, with right TLE found to exert a greater maladaptive influence on emotion-related networks than left TLE. Rayner (60) discussed the role of diseased neural networks in the development of epilepsy, depression and behavioural disorders. The characteristic hypersynchrony of large-scale cognitive brain networks observed in epilepsy has also been implicated in the pathogenesis of primary depressive disorders. EEG-fMRI has shown that epileptiform discharges can, over time, disturb the normal organisation and functioning of cognitive networks, with evidence that network dysfunction in PWE with comorbid depression is more extensive than that seen in patients with epilepsy alone, and very closely analogous to the frontal lobe pathology associated with primary depression. The extent of the underlying network disruption, together with variables such as age at onset, may affect the degree to which disturbed cognitive networks contribute to depression in PWE. Rayner suggested that cognitive impairments, depressive symptoms and seizures may arise independently from the same network pathology.

4.4.2 Neurotransmitter disruption

Evidence for the abnormal functioning of serotonergic, glutamatergic and GABAergic mechanisms has been found in studies of both TLE patients and patients with primary mood disorders, suggesting that the same pathogenic neurotransmitter processes may be characteristic of both conditions. Abnormalities in serotonergic activity are a recognised biomarker in primary depressive disorders while similar deficiencies in serotonin receptor binding have been observed in the hippocampus, amygdala, cingulate gyrus, insula and raphe nucleus of PWE without depression and patients with primary major depression. An increase in glutamatergic activity is indicated in the emergence of seizure activity and may be a factor in the development of epilepsy itself. Elevated cortical glutamate levels are also a feature of primary mood disorders (21). Furthermore, a correlation between the ratio of glucose/creatine in the right hippocampus in PWE with comorbid depression and the severity of depressive symptoms was found in a study by Peng et al. (61). A reduction in the inhibitory function of GABA is one of the primary characteristics of brain dysfunction in epilepsy, with indications of a similar deficiency in major depression. Decreased GABA concentrations have been found in the cerebrospinal fluid of patients with MDD and in the dorsomedial, dorsal anterolateral prefrontal and ventromedial prefrontal, and occipital regions of affected individuals (21). Compromised cortical inhibition was reported in 35 patients with MDD compared with healthy controls in a study by Lefaucheur et al. (62) and loss of GABA-mediated inhibitory function was associated with treatment resistance in patients with MDD in a further study by Levinson et al. (63).

4.4.3 Other underlying structural determinants

Abnormalities in temporal lobe regions, specifically the hippocampus and amygdala, have been implicated in an increased risk of depression in PWE as well as in the otherwise neurologically normal population. Hippocampal atrophy of between 8% and 19% has been found in studies of patients with primary depressive disorders compared with controls, with an inverse relationship observed between duration of depression and hippocampal volume loss. Furthermore, reduced hippocampal volume is the most commonly observed abnormality in temporal lobe epilepsy and primary depression (21). Grimes et al. (64) investigated the correlation between hippocampal volume and interictal mood and anxiety, and improvement in post-ictal mood in patients with temporal lobe epilepsy. They found that reduced hippocampal volume was associated with less mood improvement after seizures and higher baseline anxiety levels. These findings were inconsistent with those of a recent study by Hecimoviç et al. (65), however, which revealed an inverse relationship between hippocampal volume and BDI scores in patients with temporal lobe epilepsy. Total hippocampal volumes were significantly smaller in the sub-group of patients with BDI < 15 ($p < 0.007$); significant symptoms of depression were indicated by scores greater than 15. Patients in the quartile with the smallest left hippocampal volume all had BDI < 15 while 57% of the patients in the upper three quartiles by hippocampal volume had BDI scores above this threshold. The authors suggested that this effect might be explained by a minimum degree of hippocampal integrity being required to maintain depressive symptoms in patients with mesial temporal lobe (MTL) epilepsy. They argued that their findings supported a unique mechanism responsible for depression in MTLE, mediated by the effect of hyperexcitable neurons in the hippocampus on the limbic network. In a separate study, Quiske et al. (66) found that the presence of mesial temporal sclerosis was significantly associated with higher mean BDI scores in a sample of 60 patients with temporal lobe epilepsy. Other studies have reported that enlargement of the amygdala is characteristic of TLE patients with comorbid depressive symptoms (21). In addition, there is evidence of an association between primary depression and reduced grey matter volume in the orbito-frontal cortex, cingulate gyrus and thalamus, while a study by Lin et al. (67) found evidence of a reduction in cortical thickness in the lateral temporal and extratemporal cortex in patients with mesial temporal lobe epilepsy. While these studies show similarities in brain dysfunction between depressive and epileptic disorders, an exact correlation between the presence of one disorder, reflected in specific abnormal neurological features, and the consequent emergence of the other, has yet to be established. As Kanner and co-authors observed in their 2014 review, since not all PWE have comorbid depression and not all patients with primary depressive disorders develop epilepsy, a combination of circumstances may be required for the development of either comorbidity (21).

4.5 Hyperactive hypothalamic-pituitary-adrenal axis, neuroinflammation and hypometabolism/ hypermetabolism

High cortisol levels resulting from a hyperactive hypothalamic-pituitary-adrenal axis is the earliest biomarker of major depression. An abnormal dexamethasone (DEX) suppression test, in which the adrenal gland is unable to suppress the release of cortisol in response to the introduction of dexamethasone (DEX), has been observed in 50% of patients with major depression as well as being reported in patients with temporal lobe epilepsy. One effect of elevated cortisol may be the reduction of 5-HT_{1A} receptor binding as a response to tonic inhibition due to glucocorticoid receptor stimulation. Elevated cortisol levels have furthermore been implicated in reduced glial density and neuronal size in cortical structures and reduced and disrupted astrocytic activity (21).

There is consistent evidence of an association between depression and chronic inflammation, with a significantly increased risk of depression in chronic inflammatory diseases including rheumatoid arthritis, for example. In addition, pro-inflammatory cytokines, including interleukin (IL)-1β, have been found in patients with major depression. Evidence of the proconvulsant effects of various cytokines, including IL-1β has been found, along with an overexpression of IL-1β and IL-1β receptor type 1, in TLE patients and individuals with cortical dysplasia and tuberous sclerosis (21).

Both hypometabolism and hypermetabolism have been implicated in depressive disorders in PWE. Bromfield et al. (68) and Victoroff et al. (69) found significant correlations between hypometabolism in the inferior temporal regions and higher BDI scores and history of major depression respectively. In a review of studies of psychiatric comorbidity in PWE, Hermann et al. (11) found that hypermetabolism and decreased cerebral blood flow were among the variables that were consistently associated with depression in PWE. The same biomarkers have been found in studies of patients with primary psychiatric disorders, notably major depression.

5. QOL

5.1 What are the determinants of quality of life in people with epilepsy and depression?

Clinical investigations have indicated that comorbid depression has a large negative impact on the subjective quality of life in people with epilepsy. In many cases the effect of the depressive disorder has a greater influence than seizure rate on subjective quality of life assessments (70), and is second only to medication toxicity as the clinical factor with the greatest influence on quality of life measures. People with epilepsy and co-occurring depressive symptoms use more health services, have a higher risk of suicide and premature mortality (31), lower treatment adherence, reduced quality of life and poorer control of seizures (29). Lower medication compliance is linked to a lower tolerance of ASDs in depressed patients with consequences for seizure remission in these individuals (31).

A study by Gaus et al. (18) used subscales of the Patient-weighted Quality of Life in Epilepsy Inventory-31-P to assess predictors most closely associated with depression in 302 adult PWE. The detrimental effects of medication (QOL medication effects) and seizure worry (QOL seizure worry) were found to be the most important contributory factors. In a review of psychiatric comorbidity in epilepsy, Hermann and co-authors (11) cited studies by Wiegartz et al. (13) and Lehrner et al. (71) which demonstrated a negative impact of depression across a range of self-reported quality of life scales, including physical, well-being, activity and capability, relations and family, independence, coping and control, and emotion and mood.

Treatment non-compliance appears to be higher in PWE with depressive symptoms. Other barriers to successful implementation of epilepsy care in depressed patients have also been discussed. The effect of comorbid depression and anxiety on epilepsy management in patients with refractory epilepsy was investigated in a study by Hamilton et al. (72). The authors found that patients with depression were more likely to miss outpatient appointments, and those with the most severe psychiatric comorbidities were more likely to be admitted for inpatient treatment than controls without depressive symptoms.

Mula and Sander (70) reviewed the psychosocial aspects of epilepsy and observed that the stigma associated with epilepsy can lead to depression, anxiety and poor medication adherence. Feelings of stigmatisation are also evident in mothers of children with epilepsy and the resultant increased perception of burden is seen to correlate with depressive symptoms in the child (54).

PWE are at significantly higher risk of premature mortality than the general population. Fazel et al. found an approximately 11-fold greater frequency of premature death in PWE than either the general population or unaffected siblings. 15.8% of all deaths in PWE were attributed to external causes which included suicide and accidents (including falls, drowning, drug poisoning, assault and motor accidents). 75% of PWE who died as a result of external causes had a history of psychiatric disorder, mainly depression and drug misuse (73).

5.2 Suicide

Suicide is a severe complication of untreated and undiagnosed depression. The risk of suicide in PWE is up to three times higher than in the general population (74-76) and has been found to represent the greatest risk of mortality in epilepsy. However, the increased suicide rate is not solely due to the elevated rate of depression (70). A Danish population-based study by Christensen et al. (76) found a 32-fold greater risk of death by suicide in PWE with comorbid mood disorders. Individuals were most at risk within the first 6 months after epilepsy was diagnosed. However, the rate ratio of suicide in PWE reported in this study was still double that in the general population when excluding people with psychiatric comorbidity from the sample. A study by Hecimoviç et al. (77) examined the predictive risk factors of suicidality in a sample of 193 epilepsy outpatients and found that in logistic regression analysis, only BDI score remained significantly correlated with suicidal ideation. Gender, age, seizure factors, medication toxicity and self-perceived quality of life were also evaluated but were not found to predict suicidality in bivariate analyses. Early evaluation of the psychiatric history may help to identify those at most risk and mitigate the possible emergence of suicidal ideation with appropriate interventions (20).

6. Conclusion

Psychiatric disorders are relatively frequent comorbidities in PWE, with mood and anxiety disorders being the most frequent. The interplay between epilepsy and comorbid depression is complex and a number of interconnected factors have been implicated, including previous personal or family psychiatric history, neurobiological changes associated with epilepsy, seizure-related phenomena, iatrogenic factors and reactive processes. The recognition of a bidirectional relationship between the disorders suggests the possibility that shared pathogenic mechanisms may be implicated. Depression in PWE is under-recognized and undertreated, despite the high prevalence and negative consequences for QOL. In most cases, depression is mild to moderate and responds well to antidepressant and/or cognitive behavioural therapies. Identification of lifetime personal or family history of psychiatric disorders can help in the prediction of the risk of emergence or re-emergence of depressive symptoms. Prompt intervention with skilled management of both the epilepsy and the depression can greatly improve the quality of life of individuals with both conditions.

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