Depression in women with epilepsy: clinical and neurobiological aspects

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Summary

Patients affected by epilepsy show a considerably higher incidence of depression compared with the general population. Since women are twice as likely as men to suffer from depression, female gender could be considered a major risk factor for developing this condition. Converging lines of evidence suggest that sex hormones, which are known to contribute to remodelling the hippocampus, play a pivotal role in both epilepsy and depression. In women, the role of sex hormone levels may be more important because of their physiological cyclic fluctuations. Oestrogens, more than other ovarian hormones, show an effect similar to antidepressant drugs by stimulating hippocampal synaptogenesis, thus exerting a protective role against seizures as well. This paper reviews the current knowledge on the neurobiological basis of depression in women with epilepsy. The emerging picture informs therapeutic strategies to improve the clinical management of this common comorbidity.

KEY WORDS: antiepileptic drugs, depression, epilepsy, sex hormones, SSRIs, women.

Introduction

The term epilepsy, or more correctly, the epilepsies, refers to a group of chronic neurological disorders characterised by recurrent epileptic seizures. Epileptic seizures are the clinical manifestations (signs and symptoms) of excessive and/or hypersynchronous, usually self-limiting, abnormal activity of neurons in the brain. It was once believed that this abnormal neuronal activity occurred only at the level of the cerebral cortex; however, it is now recognised that sub-cortical structures can also be involved; indeed, some epileptic seizures may be primarily generated at sub-cortical level (1). Since the behavioural manifestations of epileptic seizures depend on the functions of the brain areas involved, they may take the form of a variety of signs and symptoms, including impaired higher mental function or altered consciousness, involuntary jerk-like movements or cessation of movement, sensory or psychic experiences, autonomic disturbances, or combinations of these. Specific epileptic seizure types are defined by their ictal behavioural and electroencephalographic (EEG) features. From an electrophysiological point of view, the epileptic focus is defined as the brain area that appears to generate the most prominent interictal epileptiform EEG discharges. Epileptic conditions may be due to a single focus, bilateral independent foci, multiple foci, or there may be diffuse unilateral or generalised epileptiform abnormalities with no focal features. The International League Against Epilepsy's current classification of epilepsy and epileptic syndromes (2) makes a fundamental distinction between partial (or focal) epilepsies and generalised epilepsies; this distinction is based on the presence or absence, respectively, of clinical and electrophysiological evidence of a clear-cut epileptogenic focus. The seizures, on the other hand, are classified as simple or complex according to the presence or absence of ictal consciousness (3).

The exact prevalence of epilepsy is not known as figures vary among different countries, but it is estimated that there are about 50 million people affected by the disorder worldwide. An increasing amount of evidence suggests that people with epilepsy show a tenfold higher incidence of depression (4-6) compared with the average population (over 55% versus over 5%). Specifically, it has been suggested that 20% of patients with temporal lobe epilepsy will eventually develop depression and that up to 62% of patients with intractable complex partial seizures have a history of previous depressive episodes, sometimes recurrent (7).

This paper reviews current knowledge on: i) the clinical phenomenology of depression in patients with epilepsy, ii) the influence of female sex hormones on seizure activity, and iii) the neurobiological basis of clinical depression in women with epilepsy.

Depression in patients with epilepsy: diagnostic and therapeutic issues

The relationship between epilepsy and depression has been thoroughly investigated in the neuroscientific liter-

ature, in order to promote an effective approach to patients affected by this comorbidity (8,9). Epilepsy occurring in association with depression is usually one of two main types: peri-ictal or interictal. In the first case, the depressive symptomatology, which can include prodromata, epileptic aura, ictal and postictal disturbances (10-13), is present around the time of the seizure. In the second, the depression is characterised by chronic psychiatric disturbances not temporally related to ictal electro-clinical features (14).

Furthermore, intermittent affective-somatoform symptoms are frequently observed in chronic epilepsy; these psychological symptoms, which can include irritability, depressive moods, anergia, insomnia, atypical pains, anxiety, phobic fears, and euphoric moods, manifest themselves in pleomorphic patterns. They occur at various intervals and tend to last from hours to a few days. In the event of intermittent dysphoric symptoms (at least three of the above), each present to a troublesome degree, a few authors have proposed a diagnosis of interictal dysphoric disorder (15). In women, this disorder is accentuated in the premenstrual phase (16).

A rapidly-growing group of patients with epilepsy at greatly increased risk of developing depressive disorders are those who undergo surgical treatment following failure to obtain pharmacological seizure control. In the past two decades the rate of surgical resections of the antero-temporal lobes has increased substantially, leading to a proportional increase in iatrogenic depression. It is not unusual to see mood lability within the first six weeks of this surgery. Although these symptoms often subside, up to 30% of patients show overt signs of depression within the first six months of surgery. The depression can vary in severity from mild to extremely severe, and can even culminate in suicide attempts. Patients with a prior history of depression are at greater risk. Interestingly, this risk seems to be independent of the postsurgical control of seizures. All candidates for epilepsy surgery should therefore be informed of this potential complication before undergoing the procedure.

Diagnosis of epilepsy-related depression is often a major challenge. Indeed, the forms of depression experienced by patients with epilepsy are usually identical to those experienced by non-epileptic patients. Nevertheless, depressive disorders can have an atypical presentation in a significant percentage of patients with epilepsy, who do not fall into any of the DSM Axis I categories (17). Depressive symptoms and disorders can be present before or after the onset of seizures and their temporal relationship with seizure occurrence is an important factor when classifying them. Moreover, depressive symptoms can constitute a manifestation of the actual seizure or be completely unrelated to seizure occurrence (18). When the latter occur very close to a seizure they can be misinterpreted by clinicians, which accounts for the paucity of data on their prevalence and response to treatment.

Although the exact nature of the relationship between epilepsy and depression is not fully understood, a picture is emerging that is informing therapeutic strategies aimed at improving the clinical management of women with epilepsy. Having said that, clinical trial results and clinical practice experience seem to suggest that the problem of managing depression in epilepsy is often exaggerated. Results from preliminary clinical trials indicate that selective serotonin reuptake inhibitors (SSRIs) can efficiently control major depressive symptoms in patients with epilepsy without inducing unacceptable increases in seizure frequency (19). Specifically, paroxetine and citalopram are drugs of choice because they do not interact with the most common antiepileptic drugs and are known to have lower epileptogenic potential (20). Moreover, there is converging evidence in favour of moclobemide whose dual action on depression and seizure status (21) may make it a suitable option. Clinical data have also shown that the dual antidepressant venlafaxine, which modulates both serotonergic and noradrenergic pathways, has low epileptogenic potential (22). The multiple mechanisms of action of antidepressant drugs may partly explain their efficacy in populations with epilepsy. For example, a lack of influence on hippocampal plasticity may be compensated for by an ability to inhibit serotonin reuptake and stimulate aminergic receptors that is enough to effectively contrast depression (23). Electroconvulsive therapy (ECT), which is used in selected patients to treat psychiatric disorders, can have significant effects on patients with epilepsy. It has been argued that this treatment can result in an at least transient cessation of seizures by increasing the seizure threshold (24). The main benefit of ECT is the rapidity of the response, which, however, may not always be sustained. Counselling and/or psychotherapy, in particular cognitive-behavioural therapy and interpersonal therapy, can also be effectively used in the management and prevention of relapses of depression (25). Vagus nerve stimulation (VNS) has recently gained considerable support as an approach to patients with treatment-refractory partial seizures unable to undergo surgical procedures. The advantage of VNS for people with epilepsy and comorbid depression is that it has proved effective in both disorders separately (26,27).

Female physiology and epilepsy

Since women are twice as likely as men to suffer from depression, female gender could be considered a major risk factor for developing this condition, although in this regard epidemiological data are somewhat controversial. Overall, women with epilepsy appear to be at greater risk of developing depression than the general population (16). Over the past few years, several authors have investigated the neurobiological links between epilepsy and depression (23,28). In female patients, these links are further complicated by gender-specific physiological issues. It is currently acknowledged that, after the menarche, ovarian steroid hormones affect seizure activity. In women, seizure threshold may vary in relation to their menstrual cycle, but also in relation to the different stages in their reproductive life (puberty, pregnancy, and the menopause), when the levels of both oestrogens and progesterone in their body change dramatically. Fertility and reproductive functions may also be affected in some women with epilepsy. There is an important bi-directional relationship between hormones and epilepsy, with each influencing the other in several ways. Specifically, seizures have been associated with sexual dysfunction (16).

Ovarian steroid hormones affect the activity of the central nervous system by altering the excitability of neu-

rons. This modifies both the frequency and the severity of seizures. Experiments on animal models have consistently demonstrated both proconvulsant effects of oestrogens and anticonvulsant effects of progesterone (29). Oestrogens increase the activity of excitatory neurotransmitters and also alter dopamine pathways, thus disrupting inhibitory neurotransmission. Oestradiol hormones may also alter the structure of the synaptic area of neurons, increasing the number of dendritic spines and synapses. Oestrogens and progesterone are highly lipophilic; easily crossing the blood-brain barrier, they diffuse through cell membranes and bind to intracellular receptors, forming hormone-receptor complexes. This is how fluctuations in ovarian steroids and peptides directly affect the brain. Hormones secreted by the hypothalamus and pituitary gland regulate the amounts of oestrogens and progesterone circulating in the body. The hypothalamus receives many direct connections from the temporal lobes, which are often involved in seizure generation. Research has shown that seizure discharges can disrupt the production of hormones such as follicle stimulating hormone (FSH) and luteinising hormone (LH), which, in turn, can alter the balance of oestrogens and progesterone and affect seizure control. Progesterone metabolites produce anticonvulsant, antianxiety, and sedative effects similar to those of the benzodiazepines. Women with epilepsy display a variety of endocrine disturbances (30). Several lines of evidence suggest that changes in the levels of the female sex steroids may contribute to the risk of depression.

Neurobiological basis of depression in women with epilepsy

Clinical data show that alterations in oestrogen secretion, common in women affected by epilepsy, seem to play a critical role in the aetiology of depressive disorders (31,32). Consistent with animal studies, oestrogens appear to be effective in treating postpartum and perimenopausal depression (33). Moreover, since androgens appear to have an antidepressant effect comparable to that of oestrogens (33), the higher incidence of depression observed in women may be convincingly explained by their different pattern of gonadal hormone secretion. The mechanisms responsible for the antidepressant effect of gonadal steroids are not yet fully understood. However, current evidence suggests that the effects of sex hormones on the brain, including their effects on the structure and function of the hippocampus, mimic those of antidepressants. Oestrogens, in a manner similar to SSRI antidepressants, seem to modulate the reuptake of serotonin, leading to increased concentrations in key mood-determining areas. The hippocampus itself is sensitive to oestrogens and androgens (34), containing receptors for both these groups of steroids. Oestrogens induce brain-derived neurotrophic factor (BDNF) synthesis in the hippocampus, bringing about significant increments in hippocampal BDNF expression with every ovarian cycle (35). The observation that loss of gonadal steroids leads to atrophic changes in the hippocampus could explain why the risk of developing depression appears to be higher when oestrogen levels are low. These data are also consistent with the findings, from both animal research and clinical trials, that hormone replacement therapy may potentiate the effects of antidepressant therapy (36,37). A possible explanation for this is that the effects of gonadal steroids on the hippocampus could synergise with those of antidepressants. This hypothesis seems to be supported by clinical observations of different times to measurable therapeutic effect: improvements after treatment of postpartum depression using antidepressant drugs can take up to six weeks to appear, whereas oestrogen seems to be effective within one week (38). Further research in experimental animal models confirmed that these are the latencies necessary to obtain detectable hippocampal neuroplastic responses to oestrogens and antidepressant drugs. Oestrogens are likely to induce rapid increases in hippocampal spine synapse density (39) as well as rapid, but transient, increases in dentate gyrus neurogenesis (40). Although the time course for the effects of antidepressants on synaptogenesis has not been determined definitively, neurogenetic changes appear to require weeks of antidepressant treatment to become fully established.

It has been shown that female sex hormones influence both epilepsy and depression, and that when these conditions coexist there is a deep intertwining of their pathophysiology. Hippocampal plasticity, which is affected by female sex hormones, appears to be involved in both mood disorders and epilepsy. This shared mechanism could provide a theoretical basis for the increased frequency of depression in women with epilepsy. Aspects of the endocrine and anatomical sequelae of epilepsy appear to be consistent with findings from studies on depression, suggesting possible parallels between the two disorders. First, epileptic seizures can lead to a derangement of the hypothalamic circuitry controlling pituitary gonadotropin release (41) and consequently dysregulation of female sex hormones. This alteration leads to marked physiological and anatomical changes in the hippocampus. Therefore, it is possible that the increased incidence of depression observed in women with epilepsy could reflect a hormonal deficiency (abnormally low levels of oestrogen) that contributes to the intrahippocampal deficits that predispose to depressive symptoms.

Moreover, changes in gonadal steroid production probably represent a critical contributing factor in determining seizure frequency in women with catamenial epilepsy, a condition characterised by changes in seizure frequency in relation to the menstrual cycle. Taking an at least twofold increase in daily seizure frequency during or around menstruation as the criterion for definition, catamenial epilepsy is seen in approximately 30% of women with epilepsy. The abovementioned proconvulsive effects of oestradiol and the anticonvulsive effects of progesterone seem to play a central role in the aetiology of catamenial epilepsy, although this aspect is not entirely understood. In particular, 5α-reduced metabolites of progesterone, such as allopregnanolone, seem to modulate $GABA_A$ receptor function (42), while oestradiol mediates an increase in hippocampal excitation, increasing hippocampal expression of BDNF. A lower hippocampal excitability threshold means easier seizure generation. Circumstantial evidence supporting this view also comes from observations on one of the potential adverse effects of antidepressant drugs, namely an increased susceptibility to seizures (43).

These findings seem to explain the link between oestrogen activity, depression, and seizure frequency. However, they also raise an apparent paradox. An extensive body of evidence indicates that the seizure activity itself is associated with marked increases in hippocampal neurogenesis and BDNF synthesis (44,45). Since insufficient hippocampal neurogenesis and BDNF synthesis are critical contributory factors in depression (46), it seems difficult to accept that depression has a higher prevalence in epilepsy, under conditions of increased neurogenesis and facilitated BDNF release. An explanation might lie in the particular hippocampal environment resulting from recurrent seizure activity. From this perspective, it can be hypothesised that the positive effect of increased neurogenesis may fail to compensate for the massive seizure-induced loss of neurons. Normally, increases in BDNF synthesis and neurogenesis are likely to contribute to the enhancement of hippocampal function, increasing the pool of developing neurons available for incorporation into the circuitry and stimulating synaptogenesis. But under the aberrant conditions of recurrent seizures, neurogenesis is unlikely to be a sufficient response. Despite increased cell proliferation, there may be a net loss of neurons in the hippocampus as a result of seizure-induced cell death (47). Moreover this pathological neurogenesis appears to be dysregulated, with some of the newly created neurons ending up at ectopic sites, where they form inappropriate connections (48). Both the number of cells and their connections are crucial in developing a correctly functioning hippocampal circuitry. Several studies indicate that there is a fairly hefty loss of dendritic spines both in epilepsy patients (49) and in animal models of epilepsy (50). These data provide another possible explanation for the inefficacy of post-seizure neurogenesis. An important factor determining the likelihood of developing depression is the extent to which the hippocampal circuitry retains the capacity for growth and repair. If this capacity is diminished, for whatever reason, the final result may be an increase in the risk of developing clinical depression.

In summary, the reviewed literature suggests that there is an increased incidence of depression in epilepsy: however, much work remains to be done in order to fully clarify the neurobiological basis of this relationship. The contributions of both genetic and epigenetic factors to the development of affective disorders in women with migraine have recently been reviewed by Guidetti et al. (51). With regard to epilepsy, rigorous experimental data can be difficult to obtain and much of the available evidence is circumstantial. Despite these limitations, it is possible to advance a plausible state-of-the-art theory to explain the clinical manifestations shared by epilepsy and depression. The hippocampus, which is subject to rapid structural changes in order to respond effectively to an ever-changing environment, seems to play a pivotal role (23). Neurological disorders, like epilepsy, or conditions causing deficient trophic stimulation by gonadal steroids, severely undermine its plasticity and eventually predispose to the development of depression. Moreover, in women, in whom the hippocampus is also physiologically under stress because of cyclically fluctuating sex hormone levels, this phenomenon is exacerbated, which accounts for the increased prevalence of depression.

Concluding remarks

Current evidence suggests that patients affected by epilepsy show a considerably higher incidence of depression compared with the general population. Since women are twice as likely as men to suffer from depression, female gender could be considered a major risk factor for developing this condition, although in this regard epidemiological data are somewhat controversial. As regards the neurobiological and psychological basis of these conditions, the key elements to be considered are the partial overlap of neurochemical mechanisms involved both in depression and in epilepsy, and the large number of interlinked psychosocial factors, including the clinical features of epilepsy, such as seizure type, frequency, and cortical focus. Sex hormones are also important as they are known to affect the hippocampus, which plays an important role in both epilepsy and depression. It has been consistently shown that decreased oestrogen levels are linked to significantly increased seizure frequency. The exact nature of the relationship between epilepsy and depression remains to be elucidated. It is, however, important to control seizures by medication or newer strategies. The choice of antiepileptic drug should take into due account the behavioural profile of the medication, as some of these drugs (e.g. lamotrigine, carbamazepine) can have a positive effect on mood (52). SSRIs and dual-action antidepressant medications are considered first-line therapy.

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