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Review

Stress regulation in drug-resistant epilepsy

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ABSTRACT

The prevalence of psychological distress, especially depressive and anxiety disorders, is higher in epilepsy than in other chronic health conditions. These comorbid conditions contribute even more than epileptic seizures themselves to impaired quality of life in patients with epilepsy (PWE). The link between these comorbidities and epilepsy appears to have a neurobiological basis, which is at least partly mediated by stress through psychological and pathophysiological pathways. The impact of stress in PWE is also particularly important because it is the most frequently reported seizure trigger. It is therefore crucial for clinicians to take stress-related conditions and psychiatric comorbidities into account when managing PWE and to propose clinical support to enhance self-control of stress. Screening tools have been specially designed and validated in PWE for depressive disorders and anxiety disorders (e.g. NDDI-E, GAD-7). Other instruments are useful for measuring stress-related variables (e.g. SRRS, PSS, SCS, MHLCS, DSR-15, ERP-R, QOLIE-31) in order to help characterize the individual "stress profile" and thus orientate patients towards the most appropriate treatment. Management includes both pharmacological treatment and nonpharmacological methods for enhancing self-management of stress (e.g. mindfulness-based therapies, yoga, cognitive-behavioral therapies, biofeedback), which may not only protect against psychiatric comorbidities but also reduce seizure frequency.

1. Introduction

Unpredictability of seizures remains one of the most disabling aspects of epilepsy, but comorbid disorders may have an even more important contribution to impaired quality of life (QOL) in patients with epilepsy (PWE). Among epileptic comorbidities, psychiatric disorders are in the foreground, especially depressive disorders and anxiety disorders [1]. Prevalence of these disorders is higher in epilepsy than in other chronic diseases [2] due to specific psychophysiological and neurophysiological mechanisms, especially those involved in stress responses [3]. From a psychological perspective, it is conventional to conceptualize depression and anxiety in epilepsy as indicating a heightened emotional response in response to the unpredictable nature of seizures, and to the restriction of activities resulting in low self-esteem, stigma and social rejection. In addition, stress is frequently identified by patients as a precipitant factor of seizures [4]. As well as this psychological model there is also a well-established neurobiological model of depression and anxiety, which is useful to consider in the context of epilepsy. The pathophysiological links between stress, depressive disorders and anxiety disorders are well-known. Animal models provide accumulating evidence that epileptic activity alters the neurophysiological pathways involved in stress responses, and that stress response also affects epileptic activity [5].

Identifying and managing depressive and anxiety disorders and stress has been highlighted as a crucial issue in patients with epilepsy (PWE), with a need to individualize treatment according to individual patient profiles [6]. In the present article we aim to present an overview of current knowledge of stress and epilepsy and then focus on the various health psychology tools available for characterizing patient profiles of depression, anxiety and stress and their capacity to cope with these. We will also discuss the different stress management therapies currently available for PWE, and reflect on how patient profile might influence choice of therapy.

Abbreviations: AED, Anti Epileptic Drug; MDD, Major Depressive Disorder; GAD, Generalized Anxiety Disorder; QOL, Quality of Life; PWE, Patient With Epilepsy; TLE, Temporal Lobe Epilepsy; PSC, Perceived Self-Control; LOC, Locus Of Control.

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1.1. Stress, depressive and anxiety comorbidities and epilepsies

General understanding has emerged about the role of stress in the etiology and maintenance of psychopathologies [7]. The prevalence of psychological distress is higher in epilepsy compared to other chronic health conditions [2]. Many clinical and epidemiological studies have shown high proportions of PWE suffering from psychosocial difficulties directly linked to emotional and cognitive disorders [8]. Major depressive disorder (MDD) and generalized anxiety disorder (GAD) are the two most prevalent psychiatric comorbidities in PWE [1] and particularly in temporal lobe epilepsy (TLE) [9]. In addition, it has been suggested that these psychological comorbidities can precede the onset of seizures [10]. This observation indicates a possible bidirectional relationship and it has been postulated that some shared neurobiological mechanisms exist underlying epilepsy, depression, anxiety and vulnerability to stress [11,12]. Epilepsy is the cause of an important burden on quality of life with frequent impairment in social functioning that can be explained largely by comorbid depression and anxiety. Indeed, stress plays a key role in the onset of depression and anxiety disorders and is known to worsen these conditions. Stress is also frequently described as a factor precipitating seizures, or even as the trigger for development of epilepsy. Neurological and endocrine pathways of stress regulation are known to be impaired in epilepsy, especially in TLE [5] and ongoing research aims to better characterize the interactions of stress and epilepsy from a neurobiological perspective.

1.1.1. Major depressive disorder and anxiety disorder comorbidities in epilepsies

1.1.1.1. Major depressive disorder. MDD is the psychiatric comorbidity the most frequently associated with epilepsy [13,14]. Between 30% and 35% of PWE suffer from depression during their lives [13]. The proportion is highest in refractory epilepsies, accounting for 20% to 55% of drug-resistant patients compared to 3% to 9% of patients with good seizure control [8]. The prevalence of depression in drug-resistant epilepsy is 10 times greater than the general population [8]. Thus, MDD represents a global problem in PWE [15,16]. The existence of neurobiological mechanisms common to MDD and epilepsy could explain this high prevalence. Presence of MDD is associated with greater risk of unprovoked seizure [17]. Moreover, the presence of MDD in PWE is associated with a negative effect on seizure control [18], higher rates of adverse effects of antiepileptic drug (AED) therapy [19], poorer outcome of epilepsy surgery [20,21], lower quality of life [22], increased risk of suicidal behavior in PWE [23], and increased health care costs [24].

1.1.1.2. Anxiety and generalized anxiety disorder. Anxiety is described as a phenomenon that may occur in the ictal, postictal or interictal state [25]. Studies founded that the risk of anxiety disorders is higher in TLE than in other types [26,27]. These observations are supported by neurobiological mechanisms [5]. Nevertheless, the prevalence of anxiety disorders depending on the type of epilepsy is not so clear. Indeed, Swinkels et al. [28] showed that if the persons suffering from TLE are more likely to suffer from anxiety disorders (25% to 30%) than the general population (12% to 19%), they do not differ from other types of epilepsy.

Anxiety comorbidities can be classified into:

- interictal anxiety disorders, which are not chronologically linked to the seizure. The characteristic forms of DSM-5 and forms specific to the epileptic context are distinguished. According to DSM-5, interictal anxiety disorders can be characterized in order of prevalence in epilepsy as: generalized anxiety disorder (GAD) (3% to 13%, with an even higher prevalence in patients with drug-resistant epilepsy) [29]; obsessive–compulsive disorder (1% to 3%); and post-traumatic stress disorder (1% to 5%) [30].
- ictal anxiety disorders, which are directly related to the occurrence of seizures, in which anxiety is distinguished as either a prodromal symptom, a preictal phenomenon, a predictor of a seizure, or as a postictal symptom following a seizure.

Anxiety is sometimes described as a psychological response that is exacerbated in response to the unpredictable nature of seizures, and to restriction of life activities resulting in low self-esteem, stigmatization and social rejection [27]. Anxiety can also be conceptualized in neurophysiological and neurobiological terms; for example, psychosocial stress in the form of chronic anxiety has been described as a dysregulated physiological response of the organism to perceived unsafe conditions [31]. The main factors associated with anxiety are not necessarily epilepsy-related, since they concern history of depression, educational level, unemployment or female gender, chronic ill health, perceived side effects of antiepileptic medication but not the duration of epilepsy [32]. A personality trait of anxiety should be considered as a premorbid condition and is also one of the main factors determining QOL in epileptic patients [33].

Anxiety is described in terms of a specific disorder when particular psychiatric criteria are present. In particular, generalized anxiety disorder (GAD) is the second most frequent psychiatric disorder in PWE after MDD [1,34–36]. GAD is characterized by disabling and persistent free-floating worry. Occurring in the context of epilepsy, GAD is often associated with fear of future seizures, fear of disease progression, or fear of specific complications [25,37]. As for MDD, the presence of GAD in PWE is associated with a negative effect on seizure control [18,20,38], higher rates of adverse effects of AED therapy [19,39,40], increased risk of suicidal behavior in PWE [23,41,42] and lower QOL [22,43], as well as increased health care costs [24].

1.1.2. Stress in epilepsies

1.1.2.1. Stress: definition

1.1.2.1.1. The physiological model of Selye. Stress response and stressful events are often confounded. In addition, the issue of whether the stress response becomes chronic (and maladaptive) is highly relevant to clinical effect. In order to clarify the use of "stress", the following terminology will be used: stimuli that are seen as a source of stress are referred to as "stressful events" and the psychological, neurophysiological and/or biological responses to the stressful events are referred to as "stress responses". Stress responses are adaptive processes, the purpose of which is to restore homeostasis. However, prolonged or intense exposure to stressful events leading to prolonged stress responses can potentially lead to tissue damage and disease. In addition, depending on characteristics of the individual in terms of their resilience and vulnerability to stressful events, the stress response may be more or less exaggerated and/or prolonged [31]. From the physiological point of view stress is a variable arising from the physical or social environment. Cannon [44] introduced the idea that an organism's homeostasis can be threatened by an aversive situation. Homeostasis refers to the normal resistance (or equilibrium) level of the organism. The purpose of physiological changes in response to stress is to leverage resources in order to cope with the stressful event and to return to the homeostatic state. The term stress was used by Selye [45] to characterize the physiological changes and responses occurring when the homeostasis is disturbed. Selye [45] introduced the first model of stress with his General Adaptation Syndrome in which he described three stages: alarm stage, resistance stage and exhaustion stage. Alarm stage is the first reaction to a stressful event exposure. Homeostasis is disturbed, physiological resources are mobilized in order to flight or fight the stressful event. Resistance stage is an adaptation stage. The resources are restored to return at the homeostatic state in order to the organism could deal with others stressful events. The exhaustion stage appears when the stressful event occurs in long duration or strong intensity, so resources cannot be restored. Building on Selye's work, a recent model [31] has conceptualized chronic stress (and chronic anxiety) in terms of the innate default state