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Review

Epilepsy, depression, and growth hormone

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ABSTRACT

Depression affects a large proportion of patients with epilepsy, and is likely due in part to biological mechanism. Hormonal dysregulation due to the disruptive effects of seizures and interictal epileptiform discharges on the hypothalamic–pituitary–adrenal axis likely contributes to high rates of depression in epilepsy. This paper reviews the largely unexplored role of neuroendocrine factors in epilepsy-related depression, focusing on Growth Hormone (GH). While GH deficiency is traditionally considered a childhood disorder manifested by impaired skeletal growth, GH deficiency in adulthood is now recognized as a serious disorder characterized by impairments in multiple domains including mood and quality of life. Could high rates of depression in patients with epilepsy relate to subtle GH deficiency? Because GH replacement therapy has been shown to improve mood and quality of life in patients with GH deficiency, this emerging area may hold promise for patients suffering from epilepsy-related depression.

1. Epilepsy and depression

Depression is a significant yet underappreciated problem, which affects up to 55% of patients with epilepsy [1–5]. Although depressed mood may in some cases be due in part to an understandable psychological reaction to lifestyle limitations imposed by recurrent seizures, an increasing body of scientific research indicates that depression in patients with epilepsy has a specific biological basis [3,4,6–15]. Depression commonly precedes the onset of seizures [16,17] and has been associated with lower rates of seizure remission following epilepsy surgery [18], suggesting biologic links between epilepsy and depression may be bidirectional or reflective of an underlying shared causal mechanism. Mood, and not seizure frequency, may be the strongest predictor of quality of life in epilepsy [19–21], and patients with epilepsy are at remarkably high risk for suicide [22–25]. The limbic brain structures such as the amygdala and hippocampus likely represent one neurobiological link between epilepsy and depression based on their role in emotional processing, their implication in the pathophysiology of depression [26,27], and their intimate involvement in seizure generation and propagation in temporal lobe epilepsy. Another potential link between epilepsy and depression relates to hypothalamic–pituitary–adrenal (HPA) axis hormone imbalance.

1.1. HPA dysregulation, depression, and epilepsy

In depression, HPA abnormalities are well-established. Failure to suppress cortisol secretion in response to dexamethasone is a robust biologic finding in depression [28,29], which has also been demonstrated in patient with temporal lobe epilepsy and animal models of epilepsy [30]. Cortisol levels are elevated in patients with epilepsy and are further increased following seizures, and cortisol has been considered a link between seizures, stress, and depression [30–32].

With respect to sex hormones, ictal and interictal discharges appear to have specific effects on hypothalamic and pituitary hormone release, in the case of temporal lobe epilepsy, likely via direct connections between the medial temporal structures and the hypothalamus [33]. In women with epilepsy, altered hypothalamic–pituitary–ovarian reproductive endocrine regulation is considered to account for low estrogen levels, irregular menses, infertility, and early menopause, while men with epilepsy commonly have diminished sexual interest and potency [34]. Curing epilepsy through resective epilepsy surgery results in normalization of serum testosterone levels [35]. Sexual and reproductive dysfunction has been related to both epilepsy and to antiepileptic medication use [34]. Alterations in hypothalamic gonadotropin-releasing hormone (GnRH) pulsatile release affects luteinizing hormone (LH) [36,37], which also affect sex hormone levels and may contribute to cognitive dysfunction [38,39], which is common in chronic uncontrolled epilepsy [40].

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1.2. Postseizure pituitary hormone change

The existence of anterior pituitary hormonal changes due to seizures and epilepsy has been known for decades. A rise in prolactin, detectable approximately 30 min after most complex partial and generalized seizures, is commonly used to help determine whether a transient neurologic event was actually a seizure [41–43]. Adrenocorticotropic hormone (ACTH) and cortisol also rise after seizures [41–46], as they do in response to most physically or psychologically stressful events. Electroconvulsive therapy (ECT) gives rise to prolactin and ACTH/cortisol responses similar to those that follow spontaneous epileptic seizures [44,46–48]. Postseizure changes in the anterior pituitary hormone, growth hormone (GH), are less studied and are the focus of this review.

2. Growth hormone

GH is a single-chain, 22,000 molecular weight polypeptide with 191 amino acids produced by the somatotropic cells of the anterior pituitary gland. GH secretion occurs in bursts that are greatest during nocturnal slow wave sleep. During the day, serum GH levels fluctuate greatly in response to external stimuli and endogenous regulatory mechanisms, making it difficult to assess GH levels directly. For this reason, evaluation for GH abnormalities typically relies upon measurement of insulin-like growth factor-1 (IGF-1) as a more stable marker of GH functioning, or provocative dynamic stimulation tests of GH secretion. Stimulation tests consist of serial GH serum measurements after the administration of agents, such as, insulin, GH releasing hormone (GHRH), arginine, glucagon, levodopa, or clonidine, which induce GH release via direct (as in the case of GHRH, which acts directly on somatotropic cells) or indirect mechanisms [49–51].

3. Growth hormone deficiency

While GH deficiency is traditionally considered a childhood disorder manifested by impaired skeletal growth, GH and related molecules (GHRH, IGF-1) interact with receptors on virtually all cell types, including neurons, and GH supplementation is increasingly recognized to have significant therapeutic effects beyond normalization of childhood growth. Central nervous system (CNS) functions affected by GH include sleep, cognition, mood, and neuroprotection [52]. Several regions in the CNS contain specific binding sites for this hormone, including the choroid plexus, hippocampus, hypothalamus, pituitary, putamen, and thalamus [53]. Despite an early belief that GH replacement therapy was unnecessary in adulthood, adult GH deficiency is now recognized as a serious disorder characterized by impairments in physical, cognitive, and emotional functioning, which have been shown to improve with GH supplementation [54–62]. Because of lack of specificity of the clinical manifestations of adult-onset isolated GH deficiency, which are extremely common in the general population, and include obesity, decreased muscle mass and strength, decreased bone mineral density, abnormal lipid metabolism, fatigue, depression, memory impairment, sexual dysfunction, and impaired quality of life [54], it is recommended that only specific categories of high-risk patients undergo diagnostic testing to identify adult-onset GH deficiency [63]. Currently, testing is recommended for patients with known or suspected pituitary dysfunction due to prior surgery, cranial irradiation, tumor, brain injury, or laboratory evidence of other abnormal pituitary hormone levels. In such patients found to be GH-deficient, GH supplementation has been shown to result in marked improvement in mood, energy, sense of wellbeing and overall quality of life [54–62]. Unfortunately, GH deficiency is probably underdiagnosed because diagnostic testing, especially stimulation testing, is complex and not widely available, and in accord with current guidelines, is rarely considered or performed in individuals without evidence of overt pituitary dysfunction.

3.1. Postseizure change in growth hormone levels

In contrast to the well-documented effects of seizures and epilepsy on prolactin, ACTH, cortisol, and sex hormones, there is remarkable inconsistency in reported effects of seizures on GH levels. At least two studies of patients with epilepsy have shown unequivocal increases in GH following spontaneous complex partial and generalized tonic–clonic seizures [64,65]. These results are expected, since GH, like ACTH and cortisol, is released in response to stressors including major surgery, hypoglycemia, starvation, and exercise [66]. However, other studies have shown little [42] or inconsistent [41,45] GH increases following spontaneous seizures. In one study, eight patients showed a distinct postseizure GH rise, while eight did not, resulting in overall nonsignificant GH changes postseizure [41].

3.2. Could depression in epilepsy be associated with subtle GH deficiency?

Given (1) the high rates of depression in epilepsy, (2) evidence of HPA dysregulation associated with seizures and epilepsy, and (3) recent realization that GH deficiency in adulthood can cause depression, an important question is raised: Could depression in patients with epilepsy be associated with subtle GH deficiency? Answering this question is therapeutically relevant because GH deficiency is treatable with GH supplementation. We are not aware of any published studies that address this specific issue. However, the studies of postseizure change in GH levels described above suggest that some patients with epilepsy show the expected rise in GH levels following spontaneous seizures, while some do not. Could it be that patients with depression, who constitute approximately 40–50% of the population with epilepsy, are the ones unable to mount an appropriate GH response to seizures? Support for this hypothesis comes from studies of patients with depression without epilepsy undergoing ECT who demonstrate either no change in GH post-ECT [44,47,67–69] or actually show a GH decrease [46,48]. Patients with depression also generally show diminished GH levels at baseline and in response to stimulation tests, though results are quite variable [4,50,70].

4. Areas for future research

To determine whether patients with epilepsy and depression might have subtle growth hormone deficiency, it will be important to assess GH levels in psychiatrically characterized patients in at least two ways: 1) standard clinical GH stimulation testing using GHRH and/or arginine as described above and 2) measuring GH levels after spontaneous seizures — a real-world test of GH functioning.

Because GHRH and arginine act directly on the pituitary, their administration bypasses any faulty suprapituitary neurocircuitry, including the limbic–hypothalamic circuits, which are likely to be involved in epilepsy-related depression [16,18]. Unless there is an abnormality in the pituitary itself, we suspect that standard GH stimulation testing will give rise to normal results in patients with epilepsy. In support of this contention, anecdotal data from four patients with epilepsy, incompletely controlled seizures, and variable levels of depression showed normal GH responses to GHRH/arginine stimulation testing performed at Weill Cornell Medical College in 2008, indicating that none were GH-deficient (unpublished data). Consensus guidelines stating that in the absence of other pituitary hormone abnormalities or known structural pituitary disease, stimulation testing for GH deficiency is not indicated [63], are likely applicable to most patients with epilepsy, with the possible exception of patients experiencing frequent generalized tonic–clonic convulsions, in whom pituitary GH depletion could be relevant.

Normal results from GH stimulation testing do not tell us whether patients with epilepsy may be experiencing subtle GH deficiency in their everyday lives. This is why measuring GH after a seizure, a major neural and systemic perturbation that should normally result in

significant GH release, represents a more sensitive and naturalistic way of assessing real-world GH functioning. This could be done in an inpatient video-electroencephalogram (EEG) setting via serial blood sampling following spontaneous seizures. Characterizing transient postseizure hormonal and other changes and determining how such changes correlate with mood will shed new light on the pathophysiological basis of depression and other neuropsychiatric disorders in people with epilepsy.

5. Conclusion

Growth hormone deficiency in adults is now recognized as contributing to depression and poor quality of life. Assessing for GH deficiency using stimulation testing – the most accurate method of diagnosis – is usually limited to patients with known pituitary disease. Because seizures and epilepsy affect the HPA access, patients with epilepsy may also have subtle GH deficiency, though few published studies address this issue. We believe additional research is warranted to determine when GH stimulation testing may be appropriate in patients with epilepsy. Furthermore, we suggest that research to measure GH levels following spontaneous seizures, which constitute a naturalistic, real world stimulation test, may be an even more sensitive test for subtle GH deficiency in patients with epilepsy. Because GH replacement therapy has been shown to improve mood and quality of life in patients with GH deficiency, this line of research may hold therapeutic promise for patients suffering from epilepsy-related depression.

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