Hypercortisolemia in the manifestation and treatment of mental disorders: the short literature review

Hiperkortizolemijos vieta psichikos sutrikimų pasireiškime ir gydyme: trumpa literatūros apžvalga

Emilija MILASIUTE[1], Egle MILASAUSKIENE[2] , Vesta STEIBLIENE[2]

[1]Lithuanian University of Health Sciences, Kaunas, Lithuania

[2]Clinic of Psychiatry, Lithuanian University of Health Sciences, Kaunas, Lithuania

SUMMARY

Introduction. Cortisol is a glucocorticoid hormone synthesized from cholesterol through stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. Multiple studies report that persistent excess of serum levels of cortisol due to endogenous and exogenous reasons can induce hippocampal atrophy and cerebral remodeling and result in changes in body composition, metabolic manifestations, and psychiatric symptoms. Major depression, anxiety, psychosis, and impairment of cognitive functions are mental disorders most frequently associated with hypercortisolemia. Factors affecting the onset of psychiatric comorbidities are female gender, older age, higher levels of cortisol, a prolonged period of illness, and absence of a pituitary tumor. In this review, we analyzed the impact of hypercortisolemia in the manifestation and treatment of mental disorders.

Aim. To review the experience of clinical trials and the most relevant study data about the correlation between hypercortisolemia and depression, anxiety, psychosis, impairment of cognitive functions, and management of mental disorders.

Methods. A literature search was conducted using research published in the PubMed database, that analyzed hypercortisolemia and its role in the development of mental disorders.

Results. Major depression is the most significant psychiatric comorbidity in patients with hypercortisolemia, occurring at the highest prevalence, while anxiety is most frequently noticed in the state of active disease. Hypercortisolemia rarely manifests in psychosis, although there is a pattern of psychosis being a complication of severe depression or mania. Hypercortisolemia is also associated with the impairment of cognitive functions, such as reduced concentration and memory impairment. Multiple studies have reported the correlation between the normalization of the cortisol level after surgery or medication and the reduction of psychiatric symptoms, although cognitive functions and memory remain affected.

Keywords: cortisol, anxiety, depression, psychosis, mental disorder

SANTRAUKA

Įvadas. Kortizolis yra gliukokortikoidas, sintetinamas iš cholesterolio veikiant pagumburio-hipofizės-antinksčių ašiai. Tyrimų metu pastebėta, jog nuolatos padidėjęs hormono kiekis serume dėl endogeninių bei egzogeninių priežasčių gali sukelti hipokampo atrofiją ir smegenų remodeliaciją, o to pasekmė – kūno kompozicijos bei medžiagų apykaitos pasikeitimai, psichiatriniai simptomai. Dažniausiai su hiperkortizolemija siejami nerimas, depresija, psichozė ir kognityvinių funkcijų sutrikimai. Veiksniai, turintys įtakos psichikos sutrikimų atsiradimui, yra moteriška lytis, vyresnis amžius, didesnis kortizolio kiekis, ilgesnė ligos trukmė ir naviko hipofizėje nebuvimas. Šiame straipsnyje mes apžvelgsime hiperkortizolemijos įtaką psichikos sutrikimų pasireiškimui bei gydymui.

Tikslas. Apžvelgti klinikinius tyrimus ir aktualiausius literatūros duomenis apie kortizolio sąsajas su depresija, nerimu, psichoze, kognityvinių funkcijų sutrikimu ir jų gydymu.

Metodai. Literatūros apžvalga atlikta naudojantis tyrimais bei apžvalginiais straipsniais paskelbtais PubMed duomenų bazėje apie hiperkortizolemijos vaidmenį psichikos sutrikimų išsivystyme.

Rezultatai. Depresija – reikšmingiausias ir labiausiai paplitęs psichikos sutrikimas tarp pacientų su nustatyta hiperkortizolemija, kuomet nerimas dažniausiai pastebimas aktyvios ligos metu. Psichozė yra reta hiperkortizolemijos išraiška, dažniau pasireiškianti kaip sunkios depresijos ar manijos komplikacija. Kognityvinių funkcijų sutrikimai, tokie kaip sutrikusi koncentracija ir atmintis, taip pat siejami su hiperkortizolemija. Tyrimų metu pastebėta sąsaja tarp hormono kiekio normalizavimosi po operacijos ar vaistų vartojimo ir psichiatrinių simptomų sumažėjimo, tačiau kognityvinės funkcijos ir atmintis išlieka paveikta.

Raktiniai žodžiai: kortizolis, nerimas, depresija, psichozė, psichikos sutrikimas.

Corresponding author: Emilija Milasiute, Lietuvos sveikatos mokslų universitetas, Eivenių g. 2, Kaunas; E-mail: milasiutemilija@gmail.com

INTRODUCTION

Cortisol is a glucocorticoid hormone consistently assessed in psychoendocrinology research. Frequently called stress hormone, cortisol is synthesized from cholesterol in the fasciculate layer of the adrenal cortex through stimulation of the hypothalamic-pituitary-adrenal (HPA) axis [1]. Subsequently to the binding of adrenocorticotropic hormone (ACTH) at the cholesterol receptor, multiple enzymatic conversions are commenced to convert the cholesterol into a corticosteroid [2]. The main processes that are affected by cortisol are gluconeogenesis, glycogenolysis, immune response, sodium transport, and others [3, 4]. Standard values of cortisol depend on the time of the day and the clinical factors. For a blood sample taken at 8 in the morning, it is generally 140 to 690 nmol/l and by afternoon (15–16 h) it falls 50%.

Hypercortisolemia is a condition caused by persistent excess of serum levels of cortisol due to endogenous (Cushing's disease, ectopic Cushing's syndrome, cortisol-producing adenoma, adrenal carcinoma, primary pigmented nodular adrenocortical disease, bilateral adrenal hyperplasia, ACTH-independent macronodular adrenocortical hyperplasia) and exogenous (corticosteroid medications) reasons [4–6]. Prolonged excess of glucocorticoids can induce hippocampal atrophy and cerebral remodeling due to pathological mechanisms such as disruptions in neuronal homeostasis, reduced glucose utilization, and abnormalities in neurotransmitter signaling [7, 8]. Modifications result in changes in body composition and metabolic manifestations such as dyslipidemia, insulin resistance, diabetes mellitus, hypercoagulability, and hypertension [6, 9, 10].

Another major part of the clinical symptomology of hypercortisolemia in both active and remission phases of the disease is psychiatric symptoms. Multiple studies have shown that affective disorders such as anxiety, major depression, and bipolar disorder have been identified as the most frequent, whilst psychosis and mania are less common [5, 7, 11]. Patients with hypercortisolemia with higher urinary cortisol levels, longer duration of the disease, absence of pituitary tumor, and are female or older are more likely to develop psychiatric illness [7, 12–15].

In this non-systematic literature review, we had analyzed the role of hypercortisolemia in the development and treatment of mental disorders.

METHODS

This literature review was performed focusing on primary literature on keywords in the PubMed database. The keywords were "hypercortisolemia", "mental disorders", "anxiety", "depression", "psychosis". Of 177 articles, selected according to the search criteria – 51 of them were used to conduct this literature review. Due to the nature of the review, we included studies on physiology, clinical manifestations, and treatment. Only English language and full-text articles were included.

RESULTS

The rate of psychiatric manifestations in patients with hypercortisolemia range amongst studies. In reviewed literature, the most regularly reported mental disorders are depression [7, 16, 17–27], anxiety [7, 17, 28–33], psychosis [6, 28, 35–43], and impairment of cognitive functions [46–51]. Psychiatric comorbidities can vary from mild forms to severe manifestations and significantly reduce the quality of a patient's life. Although most of the psychiatric symptoms tend to reduce after surgery or drug therapy [13, 22–25, 28, 30, 36–40,44], numerous studies report that the disease can persist [6, 26–27, 32–33, 49–51].

Depression

Studies report, that from 35 to 65 % of patients with depression demonstrate evident irregularities in neuroendocrine function, such as modifications in the hypothalamic-pituitary-adrenal (HPA) axis [16]. Major depression is the most significant and life-threatening psychiatric difficulty in patients with hypercortisolemia, developing at 50–80% [17,19]. Frequently the depression is intermittent, with episodes of aggravation occurring irregularly [7].

In a longitudinal study, Starkman et al. reported 77% of the patients as having depressed mood characterized by sadness ranging from brief to constant with symptoms such as increased crying time (63%) and social withdrawal (46%). Irritability is a recurrent manifestation, occurring in 86% of patients, and having an early onset [7]. Atypical depression is also not infrequent in patients with hypercortisolemia due to hypoactivation of the stress system resulting in severe fatigue, excessive sleep, and apathy [17–19].

Differentiation between primary major depression followed by hypercortisolemia and Cushing's syndrome and secondary depression caused by hypercortisolemia is relevant but challenging. Research suggests that the main differences are that hypercortisolemia is associated with clinical features, such as facial plethora, central obesity, bruising, purplish striae, hypertension, and osteoporosis, whilst patients with primary major depression frequently have a family history of mental illness and mood changes seem to be more permanent and non-variable than those with hypercortisolism [20,21].

Multiple studies have reported the correlation between the normalization of the cortisol level after surgery and the reduction of mood disorders [22, 23] with a partial decrease in depression 1 year after pituitary surgery from 24% to 11% [24]. When the surgery can not be performed, antiglucocorticoids such as mifepristone have been reported to be as effective [25]. Although there is evidence, that even after correction of hypercortisolism mood disorders may persist, as the hippocampus, the amygdala, and the cerebral cortex have a plethora of glucocorticoid receptors and are especially sensitive to the glucocorticoid excess [6,26] and there have not been found differences between pituitary pituitary-dependent and pituitary-independent forms of hypercortisolemia [27].

Anxiety

Another common disorder in patients with hypercortisolemia is anxiety, most frequently noticed in the state of active disease [17], although the differentiation between autonomous anxiety and anxiety induced by depression remains arduous [28]. Correlation between the severity of

hypercortisolism and ACTH and psychiatric manifestations can be seen. Patients with high levels of cortisol but with low ACTH had milder symptoms of anxiety [7].

Starkman et al. reported that 66% of patients were diagnosed with generalized anxiety and symptoms such as shaking, palpitations, and sweating [7], whilst Loosen et al. stated that 79% of patients had generalized anxiety (more than major depression disorder) and 53% had panic disorder [29]. Kyung-Jee Nam et al. describe a case of a patient with a 2-year history of fatigue and anxiety induced by hypercortisolemia due to adrenal adenoma. Psychiatric manifestations disappeared shortly after the surgery [30]. A study by Dimopoulou et al. reported that hypercortisolemia was associated with anxiety-related personality traits, as patients scored higher in harm avoidance and neuroticism, and lower in novelty seeking and extraversion [31]. Findings are supported by a hypercortisolemia-induced decrease in hippocampal volume and cerebral atrophy [6, 32, 33].

Psychosis

Hypercortisolemia rarely manifests in psychosis, therefore a limited number of published articles and case reports focuses on this matter [34], although even hypercortisolemia with less prominent physical manifestations can result in acute psychosis [35]. The pattern of psychosis being a complication of severe depression or mania can be seen [28].

Tang et al. reported two cases of acute-on-chronic psychotic depression associated with hypercortisolemia, manifesting in auditory hallucinations and nihilistic delusions due to adrenal adenoma and metastatic adrenal carcinoma [6]. WU et al. described a case of psychosis with acute irritability, mania, aggressive behavior, persecutory delusions, and suicidal ideation induced by hypercortisolemia, which decreased after removal of a benign ACTH-independent adrenal adenoma [28]. Zielasek et al. reported a case of a psychotic patient with persecutory ideas, social withdrawal, self-neglect due to benign adrenal adenoma [36]. Tran and Elias described a psychosis, induced by a pituitary macroadenoma with no typical signs of hypercortisolism [37]. Górniak and Rybakowski reported a case of a patient with an acute paranoid syndrome in the course of caused by a hypophysial adenoma [38]. Chu et al. described a patient suffering from psychosis induced by hypercortisolemia due to ACTH-secreting pituitary macroadenoma [39]. Hirsch et al. reported a case report of a patient with a schizophrenia-like psychotic state, with an immediate response to the normalization of cortisol levels [40].

Multiple studies stated that injected glucocorticoids can induce a temporary secondary mania and psychosis, although there is no known correlation between the frequency or dose of the medication [41–43].

The treatment of psychosis induced by hypercortisolemia is typically arduous, as generally the response to antipsychotic medication is insufficient or it does not exist at all. Although, if surgery (resection of tumor) is performed the symptoms frequently reduce [13, 36–39, 44].

Cognitive function

Hypercortisolemia is also associated with the impairment of cognitive functions, as frequently as 66% in reduced concentration and 83% in memory impairment [46]. Starkman et al. reported patients with altered learning, delayed recall, and lower scores in visual and spatial abilities in patients with chronic hypercortisolemia [46]. Other reports stated impaired attention, reasoning, and verbal fluency compared with healthy controls [47]. Studies report that this is due to a large number of glucocorticoid receptors in the hippocampus, as it is a brain region responsible for learning and memory [32], although the wide distribution of the receptors in the cerebral cortex and other extrahippocampal sites can also be targeted [6, 33].

Subsequently to the normalization of cortisol levels, the volume of the hippocampus tends to increase [48], although cognitive functions and memory remain affected [49]. Even after the use of exogenous glucocorticoids, patients had impaired memory compared to healthy controls [50]. A study by Papakokkinou et al. demonstrated that mental fatigue, characterized by impairment during sensory stimulation and performing mentally arduous assignments, is common in patients with hypercortisolemia even in remission [51].

CONCLUSIONS

In this review, we summarised findings on the most relevant studies about hypercortisolemia induced psychiatric symptomology. Effects of cortisol are significant, thus it is crucial to be observant to avoid misdiagnosis between primary psychiatric comorbidities and secondary mental disorders due to hypercortisolemia. Further studies are needed to expand knowledge on the role of hypercortisolemia in mental disorders and adapt appropriate and timely treatment.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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