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ORIGINAL ARTICLE

Association of Cushing Syndrome's Emotional Distress and Cognitive Symptoms with Cortisol Levels

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ABSTRACT

Background: Cushing's syndrome is a rare endocrine disorder characterized by excess cortisol levels, leading to physical, emotional and cognitive symptoms. The syndrome can result from various causes, it is most commonly due to prolonged corticosteroid use, but endogenous causes can include tumors of adrenal gland, pituitary gland or ectopic adrenocorticotropic hormone producing tumors.

Objective: To determine the association of Cushing syndrome's emotional distress and cognitive symptoms with cortisol levels.

Study Design: Retrospective study

Place and Duration of Study: Medical Unit-2, Bolan Medical Complex Hospital, Quetta from 1st Jan 2009 to 31st July 2023.

Methodology: Fifty patients diagnosed with Cushing's syndrome, aged 25-40 years, with chronic hypercortisolism were enrolled. Patients with a history of psychiatric illness were excluded. The diagnosis was confirmed through either 24-hour urinary free cortisol, and/or dexamethasone suppression, late night salivary cortisol tests. Patients were categorized into "Cases" (high cortisol and emotional symptoms) and "Controls" (high cortisol, minimal emotional symptoms).

Results: High cortisol levels were significantly associated with cognitive and emotional distress symptoms (p=0.021).Emotional complaints, particularly anxiety, sadness, and emotional liabilities, were more prevalent in cases with high cortisol levels. The cognitive symptom most commonly seen was disturbance of memory. But attention, word finding and processing speed were also more commonly affected with high cortisol levels. Treatment outcomes varied between cases and controls, with pituitary-directed medical treatment being more common in controls (40%) than cases (14.2%).

Conclusion: There is a significant association between high cortisol levels, cognitive and emotional distress symptoms in Cushing's syndrome patients.

Keywords: Cushing syndrome, Cognitive, Cortisol, Emotional distress, Quality of life

INTRODUCTION

Cushing "syndrome" refers to the manifestations of excessive corticosteroids, commonly due to supraphysiological doses of corticosteroid drugs and rarely due to spontaneous production of excessive cortisol by the adrenal cortex glands. Endogenous Cushing syndrome (CS) may be adrenocorticotropic hormone (ACTH) dependent (80-85%) or independent (15%-20%). Adrenocorticotropic hormone dependent causes include, most commonly, a pituitary corticotrophic adenoma (Cushing's disease). Adrenocorticotropic hormone independent causes are from unilateral adrenocortical tumours, which can be benign or malignant, or bilateral adrenal hyperplasia.[1-4]

The major clinical symptoms include central obesity, particularly in the midsection of the body, moon face, buffalo hump, purple striae, hirsutism, acne, glucose intolerance, high blood pressure, cardiovascular diseases and fractures.[4]

Hypercortisolism affects psychological and emotional functioning in the long term. Patients with CS have lower quality of life (QoL), lower body image perception and higher levels of depression. [5,6]

In addition to medical comorbidities, patients with CS frequently report impairments in cognitive and emotional functioning. Cushing's syndrome is associated with brain atrophy and subsequent cognitive impairments. Given neuroimaging research that implicates alterations in structure and function in the brain in this population. Impairments in have been documented in the domains of memory, concentration, visuospatial functioning, and language functioning. Patients with active CS also demonstrate significant emotional changes due to the hypersecretion of cortisol, notably symptoms of depression, anxiety, and mania. Emotional distress may play a role on cognitive functioning and lead to decline in quality of life. Suicidal thoughts and suicide attempts have also been described. Neurocognitive disorders contribute to significantly impair health-related quality of life. Normalization of cortisol level plays a crucial role in the treatment of mood disorders in the course of Cushing's syndrome.[7-10]

When CS is suspected, the first step is to exclude hypercortisolemia attributed to exogenous glucocorticoid exposure. Then one of three biochemical screening tests is recommended: (a) the 24-hour urinary free cortisol (UFC) test, (b) the late-night salivary cortisol test, or (c) the 1 mg overnight dexamethasone suppression test (DST). After a diagnosis of CS is made, the primary cause should be determined, typically by abdominal or pituitary imaging to identify tumors or adrenal hyperplasia.[10]

The treatment of Cushing's syndrome includes controlin cortisol production or managing symptoms or surgery wherein the tumors or affected adrenal glands are removed. Radiation therapy is also an optional treatment for reducing the size of the tumor.[7-10]

The present study was designed to assess the association of Cushing syndrome's neurocognitive and emotional features with high levels of cortisol in patients who were chronically suffering from hypercortisolism. The results of this study provided substantial evidence that can assist in early management and treatment of the emotional and cognitive features of Cushing's syndrome and reduce the risk of poor quality of life and comorbidities.

MATERIALS AND METHODS

This retrospective study was conducted at the Medical Unit-2, Bolan Medical Complex Hospital Quetta from 1st January 2009 to 31st July 2023. A total of 50 patients diagnosed with Cushing syndrome were included. The sample size was generated through WHO sample size calculator using 80% power of test, 95% CI and 5% margin of error. The patients within the age group of 25-40 years, having chronic hypercortisolism were included in the study. Patients having psychiatric illness history were excluded from the study. The diagnosis of the disease was made through abnormal results of the screening of 24-hour urine free cortisol as well as the dexamethasone suppression and the results of the bedtime/ late night salivary cortisol. Magnetic resonance imaging (MRI) with

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gadolinium contrast enhancement was also conducted. The research study aspect was based on the presence of the emotional and cognitive symptoms and was measured through the available neurological assessment record. The records of evaluation interviews for assessing of emotional symptoms were also gathered. The interview detailed their previous and current complaints. The demographic details of each patient were separately entered in a well-structured questionnaire wherein other diagnostic and clinical information was also documented. Morning cortisol/ACTH levels were tested through 3 cc blood withdrawal and analyses through ELISA based kit method. Patients were further categorized on the basis of their hypercortisolism and emotional/ cognitive symptoms. Those patients which were having high cortisol but minimal emotional symptoms were categorized as "Control" while those having high cortisol levels and emotional distress symptoms related with Cushing's syndrome were categorized as "Cases". Cases were treated through the administration of Emotionality, Activity, Shyness and Sociability (EAS) measurements. This was followed by the treatment of the patients and was based on their cortisol and clinical symptoms, wherein surgical intervention was considered as one other main strategy of treatment. The data was analyzed using independent t test wherein p value <0.05 was considered as significant.

RESULTS

There were 72% females while 28% were males. The mean age of the participants was calculated as 31.8±3.5 years. The ACTH level was measured as 87.8±41.9 pg/ml. The normal range of ACTH is 10-50 pg/ml and hereby was observed as high. The normal range of urine free cortisol is 10to55mcg/day whereas in the enrolled participants it was as high as 383.5±281.3 mcg/day (Table 1).

The clinical features including hypertension and diabetes mellitus are the most common, followed by osteoporosis, hirsutism and amenorrhea in the women. Hypokalemia was also found among participants (Fig. 1). High cortisol levels were more commonly (p value 0.021) associated with the emotional distress/cognitive and emotional symptoms, as there were 35 (70%) such cases who had high cortisol levels as well as emotional distress symptoms while only 15 (30%) of the participants had high cortisol levels that were not associated with emotional symptoms (Fig.2).

Table 1: Demographic and laboratory test of the patients (n=50)

Variable	Mean±SD
Gender	
Males	14 (28%)
Females	36 (72%)
Age (years)	31.8±3.5
Endocrinological values at the time of testing	
ACTH (pg/mL) at 8 am	87.8±41.9
Urine free cortisol (mcg/day)	383.5±281.3
Other blood values at the time of testing	
Potassium (mEq/L)	4.1±0.4
Glucose (mg/dL)	109.1±33.6
Hemoglobin A1c (%)	6.3±1.2

Table 2: Comparison of cognitive and emotional complaints in case and control groups (n=50)

Complaint	Controls n=15	Cases n=35	P value
Cognitive			
Attention	12 (80%)	25 (71.4%)	0.211
Memory	4 (26.6%)	25 (71.4%)	0.031
Word finding	8(53.3%)	20 (57.1%)	0.756
Processing speed	4 (26.6%)	12 (34.3%)	0.519
Emotional/psychiatric			
Irritability	8 (53.3%)	20 (57.1%)	0.881
Anxiety	4 (26.6%)	14 (40%)	0.081
Sadness/low mood	4 (26.6%)	14 (40%)	0.081
Emotional liability	2 (13.3)	12 (34.3)	0.041

The comparison of cognitive and emotional complaints in controls and cases presented a significant variance within the two categories. The major emotional distress was linked with emotional liabilities which were observed in 34.3% of the cases versus 13.3% of the controls (Table 2). Treatment outcomes varied between cases and controls, with pituitary-directed medical treatment being more common in controls (40%) than cases (14.2%). These findings highlight the importance of considering cognitive and psychiatric complaints in the management of Cushing's syndrome.

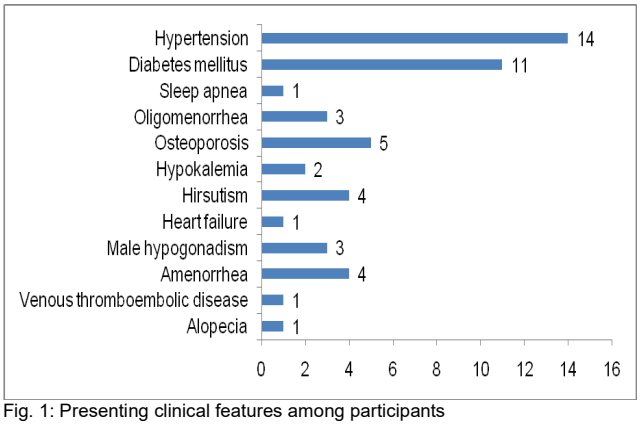

Fig. 1: Presenting clinical features among participants

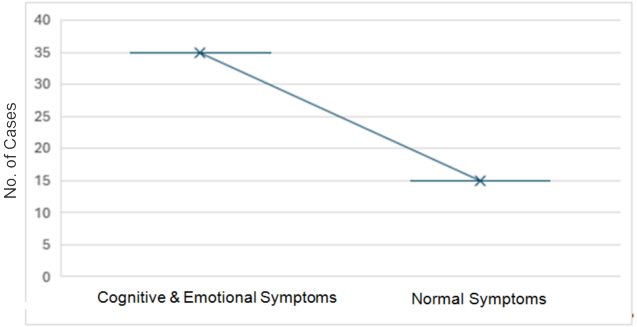

Fig. 2: Association of high cortisol with contagious symptoms

DISCUSSION

Cushing syndrome is defined as a prolonged increase in plasma cortisol levels that is not due to a physiological etiology. Although the most frequent cause of Cushing syndrome is exogenous steroid use, the estimated incidence of Cushing syndrome due to endogenous overproduction of cortisol ranges from 2 to 8 per million people annually. [11]

Many studies have been conducted conducteds of cortisol on the brain. Memory impairments are present in patients with Cushing's syndrome (CS) and are related to hippocampal damage; functional dysfunctions would precede structural abnormalities as detected by brain imaging. There is controversy concerning the reversibility of brain impairment. It seems that longer disease duration and older age are associated with less recovery of brain functioning. Conversely, earlier diagnosis and rapid normalization of hypercortisolism appear to stop progression of brain damage and functional impairments. Patients with untreated CS show significant reduction of gray matter in the cerebellum and hippocampus. [12, 13]

Other studies have been done on the affects of steroids on emotion & cognition. Cushing syndrome is associated with a specific spectrum of dementia-like symptoms, including psychiatric disorders, such as major depression, anxiety and mania, and neurocognitive alterations, like impairment of memory and concentration. This pattern of clinical complications, which significantly impair the health-related quality of life of CS patients, is sometimes referred to as steroid dementia syndrome (SDS). The

SDS is the result of anatomical and functional anomalies in brain areas involved in the processing of emotion and cognition.[14]

Therefore, CS has an adverse impact on the quality of life and life expectancy of affected patients. Most recent evidence supports the persistence of increased morbidity and mortality even after long-term remission. These findings highlight the need for early recognition and effective management of patients with CS, which should include active treatment of the related comorbid conditions. In addition, it is important to maintain a surveillance strategy in all patients with CS, even many years after disease remission, and to actively pursue specific treatment of comorbid conditions beyond cortisol normalization.[15]

Depression is also linked to the psychological effects of living with a debilitating condition, and to the lowered self-esteem caused by the physical manifestations of CS, including weight gain around the abdomen, the development of a hump between the shoulders, facial redness, hirsutism, muscle wasting, and weakness.[16,17]

Older age and depression at diagnosis predict worse long-term outcome for quality of life (QoL), regardless of aetiology. In fact, depressive symptoms, which negatively impact QoL, are present in most CS patients, either at baseline or during follow-up.[18]

The most frequent cause of Cushing syndrome is exogenous steroid use, and Corticosteroids are used to treat both acute (e.g. Asthma exacerbation) and chronic (e.g. systemic lupus erythematosus) conditions. The adverse effects such as mood liability, cognitive impairments or psychotic can present alone or in combination. In a case-control study of 20 patients receiving long-term low-dose corticosteroid therapy (prednisone, 7.5 mg/d for >6 months) and 14 volunteers with similar illnesses who were not receiving corticosteroid therapy, these patients presented more commonly with depression than with mania, a characteristic difference associated with long-term corticosteroid therapy. These findings are consistent with published reports of patients with Cushing disease, a disorder of excessive endogenous cortisol production, in which depression was identified in 67% of patients, whereas mania was identified in only 27% to 31%. Most patients will recover fully with dose reduction or discontinuation of corticosteroid therapy.[19]

Further evidence highlights that both dose and duration of corticosteroid play critical roles in determining psychiatric outcomes. Higher concentrations (e.g., >40 mg/day) are more likely to trigger manic and psychotic symptoms, especially in acute scenarios, while lower chronic doses can lead to persistent mood disturbances and anxiety over time. The discontinuation of corticosteroid may alleviate symptoms. Therefore, while corticosteroids may be essential for certain conditions, their emotional and cognitive side effects, warrant careful monitoring and dose management.[20]

Cushing syndrome, mostly is due to benign (pituitary, adrenal and ectopic tumors) CS, and few cases are malignant CS. In all cases, acute and life threatening complications are most commonly due to cardiovascular complications. Mortality was associated with higher urinary free cortisol (UFC). The other life threatening complications like hypokalemia can lead to life threatening arrhythmias. Depression with acute suicidal thoughts has been found in 0.9% of all cases.[21]

Patients with active CS also demonstrate significant emotional changes due to the hypersecretion of cortisol. Emotional distress may play a role on cognitive functioning and lead to decline in quality of life.[7]

The most important interventions are control of the cortisol level, lowering the high cortisol state, and the ultimate resolution of hypercortisolism to improve psychiatric and neurocognitive disorders, such as concentration and memory. However, it is important to note that, even after the resolution of hypercortisolism and the improvement of psychiatric and neurocognitive disorders, some patients still experience depression anxiety, memory, and concentration problems due to residual effects of hypercortisolism on the brain. The research studies show that psychiatric symptoms caused by CS have a detrimental impact on both physical and mental quality of life of patients with CS. Therefore, close and long-term monitoring of emotional symptoms, psychiatric and neurocognitive symptoms should be standard procedure in the management of CS both in the active phase of the illness and after remission.[22]

CONCLUSION

A significant association between high cortisol levels and emotional distress symptoms in Cushing's syndrome patients were found. Early recognition and intervention of these symptoms can improve treatment outcomes and quality of life. A multidisciplinary approach is necessary to effectively manage the complex symptoms of this rare endocrine disorder.

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