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CUSHING 'S SYNDROME: PATHOPHYSIOLOGY AND MANAGEMENT

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Abstract:

Introduction: *Cushing's syndrome a state of high blood cortisol level due to various reasons. The syndrome has much comorbidity like hypertension, heart diseases, pathological fractures, diabetes mellitus, and coagulopathy. the diagnosis is largely clinical based on history and examination, and treatment depends upon the cause.*

Aim of the work: *In this study, our aim was to understand the pathophysiology behind Cushing's syndrome and its various causes. We will also discuss the diagnoses and ways of management.*

Methodology: *we conducted this review using a comprehensive search of MEDLINE, PubMed and EMBASE from January 1994 to March 2017. The following search terms were used: Cushing's syndrome, Cushing's disease, adrenocorticotrophic hormone, high blood steroid levels, pathological fractures, diagnosis of Cushing's, management of Cushing's.*

Conclusion: *Cushing's syndrome is the result of any long-term pathology that leads to high levels of circulating cortisol in the bloodstream. Up to 80% of patients with Cushing's syndrome can have hypertension which will lead to significant increase in both morbidity and mortality if left untreated. Asides from blood pressure control, surgical resection remains the most ideal treatment modality in the treatment of most causes of Cushing's syndrome.*

Keywords: *Cushing's syndrome, Cushing's disease, high blood cortisol*

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INTRODUCTION:

The term 'Cushing's syndrome' is used to describe the pathological status of high cortisol levels that result from increased production of adrenocorticotropic hormone (ACTH), or abnormal adrenal production of cortisol. Cushing's syndrome is known to cause several serious comorbidities and can sometimes be fatal. Associated comorbidities include hypertension, cardiovascular disease, coagulopathy, pathological fractures, diabetes mellitus, and infections. These consequences of Cushing's syndrome make patients at higher mortality risk, even after treatment of the condition. Therefore, it is crucial to early diagnose and properly manage the disease as soon ass possible, to avoid the development of late sequalae that will lead to higher mortality **[1]**.

Generally, the diagnosis of Cushing's syndrome can be made based of clinical manifestations. However, some of these clinical manifestations are non-specific and can be found in the general population. These include increased blood pressure and abnormal weight gain. Therefore, the duration of these manifestations is also an essential information that needs to be obtained and will help distinguish the disease. In addition, when there is high suspicion of Cushing's syndrome, laboratory investigations must be considered to confirm the diagnosis **[2]**.

When a diagnosis of Cushing's syndrome has already been confirmed, the underlying cause of it should be determined. The reason of this is that the most effective treatment of Cushing's syndrome, is the treatment of its underlying cause. Usually, the best treatment is surgery to resect the abnormal tissue that causing the syndrome. When surgery is not feasible, or when there is a recurrent or a metastatic disease, cortisol levels are usually normalized used either pharmacological therapy, or bilateral adrenalectomy **[2]**.

Methodology:

We did a systematic search for blunt abdominal trauma and imaging using PubMed search engine (http://www.ncbi.nlm.nih.gov/). EMBSE, and Google Scholar search engine (https://scholar.google.com). Our search looked for radiology modalities that are used in cases of blunt abdominal trauma. All relevant studies were retrieved and discussed. We only included full articles. The following search terms were used: Cushing's syndrome, Cushing's disease, adrenocorticotrophic hormone, high blood steroid levels, pathological fractures, diagnosis of Cushing's, management of Cushing's

The study was approved by the ethical board of King Abdulaziz University.

PATHOPHYSIOLOGY OF CUSHING'S SYNDROME

ACTH-dependent Cushing's syndrome

Cushing's disease

Most causes of Cushing's syndrome are caused by a pituitary tumor releasing abnormally high levels of ACTH; hyperplasia of the pituitary, on the other hand, is relatively rare. A pituitary tumor will increase ACTH serum levels and lead eventually to the development of a bilateral hyperplasia of the adrenal cortex and an increase in cortisol secretion. When serum ACTH levels and cortisol levels are measured in the morning, there show only moderate increase. However, when they are measured in the late evening, they show significant elevations. Having a chronic status of hypersecretion of cortisol will lead to the suppression of the hypothalamic secretion of CRH, and the pituitary secretion of ACTH. The best method to test for endogenous hypersecretion of cortisol is the collection and measurement of 24-hour urinary-free cortisol, as this test will reflect the daily secretion of cortisol **[3]**.

Ectopic ACTH-producing tumors

Moderate to severe elevation in ACTH serum levels can be caused in pulmonary malignancies (most likely small cell carcinoma), foregut and bronchial carcinoids, thymomas, tumors of the pancreatic islet cells, thyroid medullary carcinomas, and pheochromocytomas. This hypersecretion of ACTH will similarly lead to development of hyperplasia of the adrenal cortex, and abnormal secretion of corticosteroids. Similar to Cushing's disease, excretion of cortisol in the urine will also be high in this case. Later, these high levels of cortisol will lead to the suppression of the hypothalamic-pituitary axis with decreased secretion of ACTH. However, the secretion of ACTH from these ectopic tumor tissues will not be regulated by the hypothalamic-pituitary axis **[4]**.

In such cases, clinical manifestations of high cortisol levels will start rapidly with dramatical increase in severity. Patients will soon start to have significant weight loss, generalized weakness, increased blood pressure, decrease potassium levels, diabetes mellitus, and hyperpigmentation. However, patients do not usually show cushingoid features because of the relatively short duration of the pathology **[4]**.

Ectopic CRH syndrome

In cases where there is an abnormal secretion of CRH from an ectopic tumor out of the hypothalamus, hyperstimulation of the pituitary occurs that will lead to hyperplasia of the corticotroph cells of the

pituitary. This will eventually lead to high serum levels of ACTH. All later steps will produce clinical manifestations that are similar to those of an ectopic tumor secreting ACTH **[5]**.

ACTH-independent Cushing's syndrome

Adrenocortical adenoma

An adenoma of the adrenal cortex can develop and lead to an elevation of cortisol secretion, which, in turn, will lead to a suppression of both CRH and ACTH secreted by the hypothalamus and the pituitary, respectively. Eventually, both the normal cells in the adrenal cortex, and the pituitary corticotrph cells will become atrophied due to becoming inactive and suppressed. This will cause serum levels of DHEAS and urinary levels of 17 KS to be normal or low. In some cases, adenomas of the adrenal cortex can also produce androgens. However, it is relatively rare for adenomas to produce estrogens **[6]**.

Adrenocortical carcinoma

Generally, carcinomas of the adrenal cortex secrete low levels of cortisol. Therefore, clinical manifestations of Cushing's syndrome are only seen when the size of the carcinoma is large enough to produce high amounts of cortisol **[7]**.

Iatrogenic Cushing's syndrome

Cushing's syndrome can be cause due to iatrogenic causes, which has been recently increasing. This most commonly occurs from the excessive administration of synthetic cortisol. This exogenous administration of cortisol will lead to the inhibition of both CRH and ACTH secretion by the hypothalamus and pituitary, respectively, and will cause bilateral atrophy in the adrenal cortex tissues. Basal serum levels of both ACTH and cortisol will be low. Several diseases are usually associated with Cushing's syndrome including cataracts, pancreatitis, benign intracranial hypertension, glaucoma, and femoral head necrosis. Sudden cessation of exogenous cortisol will most likely lead to the development of secondary insufficiency of the adrenal cortex. This must be managed using cortisol replacement until the hypothalamic-pituitary axis is fully recovered **[8]**.

Clinical Picture

Clinical signs and symptoms of Cushing's syndrome can vary among patients, and usually depend on many factors including age, sex, duration of the disease, underlying cause, and severity. The most common clinical manifestation of Cushing's syndrome is wright gain and central obesity. Central obesity results from the abdominal deposition of visceral fat. It is usually associated with limbs thinning from atrophy of skeletal muscles. Other typical features of Cushing's syndrome include 'moon face', which is having a rounded plethoric face, and 'buffalo hump', which is a result of abnormal fat deposition in the posterior neck. Purple striae in the lateral abdomen, axillae, and internal thighs can be also observed along with bruising all over the body **[9]**. It is not uncommon to develop gonadal dysfunction; it can occur in up to 75 percent of patients. However, clinical manifestations of this gonadal dysfunction differ according to sex; men will usually develop low libido and erectile dysfunction, whereas females will mainly suffer from irregularities in menstrual cycle. Alopecia and hirsutism are present in a smaller number of females, and usually result from increased androgens levels and, possibly, the concomitant presence of polycystic ovarian syndrome. Both males and females with Cushing's syndrome can develop from infertility **[10]**.

Metabolic syndrome is considered to be one of the most important systemic manifestations that can complicate Cushing's syndrome, being present in up to 75% of patients. It manifests as obesity, diabetes, increased blood pressure and dyslipidemia. Both the metabolic syndrome and coagulopathies that result from Cushing's syndrome are the main cause of increased risk of cardiovascular diseases in these patients, which persists even after treatment of the disease **[11]**.

Half Cushing's syndrome patients can develop nephrolithiasis. However, it is asymptomatic in most cases. In addition, about half of the patients with Cushing's syndrome will later develop osteoporosis which will result in pathological fractures. Osteoporosis usually improves spontaneously following treatment of Cushing's syndrome. However, in some cases, specific treatment is required **[12]**.

Many patients who suffer from Cushing's syndrome can develop psychiatric symptoms or neurologic symptoms. Psychiatric symptoms can include anxiety, depression and psychosis. On the other hand, neurologic symptoms are usually associated with reduced brain volume and manifest as impaired memory and cognition. After treatment of the disease, neurologic symptoms can recover slowly. However, psychiatric symptoms are more likely to persist. This leads to significant impairment in the quality of life of Cushing patients, even those who were completely treated. When occurs in children and adolescents, the most important clinical manifestations of Cushing's syndrome are delayed

growth, delayed puberty, and central obesity **[13]**.

Hypertension in Cushing's syndrome

Patients who have Cushing's syndrome have five times the risk of developing a vascular disease when they are compared to the general population. This is the main cause of significantly higher mortality in this population. A previous study has found that of 25 patients with Cushing's syndrome, eight had atherosclerotic plaques in their carotid arteries. On the other hand, only two of 32 of controls showed similar plaques in their carotid arteries **[14]**.

Generally, Cushing's syndrome patients develop diabetes, increased blood pressure, obesity, and dyslipidemias, all of which are considered to be risk factors for developing cardiovascular diseases. In fact, up to 80% of adults with Cushing's syndrome, and 95% of adults with ectopic Cushing's syndrome will develop hypertension. However, the prevalence of hypertension in children and adolescents with Cushing's syndrome is relatively lower and is about 47%. On the other hand, Cushing's syndrome that develops as a result of iatrogenic intake of cortisol is associated with very low prevalence of hypertension that is about 20% **[15]**.

Generally, and regardless of the presence of Cushing's syndrome, blood pressure levels proportionally correlate with the risk of heart failure, myocardial infarction, strokes, and chronic kidney diseases. A systematic review and meta-analysis of over sixty studies reported that the mortality from a stroke or an ischemic heart disease will double for each 20 mmHg increase in the systolic blood pressure, or each 10 mmHg increase in the diastolic blood pressure. Having such significant impact on morbidity and mortality, hypertension should be always addressed and properly treated in Cushing's syndrome patients **[16]**.

Diagnostic tests

1. Evaluation of the sellar region by using magnetic resonance investigation

This investigation is essential to evaluate the structure and anatomy of the pituitary gland and confirm the presence and exact location of the adenoma before performing a surgery. MRI is considered to be one of the most accurate methods that can detect pituitary adenomas with high sensitivity and specificity **[17]**.

2. IPSS with Desmopressin or CRH

This test is performed by the simultaneous injection of desmopressin (or CRH) into bilateral inferior petrous sinuses. This will be followed by measuring the basal level of ACTH in the serum **[18]**.

3. Overnight Dexamethasone 8 mg

The main use of this test is to distinguish Cushing's syndrome caused from ectopic ACTH secretion from other causes of Cushing's syndrome. It is performed be administrating dexamethasone (2 mg every six hours), then determining levels of cortisol in the serum in the next morning. If this test shows elevated secretion of cortisol, this will indicate the presence of an ectopic ACTH secretion. On the other hand, if this test shows decreased secretion of cortisol, this will indicate the presence of Cushing's disease **[19]**.

Treatment

The goal of treatment in Cushing's disease is the improvement of clinical signs and symptoms. This is mainly achieved by resecting the tumor, decompressing the optic nerve and optic chiasm, restoring normal levels of hormones secretion, and preventing the recurrence of the disease. It is also essential to reserve normal anatomical structure and integrity with avoiding the development of any possible complications. Current protocols for treatment of pituitary adenoma include surgical resection, radiotherapy, and pharmacological therapy **[19]**.

Medical Management

Despite being the ideal and best treatment modality, surgical resection is not always feasible due to several reasons, or sometimes needs to be delayed. In these cases, pharmacological therapy is indicated until the patient becomes ready for operation. Pharmacological agents usually work on modulating the release of ACTH (like somatostatin and dopamine agonists), inhibiting steroidogenesis (like mitotane, ketoconazole, and metyrapone), or blocking the action of cortisol (like mifepristone). These drugs will usually restore normal cortisol levels, and thus improve hypertension. However, metyrapone is sometimes associated with worsened hypertension due to its effects on the production of mineralocorticoids **[20]**.

Both ketoconazole and metyrapone, which inhibit steroidogenesis, have a rapid action. However, they are only effective for short-term treatment of Cushing's syndrome due to the escape phenomenon associated with them. Due to this limitation, there used is limited to being used as adjuvant therapy following radiation or surgery. On the other hand, mitotane (especially in high doses) does not show the escape phenomenon most often. This could be explained by the adrenolytic effect that mitotane has **[21]**.

Many factors work together to specify the best pharmacotherapeutic agent. When planning chronic treatment of Cushing's syndrome, secondary adrenal insufficiency. Bromocriptine, octreotide, and cabergoline are generally used due to their effects in inhibiting the secretion of ACTH. Another more recent drug that is being investigated for the same role is SOM230 **[22]**.

In addition to using pharmacological agents that treat hypercortisolemia, it is also essential to administrate drugs to treat hypertension. Generally, in order to be able to establish proper blood pressure control, more than one anti-hypertensive agent. It is recommended to start with and ACE inhibitor or an ARB, as these drugs will target cortisol-induced hypertension. ACEIs and ARBs achieve sufficient blood pressure control in up to 50% of patients who have Cushing's disease. On the other hand, CCBs are usually not effective in cortisol-induced hypertension, but they can be used as an adjuvant therapy to ACEIs. Treating hypertension is generally challenging, and almost impossible to succeed without addressing hypercortisolemia. Hypertension can be difficult to control with antihypertensive agents without normalization of hypercortisolemia **[23]**.

Surgical treatment of Cushing's syndrome

By far, the most effective modality of treatment for treating Cushing's disease remains to be surgical excision of the tumor. Cushing's disease caused by a pituitary adenoma is globally treated by transsphenoidal resection which has a success rate that can reach up to 97%. When treating primary adrenal hypercortisolemia, unilateral adrenalectomy or bilateral adrenalectomy can be performed. Even in tumors that cause ectopic secretion of ACTH, surgery is the best treatment modality when the tumor is non-metastatic and localized. On the other hand, id the tumor cannot be found, or if all the previous measurements failed, bilateral adrenalectomy could achieve cure of Cushing's syndrome **[24]**.

In some cases, some patients with Cushing's syndrome do not return to their basal blood pressure levels, even after surgery for the disease. In fact, previous reports suggest that up to one third of adult patients will continue to have hypertension following curative surgery **[25]**.

The main factor that correlates with persistent high blood pressure, is the duration of Cushing's syndrome before undergoing surgery. Severity of Cushing's syndrome, on the other hand, does not play a significant role in this. However, this is different in children and adolescents who show complete recovery of hypertension and return to their basal blood pressure levels within a year following surgical treatment of Cushing's syndrome. It is still unknown why young patients are less likely to develop persistent hypertension **[26]**.

Radiotherapy

Patients who suffer from a persistent increase in cortisol levels even after undergoing surgery can be administrated tumor-directed radiotherapy. Despite being highly effective, this modality of treatment can be associated with the development of late permeant hypopituitarism **[27]**.

CONCLUSION:

Cushing's syndrome is the result of any long-term pathology that leads to high levels of circulating cortisol in the bloodstream. Up to 80% of patients with Cushing's syndrome can have hypertension which will lead to significant increase in both morbidity and mortality if left untreated. The mechanisms by which Cushing's syndrome causes hypertension yet remains a debatable issue, with several theories present to explain it. Due to its associated increase in mortality and morbidity, it is essential to control blood pressure in patients with Cushing's syndrome. Surgical resection remains the most ideal treatment modality in the treatment of most causes of Cushing's syndrome.

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