

Endocrine hypertension – Cushing’s syndrome

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ABSTRACT

Hypertension is a major and frequent comorbid finding of Cushing’s syndrome. This review discusses the etiology and pathophysiology of hypertension in Cushing’s syndrome, while suggesting methods of management of this condition. It also provides an overview of diagnosis and management strategies in this disease.

Key words: Cushing’s, hypertension, cortisol

INTRODUCTION

It has been almost 80 years since Harvey Cushing described the clinical syndrome of glucocorticoid excess that now bears his name.^[1] The interest in this entity has gradually increased especially over the last decade as evidenced by the expanding literature on this subject. A large number of tests have been devised over the years to have a better and earlier diagnostic yield of this entity. In recent years, there has been a shift in clinical spectrum of this disease, as cases are being detected at an earlier stage. This has resulted in endocrinologists seeing the disease at an earlier stage in the natural history. Despite all the advancements, Cushing’s syndrome continues to raise considerable debate and differences amongst the endocrinologists on the ways to manage a particular case. This review briefly discusses the manifestations, causes, approaches to diagnosis, and treatments for this enigmatic entity. Hypertension in Cushing’s syndrome is discussed in more details.

EPIDEMIOLOGY

The incidence of Cushing’s syndrome varies depending

on the population studied, anywhere from 2 to 3 cases per million population per year.^[2] Recent data, however, suggest that this may be an underestimate and Cushing’s syndrome may be more common than previously thought. Cushing’s disease occurs predominantly in women (female to male ratio ranging from 3:1 to 10:1).^[3] Iatrogenic Cushing’s may be more common than the endogenous Cushing’s.

ETIOLOGY

The etiology of Cushing’s syndrome can be divided into those that are adrenocorticotrophic hormone (ACTH) dependent and those that are ACTH independent [Table 1]. The ACTH-dependent forms are characterized by excessive ACTH production from a corticotroph adenoma (known as pituitary-dependent Cushing’s syndrome or Cushing’s disease), from an ectopic tumoral source (ectopic ACTH syndrome), or (rarely) from normal corticotrophs under the influence of excessive corticotrophin releasing hormone (CRH) production (ectopic CRH secretion). ACTH-independent forms include unilateral disease (adenoma and carcinoma), bilateral disease (primary pigmented nodular adrenal disease, McCune-Albright syndrome, and macronodular adrenal disease related to aberrations of the cyclic AMP signaling pathway, or caused by ectopic expression of G-protein–coupled receptors), and hyperfunction of adrenal rest tissue.

HYPERTENSION IN CUSHING’S SYNDROME

Hypertension is a frequent feature of endogenous Cushing’s syndrome with a prevalence of approximately 80% in

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Table 1: Causes of Cushing's syndrome

ACTH-dependent form	ACTH-independent form
Pituitary-dependent Cushing's syndrome (Cushing's disease)	Adrenal adenoma
Ectopic ACTH syndrome	Adrenal carcinoma
Ectopic CRH secretion	Primary pigmented nodular adrenal disease (PPNAD), sporadic or associated with the Carney complex
Exogenous ACTH administration	AIMH AIMH secondary to abnormal hormonal signaling McCune-Albright syndrome Exogenous glucocorticoid administration

AIMH: ACTH-independent bilateral macronodular adrenal hyperplasia

adults. Hypertension is seen much more commonly in ectopic Cushing's (95%).^[4] However, it is less common in children and adolescents (about 47%).^[5]

PHYSIOLOGY OF BLOOD PRESSURE IN CUSHING'S SYNDROME

Normal healthy individuals show a diurnal variation in blood pressure. There is a nocturnal sleep-related reduction in blood pressure. This reduction occurs *pari passu* with the nocturnal reduction of serum cortisol. Several conditions are associated with absence of sleep-related decrease in blood pressure.^[6] These include glucocorticoid-induced hypertension. Several mechanisms have been postulated to explain the impact of hypercortisolemia on hypertension.^[7] These include:

- mineralocorticoid effects of cortisol;
- activation of the renin angiotensin system (RAS); and
- action of cortisol on peripheral and systemic vasculature.

Mineralocorticoid effects of cortisol

Glucocorticoid-induced hypertension is likely mediated through effects of cortisol on type 1 (mineralocorticoid) and type 2 (glucocorticoid) receptors. The enzyme 11 beta-hydroxysteroid dehydrogenase (11bHSD) modulates the effects of cortisol at cellular level. There are two isoforms of 11bHSD:

- 11bHSD1:** It has bidirectional activity and catalyzes both dehydrogenation (conversion of cortisol to cortisone) and reduction (conversion of cortisone to cortisol) reactions. *In vivo*, it predominantly functions as a reductase, converting inactive cortisone to active cortisol.
- 11bHSD2:** It is abundantly expressed in the classical mineralocorticoid target tissues; including the renal cortex, colon, and salivary glands.^[7] It predominantly acts as a dehydrogenase to convert cortisol into inactive cortisone.

It has been postulated that hypertension in Cushing's

syndrome is due to decreased renal conversion of cortisol to cortisone, which would increase mineralocorticoid action. The high cortisol levels in Cushing's syndrome overwhelm the 11bHSD2 enzyme because of substrate saturation leading to spillover of cortisol to the mineralocorticoid receptor. The end result is a functional mineralocorticoid excess state. This leads to hypokalemia, increased renal tubular sodium reabsorption, intravascular volume expansion, and hypertension. However, recent studies have brought out that a functional mineralocorticoid excess state is not the sole pathogenic mechanism and the glucocorticoid receptor is involved in the development of hypertension in Cushing's syndrome.^[8]

Activation of the renin angiotensin system

The RAS may have a role in the pathogenesis of glucocorticoid-induced hypertension through upregulation of central and peripheral angiotensin II receptors. This is borne out by animal studies which have shown that glucocorticoids increase angiotensin II receptor type 1 concentration in brain and peripheral tissue. Glucocorticoids have also been shown to enhance angiotensin II-stimulated inositol phosphate-3 production in vascular smooth muscle cells, as well as its central pressor effects.^[9,10]

Action of cortisol on peripheral and systemic vasculature

Inhibition of vasodilators

Glucocorticoid excess has been known to be associated with increased circulating levels of the vasodilator atrial natriuretic peptide (ANP). However, various *in vitro* studies have shown that it decreases the biologic activity of the ANP.^[11] Glucocorticoids also decrease the production of nitric oxide synthase, which is responsible for the synthesis of another vasodilator, nitric oxide.^[12] This inhibition may increase the blood pressure by decreasing peripheral vasodilatation.

Increased vascular sensitivity to vasopressors

Glucocorticoids have been known to increase the vascular sensitivity to the effect of catecholamines. Plasma levels of endothelin-1 (ET-1), a potent vasoconstrictor, are significantly elevated in patients with Cushing's syndrome.^[13] It has also been postulated that glucocorticoids down regulate the expression of the sodium-calcium exchanger in vascular smooth muscle cells. This leads to increase in the cytoplasmic concentration of calcium which causes vasoconstriction.

CLINICAL FEATURES

Symptoms associated with hypercortisolemia include weight gain, lethargy, weakness, menstrual irregularities, loss of libido, depression, hirsutism, acne, purplish skin striae, and hyperpigmentation. The signs associated

with Cushing's syndrome are extremely varied and differ in severity [Table 2]. Signs that differentiate Cushing's syndrome from pseudo-Cushingoid states most reliably include the presence of proximal myopathy, easy bruising, and thinness and fragility of the skin. In children, pointers toward glucocorticoid excess include weight gain associated with growth retardation.

DIAGNOSIS

According to American Endocrine Society clinical practice guideline, patients with suspected Cushing's syndrome should be screened with one of the following tests: Urine free cortisol (UFC; at least two measurements), late night salivary cortisol (two measurements), 1-mg overnight dexamethasone suppression test, and long lower-dose dexamethasone suppression test.

In case of an abnormal test result, a repeat test (any other than the one performed during screening should be done to confirm the diagnosis. A concordant result confirms the diagnosis of Cushing's disease.^[14]

The next step is to distinguish between ACTH-dependent and ACTH-independent causes of Cushing's syndrome [Figure 1]. Plasma ACTH is suppressed in adrenal-dependant forms. ACTH is normal or increased in ACTH-dependant form (pituitary or ectopic in origin, markedly so in the latter). However, overlap may exist in ACTH values between pituitary and ectopic source. ACTH may be in normal ranges in patients with adrenal tumors. CRH stimulation, however, will elicit a brisk response in ACTH-dependant Cushing's. All patients with ACTH-dependant Cushing's disease should undergo gadolinium-enhanced pituitary magnetic resonance imaging (MRI). The presence of a pituitary lesion greater than 6 mm in the presence of classical signs and concordant hormonal assay confirms Cushing's disease. Bilateral inferior petrosal sinus sampling (BIPSS) is considered in patients with ACTH-dependant Cushing's disease, whose clinical, biochemical or radiological studies are discordant. A ratio of central to peripheral levels of ACTH of 2 in the basal level and 3 after

stimulation with CRH confirms the diagnosis of Cushing's disease (ACTH-producing pituitary adenoma). Failure to identify pituitary source of excess production by MRI or BIPSS should prompt the search for extra-pituitary source. If ACTH is suppressed, adrenal computed tomography (CT)/MRI scan should be done to identify whether the lesion is unilateral or bilateral.^[15]

Morbidity and mortality in patients with Cushing's disease is largely due to cardiovascular disease. The patient should be evaluated for diabetes, dyslipidemia and hypercoagulable state. 2-D echocardiography and Doppler ultrasonography are also advised as part of the initial workup. In addition, the patient should have evaluation of bone density in view of the increased incidence of osteoporosis-related fractures.

MANAGEMENT OF CUSHING'S DISEASE

Management of hypercortisolism

Definitive therapy for Cushing's syndrome is surgical excision of ACTH or cortisol producing tumor. Excision of pituitary microadenoma by an expert surgeon leads to postoperative cure rate of 65–90%. Rates of cure are better in patients with well-localized tumor. Rates of cure are <65% in patients with pituitary macroadenoma. Postoperative levels of cortisol secretion provide good prognostic information regarding the outcome in patients with Cushing's disease. Patients whose cortisol levels decrease to less than 55.2–82.8 nmol/l (preferably undetectable) within 24–72 h after surgery usually have a clinical and biochemical remission.^[16]

Table 2: Signs and symptoms of Cushing's syndrome

Sign/symptom	Frequency (%)
Truncal obesity	97
Moon face	89
Hypertension	76
Skin atrophy and bruising	75
Diabetes or glucose intolerance	70
Gonadal dysfunction	69
Muscle weakness	68
Hirsutism, acne	56
Mood disorders	55
Osteoporosis	40
Fungal infections	10

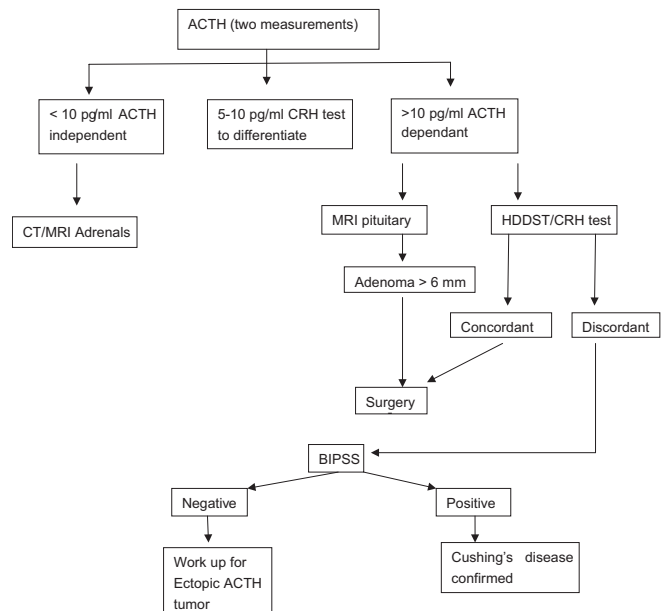


Figure 1: Flow chart depicting evaluation of case of Cushing's syndrome (HDDST: high-dose dexamethasone suppression test; BIPSS: bilateral inferior petrosal sinus sampling)^[15]

Patients with persistence of hypercortisolism postoperatively can be subjected to repeat surgery, radiotherapy or bilateral adrenalectomy^[17] Pituitary radiation (conventional or gamma knife) has been recommended as a means to treat Cushing's disease when surgery fails. Although remission rates of 53–100% have been reported with conventional radiotherapy and rates as high as 76% have been reported in patients using gamma knife radiotherapy, the normalization of cortisol secretion takes 12–36 months. Bilateral adrenalectomy is a definitive cure for patients with persistent hypercortisolism. It is indicated when enzyme inhibitors are unable to achieve eucortisolemia. Patients require to be put on lifelong gluco and mineralocorticoid replacement. They require monitoring of ACTH and MRI of pituitary due to risk of Nelson's syndrome.

Medical management

Medical management is required while awaiting surgery, when surgery is contraindicated and in occult ACTH secreting tumors. Ketoconazole, metyrapone and mitotane inhibit steroidogenesis. Ketoconazole and metyrapone lose their efficacy as elevated ACTH secretion leads to enhanced synthesis of steroids and triggers escape. Mitotane is an adrenolytic drug and has a prolonged effect. Overdosing with the drugs can lead to a state of adrenal insufficiency. Dopamine agonists (cabergoline and bromocriptine) can be used in tumors which secrete prolactin. A new multi ligand somatostatin analogue (SOM 230; Pasireotide) has been shown to be effective in Phase II trials. Mifepristone is the first potent glucocorticoid receptor antagonist. It has a long half life and lacks biochemical markers to monitor response and may be associated with significant adrenal insufficiency.^[17]

Management of hypertension

The cause of mortality in patients with hypercortisolemia is usually cardiovascular illness. Blood pressure control is difficult to achieve without control of hypercortisolemia. Control of hypertension often requires use of more than drug. Since upregulation of RAS is one of the pathophysiologic mechanisms, angiotensin converting enzyme inhibitors and angiotensin receptor blockers are the preferred drugs. Alternatively, a combination of calcium channel blockers and adrenergic blockers may be useful. Nearly one-third of the patients persistently have hypertension after achieving eucortisolemia and need to continue anti-hypertensive medication.^[18]

CONCLUSION

Multiple drugs and therapeutic strategies are needed to successfully manage Cushing's syndrome. Aggressive management of hypercortisolemia, along with simultaneous

management of hypertension, is needed to minimize the cardiovascular morbidity and mortality that these patients face.

REFERENCES

1. Cushing HW. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). *Bull Johns Hopkins Hosp* 1932;50:137-95.
2. Lindholm J, Juul S, Jørgensen JO, Astrup J, Bjerre P, Feldt Rasmussen U, *et al.* Incidence and late prognosis of Cushing's syndrome: A population-based study. *J Clin Endocrinol Metab* 2001;86:117-23.
3. Peori Giraldi F, Moro M, Cavagnini F; Study Group on the Hypothalamic- Pituitary-Adrenal Axis of the Italian Society of Endocrinology. Gender-related differences in the presentation and course of Cushing's disease. *J Clin Endocrinol Metab* 2003;88:1554-8.
4. Stewart PM, Walker BR, Holder F. II beta-hydroxysteroid dehydrogenase activity in Cushing's syndrome: Explaining the mineralocorticoid excess state of the ectopic adrenocorticotropin syndrome. *J Clin Endocrinol Metab* 1995;80:3617-20.
5. Magiakou MA, Mastorakos G, Zachman K, Chrousos GP. Blood pressure in children and adolescents with Cushing's syndrome before and after surgical cure. *J Clin Endocrinol Metab* 1997;82:1734-8.
6. Spieker C, Barenbrock M, Rahn KH, Zidek W. Circadian blood pressure variations in endocrine disorders. *Blood Press* 1993;2:35-9.
7. Fraser R, Davies DL, Connell JM. Hormones and hypertension. *Clin Endocrinol* 1989;31:701-46.
8. Connell JM, Whitworth JA, Davies DL, Richards AM, Fraser R. Hemodynamic, hormonal, and renal effects of adrenocorticotrophic hormone in sodium-restricted man. *J Hypertens* 1988;6:17-23.
9. Sato A, Suzuki H, Murakami M, Nakazato Y, Iwaita Y, Saruta T. Glucocorticoid increases angiotensin II type 1 receptor and its gene expression. *Hypertension* 1994;23:25-30.
10. Shelat SG, King JL, Flanagan-Cato LM, Fluharty SJ. Mineralocorticoids and glucocorticoids cooperatively increase salt intake and angiotensin II receptor binding in rat brain. *Neuroendocrinology* 1999;69:339-51.
11. Yasunari K, Kohno M, Murayama K, Yokokawa K, Takeda T. Glucocorticoids and atrial natriuretic factor receptors on vascular smooth muscle. *Hypertension* 1990;16:581-6.
12. Kelm M. The L-arginine-nitric oxide pathway in hypertension. *Curr Hypertens Rep* 2003;5:806.
13. Kriol G, Tomova A, Dakovska L, Kumanov P, Shinkov A, Alexandrov AS, *et al.* Elevated plasma endothelin as an additional cardiovascular risk factor in patients with Cushing's syndrome. *Eur J Endocrinol* 2003;149:549-53.
14. The diagnosis of Cushing's syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008;93:1526-40.
15. Boscaro M, Arnaldi G. Approach to the patient with possible Cushing's syndrome. *J Clin Endocrinol Metab* 2009;94:3121-31.
16. Findling JW, Raff H. Clinical Review: Cushing's syndrome: Important Issues in Diagnosis and Management. *J Clin Endocrinol Metab* 2006;91:3746-53.
17. Biller BM, Grossman AB, Stewart PM, Melmed S, Bertagna X, Bertherat J, *et al.* Treatment of Adrenocorticotropin Dependent Cushing's Syndrome: A consensus Statement. *J Clin Endocrinol Metab* 2008;93:2454-62.
18. Sharma ST, Niemen LK. Cushing's syndrome: All Variants, Detection, and Treatment. *Endocrinol Metab Clin N Am* 2011;40:379-91.

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