

Adrenal Adenoma Causing Secondary Hypertension. A Review of the Literature

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Abstract

Arterial hypertension (HTN) of endocrine origin accounts for 5 to 10% of cases of secondary hypertension. Although this form of hypertension is rare, the identification and treatment of the underlying cause could lead to healing or significant improvement in hypertension, thereby decreasing the cardiovascular risk and morbidity associated with hypertension. Endocrine causes of secondary hypertension are primary hyperaldosteronism, pheochromocytoma, Cushing's syndrome (CS), acromegaly, hyperparathyroidism, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism and secretory tumors of renin. The adrenal hypertension is the most frequent and the most frequently curable.

Epidemiological data on hypertension associated with CS are largely retrospective. However, the available data suggested that 70–85% of adult patients with endogenous CS suffer from hypertension, compared to approximately 20% of patients long-term treated with exogenous corticosteroids.

The mechanisms involved in the development of hypertension during CS are complex and only partially understood. The main data concerning the renin-angiotensin system, the mineral corticoid activity, the sympathetic nervous system and the vasoregulatory system, together with the indirect mechanisms, which contribute to the development of CS-related hypertension.

The definitive therapy of CS-related hypertension is the surgical removal of the tumor responsible for the disease. Interestingly, mortality data show that adequate control of hypercortisolemia does not always lead to BP normalization. Some studies show a normalization of increased cardiovascular risk after immediate surgical cure of Cushing's disease, while others did not.

Key words: Adrenal Adenoma; Secondary Hypertension; Cushing's Syndrome

Introduction

In our observation, we describe the case of 23-year-old man with hypertension associated with paraparesis of the lower limbs revealing a Cushing syndrome due to a left adrenal adenoma. After surgical excision of the adrenal mass, our patient normalized his blood pressure with 3 years of follow up. This case illustrates a form of endocrine hypertension of adrenal origin and the need for a careful clinical examination during the discovery of hypertension in the young subject in order to carry

out adequate balance sheets to search for a curable cause of secondary hypertension [1].

Epidemiology of endocrine hypertension

Arterial hypertension (HTN) of endocrine origin accounts for 5 to 10% of cases of secondary hypertension [2]. Although this form of hypertension is rare, the identification and treatment of the underlying cause could lead to healing or significant improvement in hypertension, thereby decreasing the cardiovascular risk and morbidity associated with hypertension. Endocrine causes of secondary hypertension are primary hyperaldosteronism, pheochromocytoma, Cushing's syndrome (CS), acromegaly, hyperparathyroidism, congenital adrenal hyperplasia, hypothyroidism, hyperthyroidism and secretory tumors of renin. The adrenal hypertension is the most frequent and the most frequently curable [3].

Definition and Classification of Cushing Syndrome

Cushing's syndrome, or chronic hypercortisolism, is a severe endocrine disease due to the prolonged exposure to glucocorticoid excess. The endogenous Cushing's syndrome, caused by the endogenous over production of cortisol by the adrenal glands, is secondary to an adrenocorticotrophin (ACTH)-secreting pituitary tumor [pituitary-dependent Cushing's syndrome (CS) or Cushing's disease (CD)] in around 70%, a cortisol-secreting adrenal lesion (adrenal-dependent Cushing's syndrome) in 15–20%, and an ACTH-secreting extra-pituitary tumor [ectopic Cushing's syndrome (ECS)] in 10–15% of the cases. The chronic administration of exogenous corticosteroids for different clinical conditions may induce the development of an exogenous CS [4–6].

The diagnosis may be late and secondary to a metabolic complication. The circumstances of discovery are essentially facio-truncal obesity; signs of skin fragility, stretch marks, muscular weakness by amyotrophy, hypertension, diabetes and osteoporosis [7].

Epidemiology of Hypertension Associated with CS

Epidemiological data on hypertension associated with CS are largely retrospective. However, the available data suggested that 70–85% of adult patients [8, 9] with endogenous CS suffer from

hypertension, compared to approximately 20% of patients long-term treated with exogenous corticosteroids [10, 11].

A particularity of hypertension associated with endogenous CS is the absence of a significant difference between the sexes or between the different etiologies of endogenous CS [8, 9, 12], as well as in the degree of hypercortisolism, the blood pressure (BP) values were not found to be correlated with circulating cortisol levels [8, 13]

HTN is present in almost 80% of patients with endogenous CS. It is most often a grade 2 hypertension (BP greater than 160 mm Hg for systolic or 100 mm Hg for diastolic), occurring in a young, often obese, subject with a frequent high blood pressure morning breakouts. Because of the suppression of the circadian rhythm of cortisol secretion, patients do not have nocturnal dipping [14], defined by a 10% decrease in blood pressure during sleep, which can be detected only by ambulatory blood pressure measure. Biologically, CS is defined by an increase in cortisolemia and urinary free cortisol.

Mechanism of Hypertension during CS

The mechanisms involved in the development of hypertension during CS are complex and only partially understood. The main data concerning the renin-angiotensin system (RAS), the mineralocorticoid activity, the sympathetic nervous system and the vasoregulatory system, together with the indirect mechanisms, which contribute to the development of CS-related hypertension.

The RAS is the most extensively investigated system as a putative contributor to hypertension in CS.

Confirmatory data on the involvement of the angiotensin pathways come from the acute lowering of BP obtained following oral administration of an angiotensin I-converting enzyme inhibitor (acei) in CS. The clear evidence of the angiotensin pathway involvement in the development of hypertension in CS suggests that this should be the first pharmacological target by using drugs as acei or angiotensin receptor blockers [15].

The mineralocorticoid activity has been traditionally considered a major player of hypertension secondary to glucocorticoid excess. The mineralocorticoid receptor is a nuclear receptor, mainly expressed at a renal level, which is able to bind two different corticosteroids, aldosterone and cortisol, with equal affinity [16].

In summary, renal mineralocorticoid receptor activation does not appear to be the main determinant of hypertension in most patients with CS, except in those with extremely elevated circulating cortisol levels where renal mineralocorticoid receptor hyper activation contributes to additional sodium and fluid retention, beyond the increased excretion of potassium and consequent hypokalemia. Renal mineralocorticoid receptor blockade with standard doses of spironolactone or epleronone is a reasonable adjunctive treatment in patients with hypokalemia [17].

The sympathetic nervous system, mediated by the catecholaminergic pathway, was supported only by limited

controlled data. The inconsistent findings and the fact that most CS patients also develop diabetes, requiring treatment with glucose-lowering drugs, suggest that adrenergic blockade should not be a first-line treatment for CS-related hypertension.

Many substances with vasoregulatory properties have been reported to contribute to hypertension secondary to glucocorticoid excess. Endothelin-1 (ET-1), a potent vasoconstrictor. Erythropoietin (EPO) mediates glucocorticoid-induced vasoconstriction. Most studies on vasodilators have demonstrated the detrimental effects of glucocorticoid excess on the nitric oxide pathway through different mechanisms: inhibition of nitric oxide synthase (NOS) expression, reduced availability of substrates due to inhibition of the arginine transporter, or impaired cofactor generation due to inhibition of the tetrahydrobiopterin synthesis [18, 19]. Atrial natriuretic peptide (ANP, a hormone with natriuretic vasorelaxant and RAS-inhibiting properties, is often reported as increased in CS [20]. CS might also be associated with impaired production of other powerful vasodilators including prostaglandins, prostacyclins and compounds of the kallikrein-kinin system, the latter due to accelerated renal kininase activity [21].

Although the prevalence of hypertension is similar among various forms of endogenous CS, however, clinical and physiopathological differences characterize CS subtypes. A tendency towards higher BP is seen in adrenal compared to pituitary tumors [17]. This difference may be related to the specific vasoactive effects of adrenal sex steroids [androgens, estrogens and their metabolites], which are generally suppressed in adrenal tumors secreting cortisol compared to pituitary tumors responsible for Cushing's disease [22, 23].

Mechanism of paraparesis during CS

The probable mechanism of the paraparesis of the lower limbs seen in our patient may be due to muscular catabolism. Cortisol causes an increase in the catabolic activity of muscle proteins [Hyper-catabolism of protein syndrome], causing muscular atrophy; it provokes paraparesis that is sometimes very debilitating. This paraparesis is often bilateral and symmetrical predominating in the thighs and can also affect the upper limbs.

Another mechanism of the paraparesis is hypokalemia, a complication that can be seen in the CS. The clinical translation varies according to the intensity of hypokalemia, it ranges from asthenia with muscle weakness to paraparesis. Patients with ectopic secretion of ACTH develop more frequently severe hypokalemia, mainly due to saturation of the activity of the 11beta-hydroxysteroid dehydrogenase 2. The rapidity and severity of onset of hypercortisolism in this condition is responsible for severe organ damage. In extreme hypokalemia, a cases of rhabdomyolysis have been described. [24].

Spinal epidural lipomatosis which is a state of pathological fat tissue overgrowth in the vertebral canal, is an unusual cause of paraparesis in a patient on chronic steroid therapy. Cases have been reported in patients with morbid obesity, Cushing syndrome, and hypothyroidism [25].

Effect of Treatment of CS on Hypertension

The definitive therapy of CS-related hypertension is the surgical removal of the tumor responsible for the disease. Interestingly, mortality data show that adequate control of hypercortisolemia does not always lead to BP normalization. Some studies show a normalization of increased cardiovascular risk after immediate surgical cure of Cushing's disease [26], while others did not [27].

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