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SIGNIFICANT SUPPRESSION OF ALDOSTERONE BY DEXAMETHASONE

Abstract: ACTH-dependent aldosteronism (Glucocorticoid-remediable aldosteronism – GRA) represents a rare, autosomal-dominant form of primary aldosteronism caused by chimerism of the CYP11B1/CYP11B2 genes, leading to increased aldosterone production. Suppression of aldosterone by dexamethasone may indicate this disorder, while genetic analysis remains the gold standard for diagnosis. We present a female patient with long-standing arterial hypertension diagnosed in early adulthood. Elevated baseline aldosterone levels were recorded with borderline aldosterone/plasma renin activity ratio values. Radiological imaging did not reveal morphological abnormalities of the adrenal glands. Confirmatory tests were performed (captopril test, saline infusion test, DST). The dexamethasone suppression test demonstrated significant suppression of aldosterone, raising suspicion of GRA and leading to the indication for genetic testing. The differential diagnosis of hyperaldosteronism includes adenoma, hyperplasia, ectopic production, and genetic forms such as GRA. Biochemical suppression of aldosterone may suggest familial hyperaldosteronism type I, but it is not sufficient to confirm the diagnosis. Genetic analysis enables definitive differentiation of GRA from other forms of primary aldosteronism. In our patient, despite biochemical findings partially suggestive of GRA, genetic testing excluded the presence of the CYP11B1/CYP11B2 chimeric gene. This case highlights the importance of genetic confirmation when GRA is suspected, particularly in younger patients with a positive family history.

Key words: GRA, CYP11B1/CYP11B2, aldosteronism.

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Introduction: Suppression of aldosterone by dexamethasone represents a key diagnostic test in establishing the diagnosis of familial hyperaldosteronism type I (GRA), which can be effectively treated with low-dose oral glucocorticoids.[1] However, the gold standard for diagnosing this disorder is genetic analysis detecting the CYP11B1/CYP11B2 gene formed between these two genes, resulting in ACTH-dependent excessive aldosterone production.[2] This disorder usually manifests with hypertension in childhood or early adulthood, and early diagnosis enables prevention of cardiovascular complications.[3,4]

Case report: The patient was diagnosed with arterial hypertension at the age of 30. During the past five years, her antihypertensive therapy had been modified once annually.

Usual blood pressure values were approximately 150/110 mmHg, while the highest recorded values reached 203/158 mmHg, with weekly episodes of sudden hypertensive surges. Her family history was positive for hypertension, as her father has been treated for hypertension since early adulthood.

As part of the evaluation for secondary hypertension, radiological imaging was performed. Computed tomography revealed a normal-appearing right adrenal gland, while the left adrenal gland showed a mildly enlarged medial limb. Recently, the patient reported frequent migraines accompanied by elevated blood pressure, leading to occasional to frequent visits to the emergency department.

Outpatient evaluation demonstrated elevated aldosterone levels (271 ng/L; reference value up to 174 ng/L), with borderline low serum potassium (K 3.7 mmol/L). Under inpatient conditions, aldosterone and renin were reassessed, showing an aldosterone/PRA ratio in the gray zone (27.1; aldosterone 325.7 ng/L; PRA 1.20 ng/mL/h). Based on clinical and anamnestic data, confirmatory tests were performed. During the captopril test, aldosterone levels were 204.3 ng/L at baseline, 109.6 ng/L after 90 minutes, and 72.5 ng/L after 120 minutes, while renin increased from 0.79 ng/mL/h to 1.5 and 2.2 ng/mL/h. The saline infusion test showed aldosterone levels of 208.6 ng/L at baseline, 137.9 after 30 minutes, 123.7 after 60 minutes, 162.9 after 120 minutes, and 119.6 ng/L after 240 minutes, with PRA values ranging from 0.84 to 1.10 ng/mL/h. The dexamethasone suppression test demonstrated a significant decrease in aldosterone, from an initial 206.2 ng/L to 82.1 ng/L after two days of dexamethasone administration, with an increase in PRA from 0.36 to 0.76 ng/mL/h.

Discussion: Aldosterone is a mineralocorticoid hormone originating from the adrenal glands and represents part of the renin–angiotensin–aldosterone system, which regulates electrolyte status, water balance, and blood pressure under physiological conditions.[5] Primary aldosteronism is one of the causes

of secondary hypertension.[6] Several conditions may lead to increased aldosterone production, including: aldosterone-producing adenoma (usually larger than 1 cm, also known as Conn's adenoma); aldosterone-producing microadenomas (smaller than 1 cm); adrenal hyperplasia (unilateral or bilateral); adrenocortical carcinoma (ACC); ectopic aldosterone secretion (aldosterone-secreting tumors, e.g., ovarian tumors); and familial hyperaldosteronism type I.[7] This condition often manifests with resistant hypertension, hypokalemia, and muscle weakness.[8] Diagnosis is established by measuring the plasma aldosterone/renin ratio and confirmed with confirmatory testing (such as saline suppression testing, captopril testing, or dexamethasone suppression testing for FH-I).[5] Treatment depends on the underlying cause: adenoma is commonly managed surgically (adrenalectomy), which may be curative, while hyperplasia or patients unsuitable or unwilling for surgery are treated with mineralocorticoid receptor antagonists such as spironolactone or eplerenone.[9] In FH-I, glucocorticoid therapy such as dexamethasone may effectively control hypertension.[10]

In the mid-20th century, Sutherland described a family in which both father and son developed arterial hypertension at an early age accompanied by hypokalemia.[11] This clinical case represents one of the first descriptions of a possible familial, autosomal-dominant form of primary aldosteronism, later known as GRA (Glucocorticoid-remediable aldosteronism).[1] Further investigations by Sutherland and colleagues demonstrated that this variant of primary aldosteronism involved ACTH-dependent increased aldosterone secretion.[11] Due to this characteristic, hypertension in these patients was successfully controlled with low doses of dexamethasone, which suppresses ACTH and thereby reduces excessive aldosterone production and its deleterious effects.[12]

Numerous studies, particularly those focusing on younger populations with GRA, indicate that patients with this genotype frequently develop severe arterial hypertension with a positive family history.[3,8] Families often report early-onset hypertension or even cardiovascular complications at a young age.[4] Therefore, particular attention to possible GRA is recommended in: 1) individuals younger than 20 years who develop hypertension, especially if associated with hypokalemia (although hypokalemia is not mandatory); 2) families with documented hypertension or cerebrovascular events before the age of 40.[5] Anamnestic data and clinical-biochemical findings are crucial for identifying patients who should be referred for further genetic evaluation.[4]

The gold standard for diagnosis is genetic analysis detecting the presence of a combined gene formed by chimerism of two different genes, CYP11B1 (11β-hydroxylase) and CYP11B2 (aldosterone synthase).[13] This newly formed chimeric gene arises due to an error during unequal crossing-over, resulting from the high structural similarity of these two genes.[2] Genetic analysis is based on

polymerase chain reaction (PCR) performed on DNA isolated from the patient's peripheral blood.[13]

Given the potential limited availability of genetic testing, the dexamethasone suppression test with monitoring of RAAS markers, particularly PRA, may be used as an alternative diagnostic approach.[1] If plasma aldosterone concentration is suppressed below 4 ng/dL after several days of dexamethasone administration (4 days, 0.5 mg every 6 hours), the finding may suggest GRA.[1] However, genetic analysis remains superior to biochemical testing.[5]

Conclusion: This is a female patient with early-onset arterial hypertension, in whom elevated baseline aldosterone was recorded with borderline "gray zone" aldosterone/plasma renin activity ratio values. The results of confirmatory testing suggest that primary aldosteronism is unlikely. However, significant suppression of aldosterone during the dexamethasone suppression test raised suspicion of glucocorticoid-remediable aldosteronism (GRA). This possibility was subsequently excluded by genetic testing, which represents the gold standard in diagnosis.

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