Primary hyperaldosteronism (PH) is a group of pathologies characterized by an increased and sustained, autonomous aldosterone secretion caused by hyperplasia and/or neoplasia in the zona glomerulosa of the adrenal cortex. It is the most common etiology of secondary systemic arterial hypertension and it is found in ≥ 12% of the cases considered as primary systemic arterial hypertension. The prevalence of PH increases in population subgroups with the following factors: severe hypertension or refractory hypertension (20-23%), hypertension and hypokalemia, younger than forty year old patients with a history of cerebrovascular disease, younger than twenty year old hypertensive patients, first degree relative with adrenal incidentalomas. PH is a group of pathologies that damage cardiovascular, renal and cerebrovascular structures even with an optimal hypertension control, and a biochemical constellation which consists of: plasma aldosterone concentration (PAC) > 20 ng/dL, plasmatic renin activity (PRA) < 0.5 ng/mL/h, when plasmatic renin concentration is low and sometimes non-detectable. It has been associated with hypokalemia and metabolic alkalosis.
Hyperaldosterism generating hypertension has a greater likelihood to be complicated with cardiovascular, renal, cerebrovascular morbidity, and mortality.

**ETIOLOGY**

Primary aldosteronism

1. Bilateral idiopathic hyperplasia (BIH) 60% of cases.
2. Aldosterone-producing adenoma (APA) 35% of cases.
3. Primary adrenal hyperplasia 2% of cases.
4. Aldosterone-producing adrenocortical carcinoma < 1% of cases.
5. Familial hyperaldosteronism (FH).
   a) Glucocorticoid-remediable aldosteronism (FH type I) < 1% of cases.
   b) FH type II (APA or BIH) < 2% of cases.
6. Ectopic aldosterone producing adenoma or carcinoma < 0.1% of cases.

**DIAGNOSIS PROTOCOL**

First stage. If there is hypokalemia, the first step will be to correct this condition. It is fundamental to do it before start diagnosis. The procedure is to increase NaCl intake up to 5 g daily; another option is to administrate orally 2-one gram NaCl tablets three times a day to achieve a total of 6 g, and then determine serum electrolytes. It is important to note that if hypokalemia remains, potassium chloride should be administered; if potassium is within the normal range, withhold all medications that substantially affect PRA, PAC/PRA, and the plasma renin for 2-4 weeks. Collect sample in the morning (preferably at 8:00 a.m.), 2-4 hours after patient being up and ambulating and determine: PAC > 20 ng/dL, PRA < 0.5 ng/dL and, plasma renin concentration (separate plasma after 30 minutes of collection). The ratio PAC/PRA ≥ 50 is diagnostic, from 49 to 25 without other criteria, probable diagnosis; if there is normokalemia withhold medications for 2-4 weeks and carry out the above mentioned tests.

**Step 2**

A) Fludrocortisone test: administer 0.1 mg fludrocortisone each 6 h/4 days with KCl supplement, collect sample for upright PRA and PAC at 10:00 a.m. on day fourth of the test. Positive test: PRA < 1 ng/mL/h and PAC > 6 ng/dL.

B) Infusion of sodium chloride at 0.9% test: have the patient in dorsal decubitus position for an hour before, and then administer to the patient a 2 sodium chloride liters of 0.9% I.V. over four hours, starting at 08:00-12:00 hours. Collect sample for electrolytes, PAC, PRA, renin and cortisol before and after saline infusion. Post infusion, if PAC < 5 ng/dL the diagnosis it is unlikely. If PAC > 10 ng/dL levels are within this range, diagnosis is probable; values between 5 and 10 ng/dL are indeterminate.

C) Captopril test: Patient sits or stands for one hour before the test. Administer captopril 25-50 mg orally; patient remains sitting for, at least, one hour. Blood samples are drawn for measurement of PRA, PAC, and cortisol basal, and at 1 or 2 h after challenge, with the patient seated during this period. Plasma aldosterone is normally suppressed by captopril (30%). In patients with PH, the PAC/PRA remains elevated, and PRA remains suppressed. Differences may be seen between patients with APA and those with BIH. However, some decrease of aldosterone levels is occasionally seen in BIH.

Another interpretation option: take plasma samples of PAC, PRA levels before and 1-2 hours after captopril administration. If PAC > 12 ng/dL and PRA < 0.5 ng/mL/hour the test is diagnostic.

**LOCATION PROCEDURES**

1. Adrenal computed tomography (CT): patient must fast for 8 hours before the procedure.
2. Adrenal magnetic resonance imaging (MRI). Fasting for 8 hours before the test is usually recommended.
3. Adrenal vein sampling (AVS) of aldosterone. I.V. catheters are placed in right and left adrenal veins and distal inferior vena cava (IVC) through the percutaneous femoral vein puncture.
b. Administer synthetic adreno corticotrophin hormone (ACTH)-250 mcg bolus injection after successful cannulation of adrenal veins, or 50 μg/hour continuous I.V. infusion, starting 30 minutes before the procedure.

c. Collect blood sample for PAC and cortisol levels from both adrenal veins and IVC before and during continuous I.V. infusion, or after bolus injection of ACTH.

d. The right and left adrenal vein PACs ratio with their respective cortisol concentrations, corrects for dilution effects of the inferior cava vein.

e. A cutoff of the aldosterone ratio from high side to low side more than 4:1 is used to indicate unilateral aldosterone excess; a ratio less than 3:1 is suggestive of bilateral aldosterone hypersecretion.

PRIMARY ALDOSTERONISM MANAGEMENT

Pharmacotherapy

1. Spironolactone is a nonselective aldosterone receptor antagonist that competitively inhibits the binding of aldosterone to the mineralocorticoid receptor. The therapeutic dose range is usually between 75 to 225 mg once daily. Adverse effects are gynecomastia (6.9% to 52%) and erectile dysfunction in men, hyperkalemia, and renal dysfunction.

2. Eplerenone is a selective aldosterone receptor antagonist with 60% of spironolactone action. Therapeutic doses are within 100 to 300 mg once daily, using a progression scheme to obtain the necessary effect. It does not have antiandrogen nor progesterone agonist effect, resulting in gynecomastia (1%) and hyperkalemia (21.1%) and renal dysfunction (6.5%).

3. Amiloride potassium-sparing diuretic. Starting with 5 mg a day, which may be increased to 10 mg daily; in scenarios when hyperkalemia persists, it may be raised to 20 mg a day. Adverse effects are hyperkalemia, renal dysfunction, nausea, vomiting, diarrhea, and loss of appetite.

4. Dexamethasone, whose dose is 0.125-0.25 mg/day, suppresses ACTH for glucocorticoid remediable aldosteronism. Adverse effects: increased appetite, restlessness, Cushing syndrome, osteoporosis, impaired linear growth in children.

Surgical treatment

Approximately 30% of all PH patients has clear lateralization of aldosterone production and will benefit from unilateral adrenalectomy. Laparoscopic adrenalectomy is the most suitable therapy for APA or unilateral adrenal hyperplasia. Complications may be developed after surgery: hemorrhage and suppression of the renin-angiotensin axis that causes transient postoperative hypoaldosteronism; then a liberal sodium diet should be allowed to prevent hyperkalemia after surgery. An I.V. infusion of 0.9% sodium chloride every 8 to 12 hours may be necessary to avoid postoperative intravascular volume depletion. All antihypertensive medications, especially spironolactone and amiloride, should be withheld and other antihypertensive medications may be cautiously reinstituted as needed within a few days.

Postoperative evolution: assess remaining adrenal gland. Postoperative PRA and aldosterone-to-renin ratio (ARR) are commonly repeated. Some authors recommend assessment of the autonomous function of the remaining adrenal gland in three months. These authors also periodically obtained CT scan in their patients at 1 to 3 yearly intervals, because they have observed that the remaining adrenal gland could slowly increase in size, become nodular, or develop adenoma after surgery.

PROGNOSIS

Approximately 33% of APA patients improved or have resolution of secondary hypertension and hypokalemia with normal PAC and PRA after unilateral adrenalectomy. Arterial hypertension is normally resolved within 1 to 6 months, and patients with persistent or residual arterial hypertension, who are likely to be older, require more than two antihypertensive medicaments before and during surgery.
FOLLOW UP

During the first year of follow-up, patients must be assessed every two months for PAC, PRA electrolytes, creatinine depuration, proteinuria, urinalysis, and having strict clinical evaluation. In case of controlling the above mentioned values, follow-up assessment must be carried out every 6 months for life. But if there is renal and/or cardiovascular deterioration, one should form a specialist team (nephrologists, cardiology, endocrinologist, radiologist and gastro surgeons with laparoscopic experience) to improve patient’s care. Since aldosterone is a toxin with deep deleterious effects in the renal and cardiovascular system; in some cases, renal function diminishes once the tumor has been excised due to pathological consequences of the aldosterone toxicity.

CONCLUSIONS

- Severe systemic hypertension (>160 mmHg systolic or >100 mmHg diastolic) in patients younger than 30 years old should be studied for primary hyperaldosteronism.
- Systemic arterial hypertension resistant to antihypertensive drugs (a three or more drug scheme) should be considered the probability of primary hyperaldosteronism.
- In patients < 40 year old with genetic background of hypertension and cardiovascular catastrophes, primary hyperaldosteronism presence should be considered.
- All hypertensive patients with first degree relatives with primary hyperaldosteronism must be studied.
- Incidentaloma concomitant with arterial primary hypertension should be studied for Hyperaldosteronism.
- Systemic hypertension with hypokalemia must be considered for primary hyperaldosteronism.
- Primary aldosteronism treatment may be pharmacological or surgical according to etiology.
- All patients treated pharmacologically or surgically must undergo a continual follow up for several years owing to the toxic sequels of aldosterone.

REFERENCES


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