Primary hyperaldosteronism in the composition of arterial hypertension: diagnosis and treatment

Abstract

Detection of primary hyperaldosteronism remains low due to the use of former recommendations based on the obligatory presence of hypokalemia and/or adrenal adenomas. Not clear clinical picture, the absence of hypokalemia and formations in adrenal glands hides primary hyperaldosteronism under the mask of essential hypertension, which leads to a lack of pathogenetic treatment. Available method of screening for primary hyperaldosteronism is the determination of the aldosterone-renin ratio. For its research needs to take into account the characteristics associated with the influence of some drugs on the level of aldosterone. As pathogenetic treatment of primary idiopathic hyperaldosteronism the mineralocorticoid receptor antagonists are recommended.

Keywords: hyperaldosteronism, arterial hypertensive dosterone, renin, spironolactone

Mini review

Primary hyperaldosteronism is a rare form of symptomatic arterial hypertension (AH), it is a clinical syndrome that develops as a result of excessive production of aldosterone by the glomerular zone of the adrenal cortex, in which the secretion of aldosterone is completely or partially autonomous towards the renin-angiotensin system, which causes the development of low-renin arterial hypertension (AH).

The syndrome of primary hyperaldosteronism (PHA) combines a number of disease similar in clinical and biochemical features, but different pathogenesis, which is based on the excessive production of aldosterone independent of the renin-angiotensin system. It was previously believed that among all patients with AH in 1% of people PGA was a cause of high blood pressure. The overall prevalence of PGA among AH patients is still unknown. The most representative data was provided by the PAPY study, which showed that among people with newly diagnosed AH, 11.2% of cases was PGA.

In general, the higher the level of blood pressure (BP), the greater the probability of PGA. With AH of the first stage, the proportion of patients with PHA is no more than 2%, at the third stage - up to 13%. However, in recent years it has been shown that even among persons with prehypertension, the frequency of PGA can be quite high. Thus, screening in subgroups of patients with AH with the highest frequency of detection of PHA can reduce the number of false positive and false negative results and avoid excessive financial costs.

Advanced screening of patients with AH will identify all patients with PGA and provide them with the opportunity to conduct appropriate treatment. The importance of this tactic is confirmed by the data of some studies indicating that in 9% of patients with PGA directed to adrenalectomy, hypertension corresponded only to the first stage, that is, they did not belong to high-risk PGA groups. Based on the results of recent studies, it has been shown that hypokalemia is detected only in a small number of patients with PGA (9-37%). Earlier it was believed that hypokalemia is a mandatory laboratory symptom in the diagnosis of hyperaldosteronism. The potassium serum level is less than 3.5mmol/l is detected in half of patients with adrenal adenoma and in 17% of individuals with idiopathic hyperplasia. Thus, in the diagnosis of PHA, hypokalemia has low sensitivity and specificity.

In the absence of hypokalemia and adenoma of the adrenal gland, the diagnosis of primary hyperaldosteronism in a patient is often excluded. However, it must be remembered that the absence of the above indicators does not exclude the presence of idiopathic primary hyperaldosteronism.

The PGA has no specific symptoms, which makes it difficult to diagnose this condition. There are three main groups of symptoms: cardiovascular, renal, neuromuscular. The most frequent clinical manifestation is AH, which occurs in 75-98%. Headaches with hyperaldosteronism can be associated with both increased blood pressure and the result of hyperhydration of the brain. The clinical significance of PGA is associated with a higher rate of cardiovascular disease and mortality compared to a similar degree of BP elevation in essential hypertension.

In most patients with diagnosed primary hyperaldosteronism, the stage of irreversible changes is revealed in target organs (diastolic dysfunction of the myocardium, interstitial nephritis, cerebral consequences in the form of acute disorders of cerebral circulation). More malignant process of arterial hypertension and rapid damage to target organs in primary hyperaldosteronism are associated with additional effects of aldosterone.

These include: the effect of elevated aldosterone levels on the enhancement of collagen synthesis by fibroblasts in the myocardium and other organs, acceleration of the processes of perivascular fibrosis of the middle and small arteries (intramyocardial, etc.), lesion of repolarization of the left ventricle with subsequent development of diastolic and systolic dysfunction of the left ventricle, the development of oxidative stress and the enhancement of endothelial dysfunction.

It is believed that the higher the aldosterone concentration, the higher the values of BP and the malignant course of hypertension. The course of hypertension can also be different: a constant with a predominant increase in diastolic blood pressure, a crisis of up to 50% of cases, and only in 6-9% of cases it is of a malignant nature.
With the long process of the disease, development of hypotrophy and dilatation of the left ventricle, changes in the fundus (angiospasm, retinopathy), visual field defects will be detected.

During studying the characteristics of the daily profile of blood pressure, it was found that in most patients with PGA, BP often increases during night hours, which may be the result of a lesion of the daily rhythm of aldosterone secretion.\textsuperscript{2} ECG changes occur in 80% of patients with PGA and manifest as sinus bradycardia, left ventricular hypertrophy. Neuromuscular syndrome includes muscle weakness, fatigue, muscle cramps, in severe cases - paresis and myopathy. Symptoms of hypokalemia are usually manifested in the syndrome of impairment of neuromuscular conduction and excitability.

These manifestations are due to the presence and severity of hypokalemia. However, at a normal level of potassium in the blood, neuromuscular manifestations are not often detected. Kidney symptoms: polydipsia, nocturia, polyuria with low relative density and alkaline urine reaction (sometimes diuresis reaches 10 liters per day). Potassium-deficiency nephropathy develops. Edema for this disease is not characteristic, since polyuria and accumulation of sodium inside cells (rather than in interstitium) do not contribute to fluid retention in the intercellular spaces. Malignant aldosteroma can be appeared by pain in the abdomen, hyperthermia, signs of intoxication. In 6-10% of cases, PHA has an asymptomatic flow. Therefore, very often the only manifestation of hyperaldosteronism is arterial hypertension.

The absence of hypokalemia and associated neuromuscular and renal manifestations is not a criterion for the exclusion of PGA. According to clinical recommendations (International Endocrinology Society, 2008), diagnosis of PGA should be performed among the followers: with arterial hypertension of the 2\textsuperscript{nd} and 3\textsuperscript{rd} stage >160/100mm Hg; with arterial hypertension, resistant to drug therapy; with a combination of arterial hypertension and hypokalemia; with a combination of arterial hypertension and adrenal gland adenoma; with a combination of hypertension and a heavier family history in relation to the early development of hypertension or acute cerebrovascular disorders before the age of 40 years.

For the primary detection of PHA in patients of these groups, the aldosterone-renin ratio (ARS) is recommended.\textsuperscript{3} The ESH/ESC (2013) clinical recommendations emphasize the need for the determination of APC in all relatives of the first line of patients with AHP who have AH manifestations.\textsuperscript{1,2} ARS is currently the most reliable and up-to-date method for screening PGA. Numerous studies confirm the diagnostic superiority of APC in comparison with the separately used methods of determining the level of potassium or aldosterone (both indicators have low sensitivity) and renin (low specificity).

Absence of hypokalemia does not exclude hyperaldosteronism, since in 50% of cases the level of potassium can be normal. Also, the normal level of aldosterone does not exclude hyperaldosteronism, since in 30% of patients the aldosterone concentration can be within the permissible limits.\textsuperscript{11-13} The definition of the aldosterone-renin relationship has some peculiarities. Many drugs can affect the level of aldosterone and renin in the blood.

Therefore, before proceeding with the research on the aldosterone-renin ratio, it is recommended to adhere to certain limitations: the patient should not limit the intake of sodium; the patient should cancel the drugs that affect the parameters of APC, not less than 4 weeks: spironolactone, eplerenone, triamterene, amiloride; diuretics; products from the root of licorice, the patient must cancel at least 2 weeks other drugs that can affect the level of APC:

a. β-adrenoblockers, central α-adrenomimetics (clonidine, α-methyl dopa), non-steroids antiinflammatory drugs (NSAIDs);

b. angiotensin-converting enzyme (ACE inhibitors), angiotensin receptor blockers (ARBs), renin inhibitors, dihydropyridine calcium channel blockers.

According to the recommendations of the International Endocrinology Society, the most common diagnostic value of APC for primary hyperaldosteronism in the indicated units of measurement is 30.\textsuperscript{2} After confirming the diagnosis of primary hyperaldosteronism, differential diagnosis of nosological forms of the disease is necessary. The significance of early diagnosis is due to the fact that this form of AH can be eliminated by surgery.

According to the recommendations of the ESH/ESC (2013), with the confirmed unilateral aldosterone, the choice method is laparoscopic removal of the affected adrenal gland (adrenalectomy).\textsuperscript{10,14} If the operation is refused, antiminalocorticoid therapy is recommended. Spironolactone (verashpiron) is the drug of choice for treating PGA. Spironolactone is a potassium-sparing diuretic, whose action in PGA is due to antagonism with aldosterone. Due to blockade of MKD located on endothelioocytes and cardiomyocytes, the drug interferes with the development of myocardial fibrosis, which occurs under the influence of an excessive level of aldosterone.\textsuperscript{15,16} Spironolactone (verashpiron) is prescribed in doses from 50-100 to 400mg per day (average dose of 150-200mg).\textsuperscript{1,2} The dose of the drug can be increased to 400mg per day to achieve normokalemia without additional administration of prolonged potassium chloride medication.\textsuperscript{7,17} Side effects of spironolactone include gynecomastia in men, muscle spasms, decreased libido, erectile dysfunction and menstrual irregularities in women.\textsuperscript{18} Eplerenone is a new MCR antagonist. The main difference between this drug and spironolactone is its greater selectivity with respect to blockade of steroid receptors.\textsuperscript{19} In the therapy of PHA, it is recommended to prescribe treatment at a dose of 25mg 2 times a day, with the subsequent selection of the dose according to the level of potassium and AD. The maximum effective dose of eplerenone is 100mg per day. Contraindications for the drug are hyperkalemia (more than 5.5mmol/L), CRF, diabetes with diabetic nephropathy at the stage of microalbuminuria, simultaneous administration of inhibitors of CYP3A4 (ketoconazole, itraconazole) or potassium-sparing diuretics. It is known that patients with PIGA are less sensitive to AMCR monotherapy, than patients with APA. In patients with PIGA, the cause of resistant hypertension is hypervolemia, and it is justified to administer small doses of thiazide diuretics (hydrochlorothiazide at a dose of 12.5-25mg per day) under the control of potassium. \textsuperscript{20} Calcium channel blockers (nifedipine, amlopidine) reduce the secretion of aldosterone, blocking the flow of calcium into the cells. In the treatment of PIGA, angiotensin-converting enzyme (ACE) inhibitors are also used, because with this nosological form of PHA, patients retain sensitivity to angiotensin II. With PGA, there is an increased expression of aldosterone synthetase,\textsuperscript{21} so the use of its inhibitors is a promising direction in drug therapy of PHA, including PIGA.\textsuperscript{22-24}

Acknowledgements

None.

Conflict of interest

The author declares that there is no conflict of interest.
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References
