

# Characteristics and features of clinical manifestations of primary hyperaldosteronism (literature review)

Viktor O. SHIDLOVSKIY<sup>1</sup>, Olexandr V. SHIDLOVSKIY<sup>1</sup>, Michael I. SHEREMET<sup>2</sup>, Natalia A. SHEREMET<sup>3</sup>,  
Nina P. TKACHUK<sup>2</sup>, Vitaliy V. MAKSYMUYUK<sup>2</sup>, Volodimir V. TARABANCHUK<sup>2</sup>, Yan V. GYRLA<sup>2</sup>,  
Oleksandr V. BILOOKYI<sup>2</sup>

<sup>1</sup>Surgery Department, I. Y. Horbachevsky State Medical University, Ukraine

<sup>2</sup>Surgery Department No1, Bukovinian State Medical University, Ukraine

<sup>3</sup>First City Polyclinic, Chernivtsi, Ukraine

## ABSTRACT

**Introduction.** Primary hyperaldosteronism as a cause of secondary arterial hypertension ranges from 4.6 to 13.0%, and among patients with refractory hypertension to medication therapy is about 20%. Meanwhile, its detectability among patients with arterial hypertension in centers of primary health care is from 6 to 13%, and in secondary care centers – from 23 to 30%. The high frequency of life-threatening cardiovascular complications dictates the need for early and timely diagnosis of primary hyperaldosteronism in the stages of the primary and secondary units of medical care. In addition, studies conducted in German and Italian hospitals among general practitioners showed a low level of knowledge about primary hyperaldosteronism.

**Objective.** To promote the knowledge of general practitioners about clinical symptoms and clinical features of primary hyperaldosteronism.

**Results.** Therefore, the main task of the work is the systematization and dissemination of knowledge for general practitioners about the symptoms and peculiarities of the clinical course of primary hyperaldosteronism. Such signs as an inadequate response to hypotensive therapy of a combination of three drugs, a manifestation of arterial hypertension under the age of 30, a rapid increase in blood pressure even in the elderly and/or the loss of efficacy of antihypertensive therapy, apnea in dream are distinguished in its non-specific clinical picture, without indicating priority. In the literature, there are recommendations to separate classical and secondary clinical manifestations. Classical include arterial hypertension, hypokalemia, hypervolemia, metabolic alkalosis, and minor ones such as headache, retinopathy, neuromuscular symptoms (paresthesia's, convulsions, general weakness), carbohydrate metabolism disorders, arrhythmias, early onset of hypertrophy and fibrosis of the heart muscle and smooth muscle vessels, hypokalemia and moderate hypernatremia.

**Conclusions.** In the clinical course of the disease, the cardiovascular, neuromuscular, renal and metabolic syndromes are distinguished, or in combination of several of them, in each particular case, the primary hyperaldosteronism may appeared (or manifested).

**Keywords:** primary hyperaldosteronism, clinical symptoms, syndromes

## Abbreviations

PHA – primary hyperaldosteronism

AH – arterial hypertension

Corresponding author:

Michael I. Sheremet

E-mail: mihayl71@gmail.com

## INTRODUCTION

The article is devoted to the study of literary sources concerning modern methods of diagnostics, treatment and prevention of primary hyperaldosteronism and its complications.

Today, primary hyperaldosteronism (PHA) is recognized as the most common specific cause of secondary arterial hypertension (AH). Its frequency as a cause of hypertension is from 4.6 to 13.0%, and among patients with refractory to medical therapy of hypertension – is within 20%. At the same time, in the centers of primary health care, the prevalence of PHA in patients with arterial hypertension ranges from 6 to 13%, and in secondary care centers – from 23 to almost 30% (1-3).

Early detection of the disease is vital, since timely undiagnosed PHA results in increase in cardiovascular, renal and metabolic morbidity and mortality associated with the effect of an excess of aldosterone on the body. However, screening of PHA as a cause of arterial hypertension depends crucially on general practitioners, who are the first link to be treated by patients with hypertension. However, a study recently conducted in German and Italian general hospitals showed a surprisingly low level of knowledge about PHA, which is the main reason for its untimely diagnosis (4).

## PHA SYMPTOMS

Peculiarities of the clinical picture of the PHA are that the disease is initially oligosymptomatic, except for the presence of arterial hypertension. In most cases, there are only subtle hints of the diagnosis of primary hyperaldosteronism, such as, for example, the resistance to drug therapy with three classes of antihypertensive drugs, including diuretics, signs of renal or heart failure, cardiac arrhythmias, metabolic disorders, hypokalemia.

Due to the non-specificity of the clinical picture of PHA, the literature has the recommendations to distinguish classical and secondary clinical manifestations of the disease. The classical ones include arterial hypertension, hypokalemia, hypervolemia, metabolic alkalosis, and secondary – headache and retinopathy, neuromuscular symptoms (paresthesia's, convulsions, general weakness), hyperglycemia, or diabetes type 2, arrhythmias as a consequence of hypokalemia, hypertrophy and cardiac muscle fibrosis and hypertrophy of smooth muscle of vessels as a direct result of aldosterone effects on the cardiovascular system, moderate hypernatremia due to changes in osmosis and sodium depletion in the body (5).

The clinical picture of the disease develops very slowly, and in the first stages it can be asymp-

tomatic, except for the presence of hypertension. Subsequently symptomatology intensifies. After some time, sometimes after many years, as a result of long-term AH there are other symptoms. Then the symptoms become more pronounced.

In the symptomatology of PHA with a certain degree of conditionality it is suggested to distinguish such clinical syndromes: cardiovascular, neuromuscular, renal failure syndrome, metabolic, and in some patients, in addition – intracranial hypertension. Cardiovascular syndrome includes arterial hypertension and its manifestations – headache, dizziness, cardialgia, and possible cardiac arrhythmias. The course of AH is different – from severe, resistant to hypotensive therapy to mild, which could be corrected by antihypertensive drugs. Minimal increase in blood pressure (BP) is observed in some patients with PHA. In connection with this, it is believed that severe hypertension is not always a reason for the diagnosis of PHA (6,7). Screening of family members with genetic forms allowed recognizing individuals with a normal blood pressure (8-10).

According to the main characteristics, arterial hypertension at PHA does not differ from the essential hypertension (EH). The degree of increase in BP may vary from moderate (150-160 / 90-100 mmHg) to very high (250-280 / 130-140 mmHg). The course of arterial hypertension is stable, but in some patients, it may be accompanied by crises. Indicators of arterial pressure in case of aldosterone-producing adenomas and carcinomas are higher than in case of bilateral hyperplasia of the adrenal glands (5,11).

In most patients with PHA, blood pressure often increases at night as a result of a violation of the daily rhythm of aldosterone secretion (12). ECG changes are observed in 80% of patients with PHA and are manifested as sinus bradycardia, left ventricular hypertrophy, inversion of the T wave, permanent or temporary (during crises) depression of the ST segment, supraventricular and ventricular arrhythmias, prolongation of the QT interval.

High frequency of complications is a characteristic feature of AH in case of primary hyperaldosteronism. In patients with PHA, compared with patients with EH, brain hemorrhage was noted 4 times more often, myocardial infarction – 7 times, and atrial fibrillation – 12 times (13).

Often, patients complain of headaches of varying intensity, which is due to hyperhydration of the brain and increased intracranial pressure. Recently, the issue of PHA associated with intracranial hypertension is discussed (14,15). Such patients complain of headache, increased BP in the range

up to 160/90 mmHg, visual impairment (reduced visual acuity). They often have visual field defect, amblyopia, and almost 50% – fundus vascular lesion (angiospasm, retinopathy). The expression of these symptoms depends on the degree of increase in blood pressure and the disease duration. Retinopathy can lead to complete loss of vision. Spinal cord puncture in such patients registered high pressure of cerebrospinal fluid.

Patients with PHA are more likely to have left ventricular hypertrophy and higher cardiovascular complications compared to patients with AH and similar levels of arterial pressure (16). In case of PHA diastolic function of the myocardium is disturbed, resulting in increased left and right ventricular end-diastolic volume (17).

Along with arterial hypertension, or even without it, spontaneous hypokalemia, which is about 30.0%, can be observed. Particular attention should be paid to patients with severe and unreduced hypokalemia after the abolition of diuretics that cause increased excretion of potassium, such as hydrochlorothiazide and furosemide (18). Potassium deficiency can cause arrhythmia. At the same time, severe hypokalemia can cause a hypokalemic crisis characterized by intense headache, nausea, vomiting, muscle weakness, superficial breathing, reduced sense of vision. In severe cases, a clinical picture of cerebrovascular accident or acute left ventricular failure develops (19). With prolonged course of the disease, there is hypertrophy and dilatation of the left ventricle. In severe chronic hypokalemia, excitability of the myocardium, insulin secretion by  $\beta$ -cells of the pancreas and glucose tolerance are disturbed (20).

Excessive secretion of aldosterone leads to an increase in extracellular fluid volume due to excessive sodium reabsorption. However, in this state, peripheral edema is rare, since excessive sodium excretion is partially regulated by an increase in the level of natriuretic peptide produced by the atria.

Hypokalemia is also a cause of the development of a syndrome of neuromuscular disorders that arise on the basis of dystrophic changes in muscle and nervous tissues – from slightly pronounced to rhabdomyolysis (21). In this case, patients are disturbed by rapid fatigability, decreased ability to work, constant or gradually increasing or pronounced neuromuscular weakness (22). Sometimes pain in the muscles of the upper or lower extremities, paresthesia, tingling and numbness in palms and soles develop, and rarer – convulsions, mono or even tetra paralysis.

Muscular weakness has a paroxysmal nature and lasts from several minutes to several days

(23). It can be provoked by physical activity, pulmonary hyperventilation, in women – onset of menstruation. Myasthenia is local, covering individual muscle groups – limbs, neck, or widespread myasthenia. Sometimes there are seizures of the type of tetanic, positive Chvostek's, Trousseau's symptoms. Often, neuromuscular symptoms are combined with polydipsia, polyuria and nocturia (24). In the instrumental study, violations of neuromuscular conduction are detected, up to the signs of bulbar disorder.

Renal impairment is observed in almost all patients with PHA. They are manifested by increased excretion of hydrogen ions in the urine, decreased renal concentration, glomerular filtration rates, metabolic alkalosis and albuminuria (25). These renal disorders are mostly reversible or weakened after surgical removal of the source of its excessive aldosterone production (26).

The changes in the quality of sleep and psycho-emotional disorders take a certain place in the clinic of primary hyperaldosteronism. Sleep disorders, which manifest themselves in sleep apnea, are dangerous for life. It is established that high concentration of aldosterone in blood correlates with the degree of severity of apnea and PHA (27). Nearly 7% of patients with PHA note the night apnea, the frequency of which is almost 4 times greater than that of patients with EH. At the same time, it was found that in female patients with PHA, apnea occurs more frequently than in men ( $8.7 \pm 3.6$  versus  $5.7 \pm 4.2$ )  $p < 0.005$  (28). Treatment of PHA by antagonists of mineralocorticoid receptors or adrenalectomy contributes to the reduction of the severity of clinical manifestations or the disappearance of sleep apnea (29).

Psychoemotional disorders in the form of depression, anxiety, unreasonable anger or panic are peculiar to some of the patients with PHA, but they are rarely documented (30). In the literature, there are few reports of the various variants of these disorders fixation when primary hyperaldosteronism was the cause of the development of recurrent panic attacks (31). Analysis of literature data suggests that psycho-emotional disorders in patients with PHA are not uncommon with respect to healthy individuals and, especially, patients with EH. According to the results of research conducted by N. Sonino et al. (2011), 12 out of 23 patients with PHA (52.2%) had anxiety disorders compared to 4 out of 23 patients (17.4%) with EH (32). These data indicate that the primary hyperaldosteronism causes anxiety and stress (33,34). During another study conducted by K. Apostolopoulou et al. (2014) a higher prevalence of de-

pression and anxiety in patients with PHA compared to healthy individuals was revealed, and women were more affected than men (35). In all the works, it was noted that psycho-emotional disorders disappear on the background of adequate treatment of PHA.

## METABOLIC SYNDROME AND PHA

Metabolic syndrome (MS) is considered as a combination of interconnected risk factors for cardiovascular complications of metabolic origin, including arterial hypertension, dyslipidemia, changes in type 2 diabetes mellitus homeostasis and obesity of the abdominal cavity organs (36).

Clinically, a diagnosis of a metabolic syndrome is authentic in the presence of any of the following five criteria: 1) obesity of the abdominal cavity organs (waist circumference more than 102 cm in men and more than 88 cm in women); 2) triglyceride level 1.69 mmol/l and more; 3) the content of high density lipoprotein (HDL) less than 1.03 mmol/l in men and less than 1.29 mmol/l in women; 4) fasting plasma glucose more than 6.1 mmol/l; 5) systolic BP – 130 mm Hg and more, diastolic BP – 85 mm Hg and more (37).

From the clinical signs of MS, abdominal adiposity with accumulation of adipose tissue in the greater omentum occupies the first place. The second most frequent component of the metabolic syndrome is arterial hypertension. Untreated MS leads to the development of explicit type 2 diabetes (if not already part of it) and early atherosclerosis (36).

The significance and role of MS in the clinical course of PHA in the literature is considered in comparison with essential hypertension, because arterial hypertension is a common and leading symptom of these three pathologies. Therefore, they are examining the question of how often other symptoms of MS, other than hypertension, occur in patients with PHA and EH (37) (Table 1).

Analysis of the data in Table 1 shows that patients with PHA with MS have a significantly higher body mass index than patients with EH. In addition, compared to patients with PHA without MS, the ratio of aldosterone to renin, waist circumference, triacylglycerol and glucose levels in the blood, the duration of arterial hypertension, and the decreased HDL score are significantly higher. Consequently, PHA in most patients is combined

**TABLE 1.** Characteristics of patients with primary hyperaldosteronism and essential hypertension, with and without metabolic syndrome

Indicators	Primary hyperaldosteronism			Essential hypertension			Value p
	total (n=85)	MS (n=35) (41.2%)	No MS (n=50) (58.8%)	Total (n=381)	MS (n=113) (29.7%)	No MS (n=268) (70.3%)	
Age, years (range)	55±9 (22-76)	59±7 (44-76)	53±10 (22-75)	53±13 (15-84)	55±12 (21-82)	53±13 (15-84)	UA
Sex% of men	63	71	57	56	53	57	UA
BMI kg/m <sup>2</sup>	27.2±3,8	28.7±2.9	25.9±3.5	27.9±4.6	30.1±4.7	25.8±4.0	<sup>1</sup>
Aldosterone, ng/dl	31,8±20	35,7±24,3	29,7±17,5	20,1±8,6	19,0±9,3	20,6±8,3	<sup>2</sup>
Renin, ng/ml; h	0.17±0.11	0.16±0.1	0.2±0.13	3.18±3.2	3.32±2.4	3.03±3.1	<sup>2</sup>
Ratio of aldosterone to renin	224±16	275±21	208±14	22±14	20±8	23±16	<sup>2</sup>
Potassium, (mmol/L)	3.7±0.5	3.7±0.6	3.7±0.5	4.2±0.5	4.2±0.4	4.2±0.4	<sup>2</sup>
Creatinine, μmol/L	81.1±19.0	85.9±22.0	77.8±16.0	80.7±18.0	80.6±18.6	80.7±18.0	UA
WC, cm	98.0±9.4	100.6±7.3	91.5±8.6	95.8±12.7	104.7±10	92.0±11.4	<sup>1</sup>
Triacylglycerols, mmol/L	1.49±0.75	1.98±0.7	1.15±0.6	1.46±0.98	2.12±1.33	1.18±0.6	<sup>1</sup>
HDL, mmol/L	1.41±0.39	1.17±0.27	1.58±0.37	1.45±0.41	1.24±0.39	1.54±0.38	<sup>1</sup>
Glucose, mmol/L	5.66±1.28	6.43±1.54	4.99±0.93	5.39±1.11	5.87±1.37	5.19±0.91	<sup>1, 2, 3</sup>
Systolic BP, mm Hg.	162±26	166±23	158±29	153±21	156±25	153±21	<sup>2</sup>
Diastolic BP, mm Hg	98±12	100±13	97±12	96±11	98±12	96±11	UA
AH duration (months)	147±111	152±92	144±123	117±100	130±114	112±94	<sup>2</sup>
Smokers, %	13	14	12	17	17	18	UA
Alcohol, %	17	20	14	18	14	20	UA
Left ventricular hypertrophy, %	27	34	22	17	21	16	<sup>2, 3</sup>

Notes: 1. BMI – body mass index; UA – unauthentic; WC – waist circumference; HDL – high-density lipoproteins; BP – blood pressure  
2. To convert the values of aldosterone in plasma to nanomol per liter, multiply by 0.0277; to convert the values of active renin plasma into nanograms per liter per second multiply by 0.2778. 3. <sup>1</sup> – significant difference between patients with MS and patients without MS; <sup>2</sup> – significant difference between PHA and EH; <sup>3</sup> – a significant difference between the PHA with MS and essential hypertension with MS.

**TABLE 2.** Comparative characteristics of combinations of components of metabolic syndrome in patients with primary hyperaldosteronism and essential hypertension

Patients with PHA, EH	MS n,%	WC↑	WC↑	TG ↑	TG↑	WC ↑	WC ↑	WC ↑	TG ↑	TG ↑	WC ↑	
		TG↑	HDL ↓	HDL ↓	FG ↑	FG ↑	TG ↑	TG ↑	HDL ↓	HDL ↓	HDL ↓	TG ↑
		BP ↑	BP ↑	BP ↑	BP ↑	BP ↑	BP ↑	BP ↑	BP ↑	BP ↑	BP ↑	BP ↑
		1	2	3	4	5	6	7	8	9	10	
PHA (n=85), %	5 1.1	4 4.7	4 4.7	4 4.7	1 1.2	8 9.4	4 4.7	6 7.0	1 1.2	2 2.4	1 1.2	
EH (n=381), %	113 29.6	31 8.2	14 3.8	12 3.2	3 0.8	20 5.2	17 4.4	4 1.0	7 1.8	1 0.3	4 1.0	

Note. n – number of the examined patients; % – percentage of the total number of examined patients; WC – waist circumference; TG – triacylglycerols; FG – fasting glucose; ↑ – indicators are over the limit; ↓ – indicators are below normal.

with the clinical signs of MS, which is confirmed by the results of studies of other authors (38-41).

F. Fallo et al. (2006) studied the possible combinations of metabolic syndrome components and their frequency in patients with PHA and EH (Table 2).

As shown the data in Table 2, in 70% of the combinations of components of the metabolic syndrome there are indicators of triacylglycerol in the blood and the waist circumference, and in 60% – the HDL content and blood glucose levels. Combinations of MS components 3, 4, 5, 7, 9 in case of PHA are more common in comparison with patients with EH. Combinations of MS components 2, 6, 8 with the same frequency take place in patients with PHA and EH. The first combination of components of the syndrome is significantly more likely to be observed in essential hypertension. In this table, you can determine the frequency of the presence of each component of the MS in the clinical course of PHA and EH. Yes, arterial hypertension was available in all combinations; increased level of triacylglycerols in the blood and circumference of the waist is more than normal – in 7, and an increased level of glucose in the blood and reduced HDL content – in 6 (37).

The analysis of the frequency of individual components of the metabolic syndrome showed that at primary hyperaldosteronism, in addition to arterial hypertension, more common hyperglycemia than in patients with EH (27.0% vs. 15.2%,  $p < 0.05$ ) (Table 1). In addition, the proportion of patients with diabetes or taking hypoglycemic drugs prior to the study was significantly higher in PHA than in EH.

Thus, it can be considered proven that the changes in glucose metabolism as a monosymptom or as a component of a metabolic syndrome are characteristic for patients with PHA. This clinical situation is due to a decrease in insulin sensitiv-

ity due to the direct effect of aldosterone on insulin receptor function (42).

In general, in most publications devoted to primary hyperaldosteronism and metabolic syndrome, it is noted that patients with PHA (aldosterone-producing adenoma or bilateral hyperplasia of the adrenal glands) are significantly more common in the MS than in patients with EH (41.1% vs. 29.6%,  $p < 0.05$ ). At the same time attention is paid, to the fact that the prevalence of MS in patients with EH is higher than in healthy individuals (23.1%) with similar demographic characteristics living in the same geographical area (37).

Later studies, conducted by V. Ronconi et al. (2010), confirmed the higher prevalence of metabolic syndrome in patients with PHA compared to the corresponding patients with EH (45% vs. 30%,  $p < 0.05$ ) (43,44). In patients with PHA, metabolic syndrome tended to develop more frequently than in patients with EH (51% vs. 32%,  $p < 0.05$ ).

In some studies, the incidence of MS with aldosterone-producing adenoma and bilateral hyperplasia of the adrenal glands was analyzed. So, G. Iacobellis et al. (2010) showed that metabolic syndrome is more common in PHA based on aldosterone-producing adenoma compared with bilateral hyperplasia of glands (29% vs. 21%,  $p < 0.05$ ) (40). The work by Z. Somlóová et al. (2010) gives somewhat different data. According to the results of their research, the metabolic profile of patients with bilateral form of PHA (due to bilateral hyperplasia of the adrenal glands) was similar to EH, but differed from the one-sided form of PHA on the basis of aldosterone-producing adenoma (45). According to these authors, the prevalence of MS in patients with bilateral hyperplasia of the adrenal glands was 62%, at aldosterone-producing adenoma – 34%, at EH – 56%.

The clinical significance of all these observations is that the role of aldosterone excess in cardi-

ovascular damage mechanisms is clearly defined. That is, the higher incidence of cardiovascular complications in patients with PHA, as compared to patients with EH, may be associated with an increased prevalence of metabolic syndrome in patients with PHA (46-48).

The presence of more than three signs of MS in patients with PHA emphasizes that this secondary form of arterial hypertension is not benign by its course. It is strongly associated with metabolic changes, which can cause a high risk of developing cardiovascular complications.

## CONCLUSIONS

Thus, the analysis of literature data indicates that PHA is the main endocrine cause of secondary hypertension and is much more frequent than previously considered.

Symptoms of primary hyperaldosteronism are not specific and do not give an impression of it as

a disease with clearly expressed clinical manifestations. An early and leading symptom of PHA is an increase in blood pressure. It is common to many diseases that cause primary and secondary arterial hypertension. Obviously, this can be explained by the low level of diagnosis of PHA as causes of arterial hypertension at all levels of medical care.

Certain values in the diagnosis of PHA have non-specific clinical and laboratory characteristics. Among them, it is possible to distinguish, without indicating priority, such as sleep apnea, inadequate response to hypotensive therapy of the combination of three drugs, manifestation of arterial hypertension at the age of 30, rapid increase in blood pressure even in the elderly and/or loss of efficacy of antihypertensive therapy, expressed increase in blood pressure more than 180/110 mm Hg, hypokalemia, especially when combined with increased creatinine plasma concentrations, proteinuria or hematuria.

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