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Primary Hyperaldosteronism in Clinical Practice

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Abstarct:
The data obtained in the study of the clinical features of aldosterone-producing adrenal adenomas indicate that aldosteromas are more common in young working age (the average age of patients was 42.4 ± 12.4 years old, and the peak incidence was at the age of 18 to 44 years old) with a predominance among females. The classical clinical triad, which includes a combination of three main syndromes (AH, neuromuscular and renal), was found only in 62.5% of the patients. The leading clinical manifestation in all the patients with aldosteroma in 100% of the cases was hypertension, which was permanent in 75% of the patients, mixed in 12.5%, while constant malignant hypertension was observed in 12.5% of the cases. At the same time, stage 1 (50%) and stage 2 hypertension (37.5%) were registered most often in patients with aldosterone-producing adenomas, and only stage 3 hypertension was registered in 12.5%. It should be noted that the combination of hypertension, especially in young people, and a burdened family history of hypertension and its complications among the relatives of the first line kinship should serve the basis for excluding aldosterone-producing adrenal adenomas.

Keywords: adrenal tumors, arterial hypertension, primary aldosteronism.

Introduction

Primary hyperaldosteronism (PHA) is one of the most common forms of secondary arterial hypertension (AH) and it makes up approximately 10%, and according to some studies even up to 30% of all hypertensions [2,3,5,6]. The causes of PHA are in 60-65% of the cases of adrenal adenoma and in 35-40% of the cases idiopathic hyperaldosteronism due to diffuse hyperplasia of the adrenal cortex [8]. Aldosterone-producing adenomas (APA) of the adrenal glands, or aldosteromas, are among the relatively rare, but the most difficult to diagnose hormone-active formations of the adrenal glands. The difficulty of diagnosis of aldosteromas is that clinically they are

practically difficult to distinguish from essential hypertension. They are also clinically difficult to differentiate from a number of symptomatic arterial hypertension kinds, such as nephrogenic hypertension, some forms of vascular hypertension or permanent and mixed forms of pheochromocytoma.

The clinical significance of APA is associated with a higher frequency of cardiovascular lesions and mortality compared with a similar degree of increase in blood pressure in cases of essential hypertension [4, 12]. The majority of patients with diagnosed APA have a stage of irreversible changes in target organs (diastolic myocardial dysfunction, interstitial nephritis, cerebral consequences in the form of acute disorders of cerebral circulation) [4,7,11]. More malignant course of hypertension and rapid damage in target organs in APA cases are associated with the additional effects of aldosterone, which enhances collagen synthesis by fibroblasts in the myocardium and other organs, accelerates the processes of perivascular fibrosis of medium and small arteries (intramyocardial, etc.), disrupts the repolarization of the left ventricle with the subsequent development of diastolic and systolic dysfunction of the left ventricle, and intensifies oxidative stress and endothelial dysfunction [10,13]. According to I.I. Dedov, the higher the aldosterone, the higher the blood pressure is and its malignant course. In their turn, early and effective detection of patients with APA will radically eliminate this cause of hypertension and thereby modify individual risks [1], improve the quality of life of the patients and reduce the frequency of cardiovascular events, including premature mortality [9].

The objective of the research was to study clinical peculiarities and progression of AH in cases of aldosterone-producing adrenal adenomas.

Materials and research methods

Among the examined patients with various adrenal gland formations (n=282) who received outpatient and inpatient treatment at the Endocrinology Center of the Ministry of Health of the Republic of Uzbekistan within the period from 2000 to 2018, there were 16 patients with APA (5.7%). Among these, there were 11 women (68.8%) and 5 men (31.2%). The age of the patients ranged from 20 to 65 years old, while the average age was 42.4±12.4.

All the patients with adrenal gland formations underwent general clinical, biochemical, hormonal and instrumental studies.

Examination of the patients with APA was carried out in several stages. At the first stage we determined the level of aldosterone and ARP and then calculated the aldosterone-renin ratio (ARR). According to the updated recommendations of the International Endocrinological Society for the Diagnosis and Treatment of Primary Hyperaldosteronism (An Endocrine Society Clinical Practice Guidelines, 2016), increase in ARR is considered to be its level of more than 30 when measuring aldosterone in ng/dl and ARR in ng/ml/h. Since in our study the level of aldosterone

was presented in pg/ml, in order to correctly determine the ARR we used unit converter (a system for converting traditional units of measurement used in laboratory and medical practice into units of the international SI system) to convert it to ng/dl and then calculated the ARR. When the ARR exceeded the threshold value a confirmatory PHA test was performed. There are several confirmatory tests, but there is no unambiguous data in the literature on the "golden standard" for the tests confirming PHA. Each of the specialized centers chooses the type of confirmation test based on their own experience. In our case we chose the saline test as the simplest, relatively cheap, the safest and most convenient to perform. Out of 16 patients 11 (68.8%) patients underwent a confirmatory test with saline solution, as a result of which the postinfusion level of aldosterone exceeded 100 pg/ml. In three (18.8%) patients after the determination of ARR without a confirmatory diagnosis we performed MSCT of the adrenal glands. These patients had a combination of spontaneous hypokalemia, severe ARP suppression, and plasma aldosterone levels above 200 pg/ml. Considering this, according to the recommendations of the International Endocrinological Society, the diagnosis of PHA is considered established without confirmatory testing. In 2 (12.5%) patients it was not possible to conduct a confirmatory test due to severe malignant hypertension in one of them and recent ACBD at the time of treatment in the other. The next step after confirming PHA according to the results of laboratory tests to confirm the topical diagnosis of all patients with diagnosed PHA was to perform MSCT of the adrenal glands.

For the assessment of clinical manifestations, the indicators of mean and standard deviation (M ± SD), as well as the frequency of occurrence of the studied signs were used. The correspondence of numerical data to the normal distribution law was evaluated. The differences between the compared mean values of independent and dependent samples were carried out by ANOVA single-factor analysis. To analyze the reliability of differences between qualitative characteristics $\chi 2$ criterion was used. The reliable level for all the analyses used was set as $p<0.05$.

Results and Discussion

To study the age characteristics of patients with APA we distributed them according to the WHO age classification 2017 (Table1). The majority of the patients (68.8%) with APA were of young working age, while the middle and elderly ones accounted for 18.8% and 12.4%,

espectively. As for the gender distribution, aldosteromas were almost 3 times more often observed in females.

Table 1 **Age and gender of the patients with APA (WHO, 2017)**

Age	male, n=5		female, n=11		Total, n=16	
	abs.	%	abs.	%	abs.	%
Children, under 18						
Young, 18-44	4	80.0	7	63.6	11	68.8
Middle, 45-59			3	27.3	3	18.8
Elderly, 60-74	1	20.0	1	9.1	2	12.4
Old, 75-90	-		-		-	

Attention is drawn to the fact that almost a third of the patients (31.2%) had a disease duration of up to 1 year, while the rest (68.8%) had 1-5 years. On average, the duration of the disease was 1.1 ± 1.0 years. The duration of hypertension up to 1 year was observed in 12.5% of patients, from 1 year to 5 years in 75%, and ≥5 years in 12.5% of the patients. The median duration of hypertension averaged 4.1±9.0 years. This also to a certain extent reflects the difficulty of aldosteroma diagnostics. This is confirmed by the fact that 31.3% of the patients were previously treated by a cardiologist, other 31.3% by a neurologist, 18.8% by a therapist, and 6.2% by an urologist.

Only 1 (6.2%) patient out of 16 initially sought medical help from an endocrinologist. In one case (6.2%) preliminary diagnosis was made by a functional diagnostic doctor. The above-mentioned doctors of related specialties treated the patients for hypertension, chronic pyelonephritis, chronic cerebral ischemia, urolithiasis, coronary heart disease, diabetes, and obesity. During the period of the disease 2 (12.5%) patients had a hypertensive crisis, 2 (12.5%) had acute cerebral circulation disorder, 2(12.5%) transient ischemic attack, and 3 (18.8%) myocardial infarction. A quarter of patients (25%) had chronic heart failure.

Analyzing the nature of the onset of the disease we found that in 81.3% of the cases at the start of the disease patients had increase in blood pressure. Other part of patients in 18.7% of the cases had general weakness observed at the beginning of the disease in combination with neuromuscular disorders, and hypertension was detected during examination. It should be noted that 87.5% of the patients did not associate the onset of the disease with anything, and only 2 (12.5%) of them associated the onset of the disease with stress. When studying the life history of the patients it was also found that6 (37.5%) patients had low physical activity, 6 (37.5%) had irrational nutrition, and 3 (18.8%) patients had too much smoking.

When studying the family history of patients with aldosteromas we revealed in relatives (first line kinship) cardiovascular diseases in men under 55 in 10 (62.5%) cases, cardiovascular diseases in women under 65 in 5 (31.3%) cases, and in particular, hypertonic disease in 12 (75%), stroke in 2(12.5%), coronary heart disease in 3 (18.8%),

hypertensive crisis in 2 (12.5%), and myocardial infarction in 3 (18.8%). Also, in 2 (12.5%) cases relatives suffered diabetes, 3 (5.9%) had kidney diseases, 1 (6.2%) had cancer and 1 (6.2%) had an adrenal tumor (pheochromocytoma). Summarising the analysis of the early signs of APA and family history, it should be noted that the combination of hypertension, especially in young people, and a burdened family history of hypertension and its complications in relatives of the first line kinship should provide grounds to suspect the presence of aldosteroma in the patient.

Classical clinical picture of aldosteroma includes three main characteristic syndromes: hypertension, neuromuscular and renal disorders. However, in our observations the classical clinical triad was found only in 10 (62.5%) patients.

The leading clinical manifestation in all the patients with aldosteroma in 100% of cases was hypertension. Their blood pressure values ranged from 130/90 to 240/140 mm Hg. At the same time, the level of maximum SAP was from 160 to 240 mm Hg. (average value 186.3±28.3 mm Hg.), DAP from 100 to 140 mm Hg. (average value 111.9± 14.7 mm Hg). In patients with hypertension without adrenal gland formation, the maximum level of SAP varied from 140 to 180 mmHg (mean value 157.7 ±13.1 mmHg), DAP from 90 to 120 mmHg (mean value 98.2±8.0 mmHg) (Table 2). The mean blood pressure levels in patients with APA for systolic one were 156.9±20.6 mmHg, for diastolic 95.6±8.1 mmHg, which also statistically significantly ($p<0.0001$) differed from both control groups.

Table 2 **Clinical characteristics of the studied groups (single-factor dispersive (ANOVA) and paired analysis)**

Parameters	Control, n=46		APA, n=16	p
	Without AH, n=24	AH, n=22		
Age	39.6±11.1	41.3±6.9	42.4±12.4	0.68
SAP (max), mm.Hg	122.4±5.4	157.7±13.1#	186.3±28.3##	<0.0001
DAP (max), mm.Hg	77.1±4.6	98.2±8.0#	111.9±14.7##	<0.0001
SAP (mean), mm.Hg	119.6±6.9	143.6±7.9#	156.9±20.6##	<0.0001
DAP (mean), mm.Hg	69.3±4.8	91.8±3.9#	95.6±8.1#	<0.0001
Term of AH, years	-	3.3±2.0	4.1±9.0	0.69
Age at the start of AH	-	38.0±7.0	38.3±10.9	0.92
Duration of the disease, years	-	-	1.1±1.0	
BMI, kg/m^2	23.8±2.6	24.5±2.7	26.7±4.5*	0.02

Note: the data are presented as M±SD; * - difference compared to the data without AH and with AH singificant (* - $p<0.05$, ●- $p<0.01$, #- $p<0.001$)

In 75% of patients the course of hypertension was constant, in 2 (12.5%) it was mixed, in other words against the background of constant hypertension crises with an increase in blood pressure of more than 200 mmHg periodically occurred. At the same time crises were accompanied by sharp headaches, visual impairment, nausea, vomiting, convulsions, sweating, trembling in the body, and tremor. Other 2 (12.5%) patients had

permanent malignant hypertension, which was accompanied by changes in the fundus and was resistant to therapy. Although these patients had small formations detected on MSCT, later due to the ineffectiveness of conservative drug therapy with antimineralocorticoid drugs, they underwent adrenalectomy. It should be noted that stage 1 hypertension was most often registered, and it was observed in half (50%) of the examined patients with aldosteroma; 6 (37.5%) patients had stage 2 hypertension and, finally, stage 3 hypertension was registered in 2 (12.5%) patients. The data obtained by us coincide with the data of other researchers [8]. Along with hypertension in APA, 3 (18.8%) patients had obesity of various degrees and 8 (50%) were overweight. At the same time BMI for all patients in this group was 26.7±4.5 kg/m2, which was significantly higher compared to the control groups without hypertension and with hypertension (p=0.02).

Among the examined patients 15 (93.8%) complained of headache of permanent or periodic nature, which worsened with rise of blood pressure. Headaches are both the result of increased blood pressure and hyperhydration of the brain. Six (37.5%) patients additionally complained of dizziness. Psychoemotional disorders in the form of asthenic and anxiety-depressive syndromes may be the result of chronic water-electrolyte imbalance. So in our observation 8 (50%) patients noted nervousness, 4 (25%) depression, and 2 (12.5%) frequent mood swings. Other 5 (31.3%) complained of sleep disorders, and 1 (6.2%) of memory loss.

According to ophthalmoscopy data hypertensive retinopathy of various degrees was detected in 9 (56.3%) patients, which was clinically manifested by flickering of "flies", the presence of "veil" in front of eyes, and decrease in visual acuity.

In addition to hypertension, patients presented the following complaints from the CVS. Thus, pain in the heart area was observed in 6 (37.5%) patients, which was dull, aching in nature, and was probably due to both blood pressure rise and potassium deficiency. Palpitations were also observed in 6 (37.5%) patients. Two (12.5%) patients had dyspnea during exercise.

ECG showed hypertrophy of the left ventricle in 6 (37.5%) patients with APA, dystrophic changes in 4 (25%), conduction disorders in 2 (12.5%), and decrease in coronary blood flow in 2 (12.5%). Metabolic disorders characteristic of hypokalemia in the form of decrease or inversion of T wave, decrease in ST segment, and extension of QT interval were detected in 8 (50%) patients with aldosteroma.

Neuromuscular manifestations were characterized primarily by muscle weakness, which was complained of by 13 (81.3%) patients. Pain in the muscles of the extremities was observed in 10 (62.5%) patients. Seven (43.8%) patients complained of paresthesia and 5 (31.8%) had muscle cramps. In addition to muscle weakness 7 (43.8%) patients

had expressed general weakness and 5 (31.3%) of them complained of fatigue, decreased performance up to its complete loss.

The development of renal syndrome in aldosteromas is associated with excessive sodium reabsorption and potassium excretion in distal parts of renal tubules under the influence of excess of aldosterone, as a result of which the renal tubules undergo dystrophic changes (calypenic nephropathy). The clinical manifestations of renal syndrome are primarily polyuria and polydipsia, which in our observations were registered in 11 (68.8%) and 4 (25%) patients, respectively. Moreover, it should be noted that a characteristic feature of polyuria in aldosteroma cases is the predominance of nocturnal diuresis nocturia, which in our case was noted in 9 (56.3%) patients. Also, 6 (37.5%) patients had periodic or persistent pain in the lower back and 3 (18.8%) complained of peripheral edema. It should be noted that edema is not quite characteristic of aldosteroma, since polyuria and the accumulation of sodium inside cells (and not in the interstitium) do not contribute to fluid retention in the intercellular spaces and the development of edematous syndrome.

Before contacting us patients received treatment for hypertension with various groups of antihypertensive drugs in various combinations from doctors of related specialties. So, in one case (6.2%) out of 16, the patient did not receive antihypertensive treatment at all, another patient was on monotherapy and, one more patient received combined treatment of 4 antihypertensive drugs. The majority of patients received combination therapy consisting of two drugs - 8 (50%) and three drugs - 5 (31.3%). At the same time, drug treatment was mainly carried out by the following groups of drugs: beta-blockers (56.3%), ACE inhibitors (50%), calcium channel antagonists (43.8%), angiotensin receptor blockers (43.8%), and diuretics (18.8%). And only 2 (12.5%) patients received antimineralocorticoid drugs. When evaluating the effect of pharmaceutical treatment, it was noted that 87.5% of the patients had insufficient effect from the received therapy and only in one patient antihypertensive drugs were effective. After the diagnosis of APA all the patients were prescribed complex drug therapy with the mandatory inclusion of aldosterone antagonists in the treatment regimen. At the same time, 5 (31.3%) patients who had a positive effect from the medication received (achieving the target blood pressure level, elimination of water-electrolyte and hormonal disorders) refused surgical treatment. For other 2 (12.5%) patients who had high risk of adverse consequences after surgery decision was made in favor of drug therapy. All the above-described 7 (43.8%) patients are still under dynamic observation. The remaining 9 (56.2%) of 16 patients subsequently underwent surgical treatment, of which 7 (43.8%) due to the lack of proper effect from drug therapy and 2 (12.5%) due to the size of the formation exceeding the threshold values (≥3cm). At the same time,

traditional laparotomic adrenalectomy was performed in 6 (37.5%) patients, laparoscopic adrenalectomy in 3 (18.8%).

It should be noted that in patients with aldosteromas left-sided localization of the tumor prevailed. Thus, in 11 (68.8%) patients with aldosteroma, the tumor was localized in the left adrenal gland and in 5 (31.2%) in the right one ($\chi 2=3.13$; $p=0.08$).

Conclusion:

Thus, summarizing the data obtained on APA we can say that aldosteromas were more common in young working age (the average age of patients was 42.4 ± 12.4 years old, and the peak incidence was at the age of 18 to 44) with a predominance among females. In our observation the classical clinical triad, including a combination of three main syndromes (AH, neuromuscular and renal), was found only in 62.5% of the patients. The leading clinical manifestation in all the patients with aldosteroma in 100% of the cases was hypertension, which was permanent in 75% of the patients, mixed in 12.5% and constant malignant hypertension was observed in 12.5% of the cases. It should be noted that most often in patients with APA we registered stage 1 (50%) and stage 2 hypertension (37.5%), while only 12.5% had stage 3.

It is noteworthy that the combination of hypertension, especially in young people, and a burdened family history of hypertension and its complications in relatives of the first line kinship should serve the basis for exclusion of a patient with adrenal APA.

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