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Research Article

ANDROGEN-SECRETING ADRENAL TUMORS

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ABSTRACT

The objective of this research was to study clinical peculiarities of androgen-secreting tumors in adrenals dependent on age and gender. Among the patients with various neoplasms in adrenals (n=282), who received out-patient and in-patient treatment in the Republican Specialized Scientific Practical Medical Center of Endocrinology of the Uzbekistan Public Healthcare Ministry within the period from 2000 to 2018, androgen-secreting tumors were diagnosed in 9(3.2%) patients: 3(33.3%) men and 6(66.7%) women aged from 1.7 to 34 years old. As well as in the other groups with adrenal neoplasms, there was double prevailing of women. However, correlation of separate age subgroups was significantly different. In this group of patients specific weight of children increased (55.6%) compared to adults under 44 years old (44.4%). In spite of similar etiopathogenetic basis analysis of clinical manifestations of adrenal androgen-secreting tumors in children and adults revealed some differences. So, performed analysis confirms the presence of several symptoms in children, symptoms which are not observed in adults. On the other hand, somatic disorders in adults are more expressed than in children.

KEYWORDS

Adrenal tumors, androgen-secreting tumors.

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INTRODUCTION

Adrenal androgen-secreting tumor is a rare pathology. Being hormonal active tumor of reticular area of adrenal cortex these neoplasms are characterized by increased production of androgens and its metabolites. According to the basic series of publications for the last 20 years the prevalence of adrenocortical tumors among the patients studied due to clinical hyperandrogenism is equal to 0.1% (4 out of 3695 patients) [4]. Recent population study included the analysis of the prevalence of adrenal androgen-secreting tumors among the patients whose level of androgens was measured independently of the presence of signs and symptoms of hyperandrogenism. The prevalence of adrenocortical tumors was equal to 1.7% (20 out of 1205 patients) [5]. In a French study including 801 adrenalectomies performed from 1970 till 2003, only in 21(2.4%) cases adrenal androgen-secreting tumors were revealed [7]. Androgen-secreting tumors more often develop in women, mostly in the age from 35-40 years old [3]. There was notable high percent of malignant tumors in children population, where tumors were observed more often in girls, than in boys [1,2]. Totally, among the patients with androgen-secreting tumors 75% of the cases (18/24 tumors) were classified to be adrenocortical cancer by means of histological tests, while the others were adenomas [4]. It should be noted that, androgen-secreting tumors producing only androgens were met relatively rarely. More often together with androgens tumors also secrete other hormones, and particularly glucocorticoids [3,8]. Clinical manifestations of a tumor are conditioned by virilizing and anabolic properties of androgens. Virilization degree depends on hormonal activity of the tumor and term of disease [3,6]. Virilization is often observed with tumors in children and represent the most prevalent characteristics of adrenocortical carcinomas in patients of that age group. However, relative data of adults population are diverse.

The objective of the research was to study clinical characteristics of adrenal androgen-secreting tumors dependent on age and gender.

MATERIALS AND METHODS

Among the studied patients with various adrenal neoplasms (n=282), who received out-patient and in-patient treatment in the Republican Specialized Scientific Practical Medical Center of Endocrinology of the Uzbekistan Public Healthcare Ministry within the period from 2000 to 2018 adrenal androgen-secreting tumors were diagnosed in 9(3.2%) patients: 3(33.3%) men and 6(66.7%) women aged from 1.7 to 34 years old.

All patients with adrenal neoplasms had common clinical, biochemical, hormonal, and instrumental tests. Common clinical tests included careful collection of complaints, history of life and disease, assessment of somatic and endocrine status, complete clinical investigation with measurement of arterial pressure (AP) and definition of body mass index (BMI); common blood and urine tests. Biochemical blood tests included definition of serum potassium, sodium, chlorine, calcium, lipid spectrum, fasting glycemia, glycemia in two hours after meal, and in some cases oral glucose tolerance test (OGTT), glycated hemoglobin, coagulogram, creatinine, and urea. We performed the study of hormonal status, including definition of plasma aldosterone concentration and rennin activity, ACTH, cortisol in blood, plasma metanephrines, normetanephrines, testosterone, and DHEAS. MSCT of adrenals was performed as a special instrumental method. The complex of compulsory research methods included

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ECG and ophthalmoscopy. For the assessment of clinical manifestations we used parameters of average and standard deviations (M ± SD), and also prevalence of the studied signs. We assessed the correspondence of numerical data to the normal distribution law. Differences between the compared average values of dependent and independent samples were determined in compliance with «ANOVA» single-factor analysis. For the analysis of difference reliability between qualitative parameters $\chi 2$ criterion was used. Reliable level for all applied tests was $p<0.05$.

RESULTS AND DISCUSSION

Adrenal androgen-secreting tumors were diagnosed in 9(3.2%) patients, among them 3(33.3%) men and 6(66.7%) women aged from 1.7 to 34 years old. As well as in the other groups of adrenal neoplasms, there was double prevailing of women. However, correlation of certain age subgroups differed much. In this groups of patients specific weight of children increased (55.6%) compared to adults under 44 years old (44.4%) (Table 1).

Table 1 Age and gender distribution of the patients with adrenal androgen-secreting tumors (WHO, 2017)

Age	Men, n=3		Women, n=6		Total, n=9	
	abs.	%	abs.	%	abs.	%
Children under 18	3	100.0	2	33.3	5	55.6
Young from 18 to 44	4	67.7	4	44.4		
Average 45-59						
Old 60-74						
Senile, 75-90						

Note * statistically significant values within groups

Further clinical analysis was performed separately in the group of adult patients (n=4) and children (n=5). So, in the group of adult patients there were only women aged from 14 to 44 years old (with average age 27.5±5.2). It should be noted that, it is extremely difficult to determine the presence of symptoms, caused by androgen excess, in male patients, as clinical presentation does not have any specific manifestations. In men these tumors can develop like hormonally inactive adrenal tumors.

Among four patients 3(75%) were initially treated by gynecologist due to amenorrhea, sterility, and two of these three were also followed by local physician due to arterial hypertension (AH). One of these four patients had independent US investigation due to menstrual dysfunction, where adrenal neoplasm was determined.

All the patients were diagnosed in the term above one year after the start of the disease. Average duration of

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the disease was equal to 2.0±0.8 years. Three patients did not relate the start of the disease with any event, and only one patient indirectly linked it with previous surgical intervention. When we studied life history of the patients, we revealed that, 3(75%) patients had low physical activity, 3(75%) had irrational nutrition, and one (25%) patient smoked. Analyzing family history of the patients we revealed cardiovascular diseases in a woman (25%) under 65, and particularly hypertonic disease, oncologic disease in two cases (50%), and renal pathology in one patient (25%).

Among the early symptoms of the disease frequent ones were disorders of menstrual cycle (amenorrhea or opsomenorrhea) and hirsutism, which were observed in 100% cases. Besides menstrual dysfunctions and hirsutism at the moment of application to clinic patients most often complained about acne (75%), head hair loss (50%), headache (50%), stomachache (50%), lumbar pain (50%), muscular pain and numbness (25%), voice change (25%), decrease in acuity of vision (25%). Twenty-five percents of the patients had total weakness and fatigability. Two (50%) patients complained about increased libido.

Objective investigation showed that, two (50%) patients had masculine type change in body architectonics. Alterations on the dermal surface such as folliculitis combined with acne vulgaris were observed in 75%. Hyperpigmentation in the area of external genitals, axillary area, shins, and elbows was also observed in 75% of the patients. Excessive hair growth on face, spine, chest, and femor was noted in all (100%) patients. Two (50%) patients had various degrees of diminishing of mammary glands. It should be noted, that one patient had a change of voice timbre worth paying attention. None of the studied patients had notable clitoris hypertrophy.

We observed 5 children with androgen-secreting tumors in the age from 1.7 to 7 years old (average age 5.2±1.9 years old). Different from adult population, in pediatric population adrenal androgen-secreting were observed similarly often among boys and girls, with some prevalence in boys (60% and 40%, respectively).

Within the assessment of the duration of the disease we noted that, children with adrenal androgen-secreting tumors were diagnosed within 1-7 years after occurrence of the initial manifestations of the disease; in two children duration of the disease was 1 year, two other children suffered for two years, and, finally, one more child had 7 years duration of the pathology. Average duration of the disease was 2.6±2.5 years. Relatively low prevalence rate of adrenal tumors in children and absence of clear understanding of clinical manifestations are the main reasons of incorrect diagnostics, choice of inadequate therapy, delay in surgery, and, as a result, non-satisfactory results of the therapy.

Prior to final diagnosis two 2(40%) children were treated due to adrenogenital syndrome, and one (20%) was treated due to preterm puberty. One more girl was incorrectly diagnosed with Cushing disease. Only in one case of a patient (1.7 years old), who came with parents complaining about child's enlargement of stomach combined with enlargement of penis and scrotum, pubic and axillary hair growth, change of voice timbre, US imaging revealed adrenal neoplasm 8.4 cm, so the primary diagnosis was correct and corresponding surgical treatment was indicated.

Similar to adults, etiology of adrenal cortical tumors in children is not clarified yet. However, some facts revealed at the study of patients' histories deserve paying attention. For example, a mother of one patient during pregnancy had long-term and severe toxicosis, while another patient received a great number of

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medications, including hormones, due to pregnancy pathology. These data suggest that, pathologic pregnancy and birth could probably be considered to be the reasons of adrenal tumor occurrence.

Clinical manifestations of adrenal androgen-secreting tumors in children are diverse and have certain characteristics. Three (60%) boys had a start of disease with symptoms of pre-term puberty, clinical manifestations of which are enlargement of penis and scrotum (60%), pubic hair growth (60%), acne (20%), and voice alteration (60%). One of them (20%) had gynecomastia, in other words, together with hyperandrogenism manifestations there were feminization symptoms (description of the case is herein below). In girls initial stages of the disease were characterized by pre-term pubic and axillary hair growth. At the same time one girl had very expressed hirsutism. Another patient with 7 years duration of the disease, besides hirsutism had clitoris hypertrophy and voice timbre change. Both girls had acne on their face. Besides that, mothers of the studied children noted complaints such as stomachache (20%), anxiety (20%), irritability (20%), total weakness (20%), polyuria (20%), nighturia (20%), and polydipsia (20%).

Two (22.2%) out of all patients with adrenal androgen-secreting tumors we studied (n=9) had AH. Average age of the patients at the moment of AH debut was 25.5±2.1 years old, which was statistically different from the parameters of control groups with and without AH ($p<0.0001$). Fluctuations of systolic AP (SAP) and diastolic AP (DAP) varied from 140-150 to 90-100 mmHg. Average levels of maximal SAP/DAP were 123.3±16.6/80.0±12.2 Hg.mm, which was significantly different from the parameters in the group with AH. Both patients with androgen-secreting tumors had AH I stage. One case of AH had a stable character, while another case had a periodic rise of AP. Average duration of AH was equal to 1.5±0.71 years and was significantly lower, than in the control group with AH ($p<0.05$) (Table 2).

Table 2 Clinical characteristics of the studied groups

(single-factor dispersive (ANOVA) and paired analysis)

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Parameters	Control, n=46		Androgen-secreting tumors, n=9	p
	Without AH, n=24	With AH n=22		
Age	39.6±11.1	41.3±6.9	15.1±12.3##	**<0.0001**
SAP (max) mmHg	122.4±5.4	157.7±13.1#	123.3±16.6#	**<0.0001**
DAP (max) mmHg	77.1±4.6	98.2±8.0#	80.0±12.2#	**<0.0001**
SAP (mean) mmHg	119.6±6.9	143.6±7.9#	113.3±14.1#	**<0.0001**
DAP (mean) mmHg	69.3±4.8	91.8±3.9#	72.2±10.5#	**<0.0001**
AH duration	-	3.3±2.0	1.5±0.71*	**0.01**
Age at the moment of AH	-	38.0±7.0	25.5±2.1#	**<0.0001**
Duration of the disease, years	-	-	2.33±1.9	
BMI, kg/m^2	23.8±2.6	24.5±2.7	20.4±5.5*●	**0.009**

Note: data are presented in M±SD values; * differences related to the data with and without AH are significant (* - p<0.05, ●- p<0.01, #- p<0.001)

Both patients with AH received a mono therapy with hypertensive agents, and particularly, ACE inhibitors, and had a positive effect of the performed therapy. It should noted that, average values of BMI in cases of adrenal androgen-secreting tumors were statistically significantly lower than in comparison groups without AH(p<0.05) and with AH(p=<0.01), but were within the range of normal weight 20.4±5.5 kg/m2. There were three (33.3%) patients with adrenal androgen-secreting tumors had increased body mass with BMI≥25. Average age of patients with adrenal androgen-secreting tumors was reliably less, than in both control groups (p<0.001).

ECG of two (50%) patients revealed metabolic changes. ECG did not register any deviations from the age-specific normal parameters in children.

None of the children had registered rise of AP. Average SAP/DAP in children was 104.0±5.5/64.0±5.5 mmHg.

CONCLUSIONS

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In spite of similar etiopathogenetic basis, analysis of clinical manifestations of adrenal androgen-secreting tumors in children and adults revealed certain differences. Thus, performed analysis confirmed the presence of several symptoms in children, which are not observed in adult population. On the other hand, somatic disorders are more expressed in adults, than in children. Similarity of clinical presentation of adrenal androgen-secreting tumors in children with some other endocrine pathologies makes its early diagnostics significantly more difficult. At the same time during careful observation it is worth to pay attention to clinical data suggesting excessive androgen secretion in children, which can be noted before puberty. It is extremely difficult to differentiate the symptoms caused by androgen excess in male patients, as clinical presentation has no specific manifestations, which probably explains low detection rate of these tumors in men.

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