COMPARATIVE CHARACTERISTICS OF CLINICAL AND HORMONAL CHARACTERISTICS IN ADOLESCENTS WITH CONSTITUTIONAL GROWTH RETARDATION AND PUBERTY AND WITH SOMATOTROPIC INSUFFICIENCY

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ABSTRACT

Purpose of the Study– *To perform a comparative characteristic of clinical and hormonal characteristics in adolescent boys with constitutional growth retardation and puberty (CGRP) and somatotropic insufficiency (HF).*

Material and Research Methods

We have examined and examined 45 adolescents (boys) with CGRP, aged 11 to 17 years. In addition, we studied 20 children with HF.20 healthy boys of the same age made up the control group of the corresponding age

All adolescents underwent all anthropometric studies based on the international Tanner-Whitehouse height-weight map, assessment of the stage of puberty according to J. Tanner, if necessary, patients were sent for further examination - x-ray (X-ray of the hand, CT / MRI of the Turkish saddle), ultrasound of the genital organs, karyotype, consultation of a surgeon, genetics and other research.

All patients underwent a range of studies, including the study of the endocrine status, general clinical, biochemical, hormonal (STH, IGF-1, LH, FSH, prolactin, TSH, testosterone, cortisol, free

thyroxine, etc.) in the laboratory of hormonal studies of the RSNPMC Endocrinology of the Ministry of Health of the Republic of Uzbekistan.)

Research Results

In patients with CGRP there was an unreliable decrease in basal values of LH, FSH (p>0.05) compared with the control group, as well as unreliably low levels of free testosterone (FT) in blood plasma (p>0.05) against the background of moderate hyperprolactinemia. While in patients with HF, the basal values of LH, FSH, STH, IGF-1 and free testosterone were significantly low (p < 0.05)

These disorders correspond to the presence of functional disorders of the hypothalamic-pituitary-gonadal axis.

In the 2nd group of patients with HF was most characteristic of a significant and pronounced decrease in the basal values of STH, LH, FSH (p < 0.05) compared with the control group, as well as significantly low levels of FT in blood plasma (p < 0.05) against the background of moderate hyperprolactinemia and normal GH values. These disorders also correspond to the presence of hypogonadotropic (secondary) hypogonadism.

Conclusions

1) In all age periods of sexual development, the examined patients had hypogonadotropic hypogonadism: there was a significant decrease in the average levels of LH, FSH, total testosterone (p < 0.05). Only 1 (0.9%) patient had hypergonadotropic hypogonadism.

2)When comparing the stages of puberty and hormonal data, it was found that as the age increases, the average values of LH, FSH, and total testosterone also increase, although they remain significantly reduced.

3) 3 degrees of severity of hypogonadotropic hypogonadism were established: mild (11.3%), moderate (16.04%) and severe(72.6%). This category of patients needs further examination (magnetic resonance imaging of the pituitary gland, ultrasound of the genital organs, etc.) and treatment.

KEYWORDS: *Delay Puberty, Growth, Constitutional.*

INTRODUCTION

The human reproductive system works on a hierarchical basis, showing four levels of organization: the central nervous system, pituitary gland, gonads, organs, and peripheral tissues as targets for sex hormones. The participation of the central nervous system is carried out through the hypothalamus, where gonadotropin-releasing hormone, also known as luteinizing hormone releasing hormone (Gn-RH, LH-RH), is synthesized and secreted. The timely onset of puberty depends on the impulse secretion of GnRH, which stimulates the release of gonadotropic hormones from the adenohypophysis - luteinizing (LH) and follicle-stimulating (FSH), which control the function of the gonads. The pulse rhythm of LH-RH secretion is carried out under the influence of numerous neurotransmitters and neuromodulators. A stimulating effect on the secretion of GnRH can have norepinephrine, neuropeptide Y, stimulating amino acids (glutamate), oxytocin, endothelin, galanin, and pituitary adenyl cyclase-activating peptide. The prepubertal increase in LH-RH is inhibited by low concentrations of sex steroids, as well as

opioid peptides and gamma-aminobutyric acid (GABA) through CNS mechanisms. GABA blocks the release of GnRH in puberty, but stimulates the perinatal and prepubertal release of GnRH[12].

In accordance with the hierarchical principle of regulation of puberty, delayed puberty may be associated with a violation at one of the levels of the hypothalamic-pituitary-gonadal axis.

The reason for the development of a functional or constitutional delay in puberty is disturbances at the level of the central nervous system, when triggers for impulse secretion of GnRH are triggered. [3].

In the clinic, in the vast majority of cases, there is a functional delay in puberty, and only in 0.1% of adolescents, the causes of delayed puberty are of an organic nature, due to the pathology of the pituitary-gonadal system or pathology of the gonads.[four].

Unfavorable dynamics of indicators of physical developmentmanifested by a discrepancy between the biological age and the passport age, a decrease in body mass and girth dimensions, a deterioration in functional parameters, a tendency to retardation, graceful gassing[5-7].

According to the authors, today in Russia there is not only a retardation of physical development, but also of sexual development, the formation of which is accompanied in adolescents by such deviations as delayed sexual development, abnormal puberty, and heterosexual sexual development. The timing of the onset of menarche in girls has shifted towards older age [8; 9]..

Constitutional growth retardation and sexual development is one of the most common forms of growth retardation. It occurs in children of both sexes, but is more common in boys.A combination of constitutional growth retardation and sexual development with elements of family short stature is possible, which worsens the final growth prognosis.The prevalence of this condition among males reaches 1:40. [ten].

Despite the relevance of this topic, the issues of early diagnosis and effective treatment of the disease remain unresolved.

Purpose of the study– to perform a comparative characteristic of clinical and hormonal characteristics in adolescent boys with constitutional growth retardation and puberty (CGRP) and somatotropic insufficiency (HF).

Material and research methods. We have examined and examined 45 adolescents (boys) with CGRP, aged 11 to 17 years. In addition, we studied 20 children with HF.20 healthy boys of the same age made up the control group of the corresponding age

All adolescents underwent all anthropometric studies based on the international Tanner-Whitehouse height-weight map, assessment of the stage of puberty according to J. Tanner, if necessary, patients were sent for further examination - x-ray (X-ray of the hand, CT / MRI of the Turkish saddle), ultrasound of the genital organs, karyotype, consultation of a surgeon, genetics and other research.

All patients underwent a range of studies, including the study of the endocrine status, general clinical, biochemical, hormonal (STH, IGF-1, LH, FSH, prolactin, TSH, testosterone, cortisol, free thyroxine, etc.) in the laboratory of hormonal studies of the RSNPMC Endocrinology of the Ministry of Health of the Republic of Uzbekistan.)

Identified adolescents with delayed puberty were subjected to a study algorithm, including the determination of the basal level of LH, FSH in blood plasma to determine the etiopathogenesis and the correct tactics for treating patients. When their values were exceeded (hypergonadotropic hypogonadism), further karyotype determination was performed in order to exclude genetic syndromes.

The obtained data were processed using computer programs Microsoft Excel and STATISTICA_6. The significance of differences in quantitative indicators (n>12) was determined by the Wilcoxon method for unrelated ranges, to determine the significance of small samples (n<12), a nonparametric Fisher component randomization test for independent samples was used, for qualitative values, the exact Fisher-Irwin test was used. Differences between groups were considered statistically significant at P<0.05. Mean values (M), standard deviations of means (m) were calculated

Research Results and Discussion. Table 1 gives the main characteristics of both groups.

TABLE 1. CLINICAL AND HORMONAL STATUS OF PATIENTS WITH IGRD AND HF

Index	**CGRP, M±SD (min-max)**	**CH, M±SD (min-max)**
Number of patients	45	twenty
Gender (male/female)	45/no	16/4
Isolated GH/MDHA deficiency	no no	14/6
Chronological age, years	11.2±0.7 years (6.3-16.6)	11.2±0.7 (6.3-16.6)
Bone age, years	12.7±0.7 (10-15)	5.7±0.7 (2-11)
Height, cm	137±7.8	-4.59±0.2 (from -6.7 to -2.6).
growth SDS	3.78±0.6 (from 4.3 to 6.6).	1.4 (0.05-9.5)
GH peak on samples, ng/ml	23±4.2	twenty

As can be seen from Table 1, in patients with HF, the main indicators significantly differed from the norm.

Table 2 gives the average values of various hormones in patients with **CGRP**, which we compared with normal values for a given sex and age periods and with patients with somatotropic insufficiency (1).

TABLE 2. AVERAGE VALUES OF VARIOUS HORMONES IN PATIENTS OF 2 GROUPS

Hormones	**Control**	**1gr n=45**	**2 gr. N=20**
STG	2.9±0.2ng/ml	2.3 ± 0.4 P>0.5	0.8± 0.02* P<0.05
IGF-1	156.5±9.8 ng/ml	149.8±12.7 P>0.05	116.4±10.4 P<0.05
LG	5.2±0.3 IU/L	4.21±0.3 P > 0.05	2.11±0.3* P < 0.05
FSH	5.3±0.1 IU/L	3.4±0,5 P > 0.05	1.9±0,one* P < 0.05

TSH	2.5±0.2IU/L	1, 82±0.7 P>0.05	4.91±0,four* P < 0.05
Prolactin	5.7±0.3 ng/ml	6.4±0,eight P>0.05	7.4±0.6 P>0.05
testosterone free	12.6 ±1.6 nmol/l	9.9±0.2 P > 0.05	4.35±0.9 P < 0.05
cortisol	norm morning 596.5 ± 11.7 nmol / l	289.25±9.3 P>0.05	400.2±8.2 P>0.05
St. thyroxine	15, 8 ±0.9 pmol/l	12.4±1.4 P>0.05	9.5±1.3 P < 0.05

P-significance of differences compared with the control group (P<0.05). The table for comparison shows fluctuations in hormone levels from 11 to 16 years of age in the control group (healthy individuals)

As follows from Table 2, in patients with CGRP, there was an unreliable decrease in basal values of LH, FSH (p>0.05) compared with the control group, as well as unreliably low levels of free testosterone (OT) in blood plasma (p>0.05) against the background of moderate hyperprolactinemia. While in patients with HF, the basal values of LH, FSH, STH, IGF-1 and free testosterone were significantly low (p < 0.05)

These disorders correspond to the presence of functional disorders of the hypothalamic-pituitary-gonadal axis. Therefore, for patients of group 2, we recommended further monitoring by an endocrinologist and, if necessary, hormone replacement therapy with chorionic gonadotropin (CG) and somatotropic genetically engineered hormone.

In the 2nd group of patients withHF was most characteristic of a significant and pronounced decrease in the basal values of STH, LH, FSH (p < 0.05) compared with the control group, as well as significantly low levels of total testosterone (TT) in blood plasma (p < 0.05) against the background of moderate hyperprolactinemia and normal GH values. These disorders also correspond to the presence of hypogonadotropic (secondary) hypogonadism. Therefore, for patients in this group, we recommended further examination with an x-ray of the sella turcica (or MRI/CT of the pituitary gland), karyotype determination, a study of smell, visual fields, observation by an endocrinologist and, if necessary, hormone replacement therapy with chorionic gonadotropin (CG) and genetically engineered growth hormone, thyroid preparations (iodmarine, euthyrox, etc.). Manifest hypothyroidism was detected only in 1 case (7.7%),

Given that our adolescents live in conditions of chronic iodine deficiency, we conducted an analysis of the state of the thyroid gland in order to compare the results withliterature data (2). Similar studies were carried out by Prof. Abusuev S.A. (2009) in the Republic of Dagestan, where 905 adolescent boys were selected living in conditions of iodine deficiency of 3 degrees of severity and who underwent genitometric and hormonal studies. The combined index of masculinization and hormonal parameters at the age of 14-17 years was shown to correspond to 14 years of age (2).

Table3 shows the average values of various hormones in patients of the 1st group according to the stages of sexual development.

TABLE 3 MEAN VALUES OF VARIOUS HORMONES IN PATIENTS ACCORDING TO 5 STAGES OF TANNER

Hormones	**Control**	I **n=0**	II **n=7**	III **n=9**	IV **n=8**	V **n=21**
STG	2.9±0.2ng/ml	-	2.3±0.2 P>0.5	2.4±0.3 P>0.5	2.5±0.5 P>0.5	2.6±0.2 P>0.5
LG	5.2±0.3 IU/L	-	1.4±0.1 P < 0.05	2.3±0.4 P < 0.05	2.0±0.3 P < 0.05	2.8±0.5 P>0.05
FSH	5.3±0.1 IU/L	-	2.0±0.2 P < 0.05	2.9±0.2 P < 0.05	3.0±0.6 P < 0.05	3.4±0.7 P < 0.05
TSH	2.5±0.2IU/L	-	1.7±0.4 P>0.5	1.2±0.3 P>0.5	2.6±0.2 P>0.5	1.82±0.2 P>0.5
Prolactin	5.7±0.3ng/ml	-	3.3±0.3 P>0.5	8.2±0.5 P < 0.05	4.9±0.1 P>0.5	7.4±0.3 P>0.5
Testosterone free	12.6 ±1.6 nmol/l	-	4.8±0.2 P < 0.05	5.4±0.6 P < 0.05	7.8±0.2 P < 0.05	8.9±0.4 P>0.5
cortisol	norm morning 596.5 ± 11.7 nmol / l	-	278±5.4 P>0.5	348±11.2 P>0.5	484±13.2 P>0.5	289.3±8.2 P>0.5
St. thyroxine	15, 8 ±0.9 pmol/l	-	15.5±3.7 P>0.5	20.4±4.2 P>0.5	14.5±3.2 P>0.5	17.4±2.2 P>0.5
Total: n=45						

P - significance of differences compared with the control group. The table for comparison shows fluctuations in hormone levels from 11 to 16 years of age in the control group (healthy individuals)

It follows from Table 3 that hypogonadotropic hypogonadism (HH) occurred in all age periods of sexual development in the examined patients: there was a significant decrease in the average levels of LH, FSH, total testosterone - WC ($p < 0.05$). At the same time, these values were the lowest in patients with the 2nd stage of puberty according to Tanner, that is, at the age11.7 ± 1.3 years (n = 17) against the background of normoprolactinemia.

Mean prolactin levels were not significantly elevated in Tanner stage 3 and 5 patients (P>0.5). It should be emphasized that the levels of growth hormone, TSH and free thyroxine, as well as cortisol were within the normal range in all patients (n = 45).

When comparing the stages of puberty and hormonal data, it was found that as the age increases, the average values of LH, FSH, total testosterone also increase, althoughthey remain significantly reduced.

Next, we analyzed among patients with IGR the cases of the lowest values of LH, FSH and total testosterone, namely, when the levels of LH/FSH ranged from 0.1 to 0.9 IU/L, OT - from 1 to 3 nmol/l (severe HH), cases of average values of gonadotropins and OT, when the levels of LH / FSH were in the range from 1 to 4 IU / L, OT - from 3 to 7 nmol / L (moderate severity of HH), as well as cases with mild HH, when LH/FSH levels fluctuated from 4 and above IU/L, OT - from 7 nmol/l and above (mild severity of HH),.

Thus, this characteristic allowed us to distinguish 3 groups of patients with 3 degrees of HH severity - moderate, moderate and severe - depending on the average values of LH, FSH, WC. These data are given in tables 3, 4, 5.

Table4 shows the number of patients with severe HH by Tanner stages. The total number of these patients was 45.

TABLE 4 THE NUMBER OF PATIENTS WITH SEVERE HH DEPENDING ON THE AVERAGE VALUES OF LH, FSH AND OT IN PATIENTS ACCORDING TO 5 STAGES OF TANNER)

Hormones	**Control**	I **n=0**	II **n=9**	III **n=6**	IV **n=3**	V **N=2**
LG	5.2±0.3 IU/L	-	0.2±0.01 P < 0.05	0.9±0.06 P < 0.05	0.1±0.05 P < 0.05	-
FSH	5.3±0.1 IU/L	-	0.3±0.04 P < 0.05	0.4±0.07 P < 0.05	0.8±0.06 P < 0.05	-
svt	12.6 ±1.6 nmol/l	-	1.0±0.02 P < 0.05	3.3±0.01 P < 0.05	2.6±0.08 P < 0.05	2.2±0.06 P < 0.05
Total	19		5	7	3	2
Total: n = 19						

Note: FT stands for free testosterone. P - significance of differences compared to control (1)

As can be seen from the data in the table4, in the analysis of the lowest values of LH, FSH and free testosterone, namely, when the levels of LH/FSH ranged from 0.1 to 0.9 IU/L, OT - from 1 to 3 nmol/l (severe HH) total the number of cases was 17(16.04%). In this group, the significance of differences was the highest (P<0.05).

Table5 shows the number of patients with an average degree of HH by Tanner stages.

TABLE 5 THE NUMBER OF PATIENTS WITH MODERATE HH SEVERITY DEPENDING ON THE AVERAGE VALUES OF LH, FSH AND OT IN PATIENTS ACCORDING TO 5 TANNER STAGES

Hormones	**Control**	I **n=0**	II **n=5**	III **n=6**	IV **n=7**	V **n=2**
LG	5.2±0.3 IU/L	-	1.2±0.03 P < 0.05	3.9±0.02 P > 0.5	1.1±0.04 P < 0.05	2.4±0.08 P < 0.05
FSH	5.3±0.1 IU/L	-	3.1±0.05 P < 0.05	2.4±0.03 P < 0.05	2.8±0.03 P < 0.05	2.2±0.09 P < 0.05
Free testosterone	12.6 ±1.6 nmol/l	-	3.9±0.07 P < 0.05	4.7±0.03 P < 0.05	3.6±0.04 P < 0.05	7.0±0.03 P < 0.05
Total	twenty		12	23	12	29
Total: n=20						

Note: FT is total testosterone. P - significance of differences compared to control (1)

As can be seen from Table 5, the total number of these patients turned out to be -twenty.When analyzing cases of moderate severity of HH, we proceeded from those average values of gonadotropins and OT, when the levels of LH/FSH were in the range from 1 to 4 IU/L, OT - from 3 to 7 nmol/l (moderate severity of HH).

Table 6 shows the number of patients with mild HH by Tanner stages.

TABLE 6 THE NUMBER OF PATIENTS WITH MILD HH DEPENDING ON THE AVERAGE VALUES OF LH, FSH AND OT IN PATIENTS ACCORDING TO 5 STAGES OF TANNER)

Hormones	**Control**	I **n=0**	II **n=0**	III **n=6**	IV **n=0**	V **n=0**
LG	5.2±0.3 IU/L	-	-	4.3±0.1 P > 0.5	-	-
FSH	5.3±0.1 IU/L	-	-	4.1±0.2 P > 0.5	-	-
FT	12.6 ±1.6 nmol/l	-	-	7.9±0.9 P < 0.05	-	-
Total	6		-	3	-	-
Total: n=6						

As can be seen from Table 6, the total number of these patients turned out to be -6.Cases with mild HH, when LH/FSH levels fluctuated from 4 and above IU/L, OT - from 7 nmol/l and above (mild severity of HH) amounted to12 patients (11.3%).

In this group of patients, the significance of differences in the content of G, FSH, OT in blood plasma was less significant, while being in the range from$P<0.05$ to $P>0.5$.

Thus, the analysis of hormonal results showed that the most frequently observed moderate severity of HH (72.6%), while severe was less common.(16.04%)and light(11.3%) of his degree.

Only 1 (0.9%) patient hadhypergonadotropic hypogonadism.

Thus, summing up, we can do the following

CONCLUSIONS:

1) Hypogonadotropic hypogonadism occurred in all age periods of sexual development in the examined patients with CGRP: there was a significant decrease in the average levels of LH, FSH, total testosterone ($p < 0.05$). Only 1 (0.9%) patient had hypergonadotropic hypogonadism.

2)When comparing the stages of puberty and hormonal data, it was found that as the age increases, the average values of LH, FSH, and total testosterone also increase, although they remain significantly reduced.

3) Among patients with CGRP, 3 degrees of severity of hypogonadotropic hypogonadism were established: mild (19 patients), moderate (20 patients) and severe (6 patients). This category of patients needs further examination (magnetic resonance imaging of the pituitary gland, ultrasound of the genital organs, etc.) and treatment.

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