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HORMONAL PROFILE OF PUBERTAL AGE GIRLS WITH CHRONIC VIRAL HEPATITIS

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Abstract

Chronic viral hepatitis (CVH) is more than 70% of the total number of children with chronic hepatitis, and in the population - 0.5%. Adolescents are the most vulnerable group of the population due to the physiological and psychological characteristics of this age. The liver coordinates both adaptive and reproductive processes in the body, and during puberty is the formation of pituitary-gonadal relationships. **The aim:** to study the features of hormonal homeostasis in adolescent girls with CVH. **Materials and methods.** We examined 300 girls aged 12-17 years, of which 120 patients with CVH (60 patients with hepatitis B and 60 - with hepatitis C) and 180 relatively healthy patients with physiological sexual development. The diagnosis of CVH was established on the basis of medical history, clinical, virological, biochemical, morphological and instrumental examination. **Results.** Analysis of the obtained data of the functional state of the liver in the examined patients with CVH revealed disorders of the morphofunctional state of the liver, manifested by cytolysis syndrome, cholestasis, hepatocellular insufficiency and mesenchymal-inflammatory syndrome. In patients with CVH there was a decrease in the production of luteinizing hormone (4.35 ± 0.09 vs. 5.13 ± 0.08 mIU / ml, p<0.01); follicle-stimulating hormone (4.40 ± 0.15 vs. 5.40 ± 0.07 mIU / l, p<0.01); prolactin (215.56 ± 4.76 vs. 282.93 ± 8.36 mIU / ml, p <0.01); progesterone (2.09 ± 0.10 vs. 2.78 ± 0.08 nmol / l, p<0.01) on the background of increasing the average level of estradiol (468.65 ± 21.32 vs. 437.45 ± 9.59 pmol / l, p<0,01) and free testosterone (1,98 ± 0,08 vs. 1,16

± 0,04 nmol / l, p <0,01). Thyroid status was characterized by a relative decrease in the production of thyroid-stimulating hormone (1.74 ± 0.04 vs. 2.15 ± 0.05 μIU / ml (p<0.01) and an increase in the secretion of free triiodothyronine (9.32 ± 0.09 vs. 5,46 ± 0.07 pmol / l, p<0.01) and free thyroxine (23.35 ± 0.76 vs. 18.55 ± 0.20 pmol / l, p<0.01). chronic infectious process, affects the morphofunctional state of the liver and leads to dysfunction of the hypothalamic-pituitary-ovarian and pituitary-thyroid systems, manifested by pathological changes in the secretion of gonadotropins, prolactin, thyroid-stimulating hormone, sex steroids and hormonal steroids.

Key words: chronic viral hepatitis; girls; puberty; liver; hypothalamic-pituitary-ovarian axis; pituitary-thyroid axis; hormonal profile.

Viral hepatitis occurs as a result of inflammation of the liver caused by a viral infection. Although "epidemic jaundice" has existed since ancient civilization, the viral etiology of hepatitis has only been identified in the last few decades. Currently, among viral hepatitis there are 7 types (A, B, C, D, E, F, G) and many genotypes (subtypes) [9]. Ways of infection in viral hepatitis are: 1) contact-household (hepatitis A, E);2) parenteral (hepatitis C, B, D, G); 3) sexual (hepatitis C, B, D, G); 4) intrauterine (hepatitis C, B) [1, 12].

Viral hepatitis is a serious public health problem that affects millions of people each year; in some cases, subsequently lead to hepatocellular carcinoma, liver cirrhosis and death of a significant proportion of patients. The WHO estimates that every third person in the world is infected with HBV or HCV and 1.3 million people died from the disease in 2015. It was reported that 2 billion people were infected with HBV, approximately 185 million of these people were infected with HCV and 20 million people were infected with HEV. About 2.3 billion people worldwide are infected with one or more hepatitis viruses. In highly endemic regions, more than 90% of children become infected with HAV before the age of 10 [4, 10].

In children, the frequency of chronic diseases caused by hepatotropic viruses differs from adults and depends on the age of infection of the child and is maximum (up to 90%) in the first year of life and early childhood, due to physiological characteristics of the child's body and immune system immaturity [9]. Chronic viral hepatitis (CVH) is an inflammatory process in the liver that is characterized by a progressive course of more than 6 months and is accompanied by hepatolienal syndrome, increased activity of liver enzymes and prolonged persistence of pathogens [3, 6-8, 11]. In general, the share of HCV is more than 70% of the total number of children with chronic hepatitis [6], and in the population - 0.5%.

Of particular concern are data on early fibrotic transformation and the development of liver cirrhosis in childhood. It was found that 42% of adult patients with CVH have the origins of the disease in childhood. The incidence of viral hepatitis in adolescents is a matter of serious concern. The largest increase in the number of cases of CVH is observed at the age of 10 to 14 years [2]. Adolescents are the most vulnerable group in terms of risk of parenteral viral infections due to physiological and psychological characteristics of this age [2]. It should be noted that in Ukraine there are no official statistics on the incidence of chronic hepatitis in children as a whole and in some etiological forms [6].

It is known that any chronic pathology of infectious or non-infectious nature affects the development of the growing body of the child in general, and somatosexual development in particular. Including chronic viral pathology of the liver, especially if it is formed before the intensive growth, complicating puberty and prepubertal periods, when there is the formation of the reproductive function of the body of girls - expectant mothers. In the pathogenesis of CVH, hormonal imbalance arises as a result of disruption of hormone metabolism at the stages of their inactivation involving glucuronic acid [9]. Given that the liver coordinates both adaptive and reproductive processes in the body, and during puberty is the formation of pituitary-gonadal relationships, the impact of liver pathology in this period is undoubtedly detrimental, and the study of hormonal hemostasis in CVH in girls puberty is relevant.

Therefore, **the aim of our research** was to study the features of hormonal homeostasis in adolescent girls with chronic viral hepatitis.

Materials and methods

300 girls aged 12-17 years were examined, of which 120 patients with CVH of the CVH group and 180 conditionally somatically healthy patients with physiological sexual development of group K. The diagnosis of CVH was established on the basis of medical history, clinical, virological, biochemical, morphological and instrumental examination. . 60 girls had chronic viral hepatitis B and 60 girls had chronic viral hepatitis C.

The viral etiology of CVH was confirmed by the presence of markers HBV, HCV by enzyme-linked immunosorbent assay (ELISA) and polymerase chain reaction (PCR). All girls studied the full range of biochemical parameters generally accepted in hepatology to determine the main biochemical syndromes of CVH (cytolysis, cholestasis, hepatocellular insufficiency, mesenchymal-inflammatory).

Fibrogenesis in the liver was assessed by the content of hyaluronic acid (HA) and profibrogenic cytokine transforming growth factor-β1 (TGF-β1) in the serum and by the

calculated APRI. Serum HA content was determined by ELISA using the Hyaluronic Acid (HA) kit (Corgenix, Inc., USA). The content of TGF-β1 was determined by ELISA (ELISA) on a set of "TGF-β1" (Biosource, Europe S.A.). The value of APRI (Aspartate-aminotransferase-to-Platelet Ratio Index) was calculated by the formula: AST Ч 100 / (upper limit of AST) / platelets (10^9 / l).

Determination of peripheral blood serum hormones was performed by immunochemical method with chemiluminescent detection using Roche Diagnostics kits (Switzerland) on a Cobas 6000 analyzer (e 601 module): luteinizing hormone (LH), follicle-stimulating hormone (FSH), free triiodothyronine (fT3), free thyroxine (fT4), estradiol (E2), progesterone (P4), free testosterone (fT).

The obtained data were processed statistically using the Excel software package 10. Calculated the mean value (M), standard deviation error (±SE). Student's t-test, Wilcolson-Mann-Whitney U-test, Fisher's φ-test, χ^2-criterion were used to identify differences between comparative indicators.

Results and discussion

Analysis of the obtained data of the functional state of the liver in the examined patients with CVH revealed disorders of the morphofunctional state of the liver, manifested by cytolysis syndrome (increased plasma levels of aspartate aminotransferase (ACT), alanine aminotransferase (ALT), increased bilirubinemia); cholestasis syndrome (increased activity of alkaline phosphatase, direct fraction of bilirubin,cholesterol, beta-lipoproteins, gamma-glutamyltransferase (γ-GT)), hepatocellular insufficiency syndrome (increased levels of indirect bilirubin, decreased blood albumin, prothrombin); increased mesenchymal-inflammatory syndrome (hypergammaglobulinemia, hyper- and dissimmunoglobulinemia, increase in thymol test) (Table 1).

Evaluation of the hormonal profile of the examined patients revealed both in girls with CVH and in the control group an increase with age in the production of gonadotropins and PRL (Table 2), but their synthesis was reduced in CVH compared with similar control indicators.

Thus, the production of LH in the total group of CVH (4.35 ± 0.09 vs. 5.13 ± 0.08 mIU / ml, $p < 0.01$) was lower than that in group K by 1.18 times, as in each age group (See Table 2). FSH secretion in patients with CVH was also statistically significantly less in the general group than in the control 1.23 times (4.40 ± 0.15 vs. 5.40 ± 0.07 mIU / l, $p < 0.01$), as in the age categories of 12, 13, 14, 15 and 16 years. In girls 17 years of age, the average level of FSH was higher than in the control - 7.51 ± 0.28 vs. 5.43 ± 0.19 mIU / ml ($p < 0.01$).

Table 1 - Indicators of the morphofunctional state of the liver of girls with HCV

Indicator	Group		Reference interval
	CVH, n=120	K, n=180	
Total protein, g / l	57.98±0.70 [k]	72.95±0.44	65-85
Albumin, g / l	30.65±0.27 [k]	40.64±0.29	32-45
α1- globulin, g / l	12.56±0.11 [k]	4.10±0.03	1.6-6.7
α2-globulin, g / l	13.56±0.12 [k]	7.97±0.05	5.6-12.4
γ-globulin, g / l	11.92±0.37 [k]	7.99±0.12	5.5-13.4
Total bilirubin, μmol / l	16.59±0.27 [k]	11.95±0.32	9-21
Direct bilirubin, μmol / l	6.01±0.05 [k]	2.51±0.07	< 5
ALT, U / l	64.59±1.96 [k]	14.77±0.28	5-42
AST, U / l	36.99±0.93 [k]	19.66±0.44	0-25
γ-GT, U / l	70.65±1.37 [k]	18.63±0.29	5-33
Thymol test, U / ml	4.36±0.07 [k]	2.03±0.07	< 4
Glucose, mmol / l	4.10±0.05 [k]	4.53±0.04	3.89-5.83
Insulin, μU / ml	10.30±0.42 [k]	6.35±0.13	2.6-24.9
Index HOMA	1.89±0.08 [k]	1.30±0.03	< 2.52
Total cholesterol, mmol / l	3.33±0.04 [k]	2.58±0.03	< 5.2
HDL, mmol / l	1.12±0.02 [k]	1.56±0.01	0.9-1.9
LDL, mmol / l	2.78±0.04 [k]	2.35±0.02	1.81-4.14
Triglycerides, mg / dl	2.38±0.02 [k]	0.85±0.01	< 2.26
Uric acid, μmol, l	258.61±4.74 [k]	158.77±1.53	2.76-8.07
Prothrombin index, %	78.18±0.78 [k]	95.03±0.36	70-130
Leptin, ng / ml	11.23±0.36 [k]	4.40±0.11	3.7-11.1
Adiponectin, μg / ml	6.27±0.25 [k]	6.51±0.16	> 10
Alkaline phosphatase, nmol / l	227.10±6.70 [k]	172.70±29.41	< 240
Glucuronic acid, ng / ml	32.88±0.64 [k]	17.80±0.28	14.8-25.6
TGF-β1, ng / ml	13.21±0.26 [k]	3.20±0.05	1.9-4.2
APRI	0.60±0.02 [k]	0.34±0.01	0.23-0.4
Notes: 1.[k] - statistically significant difference with the index of group K (p<0.05); 2. Norms of indicators are given for girls aged 12-17 years.			

The ratio of LH / FSH was in the general group K 0.98 ± 0.02 and was lower than in the group CVH - 1.05 ± 0.22 (p<0.01). The value of the ratio of LH / FSH in the control group increased with age from 0.86 ± 0.03 in the age group of 12 years to 1.11 ± 0.04 in the age group of 17 years, and in the CVH group, on the contrary, decreased according to 1.32 ± 0.03 to 0.77 ± 0.01. Statistically significant differences were observed in the groups of 12 years and 13 years, where the ratio of LH / FSH in the CVH group exceeded the same indicator in group K by 1.53 (p<0.01) and 1.33 (p<0.01) times, respectively.

Probable inhibition of pituitary prolactin-forming function was found: the level of PRL in girls with CVH was 1.31 times lower than in the control and amounted to 215.56 ± 4.76 vs. 282.93 ± 8.36 mIU / ml (p<0.01). A similar trend was registered in all age groups (see Table 2).

Table 2 - Levels of pituitary hormones in the surveyed adolescent girls, M ± SE

Age, years	Group	LH, mIU / ml	FSH, mIU / ml	LH / FSH	PRL, μMO / ml
12	CVH	3.80±0.15 [k]	2.88±0.09 [k]	1.32±0.03 [k]	212.18±7.33 [k]
	K	3,53±0,10	5,40±0,18	0,67±0,03	242,39±25,83
13	CVH	3.87±0.15 [k]	3.12±0.10 [k]	1.25±0.04 [k]	201.89±7.05 [k]
	K	3,79±0,15	5,18±0,12	0,74±0,03	258,89±11,82
14	CVH	3.68±0.14 [k]	3.90±0.14 [k]	0.95±0.01	193.67±10.53 [k]
	K	3,91±0,15	5,21±0,13	0,77±0,04	256,20±11,82
15	ХВГ	4.10±0.08	4.40±0.09 [k]	0.93±0.01	213.03±14.30 [k]
	K	4,08±0,15	5,43±0,19	1,11±0,04	302,00±18,85
16	CVH	4.85±0.15 [k]	4.63±0.18 [k]	1.05±0.01	226.16±16.88 [k]
	K	5.48±0.26	5.67±0.14	0.99±0.06	316.76±26.94
17	CVH	5.79±0.20	7.51±0.28 [k]	0.77±0.01 [k]	246.42±9.75 [k]
	K	5.98±0.25	5.43±0.19	1.11±0.04	321.34±9.29
Note. [k] - statistically significant difference with the index of group K (p<0.05).					

The study of sex hormone levels revealed an increase in the average level of E_2 in CVH by 1.07 times (468.65 ± 21.32 vs. 437.45 ± 9.59 pmol / l) (p<0.01) and fT by 1.71 times (1.98 ± 0.08 vs. 1.16 ± 0.04 nmol / l (p<0.01) on the background of a decrease in P_4 by 1.33 times (2.09 ± 0.10 vs. 2.78 ± 0.08 nmol / l (p<0,01). The tendencies found in the general group for P4 and fT were similar in the studied age groups (Table 3).

Table 3 - Levels of sex hormones in the surveyed adolescent girls, M ± SE

Age, years	Group	E_2, pmol / l	P_4, nmol / l	fT, nmol / l
12	CVH	169.35±2.44 [k]	0.95±0.10 [k]	1.55±0.14 [k]
	K	288.83±12.30	1.71±0.14	0.92±0.07
13	CVH	193.06±4.53 [k]	1.17±0.11 [k]	1.88±0.19 [k]
	K	295.83±7.92	2.28±0.16	0.99±0.07
14	CVH	535.25±11.80 [k]	2.23±0.26 [k]	2.20±0.22 [k]
	K	434.78±9.31	2.82±0.19	1.02±0.07
15	ХВГ	537.98±14.23 [k]	2.30±0.14 [k]	1.99±0.15 [k]
	K	463.89±10.62	2.87±0.16	1.16±0.07
16	CVH	586.82±12.00 [k]	2.48±0.11 [k]	2.14±0.24 [k]
	K	539.92±11.52	2.90±0.14	1.32±0.11
17	CVH	789.41±36.18 [k]	3.43±0.16 [k]	2.13±0.15 [k]
	K	601.46±9.47	4.08±0.08	1.54±0.10
Note. [k] - statistically significant difference with the index of group K (p<0.05).				

When analyzing the age characteristics of E_2 secretion, it was found that its level in patients with CVH in the age group of 12 and 13 years was reduced relative to similar indicators of group K (see Table 3), but from 14 years, began to exceed control values.

Thyroid hormones regulate the level of basal metabolism of hepatocytes. At the same time, it is known that in chronic liver disease there may be changes in the metabolism of thyroid hormones [5]. Therefore, the thyroid status of girls with CVH was assessed. The level of TSH in patients with CVH was within the reference norm, but lower than in the control - 1.74 ± 0.04 vs. 2.15 ± 0.05 μIU / ml ($p<0.01$). The content of fT_3 and fT_4 in the group with CVH was equal to 9.32 ± 0.09 pmol / l and 23.35 ± 0.76 pmol / l, respectively, and was 1.71 and 1.26 times higher than that in the control, respectively (5.46 ± 0.07 pmol / l ($p<0.01$) and 18.55 ± 0.20 pmol / l ($p<0.01$) Similar trends in the levels of TSH and thyroid hormones were observed in all age groups (Table 4).

Table 4 - Levels of TSH and thyroid hormones in the examined girls of pubertal age, M ± SE

Age, years	Group	TSH, μMO / ml	fT_3, pmol / l	fT_4, pmol / l
12	CVH	1.95±0.07 [k]	8.76±0.12 [k]	21.27±2.80 [k]
	K	2.22±0.14	4.88±0.16	19.63±0.35
13	CVH	1.89±0.12 [k]	9.13±0.27 [k]	21.62±1.25 [k]
	K	2.19±0.11	5.21±0.18	18.82±0.49
14	CVH	1.81±0.06 [k]	9.20±0.19 [k]	22.25±1.08 [k]
	K	2.37±0.13	5.39±0.13	19.22±0.35
15	CVH	1.67±0.08 [k]	9.49±0.23 [k]	23.49±1.54 [k]
	K	2.20±0.13	5.47±0.18	18.11±0.53
16	CVH	1.54±0.12 [k]	9.48±0.22 [k]	24.82±2.18 [k]
	K	1.96±0.16	5.68±0.18	18.30±0.55
17	CVH	1.61±0.03 [k]	9.87±0.22 [k]	26.63±2.01 [k]
	K	1.93±0.13	6.16±0.18	17.23±0.56
Note. [k] - statistically significant difference with the index of group K ($p<0.05$).				

During puberty, the hypothalamic system is most sensitive to the effects of adverse exogenous and endogenous factors. Apparently, the causative agent of viral hepatitis affects the hypothalamus, resulting in altered hormone metabolism, manifested by inhibition of hormonal activity, including the secretion of gonadotropins and PRL. Disturbances of functional activity of a liver in the form of decrease, including, metabolic, antitoxic and protein-forming functions also play a certain role. The pituitary-thyroid part of the

neuroendocrine system plays an important role in the development of regulation of the compensation mechanism in CVH [13]. Evaluation of the thyroid status of the examined groups showed that patients with CVH were characterized by increased activity of thyroid hormones compared with the control group.

Conclusions

CVH, as a chronic infectious process, affects the morphofunctional state of the liver and leads to dysfunction of the hypothalamic-pituitary-ovarian and pituitary-thyroid systems, which is manifested by pathological changes in the secretion of gonadotropins, PRL, TSH, sex steroids and thyroid hormones.

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