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VITAMIN D SUPPLY IN GIRLS OF PUBERTY AGE WITH AUTOIMMUNE HEPATITIS

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Abstract

Vitamin D undergoes important biotransformation and inactivation in the liver. Because vitamin D is metabolized in the liver, abnormal vitamin D metabolism can be expected to be associated with chronic liver disease, including autoimmune hepatitis (AIH). The prevalence of vitamin D deficiency in puberty was the justification for **the objective of the study–** to determine the characteristics of vitamin D supply in girls of puberty age with AIH with autoimmune hepatitis during this period. **Materials and methods.** To solve this goal, a comprehensive clinical and paraclinical examination of 66 girls withAIH and 180 relatively healthy girls of the control group aged 12-17 years. The complex included clinical and anamnestic data, biochemical study of liver function, determination of serum autoantibodies and markers of viral hepatitis, the level of 25- (OH) D in blood serum, ultrasound and elastography of the hepatobiliary system organs, liver biopsy. **Results.** The mean level of vitamin 25 (OH) D in the serum of girls with AIH of pubertal age was 17.14 ± 1.06 vs. 23.27 ± 0.53 ng / ml in the control ($p<0,01$). In 66.67% of patients with AIH there was a deficiency of 25 (OH) D, in 22.73% – insufficiency, in 10.61% – the optimal level. The supply of vitamin D depended on the histological activity of AIG. Among girls with AIH and histological activity index> 9 points, the share of patients with vitamin D deficiency was

79.41% compared with 53.13% of cases among girls with AIH, where the histological activity index was <9 points (χ^2=5.13; p<0,02). **Conclusions.** Cytolysis, cholestasis, mesenchymal-inflammatory syndrome, hepatocellular insufficiency in AIH in girls of puberty agedevelops against the background of reduced vitamin D supply, which depends on the histological activity of the disease.

Key words: girls; puberty age; autoimmune hepatitis; vitamin D supply.

Autoimmune hepatitis (AIH) is a progressive hepatocellular inflammation of unknown etiology characterized by the presence of periportal hepatitis, hepatic-associated serum autoantibodies, and a positive response to immunosuppressive therapy. The incidence of AIH varies among different segments of the population [26]. In Europe and the United States, its prevalence ranges from 3 to 17 cases, and the annual incidence is from 0.1 to 1.9 cases per 100,000 population [3]. The peak incidence of AIH occurs in childhood, when the disease is called juvenile autoimmune hepatitis [21].

Specific diagnostic criteria and a system for assessing the presence of AIH were established, which include the detection of antinuclear autoantibodies (ANA), autoantibodies to smooth muscle (SMA), microsomal autoantibodies to liver-kidney cell microsomes of type I and epithelial cells (LKM1 and anti-LKM3), immunoglobulins (IgG), viral markers (IgM anti-HAV, HBsAg, HBV DNA and HCV RNA) and histological data of liver puncture biopsy [15].

Currently, there are autoimmune hepatitis I, II and III types [17]: Type I – a classic variant of AIH, includes about 80% of all cases. The main autoantigen is liver-specific protein (LSP). In the blood of children detect ANA and / or SMA in a titer of more than 1:20. Perinuclear antineutrophil cytoplasmic autoantibodies (pANCA) are also detected in 65-95% of patients. Type II AIH is about 3-4% of all cases, most patients – children from 2 to 14 years. The main autoantigen in type II autoimmune hepatitis is LKM1. In hepatitis II type in the serum detect anti-LKM1. Type III AIH is characterized by the presence of autoantibodies to soluble liver autoantigen (soluble liver antigen) antiSLA in the absence of ANA or antiLKM1. SMA (35%), antimitochondrial autoantibodies (22%), rheumatoid factor (22%) and hepatic membrane autoantibodies (antiLMA) (26%) are most common in patients with type III AIH [6, 17, 24].

The progressive course encourages a more in-depth study of the pathogenesis and the search for factors that influence the progression and manifestation of AIH. There is growing evidence that genetic predisposition, molecular mimicry and imbalance between effector and

regulatory immunity in a particular autoimmune ecosystem are key pathological factors in the development of the disease [24]. Natural killer T cells (NKTs) are a separate branch of T cells that express both T cell receptors (TCRs) and markers of natural killers (NKs). Invariant NKTs (iNKTs) carry invariant TCRs and recognize a small amount of glycolipid antigens represented by CD1d (non-classical MHC-I). Limited CD1d iNKT cells are regulators of immune responses and produce cytokines that can be pro-inflammatory (eg, interferon-gamma) or anti-inflammatory (eg, interleukin-4). Invariant NKT cells are involved in the development and maintenance of some autoimmune diseases such as multiple sclerosis and systemic lupus erythematosus. There is an inverse correlation between the number of NKT cells and IgG levels [22].

The liver's immune system specializes in working with food and commensal microbial antigens, to which it must remain tolerant. Immune tolerance of the liver is modulated by antigen-presenting cells, such as dendritic cells, Kupffer cells, stellate and endothelial cells [22]. A variety of congenital populations of lymphocytes, including NKT cells, γδT cells, iNKT associated with the mucosa, and CD56 (+) NK cells are resident or may rapidly accumulate in the liver microenvironment after potential pathogenic load [22]. These cells can maintain or overcome the liver's immune tolerance to autoantigens, leading to the growth of autoreactive T cells. Uncontrolled synthesis of IgG-class antibodies develops by B-cells, which contribute to the destruction of membranes of normal hepatocytes, mediate liver damage, cause autoimmune disease or direct liver damage, killing hepatocytes or bile duct cells [4, 16].

Autoimmune liver diseases include primary biliary cholangitis, formerly known as primary biliary cirrhosis, AIH, and primary sclerosing cholangitis. In AIH, hepatocytes are the target for an autoimmune attack, whereas in primary biliary cholangitis and primary sclerosing cholangitis, the epithelial cells of the bile ducts are small and medium-sized and the larger bile ducts, respectively. Demographic, epidemiological and clinical characteristics of these three conditions are different, and various genetic, immunological and environmental factors are involved in the development of the disease [22].

In recent years, more and more attention has been paid to the study of the relationship between vitamin D metabolism and the course of diffuse liver disease, including AIH. Vitamin D undergoes important biotransformation and inactivation in the liver. Because vitamin D is metabolized in the liver, abnormal vitamin D metabolism can be expected to be associated with chronic liver disease [19]. According to the Cochrane Review in 2017 [6], people with chronic liver disease are deficient in vitamin D. There is evidence that low

vitamin D status is associated with increased mortality in chronic liver disease [6]. According to the research of V. S. Berezenko et al. (2018) [5], it was found that vitamin D insufficiency occurs in two thirds (68.0%) of Ukrainian children with AIH, and deficiency – in 17.0%.

Recently, a meta-analysis of all cohort studies of the European population, including the pediatric population of 14,971 patients (1-18 years) [7]. The authors applied the Vitamin D Standardization Program and developed protocols to standardize existing 25 (OH) D values based on national health / nutrition studies. The prevalence of 25 (OH) D deficiency depending on age (7-14 years and 15-18 years) ranged from 1-8% and 12-40%, respectively [19]. The prevalence of vitamin D deficiency in puberty dictates the need to study the issue of vitamin D in girls with autoimmune hepatitis during this period.

The objective: to determine the vitamin D supply in girls of puberty age with autoimmune hepatitis.

Material and methods

To address this goal, a comprehensive clinical and paraclinical examination of 66 adolescent girls of the AIH group, patients with autoimmune hepatitis aged 12-17 years, who were treated in the Department of Pediatric Hepatology of GA "The Institute of Pediatrics, Obstetrics and Gynecology named after Academician O. M. Lukyanova of the National Academy of Medical Sciences of Ukraine"in 2010-2020. The control group consisted of 180 conditionally somatically healthy girls aged 12-17 years. The age distribution of the surveyed girls is presented in table 1.

Table 1

Age distribution of examined patients

Age, in years	Number of patients	
	Group AIH, n=66	Group K, n=180
12	11	30
13	11	30
14	11	30
15	11	30
16	11	30
17	11	30

The diagnosis of AIH was established in accordance with the international recommendations of the European Association for the Study of Liver Diseases (EASL) (2015) [15].

Indicators of general clinical laboratory examination and biochemical blood test were determined in all patients, including: level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), bilirubin and its fractions, creatinine, urea - by kinetic method; γ-glutamyltransferase (γ-GT), triglycerides, cholesterol, alkaline phosphatase (AF) activity, uric acid, albumin, total protein content –by colorimetric method on a Cobas 6000 analyzer, Roche Diagnostics GmbH (Switzerland); prothrombin time and International Normalized Ratio (INR) –be coagulometric method using the analyzer and test systems Sysmex CA 1500 (Japan), Siemens (Germany); thymol test – by sediment sample followed by photometry using an analyzer and test systems Mefan 8001, Phyllis-Diagnostics (CIS); serum IgG, IgM –by immunoturbidimetric method on the analyzer Cobas 6000, Roche Diagnostics GmbH (Switzerland). The level of circulating immune complexes (CEC) was determined by the method of Yu. A. Grinevich, A. N. Alferov (1981).

AIH activity was assessed by liver tests according to V. F. Uchaikin (1998): minimal activity was characterized by an increase in transaminases to 3 norms, low - up to 5 norms, moderate – an increase in ALT and AST to 9 norms, high - more than 10 norms [27].

Serum autoantibodies were determined in all girls with AIH by immunofluorescence using a Eurostar III Plus fluorescence microscope and EUROIMMUN test systems (Germany): ANA (antinuclear antibodies), Anti-LKM-1 (antibodies to liver and kidney microsomes type 1), anti-SM (antibodies to smooth muscle), anti-LC1 (antibodies to cytosolic antibodies type 1). To exclude the viral nature of the disease, markers of hepatitis viruses were determined: anti-HAV IgM, HBsAg, anti-HBsIgM, anti-HBsIgG, HBV DNA PCR, anti-HCV IgG and HCV RNA PCR. Hereditary and acquired metabolic liver diseases were excluded in all children.

All girls with AIH underwent a puncture biopsy of the liver with morphological and immunohistochemical examination of the biopsy on the OLYMPUS BX-51 microscope (Japan). Immunohistochemical study of biopsies was performed using the immunohistochemical marker of plasma cells CD138 Ab-2 (CloneMI15, ThermoScientific, USA). The activity of the inflammatory process was characterized by the index of histological activity (IHA) by R. G. Knodell et al. (1981) [13], which is the sum of the individual components, the first of which: the severity of periportal and / or bridging necrosis of the liver lobes – is estimated in the range of 0-10 points; intralobular focal necrosis and hepatocyte

dystrophy – from 0 to 4 points; inflammatory infiltrate in the portal tract – from 0 to 4 points; fibrosis and the development of cirrhosis - from 0 to 4 points: 0 – no fibrosis, 1 – mild periportal fibrosis; 2 – moderate fibrosis with portocentral septa; 3 – severe fibrosis with portocentral septa. The degree of activity of chronic hepatitis reflects the first three components, the fourth – the stage of the process. IGA, equal to 0 points, indicates the absence of inflammation; 1-3 points correspond to chronic hepatitis with minimal activity of the pathological process; 4-8 points – weakly expressed; 9-12 points – moderate and 13-18 points – severe chronic hepatitis.

The rigidity of the liver parenchyma by shear wave elastography on the Radmir ULTIMA scanner was determined for all girls. The stage of the disease was evaluated by the histological index of fibrosis (HIF) by METAVIR (Meta-analysis of histological data in viral hepatitis): stage F0 corresponded to the hardness of the liver parenchyma> 5.8 kPa, stage F1 – ≥ 5.8 - ≤ 7.2 kPa, stage F2 – ≥ 7.2 - ≤ 9.5 kPa, stage F3 – ≥ 9.5 - <12.5 kPa and stage F4 – more than 12.5 kPa (liver cirrhosis) [4, 8].

The level of 25- (OH) D in venous blood was determined by enzyme-linked immunosorbent assay using test systems and analyzer EUROIMMUN (Germany) according to the manufacturer's instructions. The results were evaluated according to the recommendations of the International Society of Endocrinologists [11]: normal vitamin D content – 30-100 ng / ml 25-(OH) D; vitamin D insufficiency– 25- (OH) D content 21-29 ng / ml; vitamin D deficiency – the content of 25- (OH) D is less than 20 ng / ml.

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, odds ratio (OR) with 95% confidence interval(CI) were used to identify differences between the comparative indicators.

Results and discussion

Among the surveyed girls with AIH disease in 18.18% (12) cases was first diagnosed at the age of 1-7 years, in 21.21% (14) – at the age of 8-11 years, in 60.61% (40) – at the age of 12-17 years. The average age of onset of the disease was 11.74 ± 0.42 years (Table 2).

83.33% (55) of girls have type AIH, 4.55% (3) have type II AIH, and 12.12% (8) have seronegative AIH. In 31.82% (21) patients AIH was diagnosed with liver cirrhosis.

As can be seen from table. 2, in 63.64% (42) girls with AIH had an acute onset with a clinical picture of acute hepatitis, in 36.36% (24) - a subacute onset. All patients had manifestations of astheno-vegetative syndrome. Dyspeptic disorders were registered in

50.00% of patients. 36.36% (24) of patients complained of an increase in body temperature to 37-39 ° C.

Table 2

Clinical and laboratory signs of AIH in the examined girls, n (%)

Feature	Group AIH, n=66
The age of onset of the disease: • 1–7 years • 8–11 years • 12–17 years	 12 (18,18) 14 ((21,21) 40 (60,61)
Onset of hepatitis: • acute • subacute	 42 (63,64) 24 (36,36)
Astheno-vegetative syndrome	66 (100)
Dyspepsia	33 (50,00)
Rise in body temperature: 37–39 ° C	24 (36,36)
Palmar erythema	42 (63,64)
Telangiectasia	51 (77,27)
Articular syndrome	15 (22,73)
Icteric skin and sclera	53 (80,30)
Fine-spotted maculopapular rash	3 (4,55)
Hemorrhagic rash	3 (4,55)
Frequent nosebleeds	30 (45,45)
Candidiasis of the skin, mucous membranes, nail plates	5 (7,58)
Alopecia	0 (0,00)
Hepatomegaly	47 (71,21)
Splenomegaly	42 (63,64)
Hyperbilirubinemia	38 (57,58)
Transaminase activity: • 2–5 norms • 6–20 norms	 30 (45,45) 36 (54,55)
Autoantibodies: • ANA • SMA • ANA+ SMA • LKM Lack of autoantibodies	 10 (27,27) 32 (78,79) 13 (19,70) 3(4,55) 12 (18,18)

In 77.27% (51) patients, regardless of AIH activity, small hepatic signs of varying severity were detected: palmar erythema (63.64% (42)), telangiectasia (77.27% (51)). Small-spotted papular rash was observed in 4.55% (3) of patients. Skin and scleral jaundice was observed in 80.30% (53) of patients with high and moderate AIH activity. 22.73% (15) of patients had joint syndrome. Candidiasis of the skin, mucous membranes, nail plates was observed in 7.58% (5) of patients with AIH.

Manifestations of hemorrhagic syndrome in the form of frequent nosebleeds were 45.45% (30) of girls, hemorrhagic rash – 4.55% (3) of those surveyed. It should be emphasized that periodic nosebleeds were the first clinical manifestations of AIH several years before the manifestation of a detailed clinical picture of the disease. Hepatomegaly, due to enlargement of both lobes of the liver, was diagnosed in 71.21% (47) of girls, mostly with high and moderate AIH activity and severe fibrosis (according to METAVIR – F3). Splenomegaly was detected in 63.64% (42) of those examined.

In all patients, indicators of general clinical laboratory examination, biochemical blood test, which characterize the main biochemical syndromes of AIH, were determined. Cytolysis syndrome was presented in 95.45% (63) of those examined with elevated ALT levels –the average multiplicity of excess of the upper limit of norm (ULN) – 17.15 ± 0.39; AST – the average multiplicity of excess of ULN– 21.24 ± 0.70 (Table 3). In 4.55% (3) of children in the period of incomplete clinical and laboratory remission, transaminases were within the normative values.

Cholestasis syndrome was evidenced by increased AP activity (ALT / AP ratio in the AIH group of 3.81 ± 0.08 vs. 0.20 ± 0.01 in the K group) and GGT (the average multiplicity of excess of the γ-GTULN– 1.84 ± 0.06), hyperbilirubinemia mainly due to the direct fraction in 57.58% (38) of girls with AIH, significantly more often in patients with highly and moderately active hepatitis; hypercholesterolemia (see table. 3).

Mesenchymal-inflammatory syndrome was diagnosed in 83.0% of subjects and was characterized mainly by increased levels of γ-globulins, thymol test, IgG and decreased levels of albumin. Thymol test confirmed the presence of qualitative and quantitative violations of the composition of blood proteins. In the control group, its level was up to 4 U / l (on the average2.01 ± 0.07 U / l), which corresponds to a negative sample, and in girls with AIH positive amounted on the averageto 5.22 ± 0.12 U / l. The increase in the stability of the colloidal blood system in AIH is due to the fact that the synthesis of albumin decreases, and globulin, on the contrary, increases, causing a violation of the physiological balance of these protein fractions, and promotes coagulation.

Hepatocellular insufficiency was manifested by a decrease in albumin, prothrombin index, increased levels of INR, urea, creatinine (see table 3).

Table 3

Indicators of morphofunctional liver status in adolescent girls with AIH

Indicator	Group AIH, n=66	Group K, n=180
ALT, mg / dl	720.39±16.36[k]	14,77±0,28
The average multiplicity of excess of the ALT ULN	17.15±0.39	-
AST, mg / dl	531.05±17.47[k]	19,66±0,44
The average multiplicity of excess of the AST ULN	21.24±0.70	-
γ-GT, U / l	60.64±1.85[k]	18,63±0,29
The average multiplicity of excess of the γ-GT ULN	1.84±0.06	-
AP, U / l	408.11±8.85[k]	172,70±29,41
The average multiplicity of excess of the AP ULN	1.70±0.04	-
Total cholesterol, mmol / l	5.56±0.10[k]	4,21±0,05
Total protein, g / l	98.97±0.95[k]	72,95±0,44
Albumin,%	21.26±0.20[k]	40,64±0,29
γ-globulin, %	28.55±1.12[k]	15,03±0,23
Ig M, g / l	5.90±0.40[k]	1,09±0,05
Ig G, g / l	12.60±0.34[k]	10,60±0,23
Thymol test, U / l	5.22±0.12[k]	2,03±0,07
Total bilirubin, μmol / l	47.96±1.06[k]	11,95±0,32
Direct bilirubin, μmol / l	37.67±0.51[k]	2,51±0,07
Prothrombin index,%	69.26±0.76[k]	87,03±0,36
International Normalized Ratio	1.36±0.08[k]	0,99±0,01
Urea, mmol / l	6.82±0.28[k]	5,12±0,07
Creatinine, μmol / l	82.87±2.66[k]	57,45±0,78
Circulating immune complexes, c.u.	106.00±3.91	53,36±1,68
Notes: 1. [k] – statistically significant reliability with a similar indicator of group K ($p<0.05$); 2. ULN – upper limit of norm.		

Histological examination of liver biopsies showed periportal ("hepatitis interface") with stepped necrosis. Periportal tracts were expanded due to inflammatory infiltration by lymphocytes and plasma cells, which was confirmed by the presence of CD138 + -

immunopositive cells. Depending on the activity of the disease, a fairly wide range of changes was observed morphologically: from periportal to panacinar hepatitis, bridging and multiacinar necrosis with cirrhosis. Active periportal inflammation led to the penetration of inflammatory cells into hepatocytes (emperipolosis), the destruction of the original structure of the liver, and the subsequent regeneration process determined the formation of AIH-characteristic rosettes of hepatocytes. The formation of rosettes in hepatitis is a form of regeneration of liver cells preserved in the necrosis zones, which distinguishes them from cholestatic rosettes, a form of hepatocyte metaplasia associated with the formation of bile ducts in chronic cholestasis. Lobular (panacinar) and centrolobular hepatitis were registered. The cellular infiltrate was represented by lymphocytes, plasma cells and macrophages, as well as eosinophils, reflecting the autoaggressive cellular immune attack in the pathogenesis of AIH. Observed aggregation of lymphoid cells into follicles in the stroma of the portal tract.

Evaluation of the severity of fibrosis according to ultrasound elastography of the shear wave of the liver parenchyma in the diagnosis of fibrosis in girls with AIH showed that only 65.15% (43) children stage fibrosis obtained by histological examination coincided with the data of liver elastography.

When estimating the index R. G. Knodell in the group of patients with AIH, the minimum degree of clinical and biochemical activity (determined by the severity of necroinflammation in the liver) was determined in 21.21% (14) of girls, low – in 24.24% (16), moderate – in 34.85% 23), high – in 19.70% (13) patients. When assessing the severity of histological activity by R. G. Knodell mild liver fibrosis was found in 28.79% (19) cases, moderate – in 43.94% (29) of children with AIH. Morphological signs of liver cirrhosis were registered in 28.79% (19) of patients with AIH. From the above data it follows that in adolescents with AIH biochemical and histological activity are not identical: 27.27% (18) of girls with mild and moderate histological activity in the liver on the indicator of transaminases had high activity, and, conversely, in 7,58% (5) of girls with high histological activity had an increase in transaminases of not more than 5 norms.

The average level of vitamin 25 (OH) D in the serum of girls with AIH of pubertal age was 17.14 ± 1.06 vs. 23.27 ± 0.53 ng / ml in the control group ($p<0.01$). In 66.67% (44) patients with AIH there was a deficiency of 25 (OH) D, in 22.73% (15) – insufficiency, in 10.61% (7) – the optimal level, while in the control group the distribution was as follows: 43.89% (79), 36.67% (66), 19.44% (35). Respectively: the $\square^2$-criterion = 10.02 ($p<0.01$),OR = 2.56, 95 % CI:1.42-4.62;$\square^2$-criterion = 4.25 ($p<0.04$), OR = 0.51, 95 % CI:0.27-0.97;$\square^2$-criterion =2.66 ($p>0.05$), OR = 0.49, 95 % CI:0.21-1.17.

The supply of vitamin D depended on the histological activity of AIH. Among girls with AIH and IHA <9 points the share of patients with vitamin D deficiency was 53.13% (17/32) vs. 79.41% (27/34) among girls with IHA> 9 points (χ^2 = 5.13, p<0.02; OR = 0.29, 95 % CI: 0.10-0.87); with insufficiency – 31.25% (10/32) vs. 14.71% (5/34) (χ^2 = 2.57, p>0.05; OR = 2.64, 95 % CI: 0.79-8.82); the optimal level is 15.63% (5/32) vs. 5.88% (2/34) (χ^2 = 1.65, p>0.05; OR = 3.15, 95 % CI: 0.57-17.51).

Activation or inhibition of iNKT cells can cause a change in the cytokine environment in the pro-inflammatory or anti-inflammatory direction. Recent studies have examined the role of vitamin D in immunomodulation [20], including the development and regulation of iNKT cells [9, 10]. In fact, iNKT cells and intraepithelial lymphocytes CD4 / CD8 are in development and functionally dependent on sufficient levels of vitamin D [16, 25]. Numerous studies have noted vitamin D deficiency as well as vitamin D receptor (VDR) mutations in patients with autoimmune diseases [2, 23]. Low levels of vitamin D are also common in patients who do not respond to urodeoxycholic acid therapy and comorbid autoimmune diseases [1]. 1,25 (OH) (2) -vitamin D (3) prevents activation of stellate liver cells in vitro and reduces inflammatory liver damage but not fibrosis in the mouse model Abcb4 (- / -) cholestatic liver damage caused by inflammation, fibrosis and cancer [20].

Conclusion

Cytolysis, cholestasis, mesenchymal-inflammatory syndrome, hepatocellular insufficiency in autoimmune hepatitis in adolescent girls develops against the background of reduced vitamin D supply, which depends on the histological activity of the disease. Among adolescent girls with AIH, 66.67% of patients have a deficiency of 25 (OH) D, 22.73% – insufficiency and only 10.61% – the optimal level. The average level of vitamin 25 (OH) D in the serum of adolescent girls with AIH is 17.14 ± 1.06 ng / ml.

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