

Chaykivska E. F., Dyadyushko N. M. Peculiarities of the functional state of the pituitary-gonadal system of the neuroendocrinal regulation in adolescent girl with auto immune hepatitis. *Journal of Education, Health and Sport*. 2020;10(12):235-245. eISSN 2391-8306. DOI <http://dx.doi.org/10.12775/JEHS.2020.10.12.023>  
<https://apcz.umk.pl/czasopisma/index.php/JEHS/article/view/JEHS.2020.10.12.023>  
<https://zenodo.org/record/4445251>

The journal has had 5 points in Ministry of Science and Higher Education parametric evaluation. § 8. 2) and § 12. 1. 2) 22.02.2019.  
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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 09.11.2020. Revised: 25.11.2020. Accepted: 28.12.2020.

## PECULIARITIES OF THE FUNCTIONAL STATE OF THE PITUITARY-GONADAL SYSTEM OF THE NEUROENDOCRINAL REGULATION IN ADOLESCENT GIRL SWITH AUTO IMMUNE HEPATITIS

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### Abstract

Girls and women make up 75% of patients with autoimmune hepatitis (AIH). The peak incidence of AIH occurs in childhood, when the disease is called juvenile AIH. **The objective:** to determine the features of the functional state of the pituitary-gonadal system of neuroendocrine regulation in adolescent girls with AIH. **Material and methods.** During 2010-2020, 66 girls of the main group AIH, patients with AIH, and 180 conditionally somatically and gynecologically healthy girls of the control group K at the age of 12-17 years were under observation. Comprehensive examination included history taking, assessment of sexual development, clinical and biochemical blood tests, determination of autoantibodies, markers of viral hepatitis, ultrasound examination of the abdominal cavity, liver biopsy (in main group). Peripheral serum hormone levels were determined in certain age groups (12, 13, 14, 15, 16 and 17 years): luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), thyroid-stimulating hormone (TSH), free triiodothyronine (fT<sub>3</sub>), free thyroxine (fT<sub>4</sub>), estradiol (E<sub>2</sub>), progesterone (P<sub>4</sub>), free testosterone (fT). **Results.** Against the background of disorders of morphofunctional properties of the liver in 12-, 13-, 14- 15-, 16- and 17-year-old girls with AIH noted a significant decrease in the score of sexual

development in all age groups compared to the same indicator in the relevant age control groups:  $3.21 \pm 0.40$  vs.  $4.94 \pm 0.37$ ,  $3.46 \pm 1.00$  vs.  $7.91 \pm 0.58$ ,  $7.03 \pm 1.44$  vs.  $11.08 \pm 0.25$ ,  $7.80 \pm 0.65$  vs.  $11.86$ ,  $10.65 \pm 0.79$  vs.  $11.98$  points. The average total level of LH in the Group AIH was  $3.77 \pm 0.25$  against  $4.46 \pm 0.10$  mIU / ml in group K ( $p < 0.01$ ), FSH –  $3.16 \pm 0.12$  against  $4.01 \pm 0.08$  mIU / ml ( $p < 0.01$ ), PRL –  $198.92 \pm 6.96$  vs.  $282.93 \pm 8.36$   $\mu$ IU / ml ( $p < 0.01$ ),  $E_2$  –  $124.15 \pm 2.39$  vs.  $437.45 \pm 9.59$  pmol / ml ( $p < 0.01$ ),  $P_4$  –  $1.49 \pm 0.09$  vs.  $2.78 \pm 0.08$  nmol / ml ( $p < 0.01$ ), fT –  $1.96 \pm 0.10$  vs.  $1.16 \pm 0.04$  nmol / l ( $p < 0.01$ ), TSH –  $1.98 \pm 0.05$  vs.  $2.15 \pm 0.05$   $\mu$ IU / ml ( $p < 0.03$ ), fT<sub>3</sub> –  $3.50 \pm 0.06$  vs.  $5.46 \pm 0.07$  pmol / l ( $p < 0.01$ ), fT<sub>4</sub> –  $12.54 \pm 0.44$  vs.  $18.55 \pm 0.20$  pmol / l ( $p < 0.01$ ). **Conclusions.** In adolescent girls with AIH on the background of disorders of morphofunctional properties of the liver there is a delayed start of the hypothalamic-pituitary-gonadal system and suppression of hormone-producing function of the pituitary-gonadal link of the neuroendocrine system.

**Key words: autoimmune hepatitis; morphofunctional properties of the liver; adolescent girls; puberty; sexual development; pituitary-gonadal neuroendocrine regulation.**

Autoimmune and hepatitis (AIH) – a chronic liver disease that does not go away on its own, mainly affects women and is characterized by hypergammaglobulinemia (even in the absence of cirrhosis), the presence of circulating autoantibodies, binding to human leukocyte antigen (HLA) DR3 and DR4, periportal on histological examination and a favorable response to immunosuppression. Without treatment, the disease often leads to cirrhosis, liver failure and death [3].

AIH is considered a rare disease, its prevalence is 16-18 cases per 100,000 inhabitants of Europe [3]. Girls and women make up 75% of AIH patients. The peak incidence of AIH occurs in childhood, when the disease is called juvenile AIH [12, 14].

The liver, as the central metabolic organ, plays a crucial role in the homeostasis of steroid hormones [2, 4, 13, 16] and in eliminating toxic metabolites that can be destructive to tissues and ultimately lead to liver disease. There is a close relationship between liver pathology and steroid hormones [12, 14]. The effect of the liver on the metabolism of steroid hormones is not limited to the fact that it synthesizes cholesterol, immediately the latter are inactivated. Testosterone produces 17-ketosteroids, which are conjugated to sulfates and excreted in the urine. Estrogens are converted to estriol and estrone, after which they are conjugated to glucuronic acid and sulfates. In chronic liver disease, the metabolism of

estrogen and testosterone is often disrupted [5]. From the above it follows that AIH can change the functional state of the pituitary-gonadal system of neuroendocrine regulation.

Functional activity of the liver increases during puberty and reaches a maximum after puberty [7]. Hepatitis in this period worsens the processes of hepatic metabolism, affects the processes of physical and sexual development of the girl. In the available modern scientific literature, the issues of the influence of AIH on the state of the pituitary-gonadal system of neuroendocrine regulation in adolescent girls are insufficiently covered. However, this problem is relevant, as the development of a set of treatment and prevention measures for AIH can reduce not only the rate of liver damage, but also the frequency of pathology of sex development.

**The objective:** to determine the features of the functional state of the pituitary-gonadal system of neuroendocrine regulation in adolescent girls with autoimmune hepatitis.

**Material and methods.** During 2010-2020, 66 AIH girls of the main group, patients with AIH, and 180 conditionally somatically and gynecologically healthy girls of the control group K aged 12-17 years were under observation. The age distribution of the girls under examination is presented in Table 1.

Table 1

Age distribution of the patients under examination

Age, 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) [8]. The level of alanine aminotransferase (ALT) and aspartate aminotransferase (AST), bilirubin and its fractions, creatinine, urea was determined by the kinetic method;  $\gamma$ -glutamate transferase ( $\gamma$ -GT), triglycerides, cholesterol, alkaline phosphatase (AP) activity, uric acid,

albumin, total protein content – colorimetric method on a Cobas 6000 analyzer, Roche Diagnostics GmbH (Switzerland); prothrombin time and International Normalized Ratio (INR) – coagulometric method using the analyzer and test systems Sysmex CA 1500 (Japan), Siemens (Germany); evaluated the thymol test – using a sediment sample followed by photometry using an analyzer and test systems Mefan 8001, Phyllis-Diagnostics (UIS); serum IgG and IgM levels – by immunoturbidimetric method on a Cobas 6000 analyzer, Roche Diagnostics GmbH (Switzerland). 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. All girls with AIH underwent ultrasound examination of the hepatobiliary system and puncture biopsy of the liver with morphological and immunohistochemical examination of the biopsy under the microscope OLYMPUS BX-51 (Japan). The activity of the inflammatory process was characterized by the index of clinical and biochemical activity and histological activity by R. G. Knodell et al. (1981).

Determination of the level 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), prolactin (PRL), thyroid-stimulating hormone (TSH), free triiodothyronine (fT<sub>3</sub>), free thyroxine (fT<sub>4</sub>), estradiol (E<sub>2</sub>), progesterone (P<sub>4</sub>), free testosterone (fT).

The degree of sexual development was determined by the generally accepted method of the development of secondary sexual characteristics: pubic and axillary hair, the development of the mammary glands and the formation of menstruation by J. M. Tanner (1962) and L. G. Tumilovich (1975) [15]. For a comprehensive assessment of sexual development used the method of summation of points, which takes into account the degree of development of each of the secondary sexual characteristics. Accordingly, the above characteristics were evaluated taking into account the correction factor. The coefficient for mammary glands was 1.2, for the degree of pubic hair – 0.3, for axillary hair – 0.4, to assess menstrual function – 2.1. The score of the development of each individual trait was calculated as the product of the average quantitative assessment of the secondary sexual trait or

menstruation on the degree of development of each trait in a given patient [9]. The sum of the scores of the development of each individual trait was the score of sexual development (SSD).

The obtained data were statistically processed using the Excel software package 10. Calculated the mean value (M), standard deviation error (SE). Student's t-test, Wilcoxon-Mann-Whitney U-test, Fisher's  $\phi$ -test and  $\chi^2$  were used to identify differences between the comparative indicators.

### **Results and discussion**

Symptoms of autoimmune process, cytolysis, cholestasis, mesenchymal-inflammatory syndrome, hepatocellular insufficiency were observed in adolescent girls with AIH (Table 2).

When estimating the index R.G. Knodell in the group of patients with AIH, the minimum degree of clinical and biochemical activity was determined in 21.21% (14) of girls, low – in 24.24% (16), moderate – in 34.85% (23), high – in 19,70% (13) of patients. When assessing the severity of histological activity by R. G. Knodell, mild liver fibrosis was detected 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.

Against the background of disorders of morphofunctional properties of the liver in 12-, 13-, 14-, 15-, 16- and 17-year-old girls with AIH marked a significant decrease in SSD in all age categories compared to the same indicator in the relevant age control groups:  $3.21 \pm 0.40$  vs.  $4.94 \pm 0.37$ ,  $3.46 \pm 1.00$  vs.  $7.91 \pm 0.58$ ,  $7.03 \pm 1.44$  vs.  $11.08 \pm 0.25$ ,  $7.80 \pm 0.65$  vs.  $11.86$ ,  $10.65 \pm 0.79$  vs.  $11.98$  points.

The main regulators of ovarian activity are FSH, LH and PRL. During puberty, the cyclic release of gonadotropins is finally formed, the feedback between the action of estrogen and the gonadotropic function of the hypothalamic-pituitary system is fixed. The secretion of FSH and LH is under double control: by hypothalamic gonadotropin-releasing factor and peripheral sex hormones. The hypothalamic gonadotropin pulse generator triggers "basal" or "tonic" gonadotropin secretion, which is responsible for folliculogenesis, corpus luteum maintenance, and  $E_2$  and  $P_4$  synthesis in the ovaries in women [10]. An additional mode of gonadotropin release – preovulatory LH release, observed at the end of the follicular phase of the ovarian cycle – is necessary for ovulation and, consequently, for sex development in women [10]. LH and FSH are crucial for reproductive fitness. LH is necessary for sexual development and function of gonads, at insufficiency of its production hypogonadism develops. FSH deficiency leads to the absence or incomplete sexual development in women, blocking folliculogenesis to the antral stage, which leads to anovulation [6].

Table 2.

## Indicators of liver morphofunctional status in adolescent girls with AIH

Indicator	Group AIH, n=66	Group K, n=180
Autoantibody:		
• ANA	10 (27,27)	-
• SMA	32 (78,79)	
• ANA+ SMA	13 (19,70)	
• LKM	3(4,55)	
Lack of autoantibodies	12 (18,18)	
ALT, mg / dl	720.39±16.36 <sup>k</sup>	14.77±0.28
The average multiplicity of excess of the ALT ULN	17.15±0.39	-
AST, mg / dl	531.05±17.47 <sup>k</sup>	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 <sup>k</sup>	18.63±0.29
The average multiplicity of excess of the γ-GTULN	1.84±0.06	-
AP, U / l	408.11±8.85 <sup>k</sup>	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 <sup>k</sup>	4.21±0.05
Total protein, g / l	98.97±0.95 <sup>k</sup>	72.95±0.44
Albumin, %	21.26±0.20 <sup>k</sup>	40.64±0.29
γ-globulin,%	28.55±1.12 <sup>k</sup>	15.03±0.23
Ig M, g / l	5.90±0.40 <sup>k</sup>	1.09±0.05
Ig G, g / l	12.60±0.34 <sup>k</sup>	10.60±0.23
Thymol test, Od / l	5.22±0.12 <sup>k</sup>	2.03±0.07
Total bilirubin, μmol / l	47.96±1.06 <sup>k</sup>	11.95±0.32
Direct bilirubin, μmol / l	37.67±0.51 <sup>k</sup>	2.51±0.07
Prothrombin index,%	69.26±0.76 <sup>k</sup>	87.03±0.36
INR	1.36±0.08 <sup>k</sup>	0.99±0.01
Urea, mmol / l	6.82±0.28 <sup>k</sup>	5.12±0.07
Creatinine, μmol / l	82.87±2.66 <sup>k</sup>	57.45±0.78
Circulating immune complexes, c.u.	106.00±3.91 <sup>k</sup>	53.36±1.68
<i>Notes:</i> 1. <sup>k</sup> – statistically significant reliability with a similar indicator of group K (p<0.05); 2. ULN– upper limit of normal.		

PRL plays a key role in the reproductive system. PRL modulates the reproductive axis at the central level, affecting a specific population of neurons in the arcuate nuclei of the hypothalamus that express the *Kiss1* gene, which encodes neuropeptides known as kisseptins, which are critically involved in reproduction. Mutations in the loss of function in genes encoding kisseptins or the kisseptin receptor lead to impaired puberty in both human and animal models [1]. At the end of puberty, there is a normal increase in the concentration of PRL, when the percentage of ovulatory cycles increases sharply. The study of pituitary hormone levels in the examined girls with AIH revealed in all age groups a probable decrease in the levels of FSH and PRL, as well as LH in the age groups of 16 and 17 years (Table 3).

Table 3

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

Age, years	Group	LH, mIU / ml	FSH, mIU / ml	PRL, $\mu$ IU / ml
12	AIH	3.80±0.28	2.23±0.16 <sup>k</sup>	208.16±12.06 <sup>k</sup>
	K	3.53±0.10	2.82±0.08	242.39±25.83
13	AIH	3.95±0.29	2.31±0.16 <sup>k</sup>	181.39±10.69 <sup>k</sup>
	K	3.79±0.15	2.93±0.12	258.89±11.82
14	AIH	3.90±1.06	3.27±0.28 <sup>k</sup>	166.90±16.46 <sup>k</sup>
	K	3.91±0.15	4.38±0.12	256.20±11.82
15	AIH	3.88±1.08	3.43±0.39 <sup>k</sup>	193.04±22.38 <sup>k</sup>
	K	4.08±0.15	4.41±0.13	302.00±18.85
16	AIH	3.69±0.25 <sup>k</sup>	3.85±0.19 <sup>k</sup>	215.94±22.77 <sup>k</sup>
	K	5.48±0.26	4.65±0.23	316.76±26.94
17	AIH	3.43±0.48 <sup>k</sup>	3.86±0.22 <sup>k</sup>	228.10±15.74 <sup>k</sup>
	K	5.98±0.25	4.87±0.14	321.34±9.29

Note. <sup>k</sup>– statistically significant reliability with a similar indicator of group K (p<0.05)

The lack of LH reduction in the age categories of 12-, 13-, 14-, 15-year-old girls with AIH can be explained in these groups by the presence of moderate hyperandrogenism, which stimulates LH production [11]. The average total level of LH in the group AIH was  $3.77 \pm 0.25$  against  $4.46 \pm 0.10$  mIU / ml in group K (p<0.01), FSH –  $3.16 \pm 0.12$  against  $4.01 \pm 0.08$  mIU / ml (p<0.01), PRL –  $198.92 \pm 6.96$  vs.  $282.93 \pm 8.36$   $\mu$ IU / ml (p<0.01). According to the detected levels of pituitary hormones, the average age of menarche in the group AIH was

13.33 ± 0.11 versus 12.43 ± 0.04 years (p<0.01) in the control group, i.e. 10-11 months later than in practice healthy peers.

The study of levels of sex hormones revealed in AIH a decrease in levels of sex steroids, such as E<sub>2</sub>, P<sub>4</sub> in all age categories (Table 4).

Table 4

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

Age, years	Group	E <sub>2</sub> , pmol/ l	P <sub>4</sub> , nmol / l	fT, nmol / l
12	AIH	111.39±2.41 <sup>k</sup>	0.93±0.14 <sup>k</sup>	1.58±0.20 <sup>k</sup>
	K	288.83±12.30	1.71±0.14	0.92±0.07
13	AIH	118.73±3.79 <sup>k</sup>	1.12±0.18 <sup>k</sup>	1.82±0.27 <sup>k</sup>
	K	295.83±7.92	2.28±0.16	0.99±0.07
14	AIH	123.94±3.88 <sup>k</sup>	1.27±0.18 <sup>k</sup>	2.12±0.30 <sup>k</sup>
	K	434.78±9.31	2.82±0.19	1.02±0.07
15	AIH	125.72±5.55 <sup>k</sup>	1.37±0.13 <sup>k</sup>	1.98±0.22 <sup>k</sup>
	K	463.89±10.62	2.87±0.16	1.16±0.07
16	AIH	129.82±3.68 <sup>k</sup>	1.63±0.11 <sup>k</sup>	2.02±0.35 <sup>k</sup>
	K	539.92±11.52	2.90±0.14	1.32±0.11
17	AIH	135.31±11.29 <sup>k</sup>	2.64±0.13 <sup>k</sup>	2.22±0.22 <sup>k</sup>
	K	601.46±9.47	4.08±0.08	1.54±0.10

Note. <sup>k</sup>– statistically significant reliability with a similar indicator of group K (p<0.05)

The average total level of E<sub>2</sub> in the group AIH was 124.15 ± 2.39 vs. 437.45 ± 9.59 pmol / ml in group K (p<0.01), P<sub>4</sub>– 1.49 ± 0.09 vs. 2.78 ± 0.08 nmol / ml (p<0.01). Since the decrease in P<sub>4</sub> secretion is usually the result of single-phase menstrual cycles and cycles with luteal phase insufficiency, the results indicate a violation of ovulatory ovarian function in girls with AIH. Girls with AIH registered an increase compared to the same level of TV in all age groups. The average total level of fT in patients with AIH was 1.96 ± 0.10 against 1.16 ± 0.04 nmol / l in the control (p<0.01). Of course, testosterone has a biphasic effect on the production of gonadotropins in women. A moderate increase in fT levels stimulates LH production at both the hypothalamic and pituitary levels, while high fT levels suppress LH [13]. Relative hyperandrogenism, hypoestrogenism, hypoprogesteronemia on the background of decreased production of gonadotropic hormones and PRL during sexual development in the

examined patients with AIH contributed to menstrual dysfunction, among which was noted primary amenorrhea in 7.58% (5) cases, the second amenorrhea – in 6.06 % (4), oligomenorrhea – in 27.27% (18), opsomenorrhea– in 27.27% (18), juvenile uterine bleeding – in 9.09% (6), dysmenorrhea – in 31.82% (21), a combination of different disorders – in 18.18% (12).

Patients with polyglandular autoimmune syndrome were excluded from the study. The level of TSH in patients with AIH had no significant differences with a similar indicator of group K in some studied age groups, but on average in the group AIH it was lower than in the control –  $1.98 \pm 0.05$  vs.  $2.15 \pm 0.05$   $\mu\text{IU} / \text{ml}$  ( $p < 0.03$ ) (Table 5).

Table 5

Levels of TSH and thyroid hormones in the examined girls of pubertal age,  $M \pm SE$

Age, years	Group	TSH, $\mu\text{IU} / \text{ml}$	$\text{fT}_3$ , $\text{pmol} / \text{l}$	$\text{fT}_4$ , $\text{pmol} / \text{l}$
12	AIH	$1.98 \pm 0.12$	$3.33 \pm 0.09^k$	$11.07 \pm 0.79^k$
	K	$2.22 \pm 0.14$	$4.88 \pm 0.16$	$19.63 \pm 0.35$
13	AIH	$1.97 \pm 0.17$	$3.49 \pm 0.19^k$	$10.70 \pm 0.70^k$
	K	$2.19 \pm 0.11$	$5.21 \pm 0.18$	$18.82 \pm 0.49$
14	AIH	$1.86 \pm 0.11$	$3.76 \pm 0.11^k$	$11.23 \pm 0.64^k$
	K	$2.37 \pm 0.13$	$5.39 \pm 0.13$	$19.22 \pm 0.35$
15	AIH	$1.89 \pm 0.11$	$3.58 \pm 0.17^k$	$12.84 \pm 0.83^k$
	K	$2.20 \pm 0.13$	$5.47 \pm 0.18$	$18.11 \pm 0.53$
16	AIH	$2.06 \pm 0.19$	$3.46 \pm 0.14^k$	$14.21 \pm 1.64^k$
	K	$1.96 \pm 0.16$	$5.68 \pm 0.18$	$18.30 \pm 0.55$
17	AIH	$2.11 \pm 0.06$	$3.42 \pm 0.16^k$	$15.17 \pm 1.24^k$
	K	$1.93 \pm 0.13$	$6.16 \pm 0.18$	$17.23 \pm 0.56$
Note. <sup>k</sup> – statistically significant reliability with a similar indicator of group K ( $p < 0.05$ )				

As can be seen from table. 4, the levels of  $\text{fT}_3$  and  $\text{fT}_4$  in all age groups with AIH were statistically significantly lower and the average in the group AIH was  $3.50 \pm 0.06$  vs.  $5.46 \pm 0.07$   $\text{pmol} / \text{l}$ , respectively ( $p < 0.01$ ) in group K and  $12.54 \pm 0.44$  against  $18.55 \pm 0.20$   $\text{pmol} / \text{l}$  ( $p < 0.01$ ).

### **Conclusions:**

In adolescent girls with AIH on the background of disorders of morphofunctional properties of the liver, there was suppression of hormone-producing function of the pituitary-gonadal link of the neuroendocrine system. The secretion of FSH, LH and PRL in patients with AIH was lower compared to healthy peers, which suggests that the start of the hypothalamic-pituitary-ovarian system occurs in these girls later than in the control. This assumption is also confirmed by higher levels of fT in the blood at the stage of P1 pubertal development and correlates with earlier adrenarche. Analysis of LH secretion showed that there is a tendency to increase it in the final stages of pubertal development. E<sub>2</sub> and P<sub>4</sub> concentrations were significantly reduced at all stages of pubertal development in girls with AIH.

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