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Growth hormone variability in children and adolescents with helicobacteriosis

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Abstract

To study the level of growth hormone in blood serum in children and adolescents with chronic gastroduodenal pathology (CGDP) against the background of helicobacteriosis. We examined 286 children from 6 to 15 years old with chronic gastroduodenal diseases and 110 healthy children who were included in the control group. The study of the level of growth hormone (GH) was carried out according to a standard method. In children under adolescence with helicobacteriosis, compared with the control group, GH varied from 6.7% to 27.2%, depending on the type of pathology. In adolescents, the level of growth hormone varied from 11.7% to 35.1% ($P<0.05$), and with peptic ulcer - 35.1% lower than in the control group. At the same time, in patients with inflammatory forms of CGDP, the GH level was higher by 11.7%. Studies have shown that minimal changes are observed in children before adolescence and the maximum - in adolescents, coinciding with the increased physical and sexual development of children. In children and adolescents with CGDP caused by *Helicobacter pylori*, there is a decrease in growth hormone in the blood serum compared to healthy children. However, the levels remain within the age reference parameters and vary depending on the clinical form of CGDP. The most significant decrease in the level of growth hormone in comparison with it is observed in patients with peptic ulcer and with chronic duodenitis an increase.

Keywords: gastritis, gastroduodenitis, growth hormone, *Helicobacter pylori*, peptic ulcer

1. Introduction

Diseases of the gastrointestinal tract in children are one of the leading problems of modern pediatrics, and in this setting, the main factor driving the development of inflammatory processes in the digestive tract is *Helicobacter pylori* infection. *Helicobacter pylori (H. pylori)* infection is a serious problem, being the most frequent chronic infection worldwide in both adults and children, with an infection rate of up to 32% among children (1). It should be noted that the gastrointestinal tract is part of a single organism. Therefore, diseases of the digestive system affect the functioning of other organs and systems. At the same time, the disruption of the activity of any part of the body causes the dysfunction of the digestive system (2, 3).

The digestive system is the largest hormone producer in the body. In its main organs, the stomach, small and large intestines, pancreas, and others, there are diffusely located endocrine cells; together, these all form the gastroenteropancreatic endocrine system, which is part of the diffuse endocrine system (3). Therefore, any pathological process in the gastrointestinal tract can affect the hormonal status of the whole organism.

We took growth hormone (GH) for research. Fluctuations of GH were observed in children and adolescents at this age. With a disease of the gastrointestinal tract, these fluctuations are more typical. Also, the study of this hormone is more affordable from an economic point of view.

Purpose of the study is examining the level of growth hormone in the blood of children and adolescents with chronic gastroduodenal pathology in a background of *Helicobacter pylori* infection.

2. Materials and methods

2.1. Study design

The study design consisted of several stages: initial, research, and final. In the initial stage, criteria for the selection of patients were developed; contracts were written for conducting clinical, laboratory, and instrumental studies in a clinical setting; and other contracts were drawn up with urban and rural family polyclinics and private diagnostic clinics for conducting clinical and laboratory studies. An agreement was made with the clinic of the Tashkent Pediatric Medical Institute to conduct clinical and laboratory research. In the research phase, clinical and laboratory studies of children and adolescents were carried out in an outpatient setting together with a small group of pediatric specialists (pediatric gastroenterologists, pediatricians, and physiotherapists). We examined children

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and adolescents with chronic gastroduodenal pathology (CGDP; N= 286) aged 6 to 15 years living in the city of Tashkent. The average age was 11.6 ± 2.17 years. The control group included 110 healthy children of the same age and both sexes. A total of 396 children and adolescents were examined. In total, 211 (53.28%) male patients and 185 (46.72%) female patients were included.

Chronic gastroduodenitis (CGD) was diagnosed in 174 children (60.8%), chronic gastritis (CG) in 43 (15.03%), chronic duodenitis (CD) in 22 (7.69%), and peptic ulcer disease (PUD) in 47 (16.43%) patients. All examined patients, taking into account the WHO recommendations (2016), were divided into 2 study groups depending on age: group I (children from 6 to 11 years old) and group II (adolescents from 12 to 15) years old.

2.2. Eligibility criteria

Inclusion criteria:

•Children and adolescents aged 6 to 15 years;

•Children with chronic gastroduodenal pathology: chronic gastritis, chronic gastroduodenitis, chronic duodenitis, gastric and intestinal ulcers (study group) of both sexes;

•Children with confirmed carriage of *Helicobacter pylori* infection;

•Children without acute inflammatory diseases of the internal organs.

Exclusion criteria:

•Children under 6 years old and adolescents over 15 years old;

•The presence of chronic somatic diseases;

•The presence of psychosomatic and neurological disorders;

•Children receiving surgical treatment against the background of inflammatory diseases of the gastrointestinal tract.

2.3. Research methods

The studies were carried out in an outpatient setting in collaboration with an endocrinologist. In these children, together with general clinical examinations, the level of growth hormone (GH) in the blood was determined with a standard method. The study of GH in patients was performed at the start of treatment for the disease. Since the level of GH varies widely under normal conditions, the determination of its concentration in children with CGDP was carried out in compliance with certain requirements, i.e., in the morning, at least 2 hours after eating, and after 30 minutes of rest.

Tests for *H. pylori* infection based on a qualitative determination of this pathogen were carried out by two independent methods: a breath test (HELIK® test system with an indicator tube) and an immunochromatographic feces test. The quantitative determination of the pathogen was not carried out. The patient was considered *H. pylori*-infected if there was a positive result in both tests. If there was a positive result in only one test, the patient received a final diagnosis based on an invasive diagnostic method involving an enzyme immunoassay to determine the concentration of IgG antibodies against *Helicobacter pylori* antigens in blood serum.

2.4. Ethical review

The described study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. To conduct clinical and laboratory studies on children in an outpatient setting, a certificate from the Ethics Committee under the Ministry of Health of the Republic of Uzbekistan was obtained (protocol no. 3 of 20.04.2017). The study was registered on the ClinicalTrials.gov PRS site (ID: NCT04702542). Additionally, before the clinical trials, written permission was obtained from the parents and guardians to examine their sick children and adolescents. All study results were also recorded in the patients' outpatient documentation.

2.5. Statistical Analyses.

Mathematical and statistical data processing was carried out using Microsoft Excel 7.0 for Windows XP to determine the arithmetic mean (M) and standard deviation (s). When characterizing the statistical significance of the differences, Student's t-test was used, and the determination of the confidence interval limit was based on Student's distribution table. The results obtained during the study of children with CGDP were considered statistically significant at a probability level of $P<0.05$. The comparison was carried out between the groups of patients infected and not infected with *Helicobacter pylori.*

3. Results

Adolescence is characterized by the manifestation of intense physical development against a background of an increase in metabolic processes. In the pathogenesis of the development of CGDP, the main factor is malnutrition. An imbalance in food ingredients leads to a disruption in the production of certain enzymes and hormones in the body.

There was a relative increase in the GH level in patients compared to those in the control group, but levels were within normal limits (2 to 20 ng/mL). In children in group I, the average GH level was 5.04±0.739 ng/mL, and in children from group II, it was 7.13±0.887 ng/mL ($p<0.05$). These indicators varied depending on the nature of the pathology of the gastroduodenal zone (Table 1).

Table 1. GH level in children with CGDP (ng/mL)

	Group I (N=145)	Group II (N=141)
The control group	5.73±0.907	8.63±0.806
Chronic gastroduodenitis (CGD)	5.34 ± 1.041**,***	7.44±0.764**
Chronic gastritis (CG)	5.11±0.880*,**	7.14±1.085**
Chronic duodenitis (CD)	6.19±0.432***	9.63±0.788**
Peptic ulcer disease (PUD)	4.17±0.601*,**	5.60±0.833**
Average for CGDP	5.04±0.739*,**	7.13±0.887**

Reliability - *$p<0.05$ for group I compared to group II; **$p<0.01$ for groups I and II compared to the control group, ***$p<0.001$ for the groups I and II compared to the control group.

In particular, in children from the group I compared to those in the control group, GH varied from 6.7% to 27.2%,

depending on the type of pathology. In particular, a lower GH level compared to that in the control group was noted in PUD, with an average of up to 4.17±0.601 ng/mL ($p<0.05$).

It should be noted that in children with CD, the level of GH was 8.1% higher compared to the control group (6.19±0.432 ng/mL versus 5.73±0.907 ng/mL), ($p<0.005$ - $p<0.05$), which we also observe when comparing the second group with the control group.

When analyzing GH in group II compared to adolescents in the control group, the average GH level was 8.63±0.806 ng/mL and was 5.60±0.833 ng/mL ($p<0.05$) in adolescents with peptic ulcer disease, which was 35.1% lower than that in the control group. In patients with CD, the GH level was 11.7% higher than in the control group (Fig. 1).

The data obtained show the relationship between diseases caused by *Helicobacter pylori* with the physical development of children. Therefore, the data must be taken into account when assessing the physical development of children. Although hormonal fluctuations vary within the reference age range, these children need to be consulted by pediatric endocrinologists.

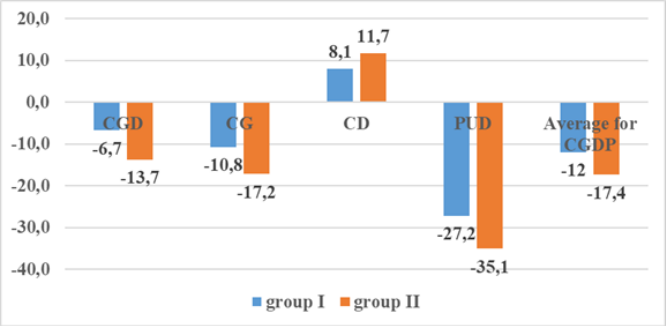

Fig. 1. The difference in blood GH levels in patients with CGDP compared to those in the control group (%)

It should be noted that in children with CD, the GH level of 8.1% was higher than that in the control group (6.19±0.432 ng/mL versus 5.73±0.907 ng/mL) ($p<0.05$), which we observed when comparing the second group with the control group.

These data show that with an isolated inflammatory process of the duodenal mucosa, there is an increase in GH synthesis, but with other types of CGDP, there is a decrease in the level of this hormone compared to that in the control group, but levels are within the generally accepted normal limits for children.

The difference between the indicators of group II and the control group was 17.4%, while the difference between those in group I and the control group was 12.0%; that is, as age increased, there was a tendency for the difference in GH synthesis to increase between CGDP patients and control individuals. These data showed a direct relationship between chronic diseases of the gastroduodenal zone in children with hormonal fluctuations, particularly with fluctuations in the growth hormone level.

4. Discussion

According to Tsay FW et al. (2018), *H. pylori* infection affects the secretion of gastrointestinal hormones, subsequently causing disturbances in gastrointestinal secretion, thereby leading to impaired growth in children (4). Perhaps there is an opinion, it has been suggested that in CGDP, in particular in the background of helicobacteriosis, the function of gastrointestinal hormones is disrupted, followed by a deviation in the physical development of children, which was shown in this study.

Considering that the main factors in the development of chronic diseases of the digestive tract are *H. pylori* infection and CagA (5, 6), the influence of infection on the hormonal status of the body should not be ruled out. In particular, there is a connection between autoimmune thyroid disorders (AITDs) and H. pylori and CagA + *H. pylori* infection.

According to Figura N et al. (2019), *H. pylori* infection can influence the development of AITD, and CagA was also the main determinant responsible for the increase in the level of thyroid autoantibodies and inflammatory cytokines (7). This opinion is supported by other scientists who have expressed opinions about the relationship of *H. pylori* with endocrine diseases in patients and their influence on the clinical degree of pathology (8, 9).

At the same time, gastrointestinal hormones play a huge role in the humoral regulation of digestive functions (10). These substances are produced by the endocrine cells of the gastric mucosa, duodenum, and pancreas. Gastrointestinal hormones are involved in the regulation of secretion, motility, absorption, trophism, the release of other regulatory peptides, and the disruption of their production affects metabolism. A representative gastrointestinal hormone is somatostatin (GHIF - growth hormone inhibiting factor, SRIF - somatotropin-release inhibiting factor).

It should be noted that the concentration of somatostatin in the islets of Langerhans of the pancreas is higher than its level in the tissues of the hypothalamic zone of the brain (11). There are also high levels of somatostatin in the antral mucous membrane of the stomach and much less somatostatin in the intestinal mucosa. In general, 3/4 of all immunoreactive somatostatin is produced by D-cells located in the digestive organs, and the rest is produced in the brain (12, 13).

At the same time, the relationship between somatostatin and somatotropin (growth hormone, GH) is indisputable. Growth hormone increases the synthesis of cartilage tissue in the epiphyseal parts of the bones, stimulates the body's growth in length, and increases the thickness and width of bones in childhood (14). An increase in the mass of tissue structures occurs in muscle and connective tissue, and the mass of internal organs also increases. Additionally, somatotropin has powerful anabolic and anti-catabolic effects; that is, it

accelerates protein synthesis and inhibits protein breakdown, providing nitrogen and phosphorus homeostasis and lowering urea levels, as well as helping to reduce the deposition of subcutaneous fat, increasing fat burning and increasing the muscle mass to fat ratio (11).

There is also research proving a relationship between growth hormone deficiency (GHD) and enzymatic deficiencies in the intestine (15). Many conflicting research results have been identified when studying the effect of inflammatory diseases of the gastrointestinal tract on the physical growth of children. In particular, many studies have proven a link between *H. pylori* infection and growth retardation in childhood (2, 15).

According to Galal YS et al. (2019), (16), and Chiu NC et al. (2017), (17), children infected with *H. pylori* exhibit growth retardation, with a simultaneous decrease in the level of serum hemoglobin, iron, and ferritin in infected children. At the same time, some authors point to the effect of *H. pylori* infection on the development of complications affecting the physical development of children (18, 19).

We determined that in CGDP, there was a decrease in GH synthesis compared to that in the control group, but GH synthesis remained within the normal range. In patients from the first group, the average GH level was 5.04±0.739 ng/mL; in patients from the second group, the average was 7.13±0.887 ng/mL ($p<0.005$).

It should be noted that depending on the nature of the pathology of the gastroduodenal zone, these indicators varied. In particular, in patients from the first group, the differences between the levels of GH in the blood depending on the type of pathology were insignificant. In children of this age in the control group, the average GH level was 5.73±0.907 ng/mL, whereas in children with CGDP, the average level of this indicator varied from 4.17 to 6.19 ng/mL.

In adolescent patients, this difference was more pronounced. In particular, the average GH level in children from the control group was 8.63±0.806 ng/mL, whereas in patients with CGDP, a relatively low GH level was observed in PUD (5.60±0.833 ng/mL), and a relatively high level was observed in children with CD (9.63±0.788 ng/mL). It should be noted that adolescence differs from all other stages of human development and life in regard to the intense physical growth and increased metabolic processes that occur. Consequently, any pathological condition of the gastrointestinal tract in this period negatively affects the endocrine system of the whole organism.

Our studies have shown that the difference in the GH level between children from the control group and the first group was 12.04%, and the difference between the GH level of children from the second group and the control group was 17.38%. Thus, the most significant difference between GH levels was noted during the period of enhanced physical and sexual development. These data showed that there is a connection between chronic diseases of the gastroduodenal zone associated with infection with Helicobacter pylori in children and age-related hormonal fluctuations, in particular, the level of growth hormone.

In children and adolescents with CGDP caused by *Helicobacter pylori*, there is a decrease in growth hormone in the blood serum compared to healthy children, but levels remain within the age reference parameters. In particular, in patients with CGDP, there is an average decrease in GH compared to that in the control group of 17.3% ($p<0.005$). At the same time, the GH level changes depending on the clinical form of CGDP; in particular, the largest decreases in GH levels compared to those in the control group are observed in patients with peptic ulcer disease (up to 35.1%) and in patients with chronic duodenitis, there is an increase in the synthesis of somatotropic hormone (up to 9.2%). At the same time, the minimum change is observed in children up to adolescence and the maximum - in adolescents, coinciding with the enhanced physical and sexual development of children.

Ethical Statement

To conduct clinical and laboratory studies of children on an outpatient basis, a certificate from the Ethics Committee under the Ministry of Health of the Republic of Uzbekistan was issued (protocol no. 3 of 20.04.2017). This study is registered on the ClinicalTrials.gov PRS site (ID: NCT04702542).

Conflict of interest

The authors declare that they have no competing and financial interests.

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Authors' contributions

Concept: T.S.T., Design: T.S.T., Data Collection or Processing: T.S.T., F.A.N., Analysis or Interpretation: T.S.T., F.A.N., Literature Search: T.S.T., F.A.N., Writing: T.S.T., F.A.N.

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