



Extragasteral Manifestations of Helicobacter Pylori Associated Gastroduodenal Pathology in Children

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ABSTRACT

Recently, there has been evidence of extragastric manifestations of *Helicobacter pylori* infection, in particular, participation in the development of allergic pathology, which can be attributed to the high prevalence of Helicobacteriosis in children with food allergies. The systemic nature of lesions of the gastrointestinal tract (GIT) in allergy causes a frequent combination of symptoms of damage to the upper and lower parts of the digestive tract and, therefore, makes it appropriate to study the digestive function of the intestine and its microbiocenosis.

Keywords:

extragastric manifestations, *Helicobacter pylori*

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The systemic nature of lesions of the gastrointestinal tract (GIT) in allergy causes a frequent combination of symptoms of damage to the upper and lower parts of the digestive tract and, therefore, makes it appropriate to study the digestive function of the intestine and its microbiocenosis.

Purpose of the study. In accordance with the objectives of the study, in order to determine the possible "extra-gastric" effects of *Helicobacter pylori*, we assessed the allergic status in the examined children.

Materials and research methods. Determination of IgG antibodies to *Helicobacter pylori* in blood serum. Study of ferrokinetic parameters: determination of serum gland (GS), serum ferritin concentration.

Determination of general and specific IgE to food antigens. Instrumental research: EGDFS, ultrasound examination of internal organs (liver, gallbladder, pancreas).

Research results. Analysis of anamnestic data showed that a history of pregnancy pathology occurred in 46.2%, more often also in children with a combined course of helicobacteriosis and food allergy, the most common complications were preeclampsia and toxicosis of pregnancy. Every fourth child had a history of an unfavorable course of childbirth: asphyxia, premature birth, or delivery by caesarean section.

Complications during childbirth were especially common in children of this group. Delivery by caesarean section was observed in 15 children from this group (17.6%), while in the second group they occurred in 13.6%. The formation of the microbial landscape is also adversely affected by preterm birth, which in the first group of children occurred 2.1 times more often than in the comparison group

(9.4%). In this case, apparently, the reasons for the development of food allergies could be transient enzyme deficiency, characteristic of prematurely born children, and antibiotic therapy, which is often noted in the anamnesis of premature infants. As expected, in the comparison groups there were features of hereditary burden. Heredity for allergic diseases or diseases of the gastrointestinal tract was burdened in 55 children (72.5%) in group I in 29 (65.9%), in group II in 15 children

(50.0%), however, the total burden (one or several diseases) was significantly higher in children with Helicobacter pylori compared with the second group, 31.8% of them had a burden of allergic pathology, which is 3 times more often than in group I (Table 1.). We noted the same trend in relation to food and drug intolerance, which occurred in the anamnesis of three quarters of children from the first group (74.3%), in a third of the children of the second group (31.7%).

Table 1.
Features of hereditary burden in the examined patients in the comparison groups

Hereditary burden	I Group (n=76)		II Group (n=30)		Significance of difference
	abs	%	abs	%	
Allergic diseases	27	35,3	2	6,6	p<0,05
Anemia	44	57,8	1	3,3	P<0,01
Other pathology of the gastrointestinal tract	24	31,8	4	5,2	P<0,05

According to our data, in the general blood test in children of the first group, there is a significant increase in the number of eosinophils, as well as a decrease in the level of hemoglobin. Individual analysis showed that in the group of children from the first group, eosinophilia occurred in every third child. In this regard, we conducted a study on parasitosis (giardiasis and helminthic invasions coprologically and by determining the level of ELISA in the blood serum). It was revealed that parasitosis aggravated the course of children of the first group, in more than a third of cases - 31 children (36.5%), which is 2.2 times higher than in the first group, where there were 7 such children (15.9%). In the structure of

parasitosis, according to our data, giardiasis and enterobiasis predominated, which accounted for up to 90% of all detected cases of invasions. According to ultrasound, most of the examined children have ultrasound signs of damage to the biliary tract and pancreas, which were regarded as reactive and more often occurred in children with a aggravated allergic background.

Especially in the first group of children with food allergies, according to our data, more often than in group I, it is accompanied by intestinal dysfunctions in the form of constipation or a tendency to diarrhea, which indicates a systemic nature of the gastrointestinal tract lesion in such patients.

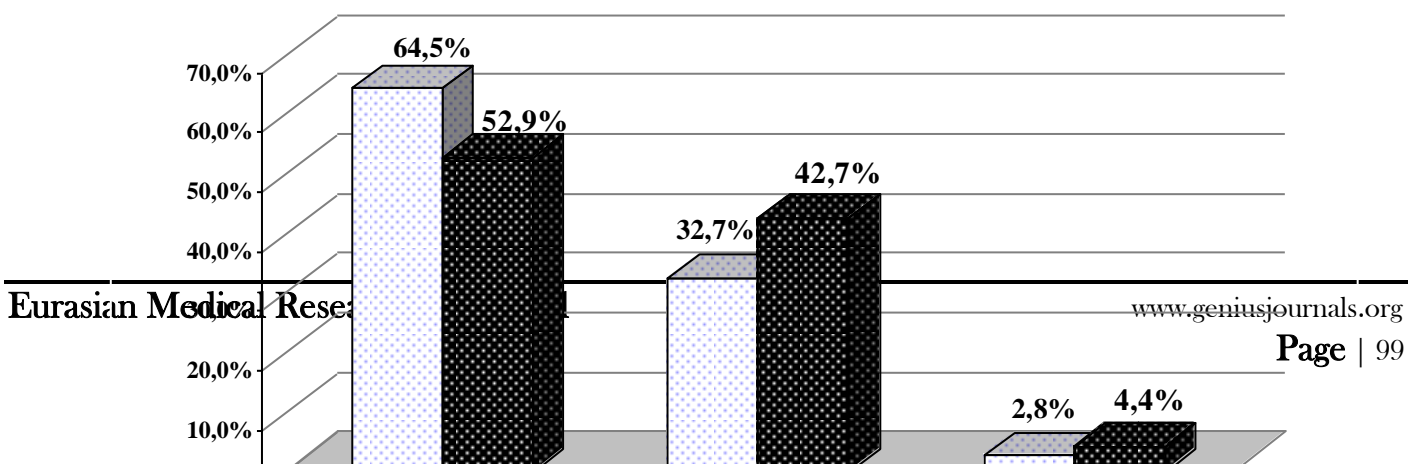




Fig .1. The frequency of lesions of the gastric mucosa in the comparison groups

A comparative analysis made it possible to establish that if a common process occurs in both subgroups almost equally often, then diffuse lesions significantly more often develop with *Helicobacter pylori*-associated, and limitedly localized with *Helicobacter pylori*-negative gastroduodenitis. (Table 2).

Table 2. Symptoms of atopic dermatitis in children with food allergy depending on the *Helicobacter pylori* association

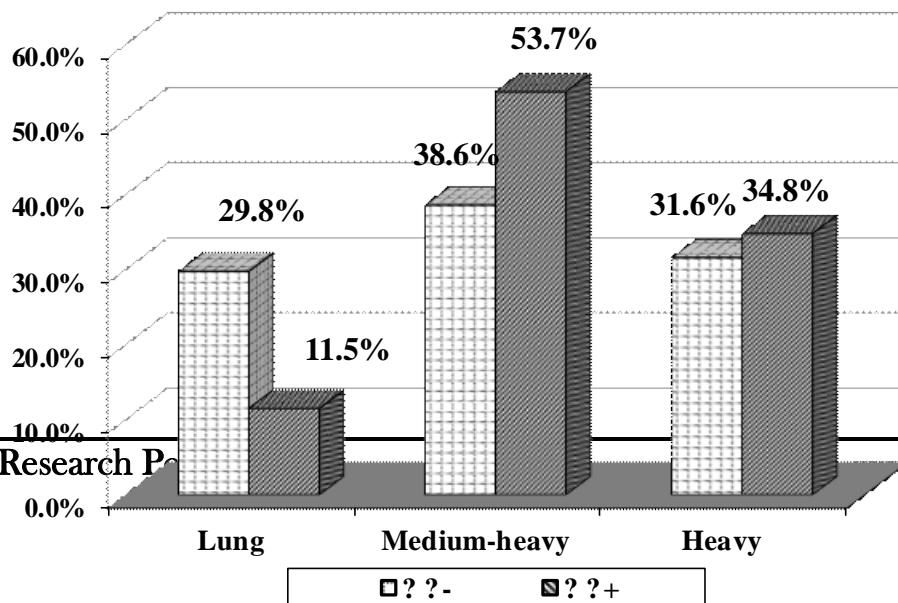
The prevalence of the process	Helicobacter pylori - infected (n = 34)		Helicobacter pylori - negative (n = 30)		Significance of difference
	Abs.	%	Abs.	%	
Limited localized	21	61,7	3	11,0	p<0,05
Common	11	32,3	4	13,3	p>0,05
Diffuse	2	2,9	-	-	p<0,05

The identified features can be explained from the standpoint of the theory of food allergy heterogeneity: it is possible that in patients infected with *Helicobacter pylori*, in some cases atopic dermatitis occurs, which is characterized by IgE-dependent reactions.

In a comprehensive assessment of the severity of food allergies, we found that a mild course was 2.7 times more common among children not infected with *Helicobacter pylori*, and moderate and severe in children with *Helicobacter pylori*-associated gastroduodenal pathology. Moreover, the severity of the flow in *Helicobacter pylori*-infected was determined not by the area.

In addition, the clinical and laboratory features that we have identified require some changes in the tactics of treating children with a combined course of helicobacteriosis with food allergies. The role of the allergic factor in the development of inflammation in gastroduodenal pathology requires the inclusion of adsorbents in the complex therapy to eliminate allergens.

Fig.2 Severity of food allergy in children infected and uninfected with *Helicobacter pylori*



In 32 (56.1%) examined children with chronic gastroduodenitis associated with *Helicobacter pylori*, early clinical manifestations were observed; clinical manifestations of food allergy in the form of a skin form were observed in 23 (71.8%) children and 9 (28.2%) in the gastrointestinal form. In most children, allergies were caused by food antigens.

At the same time, children with chronic gastroduodenitis (CGD) and food allergies were characterized by a longer duration of pain during treatment, compared with patients without food allergies. At the same time, it was noted that the prevalence of *Helicobacter pylori* in children with a combined course with food allergies is two times higher than in children without allergic pathology.

Given the high purity of functional disorders of the biliary tract, we believe it is right to investigate the contractile function of the gallbladder in all children with food allergies. In addition, the clinical and laboratory features that we have identified require some changes in the tactics of treating children with a combined course of helicobacteriosis with food allergies. The role of the allergic factor in the development of mucosal inflammation in CGD requires the inclusion of adsorbents in the complex therapy to eliminate allergens. The study of the acid-peptic factor showed that an increase in its activity contributes to the development of allergic reactions due to a direct effect on the mucous membrane of the gastrointestinal tract.

An increase in the level of IgE was determined in 64% of *Helicobacter pylori*-positive and in 1.9% of *Helicobacter pylori*-negative patients. The level of total IgE exceeded the norm in 44% of cases and averaged 142 IU/ml.

In the main group of patients, the frequency of detection of IgG antibodies to

Helicobacter pylori is higher (69.2%) than in patients without concomitant allergopathology.

At the same time, the frequency of occurrence of increased synthesis of total IgE in the group of patients with allergies and diseases of the stomach and duodenum associated with *Helicobacter pylori* infection is higher than in patients without allergic pathology. Especially in the first group of children with food allergies, according to our data, more often than in group I, it is accompanied by intestinal dysfunctions in the form of constipation or a tendency to diarrhea, which indicates a systemic nature of the gastrointestinal tract lesion in such patients. In this group of patients with a combination of *Helicobacter pylori* infection and food allergy, deeper changes in the gastric and duodenal mucosa may be associated with the formation of an allergic IgE-mediated immune response to both infection antigens and other (food) proteins. Apparently, the inflammatory process on the mucous membrane of the stomach and duodenum, induced by *Helicobacter pylori*, contributes to the course of allergic processes due to an even greater increase in the permeability of the mucous membrane.

The inflammatory process can be associated both with the direct action of *Helicobacter pylori* on the mucous membrane of the stomach and, to a lesser extent, the duodenum, and may occur indirectly, as a result of an increase in the activity of the acid-peptic factor. *Helicobacter pylori* disrupts the protective function of the gastric mucosa, so that many substances are absorbed that normally did not enter the blood directly from the stomach. The prolonged presence of *Helicobacter pylori* in the stomach triggers a complex mechanism of immune-inflammatory reactions that contribute to the occurrence of allergic diseases. *Helicobacter pylori* interacts with mast cells, initiating the release of

mediators. *Helicobacter pylori*, acting as full-fledged antigens, cause allergic reactions in the human body. *Helicobacter pylori* reduces the barrier function of the intestine, causing the entry of allergens into the blood. In particular, with prolonged persistence of *Helicobacter pylori*, a continuously relapsing course of food allergy was noted, in the absence of bacteria, the severity of the course of allergy is minimal, which corresponds to the literature data. Since *Helicobacter pylori* strains expressing CagA have a higher pro-inflammatory potential, it is reasonable to conclude that a pronounced inflammatory lesion of the gastric mucosa can increase transepithelial permeability and promote non-selective passage of allergens, which in atopics can directly stimulate an IgE-mediated response. At the same time, CagA-positive *Helicobacter pylori* infection contributes to food allergies. Thus, on the one hand, against the background of chronic gastroduodenitis, an exacerbation of latent allergies is possible. On the other hand, food allergies provoke the development of gastritis, duodenitis and support the existing process.

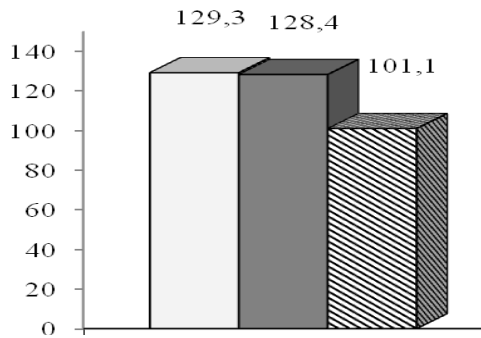
It can be assumed that food allergy in relatives may be associated not only with a hereditary predisposition to allergic conditions, but also with a family focus of *Helicobacter pylori*. Thus, an increase in blood levels of IgG antibodies to *Helicobacter pylori* in gastroduodenal pathology was revealed, indicating a decrease in the barrier function of the gastrointestinal mucosa, which provokes the development of allergies. Based on the data obtained, it can be argued that in patients with CHD, food allergy occurs quite often and its development is directly related to *Helicobacter*

pylori infection. CHD aggravates the course of food allergy, and successful treatment of the ulcer process helps to reduce the activity of the allergic process. As a result, a vicious pathogenetic circle closes. Although antiallergic therapy does not affect the healing time of the ulcer, however, it helps to improve the patient's well-being, reducing pain symptoms.

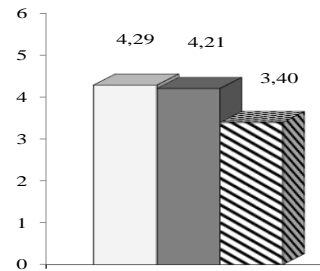
Based on this, for the treatment of patients with CHD in combination with food allergy, it is pathogenetically justified to conduct adequate therapy for the ulcerative process, including, if necessary, anti-*Helicobacter* and antisecretory therapy, in combination with antiallergic measures. To identify extragastric manifestations of *Helicobacter pylori*, an assessment of iron metabolism was also carried out, which included: The study of indicators of the general blood test: hemoglobin, MCV, MCH, MCHC on the electronic hemoanalyzer NIHON KONDEN Celltac MEK-6410K. Normative values: hemoglobin (Hb) - a decrease of less than 120 g/l was considered as anemia, as well as the number of erythrocytes, less than 4,010 l; MCV (mean erythrocyte volume) less than 80 fl is a sign of microcytosis; MCH (mean erythrocyte hemoglobin) less than 23 pg is a sign of hypochromia, MCHC (mean erythrocyte hemoglobin concentration) less than 310 g/l was regarded as anemia.

Anemia was detected in 60% of children with gastroduodenitis associated with *Helicobacter pylori*. At the same time, in patients with gastroduodenitis of a non-infectious nature, a decrease in hemoglobin levels was revealed.

Hemoglobin
g/l



Number of red
blood cells, G/l



Moreover, with the appearance of these additional complaints in patients, changes in blood tests were ascertained: lower hemoglobin levels in the range from 105 g/l to 90 g/l (average 101.1 ± 2.34 g/l with a reference norm of 129.3 ± 1.15 g/l, $p < 0.05$), color index - from 0.80 to 0.65 (average 0.74 ± 0.04 at a norm of 0.97 ± 0.07 , $p < 0.05$), erythrocyte count from $3.1 \times 10^{12}/l$ to $3.6 \times 10^{12}/l$. (average $3.4 \pm 0.15 \times 10^{12}/l$ at a rate of $4.29 \pm 0.03 \times 10^{12}/l$, $p < 0.05$), as well as iron content from 9.8

mmol/l to 7.5 mmol/l (on average 9.42 ± 1.15 mmol/l at a rate of 19.2 ± 1.86 mmol/l, $p < 0.05$). In the second group of patients, the results of a blood test, including the content of hemoglobin (average 128.4 ± 12.8 g/l), the number of erythrocytes (average 4.2 ± 0.03 T/l), color index (average 0.96 ± 0.04), the level of iron (average 18.1 ± 1.86 $\mu\text{mol}/l$) did not differ statistically significantly from the reference values.

Color indicator



Rice. 3. Results of blood tests in patients with chronic gastroenteritis depending on the persistence of Helicobacter pylori

It has been established that in schoolchildren aged 10 to 15 years infected with Helicobacter pylori, iron deficiency anemia was observed 2 times more often compared to children with children without helicobacter pylori. Iron deficiency (ferritin

below $15 \mu\text{g}/l$) was observed 5.6 times more often in Helicobacter pylori-infected (13.9%) than uninfected (2.8%) children under 10 years of age, the average hemoglobin level in the presence of HP was significantly lower ($124 \text{ g} / l$) than in its absence ($131 \text{ g} / l$), but the

relationship of iron deficiency with *Helicobacter pylori* infection is more clearly seen at the age of over 9 years. This can be explained, on the one hand, by the fact that at an early age, negative factors are possible that contribute to the development of iron deficiency anemia. On the other hand, the duration of *Helicobacter pylori* infection probably matters for the formation of iron deficiency, therefore, the longer the child is infected, and therefore the older he is, the more likely the depletion of iron stores and the development of iron deficiency anemia. A decrease in iron stores in the body during *Helicobacter pylori* infection may be the result of an increased consumption of it by *Helicobacter pylori* itself, since iron is necessary for the microorganism for its growth, and it is able to compete with the host for the creation of iron reserves. The fact that these changes are based on processes associated with iron metabolism disorders is indirectly evidenced by changes in the parameter of erythrocytes. Thus, in the group of patients infected with *Helicobacter pylori*, such indicators as the average volume of erythrocytes, the average content and the average concentration of hemoglobin in the erythrocyte are reduced compared to uninfected patients. These data are confirmed by studies of the main indicators of iron metabolism.

Findings. Thus, the proportion of persons with reduced compared to the normative level of serum iron in infected persons is about 11%, which is 3 times higher than in the compared group. Also, the level of serum iron in the group of children with *Helicobacter pylori* gastritis is $13.4 \pm 3.9 \mu\text{mol/l}$, which is on average $4.5 \mu\text{mol/l}$ lower than in uninfected individuals. Important for confirming iron metabolism disorders in the group of patients with *Helicobacter pylori* gastritis is a large proportion of children with an increase in the total iron-binding capacity of serum. Also, the presence of latent iron deficiency in this group is indicated by lower values of the coefficient of saturation of transferrin with iron compared with children suffering from non-*Helicobacter*

pylori gastritis. In general, the absence of a significantly pronounced effect of *Helicobacter pylori* infection on the indicators of the physical development of children was established. Both among infected and non-infected patients, children with average height and height above average predominated. Among patients in both groups, there was a significant proportion of patients with high stature. With regard to growth retardation, the proportion of patients with short stature was slightly higher in the group of infected patients, but short patients were somewhat more common among uninfected individuals. With regard to body weight, among those infected with *Helicobacter pylori*, patients with underweight were even slightly more often noted than in the control group.

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