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THE STOMACH AS THE TARGET ORGAN OF CELIAC DISEASE

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The aim of this study was to observe the features of chronic gastritis in children with celiac disease (CD). ***Materials and methods.*** 176 children with chronic gastritis (CG) aged from 3 to 16 years were examined. Group I consisted 58 children with CG and newly diagnosed CD not adherent to the gluten-free diet (GFD), group II consisted 49 children with CG and CD, adherent to the GFD. In the group III of comparisons were 69 children with CG and excluded CD. The examination included serological, morphological methods to confirm or exclude CD. The histological examination of the biopsy specimens of the gastric mucosa, the determination of antiparietal antibodies by the method of iIFR and ELISA (antibodies to Castle's intrinsic factor and Anti-H^+/K^+ ATPase antibodies) were carried out. ***Results.*** *Helicobacter pylori* infection was diagnosed in vast majority of patients in all groups. Autoantibodies to the gastric mucosa were found in every tenth patient in groups I and III, and did not occur in group II. In group II statistically significant the etiology of gastritis remained not determined. Endoscopically the gastric mucosa in groups I and II often remained intact. According to the morphological study in groups I and II, the pathological process was more often localized in the body of the stomach, and in group III in the antrum. Autoimmune gastritis is presented in groups without a statistically significant difference. ***Conclusion.*** Chronic gastritis is a frequent co-morbid pathology in CD, and it is also not uncommon in these patients. Data of endoscopy in children, regardless of diet, does not reflect the complete picture of CG. All children with CD, regardless of compliance with GFD, are recommended to take biopsy specimens of the gastric mucosa for histological examination in order to exclude CG, and in case of detecting atrophic changes in the gastric mucosa to define the antiparietal antibodies.

Keywords: celiac disease; autoimmune gastritis; anti-parietal cell antibodies; children.

ЖЕЛУДОК КАК ОРГАН-МИШЕНЬ ЦЕЛИАКИИ

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Целью данного исследования было изучить особенности хронического гастрита у детей с целиакией. ***Материалы и методы.*** Были обследованы 176 детей с хроническим гастритом (ХГ) в возрасте от 3 до 16 лет. Группа I — дети с ХГ и впервые выявленной целиакией, не соблюдающие безглютеновую диету (БГД), — 58 человек; группа II — дети с ХГ и целиакией, находящиеся на БГД, — 49 детей; группа III — сравнения — 69 детей с ХГ и исключенной целиакией. Обследование включало серологическое, морфологическое исследования для подтверждения или исключения целиакии. Выполнено гистологическое исследование биоптатов слизистой оболочки желудка (СОЖ), определение антипариетальных антител (АПА) методами нРИФ и ИФА: антитела к фактору Кастла и к H^+/K^+-АТФазе. ***Результаты.*** У большинства пациентов во всех группах диагностировано наличие *H. pylori*, аутоантитела к СОЖ обнаружены у каждого десятого пациента в группах I и III и не встречались в группе II.

В группе II статистически значимо чаще этиология гастрита оставалась неустановленной. Эндоскопически СОЖ в группах I и II чаще оставалась неизмененной. По данным морфологического исследования в группах I и II патологический процесс чаще был локализован в теле желудка, а в группе III – в антральном отделе. Аутоиммунный гастрит представлен в группах без статистически значимой разницы. ***Заключение.*** Хронический гастрит является частой коморбидной патологией при целиакии, АИГ также нередко встречается у таких пациентов. Данные эндоскопии у детей вне зависимости от соблюдения диеты не отражают полной картины ХГ. Всем детям с целиакией независимо от соблюдения БГД рекомендован забор биоптатов СОЖ при выполнении ФЭГДС для гистологического исследования с целью исключения ХГ, а при выявлении атрофических изменений СОЖ – определение антипариетальных антител.

Ключевые слова: целиакия; аутоиммунный гастрит; антипариетальные антитела; дети.

INTRODUCTION

Celiac disease (CD) is a systemic autoimmune disease induced by impaired gluten tolerance and develops in genetically predisposed people [4, 8]. The prevalence is approximately 1:100 among the Western population and is one of the most common autoimmune diseases [16]. Currently, CD is not considered a pathology affecting only the small intestine and is reflected in modern definitions.

The range of clinical manifestation is extensive and includes both the classic form with malabsorption and the atypical form with extraintestinal symptoms. It has been demonstrated that the atypical and "silent" forms are much more common than the typical ones [5]. In addition, many organs and systems are involved in the autoimmune process because of both the common genetic mechanisms of development of other autoimmune diseases and extraintestinal deposits of its own antibodies to tissue transglutaminase (tTG) in the lymph nodes, liver, muscles, and other organs [10, 15]. The combination of celiac disease with type 1 diabetes mellitus and autoimmune thyroiditis [4] with impaired reproductive function in women has been well-described [2].

Considerably less attention has been paid to the association of CD with other autoimmune diseases of the gastrointestinal tract. Primary biliary cirrhosis occurs in 3% of celiac disease cases [6, 9], which exceeds the population risk by 20 fold [11, 12]. The prevalence of CD among patients with autoimmune hepatitis reaches 6% [20], and hepatitis among patients with CD is observed in approximately 2% cases [19]. Primary sclerosing cholangitis (PSC) shows an association with CD in 3% of cases [17], and a four-fold increased risk of CD compared with population risk in PSC patients persists despite the exclusion of inflammatory intestinal disease [12]. Furthermore, up to 15% of patients with microscopic (lymphocytic) colitis (MC) suffer from CD [14], and the prevalence of MC among patients with celiac disease reaches 4%, which exceeds the population risk by 70 times [7, 18].

Currently, researchers have focused on chronic gastritis as comorbid pathology in CD [1, 3]; however, there is no evidence of increased prevalence of autoimmune gastritis (AIG) among patients with CD

The study aimed to analyze the aspects of chronic gastritis in pediatric patients with CD.

MATERIALS AND METHODS

We examined 176 pediatric patients with chronic gastritis (CG), aged 3–16 years. Group I consisted of 58 pediatric patients with CG and newly diagnosed CD who did not adhere to gluten-free diet (GFD), while Group II included 49 pediatric patients with CG and CD who adhered to GFD. The control group (group III) consisted of 69 pediatric patients with CG and excluded celiac disease.

All patients underwent the same examination. The diagnosis of CD was established on the Federal Clinical guidelines for the provision of medical care for pediatric patients with celiac disease[1] and the Celiac Disease Guidelines of European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPHAN) from 2012 [8], We analyzed clinical and anamnestic data that tested the presence of positive specific antibodies (IgG, IgA) against deamidated gliadine peptides and tissue transglutaminase-2. If it was necessary anti- endomysium antibodies and the level of total IgA were also determined. A morphometric study of the duodenal mucosa was performed in all patients. Detection of atrophy to a degree of no less than Marsh 3a was considered evidence in favor of CD. HLA genotyping was performed in all patients to detect *DQ2* and *DQ8* genes associated with CD.

The diagnosis of CG was verified morphologically for all studied participants. Biopsy samples of the mucous membrane of the gastric antrum and fundus were obtained by esophagogastroduodenoscopy performed using an Evis Exera 2 OLYMPUS device of the HGi

[1] A.A. Baranov, L.S. Namazova-Baranova, T.E. Borovik et al. Celiac disease in children. Clinical recommendations/Ministry of Health of the Russian Federation. – 2016. – p. 43.

180 type (Japan) using the standard procedure. Endoscopic and histological evaluation of the gastric mucosa was performed according to the Sydney system. The test for H.pylori was performed for all patients using the rapid urease test (AMA LLC, St. Petersburg, Russia).

In order to diagnose autoimmune gastritis, in 45 pediatric patients anti-parietal PCA IgG antibodies were determined by indirect immunofluorescence (iIF) using the EUROIMMUN IIFT EUROPLUS™ Stomach (Monkey) reagent kit manufactured by EUROIMMUN Medizinische Labordiagnostika AG (Germany). The normal value was <40u/ml. The study was performed on a specialized microscope for immunofluorescence studies EUROStar II of EUROIMMUN AG (Germany). Antibodies (IgG) to H^+/K^+-ATPase of the parietal cells of the gastric mucosa (GM) were detected in 58 pediatric patients in the blood plasma by enzyme-linked immunosorbent assay (ELISA) using standard kits ORGENTEC Anti-Parietal Cell (H^+/K^+-ATPase), ORGenTec Diagnostika (Germany) (negative result was 0–10 U/ml, and a positive result was more than 10 U/ml). Antibodies (IgG) to Castle intrinsic factor were determined in blood plasma by ELISA on a standard photometer using kits manufactured by EUROIMMUN Medizinische Labordiagnostika AG (Germany) from 140 pediatric patients. According to the instructions, the negative result was 0–20 RU/ml, and the positive one was greater than 20 RU/ml.

Statistical analysis was performed using IBM SPSS Statistics 23 software. The average antibody level was calculated with a 95% confidence interval, indication of the upper and lower limits, median, and mean squared deviation. For comparison of means, the Student's *t*-test was used for independent samples (two-sided significance, $p < 0.05$). The Livin's dispersion test and the normal distribution test of Kolmogorov–Smirnov and Shapiro–Wilk were taken into account. To analyze endoscopic and morphological studies in groups, the Fisher's exact test was used (significance $p < 0.05$).

RESULTS

The etiology of CG in the studied groups is presented in Table 1.

The primary etiological factor of CG in pediatric patients in all groups was *Helicobacter pylori* infection. Duodenogastric reflux was rarely observed as an independent cause of CG. An increased level of autoantibodies to GM was equally common in the group of pediatric patients with newly diagnosed CD and CG but did not occur in any patient in the CD on GFD. For patients adhering to GFD, the etiology of gastritis was more often was undetermined.

Table 1 (Таблица 1)

Etiology of chronic gastritis in the studied groups
Этиология хронического гастрита в исследуемых группах

Groups/ Группы	*n* (%)			
	I group / I группа ($n = 58$)	II group / II группа ($n = 49$)	III group / III группа ($n = 69$)	*p* Fisher's exact test / Точный критерий Фишера
	p_1	p_2	p_3	
Helicobacter infection / Хеликобактерная инфекция	37 63.8%	26 53.1%	47 68.1%	$p_{1,2} = 0.00$ $p_{1,3} = 0.00$ $p_{2,3} = 0.35$
Autoantibodies to the stomach mucous membrane / Аутоантитела к слизистой оболочке желудка	7 12.1%	0 0%	7 10.1%	$p_{1,2} = 0.01$ $p_{1,3} = 0.8$ $p_{2,3} = 0.01$
HP^+ Autoantibodies to the stomach mucous membrane / HP^+-аутоантитела к слизистой оболочке желудка	2 3.4%	0 0%	2 2.9%	$p_{1,2} = 0.14$ $p_{1,3} = 0.91$ $p_{2,3} = 0.18$
HP-reflux / Рефлюкс HP^-	3 5.17%	3 6.1%	4 5.8%	$p_{1,2} = 0.94$ $p_{1,3} = 0.91$ $p_{2,3} = 0.96$
Not determined / Этиология хронического гастрита не установлена	9 15.6%	20 40.8%	9 13.1%	$p_{1,2} = 0.03$ $p_{1,3} = 0.78$ $p_{2,3} = 0.01$

Table 2 (Таблица 2)

Endoscopic characteristics of the gastric mucosa in the studied groups
Эндоскопическая характеристика слизистой оболочки желудка в исследуемых группах

Groups/ Группы	*n* (%)			
	I group / I группа (n = 58)	II group / II группа (n = 49)	III group / III группа (n = 69)	p Fisher's exact test / Точный критерий Фишера
	p_1	p_2	p_3	
Normal / Норма	23 39.7%	26 53.1%	0 0%	$p_{1,2} = 0.00$ $p_{1,3} = 0.00$ $p_{2,3} = 0.35$
Superficial fundal gastritis / Поверхностный фундальный гастрит	2 3.4%	2 4.1%	4 5.8%	$p_{1,2} = 1.000$ $p_{1,3} = 0.687$ $p_{2,3} = 1.000$
Superficial antral gastritis / Поверхностный антральный гастрит	23 39.7%	6 12.2%	37 53.6%	$p_{1,2} = 0.002$ $p_{1,3} = 0.153$ $p_{2,3} = 0.000$
Nodular antral gastritis / Нодулярный антральный гастрит	3 5.2%	4 8.2%	6 8.7%	$p_{1,2} = 0.700$ $p_{1,3} = 0.507$ $p_{2,3} = 1.000$
Superficial pangastritis / Поверхностный пангастрит	6 10.3%	9 18.4%	18 26.1%	$p_{1,2} = 0.272$ $p_{1,3} = 0.039$ $p_{2,3} = 0.379$
Atrophic gastritis / Атрофический гастрит	0 0.0%	0 0.0%	2 2.9%	$p_{1,3} = 0.500$ $p_{2,3} = 0.510$
Erosive gastritis / Эрозивный гастрит	1 1.7%	1 2.0%	1 1.4%	$p_{1,2} = 1.000$ $p_{1,3} = 1.000$ $p_{2,3} = 1.000$
Polyp of the stomach / Полип желудка	0 0.0%	1 2.0%	1 1.4%	$p_{1,2} = 0.458$ $p_{1,3} = 1.000$ $p_{2,3} = 1.000$

The main endoscopic characteristic among patients with CB (groups I and II) was intact GM in contrast to the comparison group. In group 3, superficial antral gastritis was most often observed. These data are presented in Table 2.

Motor disorders, such as insufficiency of cardia, gastroesophageal reflux, and duodenogastric reflux, were not different between the groups. These data are presented in Table 3.

According to the morphological study, the pathological process in the mucous membrane of the gastric body was more often registered in groups I and II with celiac disease, and an antral lesion was more characteristic of isolated CG. Chronic active pangastritis was common in all groups. Chronic inactive gastritis was more often detected in group I than in group III. These data are presented in Table 4.

The average level of anti-parietal autoantibodies for the ELISA method in all groups was the same. These data are presented in Table 5.

The frequency of detection of increased levels of anti-parietal autoantibodies were significantly different between the groups. The data are presented in Table 6.

Antibodies to parietal gastric cells were more often revealed in patients with newly established celiac disease, while GFD patients had no anti-parietal autoantibodies.

Among all the examined patients, 14 were found positive for the presence of anti-parietal autoantibodies (APA). Among these patients, "classical" autoimmune gastritis (GM atrophy, the presence of APA, the absence of H.pylori) was found in only 5 patients. The frequency of "classical" autoimmune gastritis in the examined groups is presented in Figure 1.

There was no significant difference in AIG between groups: $p_{1,2} = 0.14$; $p_{1,3} = 0.85$; $p_{2,3} = 0.1$.

The main endoscopic characteristic of pediatric patients with celiac disease was an intact GM, while CG was morphologically detected in all children. There were many of these pediatric patients in the GFD

Table 3 (Таблица 3)

Endoscopic characteristic of gastric motor function in the studied groups
Эндоскопическая характеристика моторной функции желудка в исследуемых группах

Groups/ Группы	*n* (%)			
	I group / I группа (*n* = 58)	II group / II группа (*n* = 49)	III group / III группа (*n* = 69)	*p* Fisher's exact test / Точный критерий Фишера
	p_1	p_2	p_3	
Insufficiency of cardia / Недостаточность кардии	1 1.7%	4 8.2%	7 10.1%	$p_{1,2} = 0.177$ $p_{1,3} = 0.070$ $p_{2,3} = 1.000$
Gastroesophageal reflux / Гастроэзофагеальный рефлюкс	4 6.9%	5 10.2%	8 11.6%	$p_{1,2} = 0.729$ $p_{1,3} = 0.544$ $p_{2,3} = 1.000$
Duodenogastric reflux / Дуоденогастральный рефлюкс	6 10.3%	2 4.1%	12 17.4%	$p_{1,2} = 0.285$ $p_{1,3} = 0.313$ $p_{2,3} = 0.041$
Normal motor function / Нормальная моторика	48 82.8%	42 85.7%	50 72.5%	$p_{1,2} = 0.793$ $p_{1,3} = 0.205$ $p_{2,3} = 0.115$

Table 4 (Таблица 4)

Morphological characteristics of the gastric mucosa in the studied groups
Морфологическая характеристика слизистой оболочки желудка в исследуемых группах

Groups/ Группы	*n* (%)			
	I group / I группа (*n* = 58)	II group / II группа (*n* = 49)	III group / III группа (*n* = 69)	*p* Fisher's exact test / Точный критерий Фишера
	p_1	p_2	p_3	
Chronic inactive pangastritis / Хронический неактивный пангастрит	36 62.1%	28 57.1%	25 36.2%	$p_{1,2} = 0.68$ $p_{1,3} = 0.04$ $p_{2,3} = 0.1$
Chronic active pangastritis / Хронический активный пангастрит	12 21.1%	7 14.3%	19 27.5%	$p_{1,2} = 0.48$ $p_{1,3} = 0.55$ $p_{2,3} = 0.19$
Chronic active gastritis in the body of stomach / Хронический активный гастрит тела желудка	1 1.7%	0 0%	0 0%	$p_{1,2} = 0.3$ $p_{1,3} = 0.3$
Chronic inactive gastritis in the body of stomach / Хронический неактивный гастрит тела желудка	0 0%	4 8.7%	0 0%	$p_{1,2} = 0.02$ $p_{2,3} = 0.02$
Chronic inactive antral gastritis / Хронический неактивный антральный гастрит	4 6.9%	3 6.1%	1 1.4%	$p_{1,2} = 0.9$ $p_{1,3} = 0.24$ $p_{2,3} = 0.3$
Chronic active antral gastritis / Хронический активный антральный гастрит	4 6.9%	3 6.1%	20 29%	$p_{1,2} = 0.9$ $p_{1,3} = 0.02$ $p_{2,3} = 0.01$
Chronic active antral gastritis and chronic inactive gastritis in the body of stomach / Хронический активный антральный гастрит и хронический неактивный гастрит тела желудка	0 0%	0 0%	4 5.8%	$p_{1,3} = 0.06$ $p_{2,3} = 0.06$
Chronic active gastritis in the body of stomach and chronic inactive antral gastritis / Хронический активный гастрит тела желудка и хронический неактивный антральный гастрит	1 1.7%	4 8.2%	0 0%	$p_{1,2} = 0.21$ $p_{1,3} = 0.3$ $p_{2,3} = 0.002$

Table 5 (Таблица 5)

The average level of antiparietal autoantibodies in the studied groups
Средний уровень антипариетальных аутоантител в исследуемых группах

Groups / Группы	I group / I группа	II group / II группа	III group / III группа	*p* Student's *t*-test / *t*-критерий Стьюдента
Antibodies to Castle's intrinsic *factor* / **Антитела к фактору Кастла**				
Average value / Среднее значение	**4.0353**	**3.1215**	**8.0258**	$p_{1,2} = 0.347$ $p_{1,3} = 0.464$ $p_{2,3} = 0.368$
Lower bound / Нижняя граница	2.5298	1.8327	–1.3677	
Upper bound / Верхняя граница	5.5409	4.4102	17.4193	
Median / Медиана	2.4485	2.3700	2.3880	
Standard deviation / Среднеквадратичное отклонение	3.72735	3.19066	27.34546	
Anti-H^+/K^+-ATPase *antibodies* / **Антитела к H^+/K^+-АТФазе**				
Average value / Среднее значение	**16.2538**	**1.4625**	**4.7470**	$p_{1,2} = 0.352$ $p_{1,3} = 0.213$ $p_{2,3} = 0.655$
Lower bound / Нижняя граница	–2.6066	0.4039	1.1093	
Upper bound / Верхняя граница	35.1141	3.3289	8.3846	
Median / Медиана	1.9300	1.0150	1.4600	
Standard deviation / Среднеквадратичное отклонение	35.39445	1.17296	10.25888	

Table 6 (Таблица 6)

The frequency of elevated levels of antiparietal antibodies in the studied groups
Частота выявления повышенного уровня антипариетальных аутоантител в исследуемых группах

Groups / Группы	*n* (%)			
	I group / I группа	II group / II группа	III group / III группа	*p* Fisher's exact test / Точный критерий Фишера
	p_1	p_2	p_3	
Antibodies to Castle's intrinsic factor, IgG / Антитела к фактору Кастла, IgG	$n = 42$	$n = 30$	$n = 68$	$p_{1,2} = 0.08$ $p_{1,3} = 0.95$ $p_{2,3} = 0.1$
	2 4.76%	0 0%	3 4.4%	
Anti-H^+/K^+-ATPase antibodies, IgG / Антитела к H^+/K^+-АТФазе, IgG	$n = 18$	$n = 7$	$n = 33$	$p_{1,2} = 0.00$ $p_{1,3} = 0.28$ $p_{2,3} = 0.01$
	4 22.2%	0 0%	4 12.1%	
PCA IgG	$n = 10$	$n = 7$	$n = 28$	$p_{1,2} = 0.01$ $p_{1,3} = 0.01$
	1 10%	0 0%	0 0%	

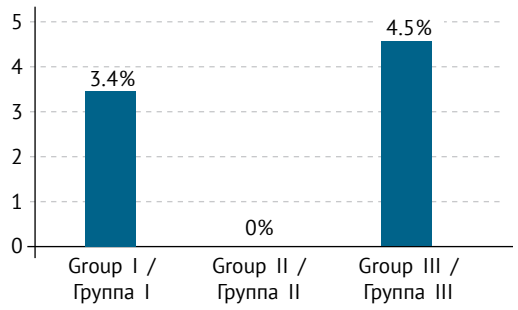

Fig. 1. Frequency of "classical" autoimmune gastritis in the examined groups
Рис. 1. Частота «классического» аутоиммунного гастрита в обследованных группах

group. Also, according to esophagogastroduodenoscopy, cases of fundic gastritis were sporadic, while morphological inflammatory changes in the fundus were observed more often in the structure of pangastritis and in isolation. Autoimmune gastritis was diagnosed in the presence of APA and GM atrophy and was mostly not combined with *Helicobacter pylori* infection. Therefore, it presented in the classical form and was not differently distributed between groups. We also observed APA patients in the absence of the GM atrophy and *H. pylori*, which requires further examination to rule out the preatrophic stage of AIG.

Among pediatric patients with CD who adhered to GFD, APA was not observed. At present, GFD appears to have a protective effect on comorbid autoimmune diseases [9]. However, in pediatric patients with GFD, active inflammation in the gastric body was observed, and thus requires additional research.

CONCLUSION

The endoscopy data in pediatric patients with CD, regardless of adherence to GFD, does not reflect the full clinical picture of CG. Biopsy specimens of the GM are recommended when performing endoscopy for histological examination of all pediatric patients with CD, regardless of adherence to GFD in order to detect CG. Also biopsy can determine anti-parietal antibodies for verification of autoimmune gastritis when detecting atrophic and inflammatory changes in the GM. The lack of APA among pediatric patients with CD who adhere to GFD may be because of the protective effect of the diet in autoimmune gastritis. Therefore, in a large proportion of pediatric patients with CD on GFD, the etiology of gastritis remains unclear.

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