European Review for Medical and Pharmacological Sciences 2015; 19: 2031-2035

Prevalence of *Helicobacter pylori* infection in pediatric celiac disease

J. JOZEFCZUK[1], B. BANCERZ[2], M. WALKOWIAK[2], A. GLAPA[2], J. NOWAK[2], J. PIESCIKOWSKA[3], J. KWIECIEN[4], J. WALKOWIAK[2]

[1]Pediatric Department with Children's Cardiologic Subunit, Specialist Hospital of Holy Spirit in Sandomierz, Sandomierz, Poland
[2]Department of Pediatric Gastroenterology and Metabolic Diseases, Poznan University of Medical Sciences, Poznan, Poland
[3]Laboratory of Nursing Practice, Department of Nursing, Faculty of Health Sciences, Poznan University of Medical Sciences, Poznan, Poland
[4]Department of Pediatrics, The School of Medicine and Division of Dentistry in Zabrze, Medical University of Silesia in Katowice, Zabrze, Poland

Abstract. – OBJECTIVE: A lower risk of celiac disease (CD) in patients with *Helicobacter pylori* (Hp) infection has been reported when Hp infection prevalence in CD patients was compared against CD-negative symptomatic persons with indications for diagnostic gastroduodenoscopy. Therefore, we aimed to determine Hp infection frequency in a group of pediatric CD patients at diagnosis and to compare obtained results to data coming from age-matched healthy population.

PATIENTS AND METHODS: The study population consisted of 74 CD subjects aged 3 to 12 years in whom the presence of Hp was diagnosed routinely in the course of differential diagnosis with the use of stable isotope breath test which is the gold standard. The control group consisted of 296 healthy age-matched subjects.

RESULTS: Hp infection was diagnosed in 4 CD patients and 20 healthy subjects. Its prevalence in CD patients and HS did not differ neither in the entire age group undergoing comparison (5.4% vs. 6.8%, $p = 0.5713$) nor in the selected age subgroups (3-6 years: 2.5% vs. 3.7%, $p = 0.8551$; 7-12 years: 8.8% vs. 11.0%, $p = 0.8742$).

CONCLUSIONS: The prevalence of Hp infection in CD patients does not seem to be different than that in general population. However, further studies are needed to assess the potential role of Hp in the pathogenesis of CD.

Key Words:
Celiac disease, *Helicobacter pylori*, Urea breath test.

Introduction

Helicobacter pylori (H. pylori) is a Gram-negative bacterium classified by Agency for Research for Cancer[1,2] as a first class carcinogen since 1994. Without any doubt, it is the causative factor in one of the most common bacterial infections. Its prevalence has been decreasing in last years and varies between different populations[3-6]. *H. pylori* is predominantly found in the human stomach and causes gastritis, peptic ulcer disease, gastric cancer and B-cell gastric lymphoma[7].

Lebwohl et al[12] have recently raised the hypothesis of decreased risk of celiac disease (CD) in patients with *H. pylori* infection. In a group of 136,179 patients who underwent esophagogastroduodenoscopy with gastric and duodenal biopsies, 2,689 subjects were diagnosed with CD. *H. pylori* presence was documented to be less frequent in patients with CD than in the remaining subjects (4.4% vs 8.8%, $p < 0.0001$). The authors suggested "hygiene hypothesis" as an explanation for this phenomenon with *H. pylori* infection protecting against CD autoimmunity. However, the comparative group of subjects comprised patients who underwent esophagogastroduodenoscopy due to various reasons and might not necessarily be representative for *H. pylori* prevalence in the general population.

Therefore, in the present study we aimed to determine the frequency of *H. pylori* infection in a group of pediatric CD patients at diagnosis and to compare obtained results to data coming from age-matched healthy population.

Patients and Methods

This was a retrospective study assessing the prevalence of *H. pylori* infection in CD subjects. The inclusion criteria comprised: newly diagnosed CD[8], age 3 to 12 years. Exclusion criteria were intravenous/oral antibiotics or PPIs for four

Corresponding Author: Jaroslaw Walkowiak, Ph.D; e-mail: jarwalk@ump.edu.pl

weeks prior to the investigation. The study population included 84 CD subjects (36 males and 48 females) in whom the presence of *H. pylori* was diagnosed routinely in the course of differential diagnosis with a use of stable isotope breath test. The basic clinical characteristics of CD patients has been given in Table I.

The control group consisted of 296 healthy age matched subjects, who did not receive intravenous or oral antibiotics or PPIs for four weeks prior to the investigation. The investigation was part of the project PL0361 "Good diagnosis - treatment – life" by the First Specialist Clinical Hospital in Zabrze evaluating the incidences of gastrointestinal diseases in randomly selected children[9].

The presence of *H. pylori* was assessed in all subjects using the ^{13}C isotope-labeled urea breath test (UBT). The test was performed as described earlier[10]. The comparison of age distribution in CD population and healthy subjects (HS) is depicted in Table II.

Statistical Analysis

The difference in the distribution of the *H. pylori* status between groups was analyzed by the χ^2-test. p value < 0.05 was considered statistically significant. All statistical analyses were performed using Statistica 9.0 software (StatSoft Inc., Tulsa, OK, USA).

The protocol of the investigation was approved by the Bioethical Committee at Poznan University of Medical Sciences, Poland.

Results

H. pylori infection was diagnosed in 4 out of 74 CD patients (5.4%) aged 3 to 12 years (Table III). Its prevalence in CD patients and HS (6.8%) did not differ (p = 0.8742). Comparisons in selected subgroups (3-6 and 7-12 years) did not reveal any significant differences either (2.5% vs. 3.7% and 8.8% vs. 11.0%, respectively).

Table I. Clinical and demographic data of CD patients.

Clinical parameters	Mean ± SD
Age [years]	6.5 ± 3.0
Sex	
Males/females	33/41
Z-score for body height	-1.5 ± 0.6
Z-score for body weight	-1.3 ± 0.5

Table II. Number of children in the age groups.

Aged [years]	CD patients (N)	Healthy subjects (N)
3-6	40	160
7-12	34	136

Discussion

This is a first study comparing the prevalence of *H. pylori* in CD patients and healthy peers with a use of urea stable isotope breath test that is the gold standard[11]. We failed to confirm the lower prevalence of *H. pylori* infection in CD patients as suggested by Lebwohl et al[12]. However, the control group was based on healthy subjects, not patients referred for a gastroduodenoscopy with subsequent histopathological assessment of biopsied specimens.

Having in mind the major criticism of our study – small number of CD patients, we would like to underline that in all studies[13-16] referring the prevalence of *H. pylori* infection to that of control populations no statistical differences were noted (Table IV). Extracting data from all five studies very similar prevalence was stated (19.3% vs. 18.4%) – non-significantly lower in healthy controls.

Lebwohl et al[12] suggested that *H. pylori* colonization may potentially protect against autoimmu-

Table III. Prevalence of *H. pylori* infection in CD patients and in healthy subjects,

Aged [years]	*H. pylori* positive		Statistical significance
	CD patients n (%)	Healthy subjects n (%)	
3-6	1 (2.5%)	4 (3.7%)	0.5713
7-12	3 (8.8%)	16 (11.0%)	0.8551
All together	4 (5.4%)	20 (6.8%)	0.8742

Table IV. Prevalence of *H. pylori* infection in CD patients and in general population.

Study	Population	Methods	*H. pylori* positive n/N (%)		p
			CD patients	Controls	
Crabtree et al, 1992[13]* (15-72 years)	Adults	Serology	29/99 (29.3)	75/250 (30.0)	0.8964
Luzza et al, 1999[14] (1-18 years)	Children	Serology	15/81 (18.5)	14/81 (17.3)	0.8376
Konturek et al, 2000[15]**	Adults	Serology	24/91 (26.4)	8/40 (20.0)	0.4342
Aydogdu et al, 2008[16] (8.2 ± 5.2 years)	Children	Histopathology	21/96 (21.8)	56/235 (23.8)	0.7025
Present study (3-12 years)	Children	Urea breath test	4/70 (5.4)	20/276 (6.8)	0.8742
All together	Children and adults	As above	83/348 (19.3)	173/769 (18.4)	0.6936

*Celiac disease and dermatitis herpetiformis; **No information on age was given.

nization and development of CD. In the extremely large cohort of patients (Table V) undergoing upper gastrointestinal endoscopy they proved that prevalence of *H. pylori* infection in CD patients is significantly lower (4.4%) than in those patients without villous atrophy (8.8%). However, the study could be biased because the so-called control group consists of subjects who – or at least majority of them – were symptomatic patients and may not necessarily represent the overall population. Only in one out of four other smaller studies comparing patients biopsied during endoscopy, higher prevalence of *H. pylori* infection in CD subjects than in patients without villous atrophy was stated (Table V)[12,17-20]. Furthermore, if the hypothesis of the impact of *H. pylori* infection on autoimmunization is to be verified, then investigation of *H. pylori* status at diagnosis is preferred since this variable may change in time.

Nevertheless, fascinating work of Lebwohl et al[12] supports their "hygiene hypothesis" postulate. Chronic *H. pylori* infection could alter the T-cell response and may result in the decrease of CD incidence. Mooney et al[21] in the correspondence suggested another option with the "second hit hypothesis" as an explanation. They referred to the example of *Campylobacter* infection that could be the environmental triggering factor required to initiate the autoimmune process in CD[21-23]. In their response Lebwohl et al[12] postulated that "second hit hypothesis" and "hygiene hypothesis" are not necessarily exclusive. The presence of *H. pylori* could prevent the "second hit" and, therefore, may protect against the development of CD.

Table V. Prevalence of *H. pylori* infection in CD patients and in subjects undergoing diagnostic gastroscopy (histopathology).

Study	Population	*H. pylori* positive n/N (%)		p
		CD patients	Controls	
Diamanti et al, 1999[17]* (13-77 years)	Adults and adolescents – non-treated adults – treated	66/80 (82.5) 21/22 (95.4)	67/75 (89.3)	0.2231 0.6510
Ciacci et al, 2000[18] (17-63 years)	Adults – non-treated adults – treated	17/82 (20.7) 34/105 (32.4)	42/76 (55.3)	< 0.00001 0.0021
Rostami-Nejad et al[19], 2009 (15-83 years)	Adults and adolescents	23/28 (82.1)	388/422 (91.9)**	0.0743
Rostami-Nejad et al[20], 2011 (16-75 years)	Adults and adolescents	20/24 (83.3)	212/226 (93.8)	0.1411
Lebwohl et al, 2013[12] (from birth up to elderly)	All age subgroups	117/2,689 (4.4)	11,207/127,619 (8.8)	< 0.00001

*Based upon histology and serology.

In a large prospective observational study comprising consecutively diagnosed CD patients, Cuoco et al[24] documented a significant association between iron deficiency anemia and *H. pylori* infection. Characterizing histologically gastric mucosa they documented greater prevalence of chronic superficial gastritis, higher grade of inflammatory activity, higher number of lymphoid follicles and slightly higher percentage of atrophic gastritis among infected patients than in those without *H. pylori* infection. The authors suggested that the existence of *H. pylori* infection might worsen inflammatory status observed in CD. In a retrospective study comprising patients infected with *H. pylori*, Santarelli et al[25] documented a significantly higher prevalence of follicular gastritis and a lower frequency of atrophic gastritis in CD patients at diagnosis than in control subjects without CD. The complex interaction potentially occurring between untreated CD and *H. pylori* infection that might influence immune Th1/Th2 mucosal balance in the stomach was suggested as a possible explanation.

Conclusions

The prevalence of *H. pylori* infection in CD patients does not seem to be higher than that in the general population. However, further studies are needed to assess the potential role of *H. pylori* in the pathogenesis of CD.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Moeller H, Correa P. Carcinogenicity of some biological agents. Cancer Epidemiol Biomarkers Prev 1994; 3: 627.
2) Ford AC, Forman D, Hunt RH, Yuan Y, Moayyedi P. *Helicobacter pylori* eradication therapy to prevent gastric cancer in healthy asymptomatic infected individuals: systematic review and meta-analysis of randomised controlled trials. Br Med J 2014; 348: g3174.
3) Mourad-Baars P, Hussey S, Jones NL. *Helicobacter pylori* infection and childhood. Helicobacter 2010; 15 Suppl 1: 53-59.
4) Ford AC, Axon ATR. Epidemiology of *Helicobacter pylori* infection and public health implications. Helicobacter 2010; 15 Suppl 1: 1-6.
5) Sýkora J, Siala K, Varvarovská J, Pazdiora P, Pomahacová R, Huml M. Epidemiology of *Helicobacter pylori* infection in asymptomatic children: a prospective population-based study from the Czech Republic. Application of a monoclonal-based antigen-in-stool enzyme immunoassay. Helicobacter 2009; 14: 286-297.
6) Breckan RK, Paulssen EJ, Asfeldt AM, Mortensen L, Straume B, Florholmen J. The impact of body mass index and Helicobacter pylori infection on gastro-oesophageal reflux symptoms: a population-based study in Northern Norway. Scand J Gastroenterol 2009; 44: 1060-1066.
7) Laszewicz W, Iwanczak F, Iwanczak B, Task Force of the Polish Society of Gastroenterology, Task Force of the Polish Society of Gastroenterology. Seroprevalence of *Helicobacter pylori* infection in Polish children and adults depending on socioeconomic status and living conditions. Adv Med Sci 2014; 59: 147-150.
8) Husby S, Koletzko S, Korponay-Szabó IR, Mearin ML, Phillips A, Shamir R, Troncone R, Giersiepen K, Branski D, Catassi C, Lelgeman M, Mäki M, Ribes-Koninckx C, Ventura A, Zimmer KP; ESPGHAN Working Group on Coeliac Disease Diagnosis; ESPGHAN Gastroenterology Committee. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J Pediatr Gastroenterol Nutr 2012; 54: 136-160.
9) Dzymała-Czyz S, Stawinska-Witoszynska B, Madry E, Krzywinska-Wiewiórowska M, Szczepanik M, Walkowiak J. Non-invasive detection of *Helicobacter pylori* in cystic fibrosis--the fecal test vs. the urea breath test. Eur Rev Med Pharmacol Sci 2014; 18: 2343-2348.
10) Dzymała-Czyz S, Kwiecien J, Pogorzelski A, Rachel M, Banasiewicz T, Pławski A, Szczawinska-Popłonyk A, Herzig KH, Walkowiak J. Prevalence of *Helicobacter pylori* infection in patients with cystic fibrosis. J Cyst Fibros 2013; 12: 761-765.
11) Di Renzo TA, D'Angelo G, Ojetti V, Campanale MC, Tortora A, Cesario V, Zuccala G, Franceschi F. 13C-Urea breath test for the diagnosis of *Helicobacter pylori* infection. Eur Rev Med Pharacol Sci 2013; 17 Suppl 2: 51-58.
12) Lebwohl B, Blaser MJ, Ludvigsson JF, Green PHR, Rundle A, Sonnenberg A, Genta RM. Decreased risk of celiac disease in patients with *Helicobacter pylori* colonization. Am J Epidemiol 2013; 178: 1721-1730.
13) Crabtree JE, O'Mahony S, Wyatt JI, Heatley RV, Vestey JP, Howdle PD, Rathbone JM, Losowsky SM. *Helicobacter pylori* serology in patients with coeliac disease and dermatitis herpetiformis. J Clin Pathol 1992; 45: 597-600.
14) Luzza F, Mancuso M, Imeneo M, Mesuraca L, Contaldo A, Giancotti L, La Vecchia AM, Docimo C, Pensabene L, Striscuglio P, Pallone F, Guandalini S. *Helicobacter pylori* infection in children with celiac disease: prevalence and clinicopathologic features. J Pediatr Gastroenterol Nutr 1999; 28:143-146.

15) Konturek PC, Karczewska E, Dieterich W, Hahn EG, Schuppan D. Increased prevalence of *Helicobacter pylori* infection in patients with celiac disease. Am J Gastroenterol 2000; 95: 3682-3683.

16) Aydogdu S, Cakir M, Yuksekkaya HA, Tumgor G, Baran M, Arikan C, Yagci RV. *Helicobacter pylori* infection in children with celiac disease. Scand J Gastroenterol 2008; 43: 1088-1093.

17) Diamanti A, Maino C, Niveloni S, Pedreira S, Vazquez H, Smecuol E, Fiorini A, Cabanne A, Bartellini MA, Kogan Z, Valero J, Maurino E, Bai JC. Characterization of gastric mucosal lesions in patients with celiac disease: a prospective controlled study. Am J Gastroenterol 1999; 94: 1313-1319.

18) Ciacci C, Squillante A, Rendina D, Limauro S, Bencivenga C, Labanca F, Romano R, Mazzacca G. *Helicobacter pylori* infection and peptic disease in coeliac disease. Eur J Gastroenterol Hepatol 2000; 12: 1283-1287.

19) Rostami-Nejad M, Villanacci V, Mashayakhi R, Molaei M, Bassotti G, Zojaji H, Mirstatari D, Rostami K, Zali MR. Celiac disease and Hp infection association in Iran. Rev Esp Enfermedades Dig 2009; 101: 850-854.

20) Rostami Nejad M, Rostami K, Yamaoka Y, Mashayekhi R, Molaei M, Dabiri H, Al Dulaimi D, Mirsattari D, Zojaji H, Norouzinia M, Zali MR. Clinical and histological presentation of *Helicobacter pylori* and gluten related gastroenteropathy. Arch Iran Med 2011; 14: 115-118.

21) Verdu EF, Mauro M, Bourgeois J, Armstrong D. Clinical onset of celiac disease after an episode of Campylobacter jejuni enteritis. Can Gastroenterol 2007; 21: 453-455.

22) Sabayan B, Foroughinia F, Imanieh M-H. Can Campylobacter jejuni play a role in development of celiac disease? A hypothesis. World J Gastroenterol 2007; 13: 4784-4785.

23) Riddle MS, Murray JA, Cash BD, Pimentel M, Porter CK. Pathogen-specific risk of celiac disease following bacterial causes of foodborne illness: a retrospective cohort study. Dig Dis Sci 2013; 58: 3242-3245.

24) Cuoco L, Cammarota G, Jorizzo RA, Santarelli L, Cianci R, Montalto M, Gasbarrini A, Gasbarrini G. Link between *Helicobacter pylori* infection and Iron-deficiency Anaemia in Patients with Coeliac Disease. Scand J Gastroenterol 2001; 36: 1284-1288.

25) Santarelli L, Gabrielli M, Sntoliquido A, Cuoco L, Cazzato A, Candelli M, Nista EC, De Lorenzo A, Silveri NG, Pola P, Gasbarrini A, Gasbarrini G. Interaction between *Helicobacter pylori* infection and untreated coeliac disease on gastric histological pattern. Scand J Gastroenterol 2006; 41: 532-535.