Helicobacter pylori *prevalence and risk factors among children with celiac disease*

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ABSTRACT

Background/Aims: *The relationship between* Helicobacter pylori *and celiac disease (CD) remains controversial. The aim of this study was to assess the prevalence and risk factors for* H. pylori *infection among children diagnosed with CD.*

Materials and Methods: *This study included 70 patients diagnosed with CD at a tertiary referral center in Romania. Age, gender, and indicators of environmental conditions were evaluated via interviews with the children's caretakers. A multivariable logistic regression analysis was performed to identify the independent predictors for* H. pylori *infection.*

Results: *Of the 70 patients, 37 (52.9%) were females, and the mean age was 4.04±3.26 years.* H. pylori *infection was diagnosed in 23 (32.8%) patients, of whom 12 (52.1%) were females, and the mean age was 6.2±4.5 years. Of the total number of children with CD and* H. pylori *infection, 18 (78.2%) had milder forms of enteropathy (Marsh I-II), whereas the remaining 5 (21.7%) had villous atrophy compared to the other 47 (67.2%) patients who were negative for* H. pylori*-infection and showed more severe intestinal damage. The development of* H. pylori *infection was independently related to children with one parent only [odd ratio (OR), 9.04; 95% confidence interval (CI), 1.29-62.89; p<0.001], living in houses without sanitary facilities (OR, 3.88; 95% CI, 1.27-14.22; p=0.016), belonging to low-income families (OR, 8.52; 95% CI, 2.52-71.39; p=0.002), and of parents with a prior history of gastritis (OR, 2.68; 95% CI, 1.49-14.50; p=0.004).*

Conclusion: *Children with CD and* H. pylori *infection had milder forms of enteropathy compared to children who are negative for* H. pylori*, suggesting that H. pylori infection may confer some protection against the development of severe degrees of villous atrophy.*

Keywords: Helicobacter pylori*, celiac disease, children, prevalence*

INTRODUCTION

Celiac disease (CD) is a chronic, multiorgan autoimmune condition affecting the small intestine in genetically predisposed children and adults, precipitated by the ingestion of gluten-containing foods (1). The etiology of CD is not yet completely understood, and its increasing prevalence has led to a change of optics concerning a number of environmental risk factors, such as exposure to bacterial antigens, including *Helicobacter pylori*, that may trigger an autoimmune process in the small bowel (2). Although *H. pylori* is one of the most common chronic bacterial infections worldwide and the causative agent of several gastric conditions [chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue (MALT) lymphoma, and gastric cancer], the majority of infected individuals remain asymptomatic (3).

Data are scarce on the epidemiology of CD in Romania, with a reported prevalence ranging from 3.9% to 6% for adult patients (4,5) and from 4.09% to 9.2% for children with type I diabetes mellitus (6,7). In a multicenter study including 2436 adult patients who underwent esogastroduodenoscopy in Romania, the overall prevalence of CD was estimated to be 2.22% (8). Regarding the prevalence of *H. pylori* infection in Romania, the studies are also scarce and heterogeneous with respect to reporting significant differences among geographic regions and the methods of diagnosis (culture, histology, rapid urease test, real-time polymerase chain reaction, serology, stool antigen test, and urea breath test). One study has reported a prevalence of 53.3% for *H. pylori* infection in adult patients with gastroesophageal reflux disease (9). Another study investigating the prevalence of *H. pylori* infection using the urease test reported an increased prevalence with age, ranging from 50% in patients younger than 20 years to 81.4% among adult patients (51-60 years) (10).

In children, the studies are also few, with an estimated prevalence of 10.5% among those younger than 7 years of age, 39.1% among school children, and 46.3% among

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adolescents (11). A high prevalence rate of 20% was also reported for *H. pylori* infection among the adopted Romanian children who underwent serological screening (12). In the northeastern part of Romania, Burlea et al. (13) found an overall prevalence of 48.25% for *H. pylori* infection among 2130 children with dyspeptic symptoms that was more common in older children (13-16 years, 57.76%).

Several studies have shown that the prevalence of *H. pylori* infection is decreasing in both adults and children, whereas the prevalence of CD has an increasing trend (14). This paradigm, which is common in infectious conditions, may also apply to CD wherein luminal factors may trigger a clinically overt disease in genetically susceptible hosts (15,16). *H. pylori* is typically acquired during the first few years of life, whereas CD can develop at any time, nevertheless, much later than infancy (17).

Data are limited on the relationship between *H. pylori* infection and CD, which remains controversial (18). Specifically, *H. pylori* bacterium induces microscopic duodenal inflammation and can consequently be related to more severe damage when associated with CD although other publications have suggested an inverse relationship between these two conditions, suggesting the possibility that *H. pylori* infection may have a protective role against the risk of CD development (19,20).

We aimed to determine the prevalence and risk factors for *H. pylori* infection among children with the diagnosis of CD from the northeastern part of Romania.

MATERIALS AND METHODS

This is a retrospective analysis of children admitted and diagnosed with CD from January 10, 2014, to December 10, 2016, at the Gastroenterology Department, a tertiary center in the northeastern part of Romania. Children between 3 and 14 years of age diagnosed with CD were eligible for the study. The patients' medical charts were carefully reviewed, and demographic information including age, gender, clinical and laboratory parameters, prior hospitalizations, and environmental and socioeconomic statuses were assessed.

The positive diagnosis of CD was based on the presence of characteristic duodenal enteropathy, which can range from intraepithelial lymphocytosis (LIEs) to total villous flattening; positive serology for specific antibodies, mainly those directed against type 2 tissue transglutaminase (tTG); and CD-associated symptoms.

The total immunoglobulin A (IgA) level was tested in all subjects. In case of IgA deficiency, the corresponding antibodies were measured in the IgG class. Serum IgA-tTG and IgA-antigliadine (AGA) antibodies were determined using a commercially available enzyme-linked immunosorbent assay kit according to the manufacturers' instructions and cutoff values. Serum tTG values ≥8.0 U and serum AGA values ≥12.0 U were considered positive (Celikey, Phadia GmbH, Freiburg, Germany).

During upper endoscopy, minimum three biopsy specimens were obtained from the bulb and distal duodenum. The degree of mucosal damage was further graded according to the standard Marsh-Oberhuber classification: Marsh 0 represents normal mucosa; Marsh I stands for increased LIEs (>25/100 enterocytes); Marsh II for hyperplastic crypts; and Marsh III grades are partial (a), subtotal (b), or total (c) villous atrophy (21,22). A single experienced pathologist who was blinded to all of patients' clinical data examined the biopsies. In case of patchy mucosal lesions, the final Marsh score for each patient was graded according to the most affected site. Two biopsy specimens were obtained from the gastric antral mucosa. Biopsies were fixed in formalin overnight, embedded in paraffin, and stained with hematoxylin-eosin and Giemsa for routine evaluation. *H. pylori* infection was considered positive when bacterium was present in at least one of the stained sections of the biopsy. Upper endoscopy and biopsy sampling were performed with parents' or legal guardians' prior informed consent.

The participants were classified into two groups according to the presence/absence of *H. pylori*: patients with CD and *H. pylori* infection (study group) were compared with those without *H. pylori* infection (control group).

This retrospective study was performed in accordance with the principles outlined in the Declaration of Helsinki. Given the retrospective nature of the study, no institutional approval was required.

Statistical analysis

Continuous variables were presented as mean±standard deviation and categorical variables as frequency and percentage. The Student's *t* test was used to compare normally distributed continuous variables, and the Mann-Whitney U test was used for variables without normal distribution. The chi-square test and Fisher approximation method were used to compare categorical variables. Univariate analysis was performed for each recorded variable. Variables with $p < 0.1$ in the univariate analysis were included in

the multivariate analysis. For adjusted effect, we used the logistic regression. The level of statistical significance was defined as p<0.05. Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 19.0 for Windows (IBM Corp.; Armonk, NY, USA).

RESULTS

Of the 70 children who were enrolled, 37 (52.9%) were females, and the mean age was 4.04±3.26 years (range, 3-14 years). Among them, 23 (32.8%) patients were diagnosed with *H. pylori* infection, with 12 (52.1%) females and a mean age of 6.2±4.5 years (range, 4-14 years). Demographics, clinical and laboratory characteristics of patients with and without *H. pylori* infection are shown in Table 1. The study also investigated the epidemiology of *H. pylori* infection among Romanian children from different environments within the same geographical area. Therefore, 61.5% lived in the adjoining urban area and 38.5% came from rural villages. However, *H. pylori* prevalence was higher among children residing in the rural areas, 14 (60.8%), p=0.015. Most of those with *H. pylori* infection were older than 5 years (65.2%), from single-parent families (60.8%, p<0.001), belonged to low-income families (p<0.001), and of parents with a prior history of gastritis or ulceropeptic disease (p<0.001). There was no significant difference concerning gender distribution, clinical features, most laboratory parameters, and family history of CD between patients with CD and *H. pylori* infection and those with CD without *H. pylori* infection. Children with precarious hygiene and poor sanitation conditions in the selected household were more likely to present with *H. pylori* infection (p=0.004).

Table 1. Characteristics of all patients with and without *H. pylori* infection

Variables	Patients (n=70)	*H. pylori* positive (n=23)	*H. pylori* negative (n=47)	p
Gender, female, n, %	37 (52.9)	12 (32.4)	25 (67.5)	0.930
Age>5 years, n, %	23 (32.9)	15 (65.2)	8 (17)	<0.001
Rural, n, %	27 (38.5)	14 (60.8)	13 (27.6)	0.015
Family history of CD, n, %	7 (10)	4 (17.4)	3 (6.4)	0.30
Low family income, n, %	24 (34.2)	19 (82.6)	5 (10.6)	<0.001
Attending school, kindergarten, nursery, n,%	24 (34.2)	14 (60.8)	10 (21.2)	0.003
Houses without toilets or sanitary facilities, n, %	28 (40)	15 (65.2)	13 (27.6)	0.004
Parents with a prior history of gastritis or peptic ulcer disease, n, %	26 (37.1)	17 (73.9)	9 (19.1)	<0.001
Single parent family, n, %	18 (25.7)	14 (60.8)	4 (8.5)	<0.001
Biochemical and serological parameters (mean±SD)				
Hemoglobin (g/dL)	11.67±1.35	12.23±1.76	11.62±1.12	0.207
Iron (µg/dL)	57.69±38.02	32.1±21.3	36.9±19.1	0.361
AST (IU/L)	60.55±16.4	73.73±35.44	44.79±5.19	0.198
ALT(IU/L)	36.18±86.96	95.6±21.2	44.2±2.8	0.273
IgA-tTG (U/mL)	58.48±19.4	73.5±2.5	59.6±7.8	0.790
IgA-AGA (U/mL)	42.66±28.61	51.8±3.3	38.5±2.5	0.048
Histology				
Marsh I-II, n, %	32 (45.7)	18 (78.2)	14 (29.7)	<0.001
Marsh IIIa-c, n, %	38 (54.2)	5 (21.7)	33 (70.2)	<0.001
Reason for referral				
Heartburn, n, %	35 (50)	15 (65.2)	20 (42.5)	0.12
Vomiting, n, %	37 (52.9)	18 (78.2)	19 (40.4)	0.064
Abdominal pain, n, %	35 (50)	18 (78.2)	17 (36.1)	0.087
Chronic diarrhea, n, %	34 (48.6)	13 (56.5)	21 (44.7)	0.44

Data given in absolute numbers, frequencies, or mean±SD. SD: standard deviation; CD: celiac disease; AST: aspartate aminotransferase; ALT: alanine aminotransferase; IgA-tTG: immunoglobulin A-type 2 tissue transglutaminase antibodies; IgA-AGA: immunoglobulin A-antigliadine antibodies

Table 2. Univariate and multivariate regression analysis of risk factors associated with *H. pylori* infection in children with CD

Parameter	Univariate analysis			Multivariate analysis		
	OR	95% CI	P value	OR	95% CI	p
Gender, female	0.96	0.35-2.60	0.93	0.24	0.012-1.45	0.733
Age>5 years	9.14	2.90-28.77	<0.001	1.91	0.13-27.00	0.630
Low family income	39.9	9.62-165.4	<0.001	8.52	2.52-71.39	0.002
Attending school, kindergarten, nursery	5.75	1.93-17.12	0.003	1.79	0.13-24.62	0.664
Houses without toilets or sanitary facilities	4.90	1.68-14.29	0.004	3.88	1.27-14.22	0.016
Parents with prior history of gastritis or peptic ulcer disease	11.96	3.67-38.96	<0.001	2.68	1.49-14.50	0.004
Single parent family	16.72	4.45-62.80	<0.001	9.04	1.29-62.89	<0.001
Rural household	4.06	1.41-11.66	0.015	-	-	-
Family history of CD	3.08	0.62-15.15	0.30	-	-	-
Marsh I-II	8.48	2.62-27.38	<0.001	-	-	-
Marsh IIIa-c	0.112	0.036-0.38	<0.001	-	-	-

*Data presented as OR: odds ratio; CI: confidence interval; CD: celiac disease

There were significant differences in the distribution of Marsh severity scores between the two study groups, with a greater proportion of the patients who were negative for *H. pylori* infections graded with villous atrophy. Of the children with CD and *H. pylori,* 18 (78.2%) had milder forms of enteropathy (Marsh I-II), and the remaining 5 (21.7%) had villous atrophy compared to 47 (67.2%) patients who were negative for *H. pylori* infections and showed more severe intestinal damage, including 19 (40.4%) with subtotal villous atrophy and 14 (29.7%) with complete villous atrophy (p<0.001). Our results suggest a slight trend toward milder duodenal lesions in patients with *H. pylori* infection compared to the non-infected patients. Variables with a p<0.1 in the univariate analysis were included in the multivariate logistic regression; the results are presented in Table 2.

Single-parent families [odds ratio (OR), 9.04; 95% confidence interval (CI), 1.29-62.89; p<0.001], houses without toilets or sanitary facilities (OR, 3.88; 95% CI, 1.27-14.22; p=0.016), low-income families (OR, 8.52; 95% CI, 2.52-71.39; p=0.002), and parents' with a prior history of gastritis or peptic ulcer disease (OR, 2.68; 95% CI, 1.49-14.50; p=0.004) were the indicators independently associated with the development of *H. pylori* infection in children with CD.

DISCUSSION

The relationship between CD and *H. pylori* remains controversial; however, some studies have reported that *H. pylori* infection appears to confer protection against CD (23). Lebowhl et al. (19) performed a cross-sectional study among patients undergoing upper endoscopy and found an inverse relationship between these two entities after adjusting for age and socioeconomic factors. Patients with CD had lower rates of *H. pylori* infection than those with normal duodenal mucosa, suggesting a guarding role for *H. pylori* against the development of CD, which was also implied by other studies (19,20).

Villanacci et al. (24) assessed the hypothesis that H. pylori could modulate gluten immunogenicity among genetically susceptible patients in a study including 80 adult patients with CD evaluated before and after the gluten-free diet. The authors concluded that patients with CD and *H. pylori* infection had milder duodenal lesions compared to those without *H. pylori* infection, and the diet was equally effective in infected as well as non-infected patients with CD (24). These histological evidences were not supported by other publications. Guz-Mark et al. (25) demonstrated that the presence of *H. pylori* infection does not influence the severity of the duodenal lesions. Similar results were reported by another study that found an identical degree of mucosal damage among patients with CD and *H. pylori* compared to non-infected individuals (26).

However, numerous epidemiological studies available in literature failed to find significant differences in *H. pylori* prevalence among patients with CD and control groups. Diamanti et al. (27) found lower prevalence rates of *H. pylori* infection compared to controls in 1999 although results were reported later in 2009 (28). Rostami-Nejad et al. (28) argue that the simultaneous presence of *H. pylori* gastritis does not influence the clinical features or the se-

verity of mucosal damage in CD. In contrast, Aydogdu et al. (29) found no differences in the prevalence of *H. pylori* infection in patients with and without CD. An interesting result was reported by Konturek et al. (30) who suggested an increased *H. pylori* seroprevalence among patients with CD with a lower prevalence of Cag-positive strains in infected subjects with CD than in infected controls, implying a potential relationship between *H. pylori* virulence and CD (31).

The frequency rate and risk factors for contamination by *H. pylori* infection were investigated in a number of studies. Yücel et al. (32) observed that poorly educated mothers, lower family income, inadequate living conditions, and higher numbers of siblings correlated with higher *H. pylori* infections in children. Children living in poor conditions, cared for by mothers lacking education were at higher risk for *H. pylori* infection. Additionally, other studies have reported that exposure to an infected subject with gastroenteritis living in the same household, residence in day-care centers, child-to-child transmission in kindergartens, and living conditions that are often crowded and lack indoor plumbing are additional factors influencing the prevalence of *H. pylori* infection (30-33).

This study investigated the prevalence and risk factors for *H. pylori* infection among children with an established diagnosis of CD. We found that *H. pylori* colonization among children with CD is not influenced by gender or household residence. No significant differences were found concerning clinical features, laboratory parameters, or a family history of CD between patients with CD and *H. pylori* infection and those with CD without *H. pylori* infection. Similar to other studies, we found minor insignificant differences related to the serum levels of IgA-tTG in patients who were positive for *H. pylori* compared to those who were negative (2). However, some children who were positive for *H. pylori* expressed mild elevation of IgA-AGA levels, compared to those who are negative for *H. pylori*. Regarding histological changes, we found that a greater proportion of patients with CD and *H. pylori* infection presented milder forms of enteropathy compared to those who were negative for *H. pylori* and showed more severe intestinal damage, including complete villous atrophy; these results were also reported by Villanacci et al. (24) and Aydogdu et al. (29). A particular finding of our study was the correlation between *H. pylori* prevalence and the severity of histological duodenal features in patients with CD. Our results suggest a slight trend toward milder duodenal lesions among patients with *H. pylori* infection.

We may conclude that the prevalence rates for CD and *H. pylori* infection differ mainly with respect to the socioeconomic status. The source of *H. pylori* is intra-familial rather than community-acquired in nursery or kindergarten attended at a young age. Contact with infected family members and crowded living conditions were associated with an increased risk of infection. Factors, such as monoparental families, houses without toilets or sanitary conditions, families with low incomes, and parents' prior history of gastritis or peptic ulcer, remained independently associated with the development of *H. pylori* infection in children with CD.

Despite its limitations, our study has a number of strengths. It is the first study conducted in the northeastern part of Romania at a tertiary referral center to evaluate the prevalence and risk factors for *H. pylori* infection in children with CD. However, as a retrospective, single center study, it is prone to bias. The main limitation of this investigation is the small size of the sample and the retrospective study design. Therefore, the temporality of exposure and outcome for study participants could not be assessed.

In conclusion, we found that the prevalence of *H. pylori* infection as well as the risk factors among children with established diagnosis of CD seems to be in range with data reported in children without CD in the northeastern region of Romania. Children with CD and *H. pylori* infection had milder forms of enteropathy compared to those who were negative for *H. pylori*, suggesting that *H. pylori* infection may have a protective role against the development of severe forms of villous atrophy. Additional studies are needed to assess the association between *H. pylori* infection and CD in children and the potential protective or damaging role of *H. pylori*-strains that could explain, at least to some extent, the conflicting results available to date.

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Informed Consent: Written informed consent was obtained from the patients' parents or legal guardians who participated in this study.

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