JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2012, 63, 2, 133-136
www.jpp.krakow.pl

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THE CLINICAL ASPECTS OF *HELICOBACTER HEILMANNII* INFECTION IN CHILDREN WITH DYSPEPTIC SYMPTOMS

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Helicobacter heilmannii (*H. heilmannii*) infection is a relatively rare causative agent of gastroduodenal diseases in children. However, *H. heilmannii* frequently colonizes gastric mucosa of animals, mainly cats and dogs, from where it can be transmitted to humans. The aim of the study was to evaluate the incidence of *H. heilmannii* infection in children with dyspeptic symptoms treated in our clinic. A number of 13,124 esophagogastroduodenoscopies in children aged 4 to 18 years were conducted from 1992 to 2010. The indications for examination were: chronic abdominal pain, nausea, vomiting, heartburn, anaemia, disturbances of intestinal absorption and other. In 11,023 cases microbiologic studies and cultures toward *Helicobacter* infection were carried out and in 22 children *H. heilmannii* infection was confirmed. *H. heilmannii* infection was diagnosed based on morphologic examination in direct microscopy of biopsy specimens from gastric mucosa. In children with *H. heilmannii* infection clinical symptoms, contact with animals, endoscopic findings of the upper gastrointestinal tract and results of diagnostic tests for *Helicobacter pylori* infection were assessed. In our studies *H. heilmannii* infection was diagnosed in 22 children. The rate of *H. heilmannii* infection was 0.2% in examination of gastric mucosa specimens. No sex-dependent difference in the rates was observed. Most of the children lived in cities and 54.5% had contact with dogs and/or cats. Children complained of chronic epigastric pain, nausea, vomiting and heartburn. Endoscopic studies most often revealed nodular gastritis and gastric or duodenal ulcer in two children. In three children result of the endoscopic study was normal. Conclusions: *H. heilmannii* infection in children is rare. However, it may be one of the causes of gastroduodenal diseases in children.

Key words: *gastroduodenal diseases, Helicobacter heilmannii, children, proton pump inhibitor, Helicobacter pylori, inflammation*

INTRODUCTION

Discovery of *Helicobacter pylori* (*H. pylori*) in 1983 instigated the development of studies on the role of this bacterium in the pathogenesis of diseases of the gastrointestinal tract, the search for new *Helicobacter* species and for sources of infection in humans (1, 2). Dent *et al.* in 1987 and Stolte *et al.* in 1994 described in the stomach of man a spiral bacterium different from *H. pylori* which is contemporarilly named *Helicobacter heilmannii* (*H. heilmannii*) initially termed *Gastrospirillum hominis* (3, 4). Various species of *Helicobacter* have been described in animals: *H. heilmannii* in pigs, dogs and cats, *H. felis* in dogs and cats, *H. mustelae* in ferrets, *H. muridarum* in rodents (5-9). It has been suggested that cats and dogs could act as animal reservoirs in the transmission of *H. heilmannii* and other *Helicobacter spp* to humans (3, 7, 8, 10-12). In humans, similar to *H. pylori*, *H. heilmannii* is accompanying the pathogenesis of chronic gastritis, peptic ulcer disease, gastric cancer and MALT-lymphoma (mucosa associated lymphoid tissue) (13-16).

H. heilmannii is a Gram-negative bacterium resembling corkscrew (spiral shaped microorganisms) two to three times larger than *H. pylori*; 4 to 10 μm in length and 0.5 to 0.8 μm in diameter, has four to eight tight spirals. There are typically 8 to 12 tufts of bipolar flagella (10, 16, 17). It possesses the greatest number of hosts in mammals. It is present in the stomach of dogs, cats, leopards, rats, pigs and various species of primates. It rarely settles gastric mucosa of man. Haesebrouck *et al.* suggested using the name *H. heilmannii sensu stricto* to refer to the novel *Helicobacter* species and the name *H. heilmannii sensu lato* to refer to the whole group of non *H. pylori Helicobacter*s (18). The prevalence of *H. heilmannii* infection in humans varies from 0.1% to 0.9% in patients presenting for upper gastrointestinal endoscopy, although it is reportedly higher in China (4%) and in Thailand where it is as high as 6% (14-16, 19, 20). *H. heilmannii* infection has an asymptomatic course, however it may lead to chronic gastritis, gastric and duodenal peptic ulcer and to other diseases in humans and animals. Diagnosis of *H. heilmannii* infection is made on the basis of bacterial morphology in direct microscopy of the specimen of the gastric mucosa and polymerase chain reaction (PCR). Attempts of cultures *in vitro* failed, but it is possible to sustain *in vivo* culture in laboratory animals (21).

The aim of the study was a clinical analysis of *H. heilmannii* infection in children, and the assessment of the incidence of *H.*

heilmannii infection in children over a period of 18 years (1992-2010) according to age, sex, clinical symptoms and living environment.

MATERIAL AND METHODS

Clinical analysis encompassed 22 children aged 4 to 18 years (11 girls and 11 boys) admitted and diagnosed in our clinic due to dyspeptic symptoms in whom *H. heilmannii* infection was diagnosed. The studied children were divided into two groups depending on the age. Into the first group nine children aged 4 to 13 years were included and into the second group children aged 14 to 18 years. In the studied children we analyzed a place of living (city, country), contact with domestic pets (dog, cat), clinical symptoms (epigastric pain, nausea, vomiting, heartburn) and the presence of concomitant diseases. In all children esophagogastroduodenoscopy was performed and specimens of mucosa from antrum were sampled for microbiology and histology studies. Erosive esophagitis, gastritis, duodenitis and ulcerative disease of the stomach and/or duodenum were taken into consideration in endoscopic diagnosis. The collected samples were studied by the mean of direct microscopy, microbiologic culture and in two children by PCR. Additionally in a part of the children urea test, IgG antibodies against *H. pylori* and study of *H. pylori* antigen in stool were performed. The specimens for direct microscopic examinations were stained using Gram stain method. Bacterial culture was conducted on medium containing Columbia agar with 7% of hemolyzed horse blood. The plates were incubated at 37°C in microaerophylic atmosphere (5% O_2, 10%CO_2, 85% N_2) for 6 days. Anti *H. pylori* IgG antibodies were detected using ELISA test (enzyme linked immunoabsorbent assay) by Microgen-recom commercial kit. Concentration of antibodies above 24 u/ml was treated as positive. *H. pylori* antigen in stool specimens was detected by EIA method using the Amplified IDEIA™HpSTAR™ test (DACO) according to the manufacturer's instruction.

RESULTS

In the period between 1992-2010 the number of 13,124 esophagogastroduodenoscopic studies were performed in children aged 4 to 18 years in the examination of 11,023 sampled specimens of gastric mucosa for *Helicobacter* infection. *H. heilmannii* infection was diagnosed in 22 children based on the examination of 11,023 samples, direct microscopic examination and culture (*Fig. 1*). The frequency of *H. heilmannii* infection was in 0.2% in direct microscopy of gastric mucosa specimens.

Table 1 presents the data of the patients, clinical symptoms and endoscopic diagnosis. No sex difference in frequency of *H. heilmannii* infection was demonstrated (p>0,05). Most children lived in urban areas. 54.5% of the children had domestic contact with a dog and/or a cat. Most of the children belonged to the group aged 4 to 13 years. In all children chronic epigastric pain was observed, nausea in 45.4%, vomiting in 27.2% and heartburn in 13.6%. Nausea, vomiting and heartburn were observed more frequently in older children. Among endoscopic diagnoses dominated chronic nodular gastritis of antrum (77%), in 22.7% duodenitis. In single cases gastric or duodenal ulcer without *H. pylori* infection as well as erosive esophagitis were diagnosed. In three children (13.6%) endoscopic studies of the esophagus, stomach and duodenum did not reveal any changes but in microscopic study chronic inflammatory changes were observed. In children with endoscopic changes of histopatologic mucosa studies revealed chronic inflammatory process, which in half of the cases was active, infiltration of mononuclear cells or neutrophils were observed. In two children bronchial asthma was diagnosed, in three lactose intolerance and in four food allergy.

In *Table 2* the results of *Helicobacter* diagnostic tests are presented. In three children mixed infection with *H. pylori* and *H. heilmannii* was diagnosed. In these children *H. pylori* infection was confirmed in direct microscopy of stomach biopsy specimen, positive culture and the presence of anti *H. pylori* IgG antibodies in serum. *H. heilmannii* infection was confirmed based on morphologic traits of *Helicobacter* in direct

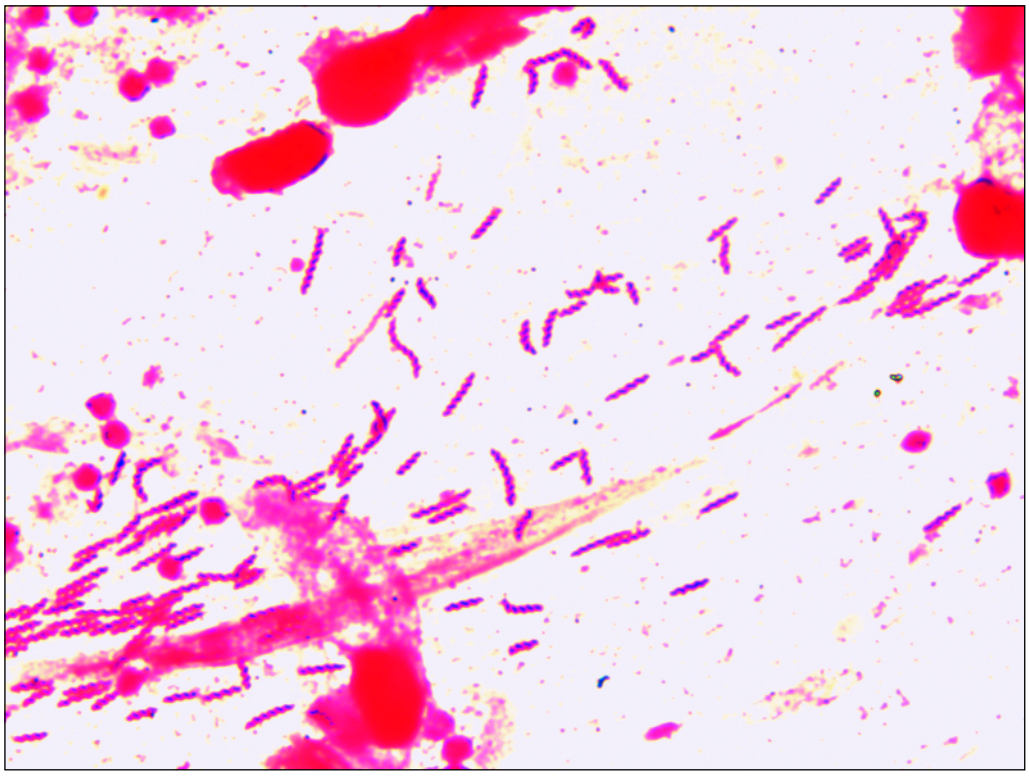

Fig. 1. Gram-stained direct smear of the antral mucosa infected with *H. helmannii* in examined patient (magnification 1000).

Table 1. Patients, symptoms and results of esophagogastroduodenoscopy.

Group	Age (years)	Number of children	Sex		Dominicile		Contact with domestic animals (dogs,cats)	Symptoms				Endoscopical diagnosis					
			f	m	city	country		epigastric pain	nausea	vomiting	heartburn	e	ng	d	gu	du	n
I	4-13	9	4	5	6	3	6 (66.6%)	9 (100%)	2 (22.2%)	2 (22.2%)	1 (11.1%)	0	8	2	0	0	1
II	14-18	13	7	6	7	6	6 (46.1%)	13 (100%)	8 (61.4%)	4 (30.7%)	2 (15.3%)	1	9	3	1	1	2
Total	4-18	22 (100%)	11 (50%)	11 (50%)	13 (59.1%)	9 (40.9%)	12 (54.5%)	22 (100%)	10 (45.4%)	6 (27.2%)	3 (13.6%)	1 (4.5%)	17 (77.2%)	5 (22.7%)	1 (4.5%)	1 (4.5%)	3 (13.6%)

e- erosive esophagitis, ng- nodular gastritis, d- duodenitis, gu- gastric ulcer, du- duodenal ulcer, n- normal

Table 2. The results of *Helicobacter* species identification. nt-not tested, O- proton pump inhibitor, A-amoxicillin, C-clarithromycin, M-metronidazole, B-bismuth subcitrate potassium.

Group	Number of children	Urease test		Direct microscopy		Culture	PCR *H. heilmannii*		IgG anti *H. pylori* antibodies		Antigen of *H. pylori* in stool specimen			Eradication therapy	Results of eradication	
		+	nt	*H. pylori*+	*H. heilmannii* +	*H. pylori* +	+	nt	+	nt	+	nt	OAC (7 days)	OAM (10 days) or BAM	+	nt
I	9	0	9	1	9	1/9	1	8	1/5	4	0/2	7	7	2	5/5	4
II	13	4/4	9	2	13	2/13	1	13	2/5	8	0/3	10	10	3	6/6	7
Total	22	4/4	18	3	22	3/22	2/2	20	3/10	12	0/5	17	17	5	11/11	11

microscopy, negative culture for *H. pylori* and in some cases PCR, the lack of antibodies anti-*H. pylori* and the lack of *H. pylori* antigen in stool. All children with *H. pylori* and/or *H. heilmannii* infection were treated with proton pump inhibitor - omeprasole, amoxicillin and clarithromycin (OAC) for 7 days or with proton pump inhibitor, amoxicillin and metronidazole (OAM) for 10 days. Alternatively, instead of proton pump inhibitor - bismuth salts, amoxicillin and metronidazole (BAM) were administred. The result of eradication was examined after 8 weeks in 11 patients (50%). In all examined children eradication was successful. In 11 children the effect of eradication was not controlled.

DISCUSSION

H. heilmannii infection in children occurs relatively rarely. Based on earlier observations, the frequency of infections in children with dyspeptic symptoms was 0.5% (14). The present study on *H. heilmannii* infection based on a very large material demonstrated a rate of *H. heilmannii* infection to be 0.2% in direct microscopic examination of gastric mucosa specimens. Our results are similar to those in Europe: 0.3% in Bulgaria and 0.9% in Czech Republic. Also in other countries *H. heilmannii* infection is diagnosed rarely, for example 0.1% in Japan, with the exception of China - 4% and Thailand - 6.2% (15, 16, 20, 22). However, *H. heilmannii* infection is frequent in the animals. Interesting studies on *Helicobacter spp* infection in cats in our region have been conducted by Kubiak *et al.* (11). The authors studied species of *Helicobacter* in the stomach of 35 cats of European breed aged 1 to 10 years. Depending on the symptoms the cats were divided into two groups: the first one containing 10 cats without symptoms (control group) and the second group consisting 25 cats with dyspeptic symptoms (chronic nausea, *fetor ex ore*, lack of appetite, abdominal pain). Gastric biopsy samples taken from animals during endoscopy were analyzed by PCR. In the control group *H. heilmannii* infection was identified in seven cats (70%) including four cats with mixed infection with two species: *H. heilmannii* and *H. felis*. In the second group *Helicobacter* spp infection was found in 18 out of 25 animals (72%). *H. heilmannii* was present in five cats (27.8%), mixed infection with two species, *H. heilmannii* and *H. felis* or other species not identified by PCR, were observed in 13 cats (72.2%). The authors demonstrated a very frequent *H. heilmannii* infection in cats, both healthy and sick. Also in other studies frequent *H. heilmannii* infection in animals was demonstrated. Hwang *et al.* using PCR assay showed the presence of *H. heilmannii* in 85% and *H. felis* in 95% of cats (23). By contrast, in dogs *H. heilmannii* was observed in 76% of the cases while H. felis only in 4.8% (23). Moreover, the possibility of transmission of *H. heilmannii* infection from domestic animals to humans was proven. Gosciniak *et al.* described 14 years old girl living in a rural area in whom gastrointestinal endoscopy was conducted due to chronic abdominalgia (8). Chronic nodular gastritis and *H. heilmannii* infection has was diagnosed. Endoscopic study was also conducted in the dog and the cat with which the girl had had everyday contact. Endoscopic and histologic studies in the animals showed inflammation of the gastric mucosa with erosions and infection with the same species of *H. heilmannii*, which was proven by PCR, in the animals and the girl. The results of that study confirmed that *H. heilmannii* infection in the girl might have been of zoonotic origin (8). Other routes of infection also exist. Kato *et al.* documented *H. heilmannii* infection in 11-years-old boy three years after successful eradication of *H. pylori* and the healing of duodenal ulcer. The patient had had no contact with domestic animals, such as cats and dogs (24). In the material analyzed in our study 13 children (59.1%) with *H. heilmannii* infection had contact with a dog and/or a cat, however 9 children (40.1%) did not have any contact with domestic animals and the majority of them lived in urban area.

Diagnosis of *H. heilmannii* infection is based on morphology of biopsy specimens of the gastric mucosa, positive rapid urease test, and PCR. Culture, serum IgG anti-*H. pylori* antibodies test and stool test produced negative results. Our diagnostic studies allowed for diagnosis of mixed *H. pylori* and *H. heilmannii* infection in three children. Besides chronic modular gastritis, gastrointestinal examination of the patients infected with *H. heilmannii* revealed duodenitis (in five children) and gastric and duodenal ulcers (in two children). Histopathologic studies of the biopsy specimens from the prepyloric part of the stomach demonstrated a chronic inflammatory process of mild grade and in some of the children active inflammation of gastric mucosa. Previous experience in the treatment of *H. heilmannii* infection has indicated that *H. heilmannii* is sensitive to antibiotics used in the eradication of *H. pylori* (14, 15, 24). In our study on children *H. heilmannii* infection was successfully eradicated by the treatment with proton pump inhibitor, amoxicillin, clarithromycin or metronidazole.

In summary, *H. heilmannii* infection may be one of the causes of chronic gastritis and ulcerative disease in children. The diagnosis of *H. heilmannii* infection is generally made by the detection of its characteristic morphology in gastric biopsy specimens, since culture is extremely difficult and up till now has not been accomplished succesfully. *H. heilmannii* infection should be differentiated from *H. pylori* infection based on morphologic traits in direct microscopy, negative culture and absence of *H. pylori* antigen in stool.

Conflict of interests: None declared.

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Received: February 21, 2012
Accepted: April 23, 2012

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