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Endoscopic Features of Gastric Mucosa in Children Having Pathohistological Evidence of *Helicobacter Pylori* Infection

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A B S T R A C T

Infection with Helicobacter pylori (Hp) is common in children from developing countries, particularly in adolescents. It is associated with chronic gastritis and stomach cancer. A characteristic endoscopic finding in children is nodular gastritis. The aim of this study was to assess and confirm association of nodular gastritis, mainly of anthral mucosa, with Hp infection in children. A total of 195 children 1 to 15 years of age were studied during a two-year period (2004–2006). There were 107 girls (54.9%) and 88 boys (45.1%). The patients presented with recurrent epigastric pain, nausea, vomiting, heartburn, sour mouth, regurgitation, bloating or other dyspeptic symptoms. The complaints were recorded by a structured interview with parents and older children. Upper endoscopy was performed in all children. The presence and degree of mucosal granulation was recorded and two samples of mucousa from the antrum and the small curvature were taken. Biopsy material was processed for histology as usual, stained with 2% Giemsa and examined by a pathologist for the presence of Hp. A total of 40 of 195 children (20.5%) have had positive Hp infection and a 27 of 40 (67.5%) have had a granular aspect of anthral mucosa at the endoscopy. Sensitivity of the finding was 87.5%, specificity 93.5%, positive predictive value 73%, negative predictive value 91.8%, $p<0.05$. Average age of those patients was 11.5±3.0 years. Subjective symptoms of dyspepsia (as recorded by the questionnaire) were often associated with Hp positivity, but short of statistical significance. No difference between boys and girls was noted. Endoscopic finding of nodular gastritis, especially in areas of antrum and small curvature, showed a highly positive correlation with Hp infection.

Key words: *nodular gastritis, Helicobacter pylori, recurrent abdominal pain, children, upper endoscopy*

Introduction

Barry Marshal and Robin Warren won Nobel prize in medicine in 2005 for the discovery of bacterium *Helicobacter pylori* (*Hp*) as being responsible for gastritis and peptic ulcer. *Hp* infection affects almost a half of the world's population, in particular adolescents in developing countries. Eradication of *Hp* helps healing verified peptic ulcers. Vaccination against *Hp* in early childhood has been being considered as a prevention of peptic ulcer and subsequent development of adenocarcinoma[1]. Epidemiological evidence indicates that the bacterium spreads by fecal-oral, oral-oral or gastro-oral ways[2,3]. Recent studies indicate a possibility of the existence of *Hp* reservoir in the mouth, tonsils and adenoids, especially if damaged due to intercurrent infections. Oral carriership might contribute to oral-oral way of infection spread[4,5]. *Hp* can be found in dental enamel[6], saliva and vomit[7]. The infection is more likely to occur with crowded housing, in children who share bed with parents, and due to a shortage of running hot water. Breastfeeding lowers the risk of infection[8]. Children with repeated abdominal pain and positive urease (Campylobacter-like organisms) test who have had close contact with their cats have been described to share the same type of *Helicobacter heilmanni* in preparations of gastric mucosa. That finding favors theory of possible animal-to-human transmission of *Hp*[9,10]. The European Association for Feline Medicine

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emphasized in 2000 epidemiological significance of so-called »gastric helicobacter-like organisms« (GHLO) residing in stomachs of carnivore pets, especially cats[11].

Hp infection is accompanied by a characteristic endoscopic finding of nodular gastritis[13]. Nodular changes are more often found in the antral area, are more common in children, and are called *antral nodular gastritis*, *nodular antritis*, or *gastric lymphonodular hyperplasia*. Many authors associate such morphological changes with the existence of *Hp* infection. The aim of this work was to assess and possibly corroborate that view[13–15]. To that end, a cross-sectional study was carried out with children reporting repeated abdominal pain, and the correspondence of endoscopic finding of nodular gastritis with *Hp* presence in bioptic material was investigated.

Patients and Methods

One hundred and ninety-five (195) children (54.9% girls, 45.1% boys) 1 to 15 years of age (average age 11±4 years) were examined during a period of two years (2004–2006). The patients were hospitalized or treated as outpatients at the Department for Children's Diseases of the University Clinical Hospital Mostar. Inclusion criteria were: age 1 to 15 years, repeated abdominal pain above the navel lasting for at least six months or longer, nausea, vomiting, heartburn and/or various »dyspeptic« symptoms such as sour mouth, burping, feeling bloated, feeling stuffed after small amounts of food etc. Exclusion criteria were: previous triple therapy for *Helicobacter* as documented by reliable history, questionnaire or medical records. Three patients that had used anti-ulcus therapy were also excluded.

After appropriate explanations, a structured questionnaire recording the symptoms of dyspepsia (mentioned above) was completed by the parents and older children. A pediatrician from the Department of Pediatrics, member of intensive care team assisted with the questionnaire. Informed consent for upper endoscopy was obtained from the parents and, depending on the age, from the children themselves.

Fig. 1. Endoscopic finding of nodular gastritis.

An endoscope *OLYMPUS GIF type P30*, Olympus Optical CO, LTD, Tokyo, Japan was used. The procedure was carried out at the endoscopy cabinet of the Clinical Hospital Mostar, with assistance of two educated nurses. The room as well as the equipment were disinfected. A reanimation kit, laryngoscope with corresponding sizes of the spoon and tubus, spare batteries, ambu-baloon, and intravenous antishock therapy set had been at hand[16].

Two samples of stomach epithelium were collected by the biopsy, one from the antrum next to the incisure, and the other from the small curvature of the stomach. The preparations were stained with 2% Giemsa and examined by an experienced pathologist. All endoscopies were recorded by means of video (VHS) technique. A representative photograph is shown in Figure 1.

After endoscopy, a written record was put down describing the appearance of mucosa (stating the presence or absence of granulation), location of the biopsies, and the presence of stomach contents, if any. The collaborating pathologist was not aware of the endoscopic findings.

Children meeting the inclusion criteria were divided into two groups after the endoscopy: with or without granulation of stomach mucosa. Arithmetic means, medians and the χ^2-test were used for the statistical analysis. The data were processed by means of Excel 2000 (Microsoft, USA) and SPSS 9.0. The level of significance was set at $p < 0.05$. The study was endorsed by the Ethics Committee of the Clinical Hospital Mostar.

Results

As seen in Table 1, infection with *Helicobacter pylori* was documented in 40 of 195 examined children (20.5%). The prevalence was somewhat higher among the children 5 to 8 years of age (10 of 29, i.e. 34.5%) but an overall difference regarding the age distribution does not reach statistical significance ($\chi^2=5.32$, df=2, p=0.069). In 70% of the children who did have *Hp* infection the bacterial infiltration in the stomach wall was of mild to moderate degrees.

Figure 1 illustrates endoscopic appearance of granulated stomach mucosa and Table 2 shows correlation of endoscopic findings with verified *Hp* infection. Granulated appearance of the mucosa was significantly correlated

TABLE 1
AGE DISTRIBUTION OF CHILDREN HAVING *HELICOBACTER PYLORI* (HP) INFECTION

Age (years)	Hp in gastric mucosa[1]		Total
	Yes	No	
1–4	0	6 (3.9%)	6
5–8[1]	10 (25.0%)	19 (12.3%)	29
9–15	30 (75.0%)	130 (83.8%)	160
Total	40 (100.0%)	155 (100.0%)	195

[1] $\chi^2=4.077$, df=1, p=0.043

TABLE 2
CORRELATION OF GRANULAR APPEARANCE OF GASTRIC MUCOSA AT ENDOSCOPY TO THE PRESENCE OF *HELICOBACTER PYLORI* (HP) IN THE BIOPSIES

Endoscopy[1]	Hp infection[2]		Total
	Yes	No	
Positive	27 (13.8)	10 (5.1)	37 (19.0)
Negative	13 (6.7)	145 (74.4)	158 (81.0)
Total	40 (20.5)	155 (79.5)	195 (100)

χ^2=77.075, df=2, p<0.0001
[1] Evidence of granulations of gastric mucosa at upper endoscopy
[2] Evidence of *Helicobacter pylori* in biopsy specimens of gastric mucosa

to the presence of *Helicobacter* and *vice versa* (χ^2=77.08, df=1, p<0.05). Normal endoscopic finding of antral mucosa was only exceptionally associated with the presence of Helicobacter. Considering only the patients without granulation of antral mucosa there is a statistically significant difference between the presence and absence of *Hp* infection (χ^2 = 110.278; df = 1; p<0.050). In turn, positive *Hp* infection was positively correlated with the presence of granulations and negatively with their absence (χ^2=7.811, df=1, p<0.005).

Sensitivity of the endoscopic finding of nodular gastritis with regard to the *Hp* infection is 87.5%, specificity 93.5%, positive predictive value (PPV) 73.0% and negative predictive value (NPV) 91.8% (χ^2=77.07, df=1, p<0.050).

A structured questionnaire (Appendix 1) was filled out in collaboration with parents and if feasible with the patients, in an attempt to see whether some symptoms were related to *Hp* infection, and if any, to compare the result with relevant data in the literature[25,26]. It appeared that various »stomach-related« symptoms were more often reported by children without *Hp* infection (79.5%) than by those having it (20.5%) (Table 3). The overall difference between the two groups is not significant, however (χ^2=13.23, df=7, p=0.067). Heartburn was present in 38 of 195 patients (19.5%) as well as its combination with nausea (44 patients; 22.6%). Dyspepsia was more common in children who did have *Hp* (6 of 40, i.e.15.0% than in those who did not (5 of 155, i.e. 3.2%) (χ^2=8.28, df=1, p=0.004). An apparent difference with regard to dyspepsia, nausea and heartburn combined is not statistically significant (χ^2=2.203, df=1, p=0.138).

Discussion

During two years (2004–2006) we examined by upper endoscopy 195 children who have had repeated abdominal pain lasting for six months or more, together with various stomach-related symptoms as vomiting, dyspepsia, nausea, heartburn etc. That number represented 25% of all children attending the gastroenterology outpatient service. The complaints were recorded by case histories and structured interviews. Upper endoscopy was carried out and biopsy samples of gastric mucosa were collected in order to check for the presence of *Hp* infection. The patients were mainly Croats from two Herzegovinian cantons adjacent to Mostar. They were 1 to 15 years of age (average, 11±4 years), with equal representation of both genders (54.9% boys and 49.1% girls).

The study was carried out in a double-blind manner. Results of the endoscopy were documented by VHS and written records, and neither the pathologist who assessed the biopsy material nor the pediatrician who completed the questionnaires were aware of the endoscopy findings.

Hp infection was found in 40 of 195 patients (20.5%), regardless of the gender. Such prevalence resembles that in developed countries with favorable socioeconomic conditions. A similar study carried out in Turkey (a country with a comparable socioeconomic state to ours) showed a higher prevalence of *Hp* infection in children with chronic gastrointestinal symptoms, 42.7%[15]. Our finding is probably misleading in view such as a high perinatal mortality of 12–20% and a low gross national product (GNP) of $ 10,831,267 that classify Bosnia and Herzegovina among poor European countries. An explanation for the discrepancy might be that in our country antibiotics are being used without strict medical indication and can be acquired without official prescriptions. Indiscriminate use of the antibiotics might have eradicated *Hp* as a collateral effect.

The average age of children having a positive PHD test to *Hp* was 11.5±3.0 years and that of children with-

TABLE 3
CORRELATION OF PRESENTING SYMPTOMS WITH HP INFECTION

Symptom	Hp in gastric mucosa[1]		Total[2]
	Yes	No	
Vomiting	5 (12.5 %)	22 (14.2 %)	27 (13.8 %)
Nausea	6 (15.0 %)	11 (7.1 %)	17 (8.7 %)
Heartburn	7 (17.5 %)	31 (20.0 %)	38 (19.5 %)
Dispepsy[3]	6 (15.0 %)	5 (3.2 %)	11 (5.6 %)
Nausea and heartburn	8 (20.0 %)	36 (23.2 %)	44 (22.6 %)
Dispepsy and nausea	0	4 (2.6 %)	4 (2.1 %)
Dispepsy and heartburn	3 (7.5 %)	10 (6.5 %)	13 (6.7 %)
Dispepsy, nausea and heartburn[4]	5 (12.5 %)	36 (23.2 %)	41 (21.0 %)
Total	40 (100.0 %)	155 (100.0 %)	195 (100.0 %)

[1] The percentages in columns *Yes* or *No* have been calculated on the basis of total numbers of patients in those columns (40 *viz.* 155)
[2] The percentages have been calculated on the basis of all patients (195)
[3] χ^2=8.28, df=1, p=0.004
[4] χ^2=2.203, df=1, p=0.138 (n.s.)

out *Hp* infection 11.0±2.9 years. As seen from data in table 1, *Hp* infection appeared to be more common (34.5%) in children five to eight years of age. That age is lower than described in relevant literature[3,22], but our observation is based on a small sample and does not reach statistical significance.

There was not a single case of *Hp* infection in children one to four years of age. That could be explained in view of our criteria for endoscopy that were strict for younger patients and more liberal for the older ones. The number of very young children was therefore limited (only 6) and positive findings might have been missed. As regards the gender, the prevalence of *Hp* infection in boys (8.2%) and girls (12.3%) were comparable.

A reliable assessment of repeated abdominal pain and dyspepsia in children is difficult due to ambiguous descriptions by the parents as well as by the children. Exact role of *Hp* in generating subjective symptoms is not clear. Vomiting and acute abdominal pain can be connected to *Hp* infection, but the opinions differ regarding the role of *Hp* in children having repeated abdominal pain and signs of non-ulcerative dyspepsia[17–19].

Bedoya et al.[20] compared *Hp* infected children from populations with high and low gastric carcinoma risks. Higher degrees of stromal and intraepithelial infiltration with polymorphonuclear leukocytes and lymphocytes, *Hp* density and mucus depletion were found in the high-risk population. T-lymphocyte and macrophage representation was higher in the high-risk population, a majority of T-lymphocytes being $CD8^{+}$[20]. On the other hand, regenerative activity was significantly higher in the low-risk population. Bode et al.[21] analyzed in a cross-section study the relationship between social and domestic factors, *Hp* infection, and repeated abdominal pain in 1,221 children of pre-school age and showed association of repeated abdominal pain with social/domestic factors, but not with the *Hp* infection.

In our experience, 72.90% of children who have had a granulated aspect of stomach antrum at the endoscopy were *Hp* positive and 27.02% were *Hp* negative. In comparison, Bahú et al.[13] found 44.0% of *Hp* infection in Brazilian children having endoscopic features of nodular gastritis. In Italy, Luzza et al.[12] found 45.3% *Hp* positive and 1.5% *Hp* negative children to have granulated stomach mucosa and De Giacomo et al.[24] found 43.0% *Hp* positive and 4.0% *Hp* negative patients respectively.

The specificity of endoscopically evidenced nodular gastritis as an indicator of *Hp* infection was 98.5%, sensitivity 87.5%, positive predictive value 91.7%. Similar observation was reported by Prieto Bozano et al.[16]. Thus, endoscopic finding of nodular gastritis indicates a probability of *Hp* infection of stomach mucosa. On the other hand, absence of nodular aspect of stomach mucosa does not exclude *Hp* infection[14]. According to De Giacomo et al.[23] a higher degree of bacterial colonization of the stomach wall is associated with endoscopic evidence of nodular gastritis.

Comparing the complaints of the patients to the presence of *Hp* infection (Table 3) it appeared that various »stomach-related« symptoms were more often reported by children without *Hp* infection (79.5%) than by those having it (20.5%). The overall difference between the two groups is not significant, however ($\chi^2=13.23$, df=7, p=0.067). With regard to particular symptoms, dyspepsia was significantly more common in children who did have *Hp* (6 of 40, i.e.15.0% than in those who did not (5 of 155, i.e.3.2%; $\chi^2=8.28$, df=1, p=0.004. An apparent difference with regard to dyspepsia, nausea and heartburn combined was not statistically significant ($\chi^2=2.203$, df=1, p=0.138).

In essence, our experience has shown a high degree of concordance of granulated appearance of stomach mucosa at endoscopy with pathohistological evidence of *Hp* infection in the biopsies. Subjective symptoms of dyspepsia were also correlated with presence of *Hp* infection. The endoscopy finding is highly specific and sensitive, and confirms similar observations of other authors[12,23,24]. The concordance does not, however, justify the institution of therapy aimed at eradication of *Helicobacter* without a firm evidence based on the biopsy material.

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ENDOSKOPSKE ZNAČAJKE SLUZNICE ŽELUCA U DJECE S PATOHISTOLOŠKIM NALAZOM INFEKCIJE *HELICOBACTER PYLORI*

S A Ž E T A K

Cilj istraživanja bio je dokazati koliko je nodularni gastritis, osobito želučanoga antruma, pouzdan pokazatelj infekcije bakterijom *Helicobacter pylori* (*Hp*) u djece. Tijekom dvogodišnjeg razdoblja (2004.–2006. godina) endoskopski je na Odjelu za dječje bolesti Kliničke bolnice Mostar pregledano 195 djece (107 djevojčica, 54,9%, i 88 dječaka, 45,1%) u dobi od 1 do 15 godina (prosjek, 11,0±2,9 godina) koja su upućena na gastroenterološku obradu zbog bolova u trbuhu iznad pupka, mučnine, povraćanja, »žgaravice« (osjećaja kiselosti u ustima i/ili vraćanja sadržaja iz želuca u jednjak) i dispepsije (osjećaja nadutosti, napuhnutosti, brze sitosti). Simptomi su registrirani strukturiranim upitnikom. Svoj djeci je učinjena gornja endoskopija, uz uzimanje dvaju uzoraka želučane sluznice s antruma i male krivine. Posebna se pozornost obratila na postojanje ili nepostojanje granulacija sluznice. Nalazi su dokumentirani snimkama VHS-a i pismenim opisom. Uzorke sluznice obojene 2% Giemsom pregledao je patolog kojem nalaz endoskopije nije bio poznat. Infekcija helikobakterom utvrđena je u 40 od 195 ispitanika (20,5%). Granuliran izgled želučane sluznice registriran je u 27 od tih 40 (67,5%). Senzitivnost endoskopskog nalaza glede *Hp* infekcije bila je 87,5%; specifičnost 93,5%, pozitivna prediktivna vrijednost (PPV) 73,0%, negativna prediktivna vrijednost (NPV) 91,8%, uz $p<0,05$. Nije bilo razlike između dječaka i djevojčica glede nalaza. Simptom dispepsije češće je bio prisutan u *Hp* pozitivnih bolesnika, ali bez statističke značajnosti. Endoskopski nalaz nodularnog gastritisa, osobito u predjelu antruma i male krivine, pouzdano upućuje na postojanje infekcije želuca bakterijom *Helicobater pylori*.