Value of Antral Nodularity for the Diagnosis of *Helicobacter pylori* Infection in Children

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Statistical Analysis **C**
Data Interpretation **D**
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Background:
The aim of this study was to confirm the role of antral nodularity in the diagnosis of *Helicobacter pylori (H. pylori)* infection in children.

Material/Methods:
This prospective study included 107 children (58 male; 54.2%), between the ages of 3 and 18 years, infected with *H. pylori,* which was confirmed if the patient had at least 2 of 4 positive test results (urea breath test, urease test in gastric biopsy, histopathology – positive hematoxylin and eosin and Giemsa staining, and/or monoclonal stool ELISA test – Amplified IDEIA™ Hp StAR™). The control group consisted of 234 children with abdominal pain, of similar age, in whom urease test in gastric tissue and histopathology were negative. In both groups, photographs of the gastric antrum taken during endoscopy were evaluated for nodularity by 3 independent endoscopists, blinded to the results of other tests. Sensitivity, specificity, and negative and positive predictive value of nodularity were assessed. Indication for upper endoscopy was chronic abdominal pain not considered to be functional.

Results:
There were no statistical differences between groups regarding sex (chi-square test with Yates's correction: p=0.8763) or age (mean ±SD) 11.77±3.49 and 12.43±3.32, study and control groups, respectively (Mann-Whitney test: p=0.1352). The sensitivity of the presence of nodularity as an indication of *H. pylori* infection was 91.6% and specificity was 91%. PPV of gastric nodularity was 81% and NPV was 96%.

Conclusions:
Antral nodularity is reliable test. Physicians could start treatment of *H. pylori* infection whenever gastric nodularity is observed and the urease test result is positive, without waiting for histopathology results.

MeSH Keywords:
Child • Diagnosis • Endoscopy • *Helicobacter* Infections • *Helicobacter pylori* • Pyloric Antrum

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Background

The significance of antral nodularity as an endoscopic sign of *Helicobacter pylori* (*H. pylori)* infection is still controversial. Sensitivity of this sign is estimated in the literature as being as low as 39.8% [1], 40.5% [2], to 61% [3], 63.4% [4], and even 96.4% [5], while the specificity is reported as ranging from 83.6% [1], 85.2% [4], 87.5% [5], 98.5% [6] to 100% [2]. According to Sykora et al. [7 the correlation between nodularity and infection is highly significant (p<0.000001). A high correlation between nodularity and CagA(+) as opposed to CagA(–) was shown by Luzza et al. [2] However, in a recently published study by Prasada et al. [8] it was shown that the presence of nodularity had a low correlation with *H. pylori* infection in children (nodularity was present in 50/118 cases, 42.4% of children with positive histopathology *H. pylori* test and in 69/607 cases, 11.4% with negative histopathology; sensitivity: 42%; positive predictive value: 42.4%). These discrepancies prompted us to carry out the current study in a large group of children.

Material and Methods

The study started in December 2006 and ended in September 2009. Children of the study group were participants of a prospective, randomized, double-blind study, which analyzed the effectiveness of different schemes of eradication of *H. pylori* [9].

Enrollment was according to the following criteria:

Study group Age 3–18 years and confirmed *H. pylori* infection and abdominal pain, which was the indication for endoscopy. *H. pylori* infection was diagnosed when at least 2 of the following tests were positive: C^{13} urea breath test (UBT), rapid urease test in gastric biopsy, histopathological sample of mucosa taken from the stomach's antrum (*H. pylori* positive gastritis proved by hematoxylin and eosin and Giemsa staining), stool test (monoclonal ELISA test – Amplified IDEIA™ Hp StAR; DakoCytomation Ltd., Denmark House, Angel Drove, Ely Cambridgeshire, CB7 4ET, UK).

Exclusion criteria:
– Use of antibiotics and/or proton pump inhibitors 4 weeks prior to the investigation.
– Treatment of *H. pylori* infection in the past.

Control group

Inclusion criteria:
Patients between 3 and 18 years of age who had undergone gastroscopy between 2008 and 2009 for chronic and/or recurrent abdominal pain. *H. pylori* infection was excluded by at least 2 different tests (rapid urease test + histopathology). Patients in the control group were evaluated retrospectively. Their final diagnosis was functional abdominal pain.

Exclusion criteria:
– Use of antibiotics and/or proton pump inhibitors 4 weeks prior to the investigation.
– Treatment of *H. pylori* infection in the past.

Endoscopies were performed using an Olympus GIF-160 gastroscope. Evaluation of antral nodularity was performed in both groups by 3 pediatric gastroenterologists, blinded for the results of *H. pylori* testing, from photographs obtained at the time of endoscopy.

Statistical analysis

The following parameters were evaluated: sensitivity, specificity, positive predictive value (PPV**)** and negative predictive value (NPV**)** were calculated using standard equations.

Positive predictive value (PPV) was calculated with a formula:

$$P(ill|+) = \frac{P(+|ill) * P(ill)}{P(+|ill) * P(ill) + P(+|healthy) * P(healthy)}$$

Negative predictive value (NPV) was calculated with a formula:

$$P(healthy|-) = \frac{P(-|healthy) * P(healthy)}{P(-|healthy) * P(healthy) + P(-|ill) * P(ill)}$$

To determine if there were statistically significant differences between groups, chi-square analysis with Yates's correction for gender and Mann-Whitney test for age were performed using platform R (*www.r-project.org*).

The study protocol was approved by Bioethical Committee Medical University of Warsaw (Decision KB/183/2006). Written informed consent was obtained from the parents and if the patient was 16 years or older, her/his assent was also obtained.

Results

One hundred and seven children (58 male; 54.2%) were enrolled in the study group and 234 in the control group. There were no statistical differences between groups regarding gender (chi-square test with Yates's correction: p=0.8763) or age (mean ±SD) 11.77±3.49 and 12.43±3.32, study and control groups, respectively (Mann-Whitney test: p=0.1352). Antral nodularity was the only endoscopic finding in all patients (Table 1).

Table 1. Characteristics of the control and the study group.

	Study group	Control group	p
Number of patients	107	234	
Age (mean ±SD)	11.77±3.49	12.43±3.32	0.1352
Abdominal pain only	100%	100%	
Nodularity (positive)	98/107	21/234	

Table 2. Sensitivity, specificity, PPV and NPV for the nodularity as the diagnostic test for *H. pylori* infection.

		Patients *H. pylori* positive according to criterion standard test		Sum		
		Positive	Negative			
Nodularity	Positive	98	21	119	82%	PPV*
	Negative	9	213	222	96%	NPV**
Sum		107	234	341		
		91.6%	91%			
		Sensitivity	Specificity			

* PPV (*positive predictive value*) – True positive/(True positive + False positive); ** NPV (*negative predictive value*) – True negative/(False negative + True negative); Sensitivity – True positive/(True positive + False negative); Specificity – True negative/(False positive + True negative).

The sensitivity of the presence of nodularity as an indication of *H. pylori* infection was 91.6% and specificity was 91%. PPV of gastric nodularity was 81% and NPV was 96% (Table 2).

Positive Predictive Value (PPV), which in our study was 81%, was calculated with a formula presented in the Methods section, using the results of this study and the data from the Polish literature [10] which show that in Poland about 30% (0.3) of children ages 0–18 are infected with *H. pylori*:

$$P(+|ill) = \frac{98}{107} = 0.916$$
$$P(ill) = 0.3$$
$$P(healthy) = 1 - 0.3 = 0.7$$
$$P(+|healthy) = 21/234 = \textbf{0.09}$$

therefore:

$$P(ill|+) = \frac{0.916 * 0.3}{0.916 + 0.3 + 0.09 * 0.7} = 0.81$$

Negative Predictive Value (NPV), which in our study was 96%, was calculated with a formula presented in the Methods section, using the results of this study and the data from the Polish literature [10] which show that in Poland about 30% (0.3) of children aged 0–18 are infected with *H. pylori*:

$$P(healthy|-) = \frac{0.91 * 0.7}{0.91 * 0.7 + 0.084 * 0.3} = 0.96$$

Figure 1 presents pictures from our study showing various degrees of antral nodularity which were considered positive.

Discussion

Although antral nodularity seen at endoscopy has been associated with *H. pylori* infection, the accuracy of this finding varies from one author to another. Several studies were retrospective, some involved a small number of patients, different tests were used to diagnose infection, studies were performed in countries with different rates of infection, and/or there were differences in indications for endoscopy [1–5,7].

The sensitivity of antral nodularity in presence of *H. pylori* in our study (91.6%) is similar to that reported by Conti-Nibali et al. [5] 96.4%. However, sensitivities observed by other investigators are lower and: range from 39.8% to 87.5% [1–4,6,12,13]. In those studies, different methodologies were used particularly regarding the different kind and number of tests used to confirm *H. pylori* infection. The importance of the tests to confirm infection in correlation to the endoscopic signs may be crucial.

Figure 1. Various degrees of nodularity (mild to massive) or „cobblestone" appearance of the antral mucosa of *H. pylori*-infected children (own material).

High specificity of antral nodularity, similar to our results (91%), were also found by several authors and ranged from 87.5% to 100% [2,5,6]. Slightly lower specificity (64–85.2%) was found by others [1,4,11]. These results show that despite considerable differences in methodologies used to establish the diagnosis of *H. pylori* infection, the specificity of nodularity in the gastric antrum is still high. Evaluation of nodularity is simple for an experienced endoscopist. Different values are described in the literature regarding PPV and NPV. PPV in our study reached 81%, a proportion lower than that found by Bahu Mda et al. (91.7%) [6] but higher than that described by others (12–73%) [3,4,10,12]. Our results confirm that the probability of infection in the presence of antral nodularity is very high. Conversely, the lack of antral nodularity decreases the probability of *H. pylori* infection in children.

The strong aspect of our study is that the investigators assessing presence or absence of antral nodularity were blinded to the results of other tests. Another positive aspect is that the control group, although not studied prospectively, was large and homogenous.

The weak aspect of the study was the fact that the control group was evaluated retrospectively. Additionally, unlike in the study group where the diagnosis was based on rapid urease test, urea breath test, stool test, and histopathology, in the control group the absence of infection was confirmed only by 2 diagnostic methods (rapid urease test and histopathology), although the latter are considered a reliable, criterion standard diagnostic standard.

Given the continued controversies mentioned in the Discussion, it seems that at least one additional study may be warranted which would be fully randomized and would utilize all the diagnostic methods available; the cost of such a study, however, would be enormous.

Conclusions

Our study is the first in which all the evaluated markers (specificity, sensitivity, PPV and NPV) were shown to be very good predictors of *H. pylori* infection. In the hands of experienced endoscopists, the presence of antral nodularity is a reliable indicator of *H. pylori* infection. Physicians could start treatment of *H. pylori* infection, if clinically indicated, whenever gastric nodularity is observed and urease test is positive without waiting for histopathology results.

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