# Influence of *Helicobacter pylori* genetic type on gastroesophageal acid reflux disease in children and teenagers

## Wpływ typu genetycznego *Helicobacter pylori* na występowanie choroby refluksowej przełyku u dzieci i młodzieży

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**Key words:** genetic type of *Helicobacter pylori*, gastroesophageal reflux disease, gastroesophageal acid, children, teenagers.
**Słowa kluczowe:** typ genetyczny *Helicobacter pylori*, choroba refluksowa przełyku, patologiczny kwaśny refluks żołądkowo-przełykowy, dzieci, młodzież.

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## Abstract

**Introduction:** The role of *Helicobacter pylori* (*H. pylori*) infection in pathogenesis of gastroesophageal reflux disease (GERD) remains controversial. It seems that the genotype of *H. pylori* influences that dependence.

**Aim:** To assess the significance of *H. pylori* genotype in gastroesophageal reflux (GER) in children and teenagers.

**Material and methods:** Hundred and one children in whom endoscopy of the upper part of the gastrointestinal tract was performed and *H. pylori* infection was demonstrated in histopathological and/or urease test and urea breath test. *Helicobacter pylori* identification was performed using the PCR method to determine the genetic type of CagA and VacA. Triple-drug eradication therapy was introduced. pH-metric examination was performed before and after treatment.

**Results:** Infection with type I strain was found in 32.7% of patients, type II in 67.3%. Concerning the group of patients infected with type I *H. pylori*, GER was found in 57.6% of patients, while 45.6% infected with type II *H. pylori* suffered from GER. It was induced *de novo* in 15% of patients in the group of patients infected with type I and in 15% of cases was removed after eradication. Change concerning GER intensity degree did not occur in 70% of patients. Gastroesophageal reflux was induced *de novo* in the group of patients infected with type II *H. pylori* in 12.8% of cases and GER was removed

## Streszczenie

**Wprowadzenie:** Rola zakażenia *Helicobacter pylori* (*H. pylori*) w patogenezie choroby refluksowej przełyku pozostaje kontrowersyjna.

**Cel:** Ocena znaczenia genotypu *H. pylori* w patologicznym kwaśnym refluksie żołądkowo-przełykowym współistniejącym z zapaleniem błony śluzowej żołądka i/lub dwunastnicy u dzieci i młodzieży.

**Materiał i metody:** Badaną grupę stanowiło 101 pacjentów, u których wykonano badanie endoskopowe górnego odcinka przewodu pokarmowego i potwierdzono zakażenie *H. pylori* w badaniu histopatologicznym i/lub w teście ureazowym i mocznikowym teście oddechowym. Wykonano identyfikację *H. pylori* metodą reakcji polimerazy łańcuchowej (*polymerase chain reaction* – PCR) z wycinków błony śluzowej żołądka, oznaczając typ genetyczny bakterii – CagA i VacA. Włączono leczenie eradykacyjne w schemacie trójlekowym. Badanie pH-metryczne wykonano przed leczeniem i po leczeniu.

**Wyniki:** Zakażenie szczepem typu I stwierdzono u 33 (32,7%), a typu II u 68 ze 101 pacjentów (67,3%). W grupie 33 osób zakażonych typem I *H. pylori* u 19 pacjentów (57,6%) stwierdzono chorobę refluksową przełyku (*gastroesophageal reflux disease* – GERD), natomiast spośród 68 zakażonych typem II *H. pylori* schorzenie to rozpoznano u 31 pacjentów (45,6%). W grupie pacjentów zakażonych typem I w 3 przypadkach (15%) GERD

after eradication in 12.8%. Change concerning GER intensity degree did not occur in 74.4% of patients. The pH-metry result after treatment was non-diagnostic in 5 patients. These differences were not statistically significant.

**Conclusions:** Genetic type of *H. pylori* did not influence gastroesophageal reflux occurrence or change of gastroesophageal reflux intensity degree after eradication.

był indukowany *de novo*, a w 3 przypadkach (15%) ustąpił po eradykacji. U 14 pacjentów (70%) nie nastąpiła zmiana stopnia nasilenia GERD. W grupie osób zakażonych typem II *H. pylori* w 6 przypadkach (12,8%) GERD był indukowany *de novo*, natomiast w 6 przypadkach (12,8%) ustąpił po eradykacji. U 35 pacjentów (74,4%) nie nastąpiła zmiana stopnia nasilenia GERD. U 5 pacjentów wynik badania pH-metrycznego po leczeniu był niediagnostyczny. Różnice nie były istotne statystycznie.

**Wniosek:** Typ genetyczny *H. pylori* nie wpływał na częstość występowania patologicznego kwaśnego refluksu żołądkowo-przełykowego i zmianę stopnia jego nasilenia po eradykacji.

## Introduction

*Helicobacter pylori* (*H. pylori*) infection is an aetiological factor of chronic inflammatory lesions of the gastric mucosa, chronic gastric and duodenal peptic ulcer disease and gastric cancer or MALT lymphoma of lymphoid tissue of the mucosa. Bacteria eradication is the most efficient method for treatment of chronic inflammation of the gastric mucosa and chronic peptic ulcer disease with concomitant *H. pylori* infection [1].

The role of *H. pylori* infection in pathogenesis of gastroesophageal reflux disease remains controversial. The presence of *H. pylori* in the gastric mucosa can play the role of a protective and aggressive factor.

It seems that the influence of *H. pylori* infection on the frequency and degree of gastroesophageal acid reflux depends on the place where inflammation exists and on inflammation intensity [1-5].

*Helicobacter pylori* strains producing cytotoxin VacA and protein CagA are more active in inducing lesions in the gastric mucosa. Simultaneously, there are reports indicating that CagA positive strains protect better against gastroesophageal reflux disease and its complications [6, 7]. Not all results of studies confirm the presence of this connection [8]. The pathomechanism of these dependences is also not entirely known.

Clinical isolates of *Helicobacter pylori* are divided into two groups: type I – CagA-positive and VacA-positive phenotype showing vacuolising activity and strong cytotoxic effect; and type II – does not contain *cagA* in the genome and does not present vacuolising activity, but contains *vacA* homological sequences. Most likely infection with type I strain causes peptic ulcer or atrophic inflammation. Strains with allele s1m1 are characterized by strong cytotoxic activity. Type II is isolated from patients with milder course of the disease [9].

## Aim

The aim of the study was to assess the significance of *H. pylori* genotype in gastroesophageal acid reflux coexisting with inflammation of the gastric and/or duodenal mucosa in children and teenagers.

## Material and methods

A total of 101 patients older than 3 years, with gastric and/or duodenal mucosa inflammation with concomitant *H. pylori* infection, were included in the study.

The criteria excluding patients from the study were:
- earlier diagnosis of *H. pylori* infection and its treatment,
- earlier diagnosis and treatment of GERD (neutralizing drugs, PPI, H2-blockers).

To eliminate false-negative results of diagnostic tests in detection of *H. pylori* infection (urease test, breath test) and in detection of GERD (Ph-metric test) only those patients were qualified who did not undergo:
- antibiotic therapy 4 weeks before the examination,
- treatment with PPI or H2-blockers 2 weeks before the examination.

Patients were divided into two groups:
1) patients with inflammation of the gastric and/or duodenal mucosa with concomitant type I *H. pylori* infection,
2) patients with inflammation of the gastric and/or duodenal mucosa with concomitant type II *H. pylori* infection.

### Diagnostics in *Helicobacter pylori* infection

**Endoscopic examination of the upper part of the gastrointestinal tract** was performed using OLYMPUS GIF 160 or OLYMPUS XP 160, and three biopsy specimens of the gastric mucosa were taken from the prepyloric region (one to perform the urease test, one for the histological examination, one to identify *H. pylori* using the PCR method), from the stomach fundus or from the upper part of the stomach body and from unexplained macroscopic lesions. Macroscopic lesions within the mucosa of the oesophagus, stomach and duodenum

were assessed during the examination according to the Sydney System classification. Biopsy specimens for the histopathological examination were stained with haematoxylin and eosin to assess inflammation, but using the Giemsa method modified by Gray to identify *H. pylori* bacterium. The whole was assessed according to the Sydney System classification grading inflammatory lesions (low, medium, high) and infection (+, ++, +++).

**The urease test** was performed in all patients, using the rapid urease test produced by the National Food and Nutrition Institute in Warsaw. The test has been validated. Change in colour from yellow to red, raspberry red or rose was acknowledged as an abnormal result of the urease test. A normal result of the test occurred when there was no change of base colour.

**The urease breath test** was performed in all the patients. Measurement of $^{13}C$ concentration was performed using an OLYMPUS *Fanci 2* infrared analyser, assuming 4‰ as a cut-off point.

***Helicobacter pylori* identification was performed using the PCR method** in biopsy specimens from the gastric mucosa, assessing genetic type of the bacterium (CagA-positive, CagA-negative, VacA-positive, VacA-negative). **Isolation of *H. pylori DNA*** was performed using the Genomic Mini set of DNA Gdansk according to the producer's recommendations. **Reactions of *ureA* and *cagA* genes amplification** were conducted using the *PCR-Helicobacter pylori* diagnostic set of DNA Gdańsk according to the producer's recommendations. **Amplification reaction of *vacA* gene fragment** was performed using starters with the following sequence:
F: 5'-GAAATACAACAAACACACCGC-3'
R: 5'-GGCTTGTTTGAGCCCCCAG-3'.

*Helicobacter pylori* infection was diagnosed in patients with a positive result of the urease test and/or abnormal result of the urea breath test and ascertainment of bacterium presence in biopsy specimens of the stomach and/or the duodenum.

### Diagnostics in gastroesophageal reflux disease

**pH-metry** of the oesophagus was performed in all patients to assess exposure of the oesophageal mucosa to gastric contents. pH-metric measurements were accomplished using a one-channel antimony probe and the registering device Microdigitrapper 4 Mb by Synectics Medical. The probe was introduced through the nose into the oesophagus, placing the probe at the level of 4-5 cm over the lower oesophageal sphincter (LES). Lower oesophageal sphincter positions were defined using Strobel's formula (5 cm + 0.252 × child's length). More-over, all patients before placing the probe underwent endoscopic examination of the upper part of the gastrointestinal tract and the length of the stomach cardia was determined. The examination lasted for 18 h minimum and always included the period of night sleep. The total percentage of time with pH below 4, considered as the presence of acid pathological gastroesophageal reflux, called the reflux index, exceeded 4% [10].

Triple eradication therapy was applied in children and teenagers with confirmed *H. pylori* infection: clarithromycin, amoxycillin, PPI or metronidazole, amoxycillin, PPI (in patients who often received clarithromycin because of other indications) for a period of 7 days and later PPI for 3 weeks.

**Control urea breath test** and **control pH-metry** were performed to control efficacy of eradication therapy after 6 weeks from completion of treatment.

### Statistical study

Non-parametric independence test $\chi^2$ was used to verify dependences between infection with type I strains (CagA-positive VacA-positive) and GER incidence. A four-field correlation table was constructed and the value of $\chi^2$ ($\chi^2_{kr}$ = 3.81) was calculated. The result of this test was also confirmed in the test for two fractions.

Consent of the Bioethical Committee of L. Rydygier *Collegium Medicum* in Bydgoszcz was obtained to perform the study.

## Results

### *Helicobacter pylori* infection

A total of 101 patients in whom *H. pylori* infection was diagnosed were included in the study. Thirty-three patients (33/101, 32.7%) were infected with type I strain (CagA-positive VacA-positive), and 68 patients (68/101, 67.3%) with type II. The result of pH-metry was normal in the group of patients infected with type I *H. pylori* in 14 patients (14/33, 42.4%), but GER was diagnosed in 19 patients (19/33, 57.6%).

### Gastroesophageal reflux

Gastroesophageal reflux was diagnosed in 31 children and teenagers infected with type II *H. pylori* (31/68, 45.6%), but in 37 cases the result of the examination was normal (37/68, 54.4%). The precise data of this analysis are presented in Table I.

A statistically significant difference was not found in the analysis of GER incidence in the group of patients infected with type I and II *H. pylori*.

### Eradication of *Helicobacter pylori*

Eradication of *H. pylori* infection was obtained in 20 patients with type I infection (20/34, 58.8%) and in 52 patients infected with type II (52/67, 77.6%).

### Genetic type of *Helicobacter pylori*

Considering the group of patients infected with type I (CagA-positive VacA-positive), GER was *de novo* induced in 3 cases (3/20, 15%) and in 3 cases was withdrawn after eradication (3/20, 15%). No change in GER intensity was noted in 14 patients (14/20, 70%).

### Gastroesophageal reflux post-eradication

Gastroesophageal reflux was *de novo* induced in the group of patients infected with type II *H. pylori* in 6 cases (6/47, 12.8%) and in 6 cases was removed after eradication (6/47, 12.8%). No change in GER intensity was noted in 35 patients (35/47, 74.4%) in this group of patients. The result of pH-metry after treatment had no diagnostic value in 5 patients.

Differences concerning changes of GER intensity, its withdrawal and *de novo* induction after eradication of type I and II *H. pylori* infection were not statistically significant. Precise data of this analysis are presented in Table II.

## Discussion

Studies of recent years indicate that the incidence of gastroesophageal reflux disease varies depending on the geographic region. Incidence is higher in countries well developed economically. However, it was also observed that the percentage of persons with GERD symptoms and with *H. pylori* infection is lower than in the group without *H. pylori* infection, which may suggest a protective role of this bacterium on GERD [11]. Results of epidemiological studies indicate the presence of an inverse correlation between GERD and *H. pylori* infection [12, 13].

In our own studies *H. pylori* infection did not influence GER incidence in children and teenagers. Two hundred and fourteen patients with dyspeptic symptoms at the age of over 3 were included in the study. All the children underwent endoscopic examination of the upper part of the gastrointestinal tract and pH-metry. There was no difference concerning GER incidence (%) in the compared groups ($p = 0.99$ – *ns*). At that time there was no analysis of the significance of the bacteria's genetic type [14].

The following mechanisms should be considered in pathogenesis concerning the effect of *H. pylori* infection on GERD:

- influence on LES tension,
- influence on gastric secretion and induction of atrophic changes of the gastric mucosa,
- neutralizing activity of ammonium ions [2].

*Helicobacter pylori* infection causes disorder of the gastrin–somatostatin axis through diminishing the activity and amount of D cells in the pyloric part of the stomach. The dependence concerning *H. pylori* infection and the mechanism of D cell inhibition is not entirely known. It is supposed that inhibiting factors could be proinflammatory cytokines and TNF-α released by activated cells during infection. Interleukin-8 (IL-8) can be released by lipopolysaccharides (LPS) in the bacteria cell membrane and additionally can activate secretion of pepsinogen and gastrin [1].

**Table I.** Results of analysis concerning GER incidence in patients infected with type I and II *H. pylori*
***Tabela I.*** *Wyniki analizy występowania GER u pacjentów zakażonych I i II typem* H. pylori

| Genetic type of *H. pylori* | Without GER | GER | Total | % GER | Test for two fractions *p* |
|---|---|---|---|---|---|
| Type I | 14 | 19 | 33 | 57.6 | 0.26 (*ns*) |
| Type II | 37 | 31 | 68 | 54.4 | |
| Total | 51 | 50 | 101 | | |
| $\chi^2$ | | 1.28 | | | |
| *p* | | 0.26 (*ns*) | | | |

**Table II.** Results of analysis concerning *H. pylori* genetic type on change of GER intensity after eradication therapy
***Tabela II.*** *Wyniki analizy wpływu typu genetycznego* H. pylori *na zmianę stopnia nasilenia GER po eradykacji*

| GER intensity changes | Type I *H. pylori* | | Type II *H. pylori* | | Test for two fractions *p* |
|---|---|---|---|---|---|
| GER withdrawal | 3 | 15.0% | 6 | 12.8% | 0.81 (*ns*) |
| Without GER intensity changes | 14 | 70.0% | 35 | 74.8% | 0.85 (*ns*) |
| GER *de novo* | 3 | 15.0% | 6 | 12.8% | 0.81 (*ns*) |
| Total | 20 | 100% | 47 | 100% | |

Lopez *et al*. [15], noting *H. pylori* infection in the prepyloric region, measured the blood concentration of pepsinogen I and II, obtaining high concentrations accompanying infection and depending on infection of type CagA-positive VacA-positive.

It seems that differences concerning virulence among *H. pylori* strains can significantly influence the GERD pathomechanism. The influence of CagA-positive VacA-positive strains on gastroesophageal reflux disease is based on the effect on gastric secretion. More significant inflammation and induction of atrophic lesions in the gastric mucosa during infection with type I *H. pylori* causes a decrease of gastric juice acidity. The region *Cag PAI* also contains genes stimulating production of IL-8 by epithelial cells [9].

Hypergastrinaemia accompanying infection causes an increase of acidity and the volume of gastric acid, acceleration of gastric emptying and decrease of LES tension [2, 3, 5]. These are essential mechanisms in GER pathogenesis.

The presence of the CagA-positive strain was discovered in 33% of patients with *H. pylori* infection in the study of Mierzwa *et al*. [16], but infection with this strain did not correlate with more severe course of the disease.

Similar absence of dependence concerning *H. pylori* genotype (presence of *cagA* gene and *vacA* gene composition) and intensity of inflammatory lesions in the stomach were obtained in subsequent studies expanded with typing alleles of the *vacA* gene. A large majority of patients (50/56; 89%) were infected with strains possessing the *cagA* gene. Alleles s1 and s2 of the *vacA* gene were found in 47 (84%) and 2 patients (4%) respectively, but in 3 (5%) mixed genotypes s1 and s2 were noted, and in 4 (7%) allele s was not identified. Alleles m1 and m2 occurred with the same frequency, each of them being found in 24 patients (43%); in 7 (12%) alleles m1 and m2 were noted simultaneously, while in one patient (2%) allele m was not identified. Together mixed infections were discovered in 9 patients (16%), but 4 (7%) were infected with strains not typing alleles of the *vacA* gene [17].

Results of the study of Arents *et al*. [18] indicate the protective character of CagA-positive and iceA1 strains. Researchers in this study isolated CagA-negative and IceA1-negative strains from patients suffering from gastroesophageal reflux disease.

Deterioration of gastroesophageal reflux disease and its *de novo* induction was observed by Reshetnikov *et al*. [19] for 2 years in teenagers with type I infection in the pyloric region.

A lower rate of *H. pylori* incidence in patients with GERD is observed and this fact can confirm the protective role of this bacterium [6, 7]. Some researchers assume that this role is caused mainly by CagA-positive bacterium strains [20, 21] and occurs during infection of the entire stomach – pangastritis [2].

Parzęcka *et al*. did not observe a significant dependence in the analysis of the impact of pangastritis of *H. pylori* infection on the incidence of GERD in children and young people, without taking into account the significance of the genetic type of bacteria [22].

Most likely infection with type I strain causes peptic ulcer or atrophic inflammation. Strains with s1 alleles have strong cytotoxic activity, but s2 strains produce only a minimal amount of VacA toxin (or they do not produce toxin at all). Strains with genotype s1m1 are more virulent than s1m2 strains, causing more severe forms of infections. Type II is isolated from patients with a milder course of disease [9].

The protective character of CagA-positive strains results from extension and severity of induced inflammation due to the fact that severe inflammation causes significant impairment of acid production [8, 20, 21].

The protective role of CagA-positive strains was confirmed by Brazilian researchers in their studies [23]. They divided 108 patients infected with *H. pylori* (with diagnosed chronic peptic ulcer disease/gastritis and/or duodenitis or with symptoms of dyspepsia) into two groups: not suffering from gastroesophageal reflux disease and with oesophagitis measured on the scale I-IV. Colonization by CagA-positive strains did not differ statistically significantly between the two groups, but patients suffering from gastroesophageal reflux disease of degree II-IV were less colonized by bacteria than patients with degree I of the disease. Based on the results of these studies it is possible to conclude that CagA-positive strains protect the oesophageal mucosa from severe forms of gastroesophageal reflux disease.

Considering our studies, the genetic type of *H. pylori* did not influence GER occurrence and change of GER intensity after eradication therapy.

Fallone *et al*. [8] in their study assessing chronic duodenal ulcer disease also found that the type of *H. pylori* strains does not influence GERD occurrence.

## Conclusions

Genetic type of *H. pylori* did not influence gastroesophageal reflux occurrence or change of gastroesophageal reflux intensity degree after eradication.

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