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The potential role of *Helicobacter pylori* in chronic rhinosinusitis with or without nasal polyposis

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Abstract

Background Certain gastrointestinal and extra-intestinal diseases are caused by the gram-negative bacterium *Helicobacter pylori* (*H. pylori*). We aimed to determine the potential *H. pylori* role in chronic rhinosinusitis (CRS) with or without nasal polyposis. This cross-sectional study was conducted on 80 subjects of any age and sex diagnosed with CRS (CRSWNP and CRSSNP) who had failed medical treatment and scheduled for surgery. Patients were further categorised into two equal groups: study group ($n=40$) were diagnosed with CRS with or without nasal polyposis (CRSWNP and CRSSNP) who had failed medical treatment and scheduled for surgery, and control group (40 patients) were admitted for septoplasty. All patients had clinical assessment, physical assessment, diagnosis of rhinosinusitis (according to EPOS), based on symptoms, rhinoscopic/endoscopic findings, CT scan findings, questionnaire for gastroesophageal reflux disease (GERD), and questionnaire for laryngopharyngeal reflux (LPR). Samples were collected in the operating room during surgery from both groups and PCR tissue was done.

Results The study group patients demonstrated significantly higher history of GERD, LPR, and *H. pylori*. *H. pylori* patients had significantly lower ages than those without ($P=0.03$). Patients with *H. pylori* revealed significantly higher GERD history ($P<0.001$) and LPR ($P=0.002$) than those without *H. pylori*. History of GERD ($P=0.003$), LPR ($P=0.043$), and *H. pylori* presence ($P=0.028$) were significant predictors, controlling for the abovementioned variables.

Conclusions We concluded that a significant correlation was observed between the *H. pylori* presence in the sinonasal mucosa and nasal polyps and the development of chronic rhinosinusitis with or without nasal polyps.

Keywords Chronic rhinosinusitis, *Helicobacter pylori*, Nasal polyposis, Potential role

Background

Nasal polyposis is an inflammatory condition affecting the paranasal sinuses and nasal mucous membranes which arises in response to allergens and other microbes, among other stimuli with the prevalence of 1% and 4% in the general population between [1].

Common teardrop-shaped growths that develop in the nose or paranasal sinuses are nasal polyps. Although they have the potential to form in any paranasal sinus, they are most commonly observed in the region encompassing the middle meatus and osteomeatal complex. These are frequently associated with allergies and chronic infections, particularly fungal sinusitis [2].

Nasal polyps can arise due to various etiological factors, including inflammation, infection, or an imbalance in a metabolic pathway, such as the arachidonic acid pathway [3]. Although numerous bacteria and fungi have been cultured from nasal polyps, sterile cultures comprise approximately 35% of the total [4].

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Most people with nasal polyps have rhinorrhea, sneezing, anosmia/hyposmia, and post-nasal drip. When combined with an oral antihistamine, topical nasal steroid drops are typically very effective at alleviating symptoms. Short-term courses of systemic steroids are occasionally prescribed as well. Surgery (endoscopic sinus surgery) is the last resort to improve quality of life. The popularity of conventional nasal polypectomy has diminished as a result of its high recurrence rate [5].

Recent research has examined the role of gastroesophageal reflux disease (GERD) in the chronic rhinosinusitis (CRS) development and nasal polyp formation [6]. Due to the high *H. pylori* prevalence infection among GER patients, nasal mucosa may be exposed to the bacterium indirectly [7].

Certain gastrointestinal and extra-gastrointestinal diseases are caused by the gram-negative bacterium *H. pylori* [8]. There has been documented evidence of an association between specific extra-gastric manifestations and *H. pylori*, including neural disorders, diabetes mellitus (DM), ear and eye diseases, head and neck cancers, and cardiovascular and respiratory disorders [9].

Additionally, saliva, human dental plaques, ulcers and oral lesions, and adenotonsillar tissue have been found to contain this substance [10]. Subsequent research has identified *H. pylori* in the nasal mucosa of CRS [11] and nasal polyps with inconsistent outcomes, which may be ascribed to differences in sample size and detection techniques [12].

The aim of this study is to determine the potential *H. pylori* role in CRS with or without nasal polyposis.

Methods

This cross-sectional study was conducted on 80 patients of any age and sex. Patients were further categorised into two equal groups: study group (40 patients) were diagnosed with CRS and scheduled for surgery, and control group (40 patients) were admitted for septoplasty. The work was done at Department of Otorhinolaryngology, Benha University Hospitals, during period of 6 months with the Microbiology Department, Faculty of Medicine, Mansoura University, where all laboratory work was done. Written informed consent was obtained from the patient or their legal guardians.

Exclusion criteria for both groups were patients who received bismuth-containing drugs, antibiotics, proton pump inhibitors, H_2 receptor blockers, or antacids at least 4 weeks before surgery, who had previous functional endoscopic sinus surgery, with immunodeficiency states, DM, with known malignancy, and renal failure, and unfit for general anaesthesia.

All patients had clinical assessment involving personal history [residence, name, age, sex, marital status, occupation, family history, and special habit (smoking, alcohol)], present history: onset, course and duration of symptoms, history of GERD (acid regurgitation, heartburn), past history by asking about systemic medical disorders, medications and/or previous surgeries, prior *H. pylori* history infection treatment and diagnosis, current medication with proton-pump inhibitors, antacids, histamine 2-receptor antagonists, or prokinetic agents.

Physical assessment including general examination with stress on heart rate, respiratory rate and temperature, ENT examination [all patients had a full ORL, head and neck examination, anterior rhinoscopy: nasal polyps, and endoscopic nasal examination], and investigations [pre-operative computed tomography (CT) nose and paranasal sinuses, bone window, coronal and axial cuts, and routine pre-operative investigations (random blood sugar, complete blood count, etc.)].

Diagnosis of chronic rhinosinusitis, based on The European Position Paper on Rhinosinusitis (EPOS) 2012 guidelines which describe CRS as an inflammatory disorder defined by the presence of two or more cardinal symptoms [obstruction, drainage (anterior or posterior), smell loss, and facial pain or pressure] for at least 12 weeks duration, confirmed by objective evidence using sinus endoscopy or computed tomography (CT) scan. For study inclusion, the guideline requires at least two of four symptoms for at least 3 months duration, one of which must be either nasal obstruction or discharge.

Questionnaire for GERD

The GERD-Questionnaire (GERD-Q) had a sensitivity of 65% and specificity of 71% [13]. It covers four positive predictors of GERD: heartburn and regurgitation, sleep disturbance because of these two reflux symptoms and use of OTC medication and two negative predictors of GERD, epigastric pain and nausea. Patients were asked to reflect on symptoms over the preceding week. Scores ranging from 0 to 3 were applied for the positive predictors and from 3 to 0 (reversed order, where 3 = none) for negative predictors. The GERD-Q score was calculated as the sum of these scores, giving a total score ranging from 0 to 18.

Total score: 0 to 2 points = 0% had GERD possibilities, 3 to 7 points = 50% had GERD possibilities, 8 to 10 points = 79% had GERD possibilities, and 11 to 18 points = 89% had GERD possibilities.

Questionnaire for laryngopharyngeal reflux (LPR)

The reflux symptom index is in common use as a semi-quantitative tool to assess symptoms associated with LPR [13]. Reflux symptom index is a 9-item self-administered outcome instrument for LPR. This index appears to be valid and is highly reproducible.

The scale for each individual item ranges from 0 (no problem) to 5 (severe suffering), with a maximum score of 45. This questionnaire displays high reproducibility and validity for the diagnosis of reflux, if reflux symptom index (R.S.I) score more than 13 is defined as abnormal.

Sample collection

Under sterile conditions in the operating room, nasal polyps and/or ethmoid tissue samples for the case group and mucosa of the middle conchae samples for the control group were collected.

Sample preparation and nucleic acid extraction

A 25 mg tissue was cut into tiny pieces and placed in a 1.5 ml micro conical tube and GeneAll® Exgene™ 96 T mini kit (GeneAll Biotechnology Co, Seoul, Korea) was utilised for DNA extraction in accordance with manufacturer instructions.

Purified DNA can be kept at 4 °C or instant analysis and can be kept at 70 °C for long-term storage.

H. pylori Ure-A gene detection and Cag-A genes by polymerase chain reaction (PCR)

Using an automatic thermal cycler, the extracted DNA from both the case and control groups was amplified for the Ure-A gene via PCR. The samples that was positive for ureA *H. pylori* gene was further amplified for cag-A gene.

Ure-A gene detection by PCR

A total of 50 µl of master mix (2X TOP simple™ Dye MIX-NTAQ) was utilised for the PCR assay. This mix comprised 1 µl of extracted DNA and 0.5¼M of each primer. HPU1 Ure-A 5-GCCATGGTAAATTAGTT, while HPU2 Ure-A 5 CCCTGTTTTTAC. Thermal cycles were utilised to amplify the samples (Norwalk, CT, USA). Specimens underwent 35 cycles of amplification.

CagA gene detection by PCR

A 50 µl master mix (2X TOPsimple™ DyeMIX-nTaq) was utilised for PCR, which included 1 µl of extracted DNA and 0.5 µM of each primer (CagA forward 5 AATACA CCAACGCCTCCAAG-3 and CagA reverse 5 ATCTCA AGCTAACAGCCAAAA-3). The specimens were amplified for four cycles using an oil-free automated thermal ABI variation, manufactured in the USA. The initial cycle involved denaturation at 94 °C for 5 min. Subsequent cycles consisted of annealing at 500 °C for 30 s, extension at 72 °C for 40 s, denaturation at 94 °C for 5 min, and a final incubation at 72 °C for 5 min. PCR products were isolated and stained using a 3 g/ml solution of ethidium bromide (EtBr) on an agarose gel containing 3%. The stained gel was photographed utilising a digital imaging camera system.

Gel electrophoresis

Agarose gel electrophoresis system was used for detecting an amplified DNA target.

Statistical analysis

A SPSS v28 statistical analysis was performed (IBM Inc., Armonk, NY, USA). The quantitative variables were expressed as the mean and standard deviation (SD), and an unpaired Student's *t*-test was utilised to evaluate them between the two groups. It was utilised the Fisher's exact test or chi-square test, as applicable, to analyse qualitative variables expressed as frequency and % age (%). The relationship between additional independent variables was estimated utilising multivariate logistic regression. A two-tailed P value < 0.05 was deemed to indicate statistical significance.

Results

The study group consists of 40 CRS patients (25 (62.5%) patients with nasal polyps and 15 (37.5%) patients without nasal polyps). The study group demonstrated 17 (42.5%) patients positive for *H. pylori*. The *H. pylori* positive patients were 17 (13 CRS with nasal polyps and 4 CRS without nasal polyps).

The study group patients demonstrated significantly higher *H. pylori* (42.5%) than controls (20%) ($P=0.03$) (Table 1).

Patients with *H. pylori* revealed significantly higher history of GERD (76.5% vs. 17.4%, $P<0.001$) and laryngopharyngeal reflux (52.9% vs. 8.7%, $P=0.002$) than those without *H. pylori* (Table 2).

The study group patients demonstrated significantly higher GERD history ($P=0.007$), LPR ($P=0.045$), and *H. pylori* ($P=0.03$). Insignificant difference was reported between the two studied groups regarding sex, marital status, age, residence, and history of a similar condition (Table 3).

H. pylori patients had significantly lower ages than those without ($P=0.03$). Patients with *H. pylori* revealed significantly higher GERD history ($P<0.001$) and LPR ($P=0.002$) than those without *H. pylori*. No significant

Table 1 Presence of *H. pylori* in the studied groups

		Patients ($n=40$)	Controls ($n=40$)	*P* value
Presence of *H. pylori*	*n* (%)	17 (42.5)	8 (20)	**0.03***

H. pylori Helicobacter pylori

* Significant *P* value

Table 2 Clinical findings according to *H. pylori* in the studied patients

		Presence of *H. pylori*		*P* value
		Yes (*n* = 17)	No (*n* = 23)	
History of similar condition	*n* (%)	0 (0)	0 (0)	–
History of GERD	*n* (%)	13 (76.5)	4 (17.4)	**< 0.001***
History of laryngopharyngeal reflux	*n* (%)	9 (52.9)	2 (8.7)	**0.002***

H. pylori Helicobacter pylori, *GERD* gastroesophageal reflux disease

* Significant *P* value

Table 3 Demographics, clinical findings, and presence of *H. pylori* of the studied groups

		Study group (*n* = 40)	Controls group (*n* = 40)	*P* value
Demographics data				
Age (years)		27 ± 5	28 ± 6	0.626
Sex	**Males**	22 (55%)	19 (47.5%)	0.502
	Females	18 (45%)	21 (52.5%)	–
Marital status	**Single**	16 (40%)	13 (32.5%)	0.485
	Married	24 (60%)	27 (67.5%)	–
Residence	**Urban**	20 (50%)	20 (50%)	1.0
	Rural	20 (50%)	20 (50%)	–
Clinical findings				
History of similar condition		0 (0%)	0 (0%)	–
History of GERD		17 (42.5%)	6 (15%)	**0.007***
History of LPR		11 (27.5%)	4 (10%)	**0.045***
Presence of *H. pylori*		17 (42.5%)	8 (20%)	**0.03***

Data are presented as mean ± SD or number (%)

GERD gastroesophageal reflux disease, *LPR* laryngopharyngeal reflux, *H. pylori Helicobacter pylori*

* Significant *P* value as < 0.05

differences were observed regarding sex, marital status, and residence (Table 4).

Table 5 reports that the model revealed that history of GERD (OR = 6.479, 95% CI = 1.853–22.653, *P* = 0.003), history of LPR (OR = 3.781, 95% CI = 1.045–13.689, *P* = 0.043), and presence of *H. pylori* (OR = 3.358, 95% CI = 1.139–9.903, *P* = 0.028) were significant predictors, controlling for the abovementioned variables.

Discussion

CRS is a prevalent upper airway disorder and a significant health concern that, as its incidence rises, places a considerable economic strain on society [14]. CRS is a multifactorial disease whose pathophysiology is influenced by a multitude of systemic, host-related, and environmental triggers [15].

The cases included in our study had an approximate mean age of 27 years. This finding is similar to the research conducted by Bansal et al. [11] which examined the *H. pylori* prevalence in nasal polyps. The study's patients had an average age of 32 years. Conversely, Chaaban et al. [16] documented that their patients had respective mean ages of 42.5 and 38.4 years. This finding was comparable to that of Lathi et al. [17], who discovered that the optimal age range for affection was between the second and fourth decades.

In our study, CRS prevalence was slightly elevated in males with male:female ratio of 1.5:1. Bansal et al. [11] also documented a greater prevalence among males, with a ratio of males to females of 1.3:1. However, a Nigerian study revealed a preponderance of females (M:F = 1:1.2) [18]. All these results as regards sex distribution were statistically non-significant.

In our study, GERD symptoms were positive in 42.5% of study group in contrast to 15% in control group with heartburn being the most frequent presentation and this was statistically significant (*P* = 0.007).

Similarly with Ahmed Muhamad and Aseel Hamid [19], who examined 28 patients with CRS and reported that GERD symptoms were positive in 53% of their patients. Also, Bansal et al. [11] reported that GERD

Table 4 Demographics and clinical findings according to *H. pylori* in the study group patients

		Presence of *H. pylori*		*P* value
		Yes (*n* = 17)	No (*n* = 23)	
Demographics				
Age (years)		25 ± 5	29 ± 5	**0.03***
Sex	**Males**	7 (41.2%)	15 (65.2)	0.131
	Females	10 (58.8%)	8 (34.8%)	
Marital status	**Single**	8 (47.1%)	8 (34.8%)	0.433
	Married	9 (52.9%)	15 (65.2%)	
Residence	**Urban**	8 (47.1%)	12 (52.2%)	0.749
	Rural	9 (52.9%)	11 (47.8%)	
Clinical findings				
History of similar condition		0 (0%)	0 (0%)	–
History of GERD		13 (76.5%)	4 (17.4%)	**< 0.001***
History of LPR		9 (52.9%)	2 (8.7%)	**0.002***

Data are presented as mean ± SD or number (%)

H. pylori, *Helicobacter pylori*; *GERD*, gastroesophageal reflux disease; *LPR*, laryngopharyngeal reflux

* Significant *P* value as < 0.05

Table 5 Multivariate logistic regression analysis to predict rhinosinusitis

	OR (95% CI)	*P* value
History of GERD	6.479 (1.853–22.653)	**0.003***
History of LPR	3.781 (1.045–13.689)	**0.043***
Presence of *H. pylori*	3.358 (1.139–9.903)	**0.028***

OR odds ratio, *CI* confidence interval, *GERD* gastroesophageal reflux disease, *LPR* laryngopharyngeal reflux, *H. pylori Helicobacter pylori*

* Significant *P* value as < 0.05

symptoms were positive in 23.3%, 27.3%, and 20% of their cases respectively.

In our study, LPR symptoms were positive in 27.5% of study group in contrast to 10% in control group with throat clearing being the most frequent presentation and this was statistically significant ($P = 0.045$).

Loehrl et al. [20] assessed 20 CRS patients and reported that 95% (19/20) of the patients had LPR symptoms. Ahmed Muhamad and Aseel Hamid [19] examined 28 patients with CRS and reported that LPR symptoms were positive in 14% of their patients and this result was statistically significant.

In our study, LPR symptoms were present in 11 (64.7%) patients with positive GERD symptoms.

Vardar et al. [21] reported that LPR symptoms were present in 70% of positive GERD symptom patients. Mosli et al. [22] detected a total of 80 positive GERD symptom patients and found that LPR symptoms were found in 57 cases (71%).

As regards sex distribution of *H. pylori* in study group of our study, male and female distribution was 41.2% and 58.8% respectively.

Agarwal et al. [23] detected that *H. pylori* prevalence was slightly elevated in males with a female:male ratio of 1:1.7. Nikakhlagh et al. [24] examined 50 patients with CRS and reported that sinus samples of nine patients (18%) were positive for *H. pylori*. Of the nine cases, one patient was female, and eight patients were male. They reported that the higher prevalence of CRS in males might be related to higher incidence of gastritis and smoking in males than females. All these results as regards sex distribution were statistically non-significant.

In the present study, a statistically significant relation was detected between associated GERD symptoms and the *H. pylori* presence. *H. pylori* patients revealed significantly higher GERD history (76.5% vs. 17.4%, $P < 0.001$).

Bansal et al. [11] also reported an elevated GERD incidence in *H. pylori* positive cases.

Conversely, Rubenstein et al. [25] found no association evidence between GERD and *H. pylori* symptoms.

A wide range of invasive and non-invasive methods were employed for the *H. pylori* infection detection. *H. pylori* diagnosing can be challenging in situations where the bacterium is present in irregular forms, in low numbers, or in a patchy or intermittent distribution. Therefore, it may be imperative to employ various detection methods in order to arrive at a diagnosis [11].

In our study, we used PCR which is considered the gold standard technique in finding *H. pylori*.

Using PCR in our study, *H. pylori* (Urea A gene) was detected in sinonasal mucosa of 42.5% of CRS cases,

whereas it was found in only 20% of control group sinonasal specimens. This result was significant statistically ($P=0.03$). The *H. pylori* gene was amplified in samples that tested positive for urea; however, the cagA gene remained negative in all samples (both in the study and control groups).

Using PCR, Nikakhlagh et al. [24] detected *H. pylori* DNA in 18% of CRS participants. Ahmed Muhamad and Aseel Hamid [19] detected *H. pylori* DNA in 8% of nasal polyp patients.

Using both PCR and ELISA, Včeva et al. [26] investigated *H. pylori* in nasal polyp patients and they detected *H. pylori* in 28.5% of patients by PCR and 85.7% using ELISA.

In this research, *H. pylori* was more prevalent in the nasal cavity of CRS cases than in healthy controls. However, *H. pylori* transmission stays unclear, and there is little knowledge about its role in extra-gastric diseases. It has been suggested that the nasal and oral cavities serve as permanent or primary reservoirs for the *H. pylori* infection, thereby potentially promoting its transmission to others. While it is postulated that chronic inflammation can result from gastric content reflux into the nasal cavity and that GERD can disrupt lymphatic drainage or mucosal bacterial adherence, the precise mechanism by which GERD induces CRS remains uncertain [27]. It is hypothesised that *H. pylori* could potentially be accountable for tissue damage in certain instances of CRS, or that it could render the sinonasal mucosa more susceptible to the other causative agents of CRS.

According to the findings of our research, PCR is a crucial method for identifying *H. pylori* in samples of mucosal tissue.

We recommended that additional epidemiological studies with larger sample sizes are needed to check or refute the *H. pylori* role in the CRS development and to determine whether the addition of antibiotic and antireflux therapy to get rid of *H. pylori* to the treatment protocol for CRS patients has an effect.

Conclusions

Based on the results of this study, we concluded that there is a significant relationship between CRS and presence of *H. pylori* in sinonasal mucosa. This relationship may reflect the role of *H. pylori* as one of the pathogenic factors in the development of chronic rhinosinusitis.

Abbreviations

H. pylori	*Helicobacter pylori*
CRS	Chronic rhinosinusitis
GERD	Gastroesophageal reflux disease
LPR	Laryngopharyngeal reflux
DM	Diabetes mellitus
GERD-Q	GERD-Questionnaire
IC	Internal control
PCR	Polymerase chain reaction
SD	Standard deviation
Cag A	Cytotoxin associated gene A
NPs	Nasal polyps
OR	Odds ratio
ORL	Otorhinolaryngology
EPOS	European Position Paper on Rhinosinusitis and Nasal Polyps

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None to be declared.

Authors' contributions

AYY and AMA conceived and supervised the study; OAE and AYY were responsible for data collection. MAE and AMA analysed and interpreted the data. All authors provided comments on the manuscript at various stages of development. All authors read and approved the final manuscript.

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Availability of data and materials

Data and material are available on a reasonable request from the author.

Declarations

Ethics approval and consent to participate

It was approved by the ethics committee of Department of Otorhinolaryngology, Benha University Hospitals, during period of 6 months with the Microbiology Department, Faculty of Medicine, Mansoura University, where all laboratory work was done, and it was started at April 2023 and ended by October 2023. An informed written consent was obtained from the participants. Approval No. Ms16-1-2023.

Consent for publication

Written consent for publication was obtained from the patients participating in the study after informing them about the purpose of the study.

Competing interests

The authors declare no conflict of interest.

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