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ORIGINAL ARTICLE

A study on the roles of Helicobacter pylori in bile reflux gastritis and gastric cancer

Haige Huang[1]*, Jun Tian[2]*, Xin Xu[2,3]*, Qiong Liang[4], Xusen Huang[1], Jiaming Lu[1], Yongliang Yao[5]

[1]Department of Gastrointestinal Surgery, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, P.R. China; [2]Department of General Surgery, Zhangjiagang Hospital of Traditional Chinese Medicine Affiliated to Nanjing University of Chinese Medicine, Suzhou 215600, P.R. China; [3]School of Medicine, Jiangsu University, Zhenjiaing 2012013, P.R. China; [4]Department of Respiratory Medicine, The Affiliated Hospital of Youjiang Medical University for Nationalities, Baise 533000, P.R. China; [5]Department of Gastrointestinal Surgery, Qujing the Second People's Hospital of Yunnan Province, Qujing 655000, P.R. China

*These authors contributed equally to this study.

Summary

Purpose: *To observe the infection rates of Helicobacter pylori (HP) in bile reflux gastritis (BRG) and gastric cancer and the clinical significance of HP eradication in BRG and gastric cancer patients complicated with HP.*

Methods: *248 patients diagnosed with BRG and gastric cancer via gastroscopy were enrolled in this study. HP detection and infection rates of HP were evaluated. Then, BRG and gastric cancer patients complicated with HP were randomly divided into BRG group 1, BRG group 2, gastric cancer group 1 and gastric cancer group 2. BRG group 1 and gastric cancer group 1 were treated with conventional anti-inflammatory drugs for 10 days, and BRG group 2 and gastric cancer group 2 were treated with anti-HP drugs in addition to conventional anti-inflammatory drugs. One month after drug withdrawal, the infection rates of HP in each group were evaluated, and prognostic follow-up was performed to record the post-therapy patient conditions.*

Results: *HP infection rate was 35.8% (57/159) in the BRG group and 73.0% (65/89) in the gastric cancer group, with statistically significant difference ($p<0.01$). In patients treated with anti-HP drugs had the HP infection rate effectively reduced. The treatment effective rates of patients with BRG and gastric cancer complicated with HP infection after eradication of HP were 82.8 and 68.8%, respectively, while those of patients with non-eradicated HP were only 46.4 and 37.5 %, respectively. The differences between the two groups were statistically significant ($p<0.05$).*

Conclusion: *HP is directly and closely related to the occurrence of gastric diseases, HP infection rate in patients with gastric cancer is significantly higher than that in patients with BRG, and the treatment of HP can effectively improve the rehabilitation rate in patients with gastric diseases.*

Key words: *bile reflux gastritis, gastric cancer, gastroscopy, helicobacter pylori*

Introduction

HP is a helical Gram-negative bacillus that requires strict survival conditions as well as oxygen, nitrogen, hydrogen and various trace elements, and it is a unique and currently known microorganism surviving in the human stomach [1]. HP, as a main pathogen of gastric diseases, can cause a series of gastric diseases, such as gastritis, peptic ulcer and gastric lymphoma, and directly lead to the development of gastric cancer in severe cases [2]. A study by Lee et al. [3] reported that the infection

Correspondence to: Dr.Yongliang Yao. Department of Gastrointestinal Surgery, Qujing the Second People's Hospital of Yunnan Province, No.289 Qilin West Road, Qujing 655000, P.R. China.
Tel: +86 13508810661, E-mail: rgx5vg@163.com
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rate of HP is as high as 55% in populations around the world, of which BRG patients account for 62% of the infected population, and the pathogen of 70-80% of gastric cancer patients is HP infection. HP-specific toxin factor, host genetic diversity, and the regulation and influence of inflammatory response directly determine the occurrence and development of gastric diseases [4]. Therefore, this paper focused on the study and analysis of HP infection and the pathogenesis, regulation, treatment and prevention of BRG and gastric cancer.

Methods

General data

A total of 248 patients diagnosed with BRG and gastric cancer by gastroscopy and pathology in the Affiliated Hospital of Youjiang Medical University for Nationalities from October 2012 to October 2014 were included in this study. Among them, BRG patients (n=159) included 82 males and 77 females, aged 45.13±18.62 years, and gastric cancer patients (n=89) included 57 males and 32 females, aged 42.64±18.13 years.

Inclusion and exclusion criteria

Inclusion criteria: patients who had clinical symptoms and were diagnosed with BRG or gastric cancer through gastroscopy and pathology; gastric cancer patients with TNM stage I-II; and patients who did not take any antibiotics and anti-inflammatory drugs before study inclusion. *Exclusion criteria:* patients complicated with peptic ulcer, gastroesophageal reflux disease, gastric polyps, cardiovascular disease, hematological disorders and pregnant or lactating women. All of the patients provided signed informed consent. The study was approved by the ethics committee of the Affiliated Hospital of Youjiang Medical University for Nationalities.

Methods

During diagnosis with gastroscopy and histopathology, a bioptic specimen was taken from the anterior gastric antrum wall of each patient and was subjected to rapid urease strip test (Zhengzhou Wanhua Biological Technology Co., Ltd.). Meanwhile, a HP tester (by Shenzhen Zhonghe Headway Bio SCI&TECH Co., Ltd.) was applied on each patient to conduct ^{14}C-urea breath test, and a value of ≥100 dpm/mol CO_2 indicated that the test was positive. Patients who had positive results in the above two tests were considered to be infected with HP. BRG and gastric cancer patients complicated with HP infection were further randomly divided into BRG group 1 (n=28), BRG group 2 (n=29), gastric cancer group 1 (n=32) and gastric cancer group 2 (n=33). There were no significant differences in clinical data of patients between BRG group 1 and BRG group 2, as well as between gastric cancer group 1 and gastric cancer group 2. BRG group 1 and gastric cancer group 1 were treated with conventional anti-inflammatory drugs (esomeprazole, Chongqing LUMMY Pharmaceutical Co., Ltd., NMPN: H44024970) and mosapride citrate (Beihua Pharmaceutical Co., Ltd., Changchun, NMPN: H22024249), and BRG group 2 and gastric cancer group 2 were treated with anti-HP drugs (amoxicillin, Zhuhai United Laboratories Co., Ltd., Zhongshan Branch, NMPN: H44024970) and clarithromycin (Changchun Gaoxin Pharmaceutical Co., Ltd. of Xiuzheng Pharmaceutical Group, NMPN: H20050292) in addition to conventional drugs. After 10 days of treatment, the drugs were withdrawn and one month later, the results of urease and ^{14}C-urea breath tests in each group were evaluated. Patients were followed up for 1 to 3 years after discharge. The recovery situations of the patients treated with different drugs were compared and the evaluation criteria were based on the study of the therapeutic effects of gastric diseases by Kim et al. [5]. Excellent treatment effects included complete disappearance of clinical symptoms and normal gastric tissues detected by gastroscopy. Good treatment effects included disappearance of clinical symptoms, some inflammatory cytokines and bacteria but only minor gastric mucosal injuries detected by gastroscopy. Bad treatment effects included no improvement or even worsening of clinical symptoms, large numbers of inflammatory cytokines and severe gastric mucosal injuries.

Statistics

The Statistical Package for Social Sciences (SPSS) 22.0 software (Beijing Strong-vinda Information Technology Co., Ltd.) was used for data processing and analyses. Enumeration data were expressed as percents. Chi-square test was employed for comparison among groups. A p value <0.05 suggested that the difference was statistically significant.

Results

Comparisons of patient clinical data

There were no significant differences in gender, age, smoking, excessive drinking, sleep, exercise, taste, nationality, place of residence and hospitalizing time after clinical symptoms appeared (p>0.05; Table 1).

Results of HP positive infection rate detection

The results of urease and ^{14}C-urea breath tests were overtly different between BRG group and gastric cancer group (p<0.05). There were 57 (35.8%) patients who had done the two tests (urease: positive, and ^{14}C-urea breath ≥100 dpm/mol) and were diagnosed with HP infection in the BRG group and 65 (73.0%) in the gastric cancer group; the difference was statistically significant (p<0.05; Table 2).

HP infection after treatment

The HP infection rates in BRG group 2 and gastric cancer group 2 treated with anti-HP drugs com-

Table 1. Comparisons of patient characteristics

Characteristics	*BRG group (n=159) n (%)*	*Gastric cancer group (n=89) n (%)*	x^2	*p value*
Gender			1.64	0.445
Male	82 (51.6)	57 (64.0)		
Female	77 (48.4)	32 (36.0)		
Age, years			2.34	0.327
<40	72 (45.3)	33 (37.1)		
≥40	87 (54.7)	56 (62.9)		
Smoking			3.16	0.286
Yes	68 (42.8)	47 (52.8)		
No	91 (57.2)	42 (47.2)		
Excessive drinking			4.25	0.165
Yes	84 (52.8)	51 (57.3)		
No	75 (47.2)	38 (42.7)		
Sleep			3.57	0.274
Early	94 (59.1)	61 (68.5)		
Late	65 (40.9)	28 (31.5)		
Exercise			3.66	0.281
Yes	64 (40.3)	49 (55.1)		
No	95 (59.7)	40 (44.9)		
Taste			5.14	0.112
Light	81 (50.4)	47 (52.8)		
Greasy	78 (49.6)	42 (47.2)		
Nationality			2.25	0.462
Han	95 (59.7)	64 (71.9)		
Minority	64 (40.3)	25 (28.1)		
Hospitalization time after clinical symptoms appeared, hrs			3.28	0.208
<12	82 (51.6)	45 (50.6)		
≥12	77 (48.4)	44 (49.4)		
Place of residence			2.95	0.369
Urban	84 (52.8)	54 (60.7)		
Rural	75 (47.2)	35 (39.3)		

Table 2. Results of HP infection rate detection

Patient groups	*Urease*		*^{14}C-urea breath*		*HP infection*
	Negative n (%)	*Positive n (%)*	*<100 (dpm/mol CO_2) n (%)*	*≥100 (dpm/mol CO_2) n (%)*	*n (%)*
BRG group	94 (59.1)	65 (40.9)	97 (61.0)	62 (39.0)	57 (35.8)
Gastric cancer group	18 (20.2)	71 (79.8)	11 (12.4)	78 (87.6)	65 (73.0)
x^2	18.34	12.54	17.16	18.94	17.67
p					0.012

Table 3. HP infection rate after treatment in BRG subgroups

Subgroups	*Urease*		*^{14}C-urea breath*		*HP infection*
	Negative n (%)	*Positive n (%)*	*<100 (dpm/mol CO_2) n (%)*	*≥100 (dpm/mol CO_2) n (%)*	*n (%)*
BRG group 1	6 (21.4)	22 (78.6)	7 (25.0)	21 (75.0)	19 (67.9)
BRG group 2	24 (82.8)	5 (17.2)	25 (86.2)	4 (13.8)	3 (10.3)
x^2	17.16	17.67	22.67	25.47	26.54
p					0.004

bined with conventional anti-inflammatory drugs were clearly lower than those in BRG group 1 and gastric cancer group 1 treated with conventional anti-inflammatory drugs, and the differences were statistically significant (p<0.05; Tables 3 and 4).

Treatment's effectiveness

The treatment effective rates of BRG and gastric cancer patients complicated with HP infection after eradication of HP were 82.8 and 68.8%, respectively, while those of patients without eradication of HP were 46.4 and 37.5%, respectively (p<0.05; Tables 5 and 6).

Discussion

HP is a leading pathogenic factor of diseases of the digestive tract, and is closely related to the occurrence of various gastric diseases and gastric cancers [6]. Currently, ^{14}C-urea breath test is the gold standard for the diagnosis of HP infection and the detection of anti-HP drug efficacy [7]. Rapid urease test is a very simple and quick detection method for HP infection, which is usually performed together with gastroscopy [8]. The presence of HP infection is determined according to the pH value of NH_3 produced by highly active urease-decomposed urea in gastric mucosa collected through gastroscopy [9]. In this paper employed were ^{14}C-urea breath and rapid urease tests to strictly select patients by gastric diseases complicated with HP infection, and analyzed the roles of HP in RBG and gastric cancer, providing guidance and reference for future clinical therapies of RBG and gastric cancer.

The comparisons of the patient clinical data with RGB and gastric cancer revealed that gender, age, smoking, excessive drinking, sleep, exercise, taste, nationality, and place of residence did not affect the test results. The HP infection rate in RGB patients was obviously lower (35.8%) than that in gastric cancer patients (73.0%). The administration of anti-HP drugs in the course of treatment could effectively reduce the HP infection rates of patients, and patients with RGB and gastric cancer who were treated with anti-HP drugs had higher

Table 4. HP infection rate after treatment in gastric cancer subgroups

Subgroups	*Urease*		*^{14}C-urea breath*		*HP infection*
	Negative *n (%)*	*Positive* *n (%)*	*<100 (dpm/mol CO_2)* *n (%)*	*≥100 (dpm/mol CO_2)* *n (%)*	*n (%)*
Gastric cancer group 1	8 (25.0)	24 (75.0)	10 (31.3)	22 (68.8)	21 (65.6)
Gastric cancer group 2	27 (81.8)	6 (18.2)	26 (78.8)	7 (21.2)	6 (18.2)
x^2	16.87	18.34	13.14	14.16	16.54
p					0.018

Table 5. Comparison of treatment effect in BRG subgroups

Subgroups	*Treatment effect*			*Treatment effective rate*
	Excellent *n (%)*	*Good* *n (%)*	*Bad* *n (%)*	*n (%)*
BRG group 1 (n=28)	5 (17.9)	8 (28.6)	15 (53.6)	13 (46.4)
BRG group 2 (n=29)	11 (37.9)	13 (44.8)	9 (31.0)	24 (82.8)
x^2	10.62	11.31	11.54	13.64
p				0.021

Table 6. Comparison of treatment effects in gastric cancer subgroups

Subgroups	*Treatment effect*			*Treatment effective rate*
	Excellent *n (%)*	*Good* *n (%)*	*Bad* *n (%)*	*n (%)*
Gastric cancer group 1 (n=32)	5 (15.6)	7 (21.9)	21 (65.6)	12 (37.5)
Gastric cancer group 2 (n=33)	8 (24.2)	14 (42.4)	11 (33.3)	22 (68.8)
x^2	10.91	12.07	13.66	11.89
p				0.029

rehabilitation rates than those of patients treated with conventional drugs. BRG is a phenomenon of bile reflux mainly caused by decreased gastric antrum motility, and bile salts, non-binding toxic bile acids and other components in reflux bile damage the gastric antrum, triggering inflammation [10]. HP infection leads to massive release of gastrin in the gastric antrum, thus affecting the normal metabolic and motor functions of the duodenum and decreasing the peristalsis of the gastric antrum, so bile reflux is easier to occur [11]. The pathogenesis of HP infection-induced gastric cancer is that increased expressions of pathogenic factors (urease, etc.) and inflammatory mediators of chronic gastric inflammation after HP infection result in over-proliferation of gastric epithelial cells, induce the aggravation of inflammation and finally lead to the development of gastric cancer [12,13]. After entering into the digestive tract, HP can penetrate the gastric slime layer by virtue of the bacterial flagella, and reach the epithelial surface; at this moment, HP will secrete an adhesin to bind to epithelial cells, leading to the failure and apoptosis of epithelial cells [14,15]. Moreover, HP can form a barrier with immune function around the bacteria through the secretion of superoxide dismutase, catalase and urease hydrolyzed urea, which can resist the microbiocidal abilities of neutrophils and gastric acid [16]. Therefore, HP infection directly leads to development of inflammation, and in the process of inflammation development, glands in gastric mucosa are continuously damaged due to invasion of HP, and the patient's condition is aggravated accordingly. Furthermore, with aggravation of the condition, a large number of immune cells and the patient immune system are destroyed, and HP is more and more rampant in gastric tissue, forming a vicious circle, and eventually leading to the occurrence of gastric cancer [17]. The use of highly effective antibacterial drugs, like amoxicillin and clarithromycin, has a strong killing effect on HP [18]. Amoxicillin is a penicillin-based broad-spectrum β-lactam antibacterial drug that inhibits bacterial cell wall synthesis, which can wrap the bacteria into a sphere and make them dissolve and disappear from the center, and this antibiotic is the most commonly drug used for HP and streptococcal pneumonia in clinical practice [19]. Clarithromycin is a semisynthetic macrolide antibacterial agent, which inhibits bacterial protein synthesis by binding to bacterial ribosomes [20]. After HP is eliminated, the gastric mucosa and epithelial tissue regain the regulatory and metabolic functions, the effects of inflammatory cytokines in gastric tissue are abolished, and the naturally rehabilitation conditions are superior to those of patients using common anti-inflammatory drugs, which is consistent with the findings of Ghotaslou et al. [21].

This paper studied the HP infection rates in BRG and gastric cancer and the rehabilitation of patients after treatment of HP infection, and analyzed the impacts of HP on gastric diseases. However, the roles of HP in more specific gastric diseases and the positive rates in gastric cancer in different stages were not analyzed due to the limited experimental conditions, which need further experiments for study.

In conclusion, HP is directly and closely associated with the occurrence of gastric diseases, and the treatment of HP can effectively improve the rehabilitation rates of patients with gastric diseases.

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Conflict of interests

The authors declare no conflict of interests.

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