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Frequency of dyspeptic symptoms, anxiety, depression and health-related quality of life among patients with chronic gastritis according to Helicobacter pylori CagA and VacA status: a cross-sectional study

Objective — to determine the frequency of dyspeptic symptoms, anxiety and depression and to describe health-related quality of life in patients with chronic gastritis according to *Helicobacter pylori* cytotoxin-associated gene A and vacuolating cytotoxin A status.

Materials and methods. This cross-sectional study included a total of 84 patients with *H. pylori*-associated chronic gastritis (CG). Based on *H. pylori* virulence factors status patients were categorized into 2 groups: 50 patients with the cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA)-positive *H. pylori* strains (Group 1) and 34 patients with CagA- and VacA-negative *H. pylori* strains (Group 2). The *H. pylori* virulence factors were determined by the polymerase chain reaction using paraffin stomach biopsies. Serum IgA and IgG antibodies to CagA and VacA were evaluated by solid-phase enzyme-linked immunoabsorbent assay. The Hospital Anxiety and Depression Scale (HADS) was used to identify anxiety disorders and depression. The MOS 36-Item Short Form Health Survey (SF-36) questionnaire was used to assess the health-related quality of life (HRQoL). Statistical analysis was performed using Stata 11 and Statistica 6 software packages.

Results. Patients with CagA- and VacA-positive *H. pylori* strains were more likely to have epigastric pain than patients with CagA- and VacA-negative *H. pylori* strains (60 % vs. 35.3 %, $p = 0.026$). No statistical difference was observed between the frequency of epigastric burning, early satiety, and postprandial fullness in both groups ($p > 0.05$). Anxiety and depression were significantly more prevalent in patients with CagA- and VacA-positive *H. pylori* strains ($p = 0.041$; $p = 0.032$, respectively). Patients of Group 1 had significantly lower HRQoL in the domains of Role-Physical (50 vs. 75; $p = 0.0001$), Bodily Pain (57.5 vs. 77.5; $p = 0.0001$), General Health (45 vs. 75; $p = 0.0001$), Vitality (55 vs. 80; $p = 0.0011$) and Mental Health (56 vs. 84; $p = 0.0001$).

Conclusions. *H. pylori* CagA and VacA-positive status is an important factor that may have an impact on the clinical course of *H. pylori*-associated gastritis. Higher frequency of epigastric pain, anxiety, and depression, as well as lower health-related quality of life were observed in patients with CagA- and VacA-positive *H. pylori* strains.

Keywords: *Helicobacter pylori*, virulence factors, chronic gastritis, dyspepsia, anxiety, depression, health-related quality of life.

The relationship between *Helicobacter pylori*-induced gastritis and functional dyspepsia (FD) has remained in contention for many years. FD is the most common cause of chronic epigastric pain or discomfort. The causes of FD are multifactorial, but *H. pylori* infection is one likely candidate

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[18]. There is no pathophysiological explanation of how *H. pylori* may cause dyspeptic symptoms. It has been calculated that *H. pylori* eradication is associated with a 10 % (95 % CI: 6—14) therapeutic gain as compared to placebo with a number needed to treat of 14 (95 % CI: 10—25), and symptoms improvement ultimately occurs in nearly 40 % of *H. pylori*-eradicated patients [5].

The association between *H. pylori* infection and chronic gastritis (CG) is well accepted, while the role of chronic gastric inflammation in causing dyspeptic symptoms is controversial. Some studies have shown a positive association between the cytotoxin-associated gene A-positive *H. pylori* strains and the presence of dyspeptic symptoms [9, 12, 14].

The present study aimed to determine the frequency of dyspeptic symptoms, anxiety and depression and to describe health-related quality of life in patients with chronic gastritis according to *H. pylori* cytotoxin-associated gene A and vacuolating cytotoxin A status.

Materials and methods

This cross-sectional study was carried out from May 2021 to January 2023. It included patients over 18 years old who had received a diagnosis of *H. pylori*-associated CG. Patients with stomach malignant tumors, peptic ulcer disease, and other conditions that could significantly affect the study results or who had taken antibiotics or proton pump inhibitors within 2 weeks prior to the visit were excluded.

The Bioethical Expertise and Scientific Research Ethics Committee of Bogomolets National Medical University approved the study protocol, which was in accordance with the regulatory standards for research involving human beings (protocol № 159). All patients provided written informed consent before study entry.

A total of 84 patients were recruited for this study. Based on *H. pylori* virulence factors status patients were categorized into 2 groups: 50 patients with the cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA)-positive *H. pylori* strains with a mean age of 48.4 ± 5.7 years (Group 1) and 34 patients with CagA- and VacA-negative *H. pylori* strains with a mean age of 45.8 ± 5.4 years (Group 2). There was no statistically significant difference in age or sex among the two groups.

Patients' complaints like epigastric pain and burning, postprandial fullness and early satiety, history of presenting complaints, past medical history, family and social history, clinical examination findings were analyzed.

CG was diagnosed by esophagogastroduodenoscopy with proximal jejunoscopy, chromoscopy using an Olympus Evis Exera III device with high resolution, chromoscopy with magnification up to × 115, and narrow-band imaging (NBI) and followed by morphological examination of stomach and duodenal biopsies.

The *H. pylori* virulence factors (CagA and VacA) were determined by the polymerase chain reaction using paraffin stomach biopsies. Genomic DNA was extracted using a QIAamp DNA FFPE Tissue Kit (QIAGEN) according to the manufacturer's instructions. After DNA isolation, the CagA and VacA gene regions were amplified. The amplification was carried out in CFX Connect Real-Time PCR System (BioRad).

Serum IgA and IgG antibodies to CagA and VacA were evaluated by solid-phase enzyme-linked immunoabsorbent assay. A SUNRISE photometric reader (Tecan, Austria), an Elx50 automatic washer (BioTeck, USA), and incubator-shakers were used.

The Hospital Anxiety and Depression Scale (HADS) was used to identify anxiety disorders and depression [22]. The results were evaluated separately according to the subscales of anxiety (HADS-A) and depression (HADS-D). Scores were categorized as normal/no cases (0—7), mild/doubtful cases (8—10), and moderate or severe/definitive cases (11—21) of depression and anxiety.

The 36-Item Short Form Health Survey (SF-36) questionnaire was used to assess the health-related quality of life (HRQoL) [2, 21]. The results were evaluated by 8 domains: Physical Function (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Function (SF), Role-Emotional (RE), and Mental Health (MH). Then, the obtained domains were combined into two general components: physical component summary and mental component summary. The answers were scored in a standardized way, where the domains of each scale were summed and then converted into a scale from 0 to 100 (100 represents complete health).

Stata 11 and Statistica 6 software packages were used for statistical analysis. The normality of data distribution was assessed with the Shapiro-Wilk test. Continuous data were presented as mean ± standard deviation (M ± SD) or median with interquartile range (Me [IQR]), proportions were reported as number of cases and frequency. Mann-Whitney U test was used to compare means of 2 continuous not normally distributed variables. The frequency characteristics in two independent groups were compared by the chi-square (χ^2) test. A p-value < 0.05 was considered as statistically significant.

Results

Dyspeptic symptoms of varying severity were present in 64 patients (76.2 %): 37 (74.0 %) patients of Group 1 and 27 (79.4 %) patients of Group 2. Table 1 demonstrates data on the frequency of dyspeptic symptoms in patients with CG depending on the *H. pylori* virulence factors status. Patients with CagA- and VacA-positive *H. pylori* strains were more likely to have epigastric pain than patients with CagA- and VacA-negative *H. pylori* strains (60 % vs. 35.3 %, p = 0.026). No statistical difference was observed between the frequency of epigastric burning, early satiety, and postprandial fullness in both groups (p > 0.05).

Table 1. **Frequency of dyspeptic symptoms among patients with CagA- and VacA-positive and negative H. pylori strains**

Symptoms	Group 1 (n = 50)	Group 2 (n = 34)	p
Epigastric pain	30 (60.0 %)	12 (35.3 %)	0.026
Postprandial fullness	18 (36.0 %)	12 (35.3 %)	0.947
Early satiety	13 (26.0 %)	12 (35.3 %)	0.361
Epigastric burning	23 (46.0 %)	12 (35.3 %)	0.329

Table 2. **Anxiety cases among patients with CagA- and VacA-positive and -negative H. pylori strains**

Categories	Group 1 (n = 50)	Group 2 (n = 34)	p
No cases	24 (48.0 %)	25 (73.5 %)	
Doubtful case	9 (18.0 %)	5 (14.7 %)	0.041
Definitive cases	17 (34.0 %)	4 (11.8 %)	
Total subscale score	8.2 ± 5.7	6.7 ± 4.9	0.221

Table 3. **Depression cases among patients with CagA- and VacA-positive and -negative H. pylori strains**

Categories	Group 1 (n = 50)	Group 2 (n = 34)	p
No cases	30 (60.0 %)	29 (85.3 %)	
Doubtful case	13 (26.0 %)	2 (5.9 %)	0.032
Definitive cases	7 (14.0 %)	3 (8.8 %)	
Total subscale score	7.1 ± 4.4	5.0 ± 3.3	0.021

Table 2 shows data on the frequency of anxiety and depression in both groups of patients. Doubtful and definitive cases of anxiety were present in 9 (18.0 %) and 17 (34.0 %) Group 1 patients, respectively, whereas among Group 2 patients only 5 (14.7 %) doubtful and 4 (11.8 %) definitive cases were detected. Thus, we found that symptoms of anxiety were significantly more prevalent in patients with CagA- and VacA-positive *H. pylori* strains (p = 0.041).

The depression severity index was higher in Group 1 patients (Table 3). Doubtful cases of depression were detected in 13 (26.0 %) patients with *H. pylori* virulence factors positive status and 2 (5.9 %) patients with CagA- and VacA-negative *H. pylori* strains. Definitive cases of depression were present in 7 (14.0 %) patients of Group 1 and 3 (8.8 %) patients of Group 2. Cases of depression were observed statistically significantly more frequent among patients with CagA- and VacA-positive *H. pylori* strains (p = 0.032).

HRQoL scores among CG patients are shown in Table 4. Patients with CagA- and VacA-positive *H. pylori* strains reported lower physical and mental component summary scores. Patients of Group 1 had significantly lower HRQoL in the domains of RP (50 vs. 75; p = 0.0001), BP (57.5 vs. 77.5; p = 0.0001), GH (45 vs. 75; p = 0.0001), VT (55 vs. 80; p = 0.0011), and MH (56 vs. 84; p = 0.0001). PF (95 vs. 95), SF (62.5 vs. 75.0), and RE (66.7 vs. 66.7) scores were not statistically different between both groups (p > 0.05).

Discussion

Our study revealed that the majority of patients with *H. pylori*-associated gastritis had dyspeptic symptoms. R. Shrestha et al. found that CG was

Table 4. **Health-related quality of life in patients with CagA- and VacA-positive and -negative H. pylori strains, Me [IQR]**

Domains	Group 1 (n = 50)	Group 2 (n = 34)	p
Physical Function	95 [83—100]	95 [90—100]	0.7060
Role-Physical	50 [25—75]	75 [75—100]	0.0001
Bodily Pain	58 [40—68]	78 [68—100.0]	0.0001
General Health	45 [35—65]	75 [65—85]	0.0001
Vitality	55 [50—80]	80 [55—80]	0.0011
Social Function	63 [50—88]	75 [63—75]	0.1170
Role-Emotional	67 [33—100]	67 [67—100]	0.0520
Mental Health	56 [32—72]	84 [58—88]	0.0001

present in 41.66 % of patients with dyspepsia [16]. The causes of FD are multifactorial, but *H. pylori* infection is one among them [10]. *H. pylori* can cause chronic mucosal inflammation in the stomach and duodenum, which, in turn, may lead to abnormalities in gastroduodenal motility and sensitivity [4]. CG might also affect a variety of endocrine functions of the stomach including the production of the gastrointestinal hormones and neurotransmitters such as somatostatin, gastrin, and ghrelin. Although these abnormalities might cause symptoms in some patients with FD, there is no definite correlation between *H. pylori* and dyspeptic symptoms [11]. The CagA gene of *H. pylori* is a marker of the Cag-pathogenicity Island and its presence is associated with more severe disorders [3]. M. F. Moreno-Ochoa et al. supported the association between CagA-positive colonization and the presence of dyspeptic symptoms [12].

D. B. Nelson et al. found that CagA-positive *H. pylori* strains and depression may be independent factors associated with dyspepsia [14]. W.-P. Meng et al. determined that CagA-positive *H. pylori* strains can play a role in the pathophysiology of FD, but the pathogenetic mechanisms of the dyspeptic symptoms are still not fully clarified [11]. Some researchers have noted that the *H. pylori* virulent factors (CagA and VacA) positive status increases the frequency of epigastric pain and also affects the severity of morphological changes of the gastric mucosa [1, 8]. Other studies did not reveal a relationship between *H. pylori* virulent factors and clinical and morphological features [13]. Our study has shown that epigastric pain was observed more frequently in patients with *H. pylori* virulence factors positive status. Obviously, CagA- and VacA-positive *H. pylori* strains can lead to more severe grade of inflammation of the gastric mucosa, and, as a result, impaired gastric motility and sensitivity functions [1, 20]. R. D. Goodwin et al. showed a significant association between chronic gastritis, anxiety, and depression [6]. A. Takeoka et al. demonstrated that women aged under 50 years with *H. pylori*-associated atrophic gastritis more often had psychological disorders and depression [19]. Our findings confirmed that group of patients with CagA- and VacA-positive *H. pylori* strains is characterized by higher rate of cases of anxiety and depression. M. Soboka et al. also found higher frequency of depression in patients with *H. pylori* infection and dyspeptic symptoms [17].

This study also explored the HRQoL characteristics in patients with CG according to *H. pylori* CagA and VacA status. It was shown that the quality of life in patients with CagA- and VacA-positive *H. pylori* strains was statistically significantly lower in the domains of RP, BP, GH, VT, and MH. A decrease in quality of life in this group of patients can be explained by a possible change in the psychological state of patients and a higher prevalence of dyspeptic symptoms. Y. D.L. Sandi et al. revealed a significant relationship between the level of stress and quality of life in patients with CG [15]. However, there are no data from previous studies about the possible dependence of the quality of life and *H. pylori* virulent strains status. The role of CG in the occurrence of psychological disorders is still not fully understood. Nowadays several hypotheses have been proposed to explain this relationship as follows: disruption in the microbiome-brain-gut axis, changes in serotonin activity, and impaired stomach secretory function [7].

Also, we should mention that this study was limited by the cross-sectional design, small sample size, inability to study other genes associated with the Cag Pathogenicity Island, no data regarding concomitant diseases and risk factors, socioeconomic status, as well as the effect of eradication therapy on the dynamics of symptoms.

Conclusions

H. pylori CagA and VacA-positive status is an important factor that may have an impact on the clinical course of *H. pylori*-associated gastritis. Higher frequency of epigastric pain, anxiety, and depression, as well as lower health-related quality of life in the domains of Role-Physical, Bodily Pain, General Health, Vitality, and Mental Health were observed in patients with CagA- and VacA-positive *H. pylori* strains.

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acquisition of data, analysis and interpretation of data, drafting the article — L. M. N.;
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Частота диспепсичних симптомів, тривоги, депресії та показники якості життя, пов'язаної зі здоров'ям, у пацієнтів з Helicobacter pylori-асоційованим хронічним гастритом залежно від наявності штамів CagA та VacA: крос-секційне дослідження

Мета — визначити частоту диспепсичних симптомів, тривоги і депресії та оцінити пов'язану зі здоров'ям якість життя у пацієнтів з *Helicobacter pylori*-асоційованим хронічним гастритом залежно від наявності штамів CagA та VacA.

Матеріали та методи. До крос-секційного дослідження було залучено 84 пацієнтів з хронічним гастритом (ХГ), асоційованим з *H. pylori*. Залежно від наявності високотоксигенних штамів *H. pylori* (CagA, VacA) пацієнтів розподілили на дві групи. До групи 1 залучено 50 пацієнтів з ХГ зі штамами *H. pylori* CagA і VacA, до групи 2 — 34 пацієнтів з ХГ без зазначених штамів *H. pylori*. Визначення чинників вірулентності *H. pylori* проводили методом полімеразної ланцюгової реакції, імуноглобулінів (IgA, IgG) до антигену білків CagA і VacA *H. pylori* у сироватці венозної крові — методом твердофазного імуноферментного аналізу. Рівень тривоги та депресії оцінювали кількісно за допомогою Госпітальної шкали тривоги та депресії (Hospital Anxiety and Depression Scale (HADS)). Для оцінювання якості життя, пов'язаної зі здоров'ям, використовували опитувальник The MOS 36-Item Short Form Health Survey (SF-36). Статистичне опрацювання отриманих даних проводили з використанням пакетів статистичних програм Stata 11 та Statistica 6.

Результати. Біль в епігастрії статистично значуще частіше турбував пацієнтів з високотоксигенними штамами *H. pylori* (60,0 та 35,3 %; p=0,026). Статистично значущої різниці за частотою скарг на відчуття переповнення після їжі, раннього насичення та печіння в епігастрії між пацієнтами обох груп не виявлено (p>0,05). Серед пацієнтів з вірулентними штамами *H. pylori* CagA і VacA частіше реєстрували випадки тривоги (p=0,041) та депресії (p=0,032). У пацієнтів групи 1 були нижчими такі показники якості життя, як рольове функціонування, спричинене фізичним станом (50 та 75; p=0,0001), інтенсивність болю (57,5 і 77,5; p=0,0001), життєва активність (55 та 80; p=0,0011), психічне здоров'я (56 і 84; p=0,0001), загальний стан здоров'я (45 та 75; p=0,0001).

Висновки. Наявність високотоксигенних штамів *H. pylori* (CagA і VacA) — важливий чинник, що може впливати на клінічний перебіг *H. pylori*-асоційованого гастриту. У пацієнтів з вірулентними штамами CagA та VacA частіше спостерігаються скарги на біль в епігастрії, випадки тривоги та депресії, а також реєструють гірші показники якості життя, пов'язаної зі здоров'ям.

Ключові слова: *Helicobacter pylori*, чинники вірулентності, хронічний гастрит, диспепсія, тривога, депресія, пов'язана зі здоров'ям якість життя.

ДЛЯ ЦИТУВАННЯ

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