

HELICOBACTER PYLORI AND GASTRIC CARCINOMA

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Abstract: The aim of the study was to evaluate the relation of *Helicobacter pylori* (HP) infection and gastric cancer and a possible relation with a certain histopathological type of gastric cancer and localization within the stomach.

A cross-section study was conducted on 60 consecutive patients (45 men and 15 women) with an established histological diagnosis of gastric cancer. The patients were divided into 2 groups (HP positive and HP negative) and additionally, depending on histopathological type, into intestinal, diffuse and cardia cancer, and localization as cardia carcinoma, proximal and distal carcinoma. HP was detected with a rapid ureasa endoscopic test and a serologic immune essay.

Forty-two out of 60 patients 42 (70%) were HP positive. There were 36 intestinal type of gastric cancer, 34 (94.4%) HP positive (statistically significant), 19 patients with diffuse type, and 8 (42.1%) HP positive. The remaining 5 were carcinoma of cardia and all were HP negative. Thirty-seven (61.7%) were distal carcinomas, up to (76.2%) in the HP positive group, there were 18 (30%) proximal carcinomas and 5 (8.3%) localized on the cardia.

This study confirmed the high incidence of HP infection in patients with gastric carcinoma, particularly in those with an intestinal type of cancer. Carcinomas were predominantly localized in the distal part of the stomach, especially in the HP positive group of intestinal type. Carcinomas of cardia were negatively associated with HP infection.

Key words: *Helicobacter pylori*, gastric cancer.

Introduction

In the middle of the twentieth century, gastric carcinoma was the most frequently detected carcinoma. Nowadays, it is still very often detected (in some areas like Latin America, Ireland, Eastern Europe). In Japan and China it is rated as the most frequent carcinoma. In the last sixty years there has been a worldwide reduction in the frequency of and mortality from gastric carcinoma. The reason for this is not quite clear, but one of the possibilities may be an improved socioeconomic status globally. In spite of this encouraging evidence, gastric carcinoma is still the most frequent cause of mortality from malignant diseases.

It is interesting to mention that there is a tendency to a continuous reduction of distal gastric carcinoma, while in those with proximal localization and cardia cancer there is a continuous increase, suggesting the possibility of a different pathogenesis [1].

The etiological factors for the development of gastric carcinoma are divided into environmental, genetic, and predisposition factors (Table 1).

Table 1 – Табела 1

Etiology of gastric carcinoma *Етиологија на желудучној карцином*

| |
|---|
| – Environmental factors |
| HP infection |
| Dietary factors: salt excess, nitrates/nitrites, carbohydrates, fresh fruit and vegetable deficiency, frozen food, Vitamin C and E deficiency |
| Low socioeconomic status |
| Smoking |
| – Genetic factors |
| Familial gastric cancer |
| Gastric cancer associated with nonpolypose colon cancer |
| Blood group A |
| – Predisposing condition |
| Chronic atrophic gastritis with or without intestinal metaplasia |
| Pernicious anaemia |
| Intestinal metaplasia |
| Gastric adenomatous polyps >2cm |
| Gastric resection |
| Gastric mucosal dysplasia |
| Gastric peptic ulcer disease |
| Menetrier's disease |

Gastric carcinomas are classified according to histology as adenocarcinoma (85%), the remaining 15% belong to lymphomas and gastrointestinal

stromal tumours -GIST. According to the Laurens histological classification, adenocarcinomas are divided into diffuse and intestinal types, and cardia carcinoma is separated as a different type.

Since the discovery of HP in 1963 by the Australians B. Marshall and R. Warren – Nobel Prize winners for medicine in 2005 – there has been a significant change in the diagnosis and treatment of upper digestive diseases. HP is a gram negative, spiral, flagellar bacterium, widely distributed, with a high prevalence in Latin America and Africa (in some regions up to 90%), in Western Europe and USA around 30–40%, in Eastern Europe and Asia about 60–70%. The lowest incidence was registered in Australia 20% (Fig. 1).

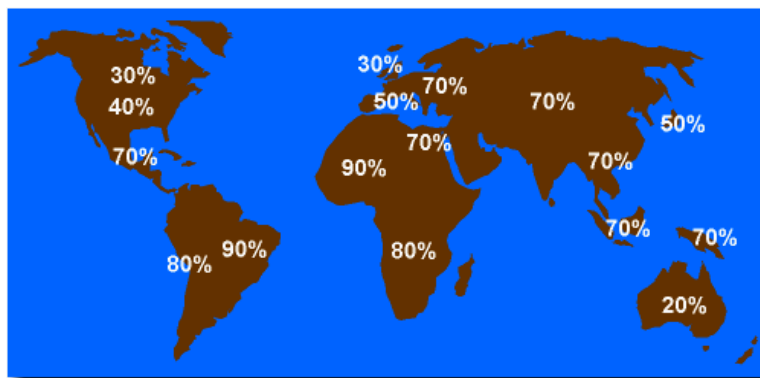


Figure 1 – Worldwide incidence of *Helicobacter pylori*
Слика 1 – Инциденца на *Helikobakter pilori* во светот

The WHO and the International Research Agency of the Cancer Consensus Group in 1994 proposed the opinion that there was sufficient epidemiological and histological evidence that HP is certainly carcinogenic [2].

The leading hypothesis explaining the role of HP infection in gastric carcinogenesis is as the induction of an inflammatory response. The inflammatory response is mainly caused by the capability of bacteria to synthesize the enzymes ureasa, phospholypasa and protease in the gastric lining membrane. These enzymes enable HP to survive in a milieu with low gastric pH but harmful for gastric mucosa, a situation that favours the development of atrophic gastritis, which leads to achilia, achlorhydria and bacterial proliferation. Bacterial overgrowth transforms nitrates into nitrites. Nitrites in combination with genetic factors provoke a metaplasia, dysplasia, abnormal cellular proliferation and genetic mutation eventually leading to cancer. Because of that, this hypothesis is called genotoxic [3].

Several studies have shown a higher prevalence of HP in patients with an intestinal type of carcinoma. In spite of this fact, the latest studies report a similar HP prevalence in intestinal and diffuse types of carcinoma. The frequ-

ency of HP in patients with non-cardia carcinoma is higher than in those with cardia carcinoma [4].

Besides all these facts supporting the rule of HP in patients with gastric carcinoma, only a portion of HP-positive patients develop carcinoma. This fact is a stimulus to further investigations.

The aim of this study is to evaluate the connection between HP and gastric carcinoma and to determine a possible relation of HP to a certain histological type of carcinoma.

Material and methods

We conducted a cross-section study which involved hospitalized patients and outpatients from the Gastroenterohepatology Clinic, Clinical Centre, Skopje, with a diagnosis of gastric adenocarcinoma.

The total number of 60 consecutive patients (Jan.-Aug. 2006) were divided into two groups depending on the results of an HP test (positive or negative). They were also divided into subgroups according to the histological type of cancer, and whether they were localized in the distal or proximal stomach or the cardia. Carcinomas were classified as intestinal or diffuse type based on the histology or as a separate entity – cardia carcinoma.

HP was detected using a rapid ureasa test with endoscopic biopsies (from antral and corporal mucosa of the stomach), and with a serologic test, considered as a positive if the titer of specific IgG was equal to 1.1 or higher.

The patients were declared HP positive when at least one of the tests was positive. If both tests were negative, the patient was declared HP negative. Inclusion criteria were gastric adenocarcinoma proved by histology.

Each patient was supplied with a questionnaire. Upper GI endoscopies were performed on all patients with Olympus GIF endoscopes in the Endoscopic Unit of the Gastroenterohepatology Clinic under local anaesthesia (Lidokain) or by intravenous application (of Diazepam, Midazolam or Propofol). From each suspected area, six biopsy samples were taken, plus two biopsies from the antral and corporal parts of the stomach for a rapid ureasa test. Blood samples were taken from each patient to determine the IgG specific HP antibodies.

Results were statistically evaluated by SPSS for Windows version 12.0 descriptive and non-parametric statistics. The level of significance was set at $p < 0.05$.

Results

The study was performed on 60 consecutive patients with proven gastric adenocarcinoma. Forty-two (70%) of the 60 patients were HP positive and the remaining 18 (30%) were HP negative, a statistically significant difference.

Thirty-six (60%) of 60 patients had an intestinal type of carcinoma, 19 (32%) a diffuse type, and 5 (8%) had cardia carcinoma.

Results show that 37 (61.7%) were distal, 18 (30%) were proximal carcinomas and 5 (8.3%) were localized on the cardia.

The average age was 64.85, with a minimal 45 and maximal 84 years. Gender distribution showed a male predominance with 49 (81.7%) with a male/female ratio of 4.45 (Table 2).

Table 2 – Табела 2

Gastric carcinoma
Желудочен карцином

| | HP | Gender | | Origin | | |
|-------------------|----------|--------|---|--------|---------|-------|
| Gastric carcinoma | Positive | 42 | m | 49 | Prox. | 18 |
| | Negative | 18 | f | 11 | Distal. | 37 |
| | | | | | Cardia | 05 |
| P < 0.05 | <0.01 | | | <0.01 | | <0.01 |

The intestinal type consisted of 36 cases, 34 (94.4%) HP positive, a statistically significant difference ($p < 0.05$). Distal carcinomas were 30 (83.3%) (Table 3).

Table 3 – Табела 3

Intestinal type
Интестинален тип

| | HP status | Gender | | Origin | | |
|-----------------|-----------|--------|---|--------|--------|-------|
| Intestinal type | Positive | 34 | m | 27 | Prox. | 06 |
| | Negative | 02 | f | 09 | Distal | 30 |
| | | | | | Cardia | / |
| P < 0.05 | <0.01 | | | <0.01 | | <0.01 |

19 cases were diffuse type carcinoma, 8 (42.1%) HP positive, 11 (57.9%) HP negative. Carcinomas were distal in 7 (36%) cases, and the remaining 12 (63.2%) were proximal (Table 4).

The HP positive group consisted of 34 (81%) intestinal type carcinoma, a statistically significant difference ($p < 0.05$), 8 (19%) diffuse type, and no case of cardia carcinoma. Distal carcinomas dominated with 32 (76.2%) and this is

of statistical significance. Gender distribution shows a male predominance (78.6%).

Table 4 – Tabela 4

| | | <i>Diffuse type</i> <i>Дифузен тип</i> | | | | |
|--------------|--------------|---|---|----|--------------|----|
| Cardia | HP status | Gender | | | Origin | |
| Diffuse type | Positive | 08 | m | 19 | Prox. | 12 |
| | Negative | 11 | f | / | Distal | 07 |
| | | | | | Cardia | / |
| P < 0.05 | <u>0.491</u> | <0.01 | | | <u>0.251</u> | |

carcinoma was detected in 5 cases and all were HP negative.

In the HP negative group 11 (61.1%) patients had diffuse type (statistically significant difference), 2 (11.1%) intestinal type and 5 (27.8%) carcinoma of the cardia. There were 8 (44.4%) proximal carcinomas, 5 (27.8%) distal and 5 (27.8%) localized on the cardia. The male predominance is more evident in this group with a ratio of 8: 1.

Discussion

In spite of the worldwide reduction in the incidence of gastric carcinoma, mainly in Western countries, particularly of the intestinal type, it is still one of the most frequent malignant diseases, and the second most common cause of cancer death [5].

Taking into account the results of the study, it may be concluded that HP infection is related to gastric carcinoma. A huge number of studies (Meta analyses) have shown that intestinal type carcinoma is strongly associated with HP infection. On the other hand, in the case of diffuse carcinoma the results are variable, ranging from highly related to those with a low association.

The study has shown that the presence of HP in the case of gastric adenocarcinoma is very high, especially in the group of the intestinal type.

HP infection is more related to distal carcinoma. It is interesting to mention that all carcinomas of the cardia were HP negative.

The sex ratio shows male predominance, regardless of equal HP distribution in both sexes.

Conclusion

In spite of the heterogeneity of the results from many worldwide studies, our results support the hypothesis that HP is an important risk factor in the development of gastric carcinoma. The results also show the indisputable relation of HP to gastric carcinoma, particularly to the distal intestinal type of gastric cancer.

Despite the facts which show the role of HP in the development of gastric carcinoma, nevertheless, a relatively small number of patients suffer from carcinomas. It is of interest to mention that in Africa, where the incidence of HP is very high (90%), the incidence of gastric carcinoma is very low (ratio 1000: 1).

This discrepancy shows that the epidemiological role of HP infection in the development of gastric carcinoma has to be taken only as an etiological factor in a multifactor process.

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Резиме

ХЕЛИКОБАКТЕР ПИЛОРИ И ЖЕЛУДОЧЕН КАРЦИНОМ

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Целта на оваа студија е да се определи поврзаноста на *Хеликобакџер ѓиллори* (ХП) со желудечниот аденокарцином, како и евентуалната поврзаност помеѓу ХП со хистолошкиот тип на карциномот и местото на појавување на желудочниот карцином (кардија, проксимален или дистален желудник).

Во оваа студија – пресек во една точка – беа вклучени 60 последователни пациенти (49 мажи и 11 жени) со патохистолошка дијагноза желудочен аденокарцином. Пациентите беа поделени во две групи, во зависност од тоа дали се *Хеликобакџер ѓиллори* позитивни или негативни. Во зависност од хистолошкиот тип беа поделени на интестинален, дифузен и карцином на кардија, а во однос на местото на појавување на карцином на кардијата, проксимален и дистален. *Хеликобакџер ѓиллори* беше определуван со брз уреаза тест и серолошки тест.

Од вкупниот број, 42 (70%) беа ХП позитивни, а 18 (30%) негативни. Интестиналниот тип на карцином беше регистриран кај 36 пациенти, а од нив 34 (94.4%) беа ХП позитивни (сигнификантна статистичка разлика). Со дифузни карциноми беа 19 пациенти, од кои 8 (42.1%) се ХП позитивни. Останатите пет беа карциноми на кардијата и сите беа ХП негативни. Од вкупната бројка 37 (61.7%) се дистални карциноми, а во ХП позитивната група (76.2%), проксимални карциноми се 18 (30%), а пет (8.3%) беа локализирани на кардија.

Студијата покажа дека застапеноста на *Хеликобакџер ѓиллори* кај желудочниот аденокарцином е висока. Интестиналниот тип на карцином е почесто поврзан со ХП инфекција. Карциномите на желудникот беа најчесто дистално локализирани, претежно во групата на ХП позитивни интестинални карциноми. Карциномот на кардија е негативно поврзан со ХП инфекцијата.

Клучни зборови: *Хеликобакџер ѓиллори*, желудочен аденокарцином.

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