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RESEARCH ARTICLE

The Age Aspect of Etiopathogenetic and Clinico-morphological Features of Chronic Gastritis

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Abstract

Chronic gastritis (CG) is a histopathologic entity characterized by chronic inflammation of the gastric mucosa with loss of gastric glandular cells. CG, pathological regeneration of the gastric mucosa, intestinal metaplasia (IM), and intraepithelial neoplasia or epithelial dysplasia (ED) of the stomach are common and are associated with an increased risk of gastric cancer. 800 patients (aged 8 to 80) were examined during the period of 2012-2017. Patients with CAG were diagnosed by endoscopy then underwent histological, bacteriological and cytological examinations. The Enzyme-Linked Immunosorbent Assay (ELISA) was used to detect antibodies to H+/K+ -ATPase and to Castle factors of parietal cells of the gastric mucosa in serum.

Keywords: *Helicobacter pylori (H. pylori) infection; Enzyme-Linked Immunosorbent Assay; gastric glandular cells.*

Introduction

Chronic atrophic gastritis (CG) is a histopathologic entity characterized by chronic inflammation of the gastric mucosa with loss of gastric glandular cells. CG, pathological regeneration of the gastric mucosa, intestinal metaplasia (IM), and intraepithelial neoplasia or epithelial dysplasia (ED) of the stomach are common and are associated with an increased risk of gastric cancer. CG and IM are considered to be precancerous conditions.

ED represents the penultimate stage of the gastric carcinogenesis sequence, defined as histologically unequivocal neoplastic epithelium without evidence of tissue invasion, and is thus a direct neoplastic precancerous lesion. ED is characterized by cellular atypia reflective of abnormal differentiation and disorganized glandular architecture.

Helicobacter pylori are Gram-negative bacteria that colonize the human gastric epithelium and represent one of the most common human infections worldwide. H. pylori infection is usually contracted in the first few years of life, and its prevalence increases with older age and lower socioeconomic status during childhood [1]. This infection is the primary inducer of CG, IM, and ED. More than half of all humans have H. pylori colonies in their stomachs; however, only a minority of H. pylori-infected individuals develops cancer of the stomach [2, 4]. Haziri et al [5].

Reported that the prevalence of H. pylori infection was high in patients with CG (66.0%), IM (71.7%), and gastric dysplasia (71.4%).At the same time, researches based on CG age-specific has been carried out long ago and there are practically no such researches in Russia [6,7]. This determined the relevance of this work. In connection with these data, in order to optimize the treatment, effective primary diagnosis of chronic hepatitis is very important, before the appearance of morphological signs of atrophy.

The Goal of Research

To study the age dynamics of chronic gastritis on the example of Russia population and to compare the data obtained with those from other countries.

Materials and Methods

800 patients (aged 8 to 80) were examined in 2012-2017.

They were divided into four groups. The first group (I) consisted of 250 children aged 8 to 12, the second group (II) included 200 adolescents aged 13 to 17, the third group (III) was represented by 190 adults aged 18 to 60, and the fourth (Iv) - 160 elderly people over 60. The survey was conducted at three clinical sites: 1) 2 Children Consultation and Diagnostic Policlinic in Saint Petersburg, 2) North-Western State Medical University named after I. I. Mechnikov (the department of Internal Medicine Propaedeutic with a course of gastroenterology endoscopy), and 3) 46 St. Eugenia City Clinical Hospital of St.

Petersburg. All patients (and / or their legal representatives) gave voluntary informed agreement to invasive examinations; the examinations correspond to the ethical standards of Declaration of Helsinki (2000) and the Order No. 266n dated Jun 19, 2003 of the Ministry of Health of the Russian Federation.

The survey did not include people with morphologically unconfirmed CG and CG related to gastric ulcer, duodenal ulcer and gastric cancer. The diagnostic criteria for H. pylori were seeding of H. pylori pure culture or coinciding of a positive H. pylorus results in all 3 methods used. The criterion for identifying a negative H. pylori status was coinciding of the negative results in all the methods used.

In the course of endoscopic examination, two biopsies were taken from the antrum (2 cm from the pylorus along the greater and lesser curves), two from the gastric mucosa of the stomach (middle third of the body along the anterior and posterior walls of stomach) and one was taken for duodenum biopsy (2 cm below the ligament of Treitz).

Cytological studies were conducted at the Central Research Laboratory of the St. Petersburg North-Western State Medical University named after I. I. Mechnikov. Azure-eosin dye by Romanovsky was used for staining a smear. The dye was diluted by exposure (1:10 proportion) with staining time - 3 minutes and according to Steedman's solution. Microscopy was carried out by micronucleus test (n = 162) and detection of H. pylori (n = 450). 400 patients underwent bacteriological examination of biopsies from the antrum of the gastric mucosa that was performed at the Laboratory of Molecular Immunology of St. Petersburg Pasteur Institute. 150 patients underwent H. pylori genotyping examination for identifying cagA, cagC, and cagH genes at Institute of Experimental Medicine RAMS.

Serology or antibody testing for H. pylori infection and Cag Antigen was conducted in 400 patients by ELISA using sets of specific testing systems developed at St. Petersburg Pasteur Institute: "Anti-H. Pylori IgG". The study was carried out at the Laboratory of Molecular Immunology of St. Petersburg Pasteur Institute.

All patients were examined using HELPIL-test produced by "Sintana SM" Ltd., St. Petersburg, Russia. The study presents a clinical trial of a new gas analyzer "HelicoSense" (Patent of Russian Federation for Utility Model No. 30545.The International Patent Classification (IPC) 61B5/00, G01N33/497). The determination of antibodies to H+/K+ -ATPase and to Castle factors of parietal cells of the gastric mucosa in serum was carried out by ELISA using standard sets produced by "ORGENTEC" (Germany).

The normal level of antibodies to H + / K + -ATPase is no more than 10 IU/ml. A double increase in the level of antibodies was considered as moderate and more than 2 times increase was considered as significant. The normal level of antibodies to Castle factor is no more than 6 IU/ml. The analysis was carried out at the Laboratory of Molecular Immunology of St. Petersburg Pasteur Institute.

The study used also non-morphological approaches for gastric mucosa assessment. The pepsinogen I (PGI), pepsinogen II (PGII), Helicobacter pylori Antibody, Gastrin-17 (G-17) were determined in serum by ELISA method using BIOHIT Gastro Panel, produced in the BIOHIT Service Lab, Finland.

Antibodies IgG-EA-EB V and IgM-NA-EB N were determined by ELISA using standard kits produced by "Vector-Best". The assessment was carried out according to the level of negative control, the extinction

coefficient for IgG antibodies was 0.308, and for the IgM antibodies - 0.502 including "gray zone" measuring. Higher coefficients indicate the presence of antibodies to EBV proteins (Epstein-Barr virus). Student's t-test with significance assessment ($p < 0.05$) by values $M \pm t$ was used for compering mean value of quantitative indicators in the study groups.

The *p*-value ($p < 0.05$)/Pearson Chi-square test were used while evaluating the relationships of qualitative indicators.

Results and Discussion

Clinical Features of Chronic Gastritis in the Examined Patients

Various disorders of trophological status among children and adolescents were determined during objective examination. They were underweight (13.4% and 20.6%, in the I and II groups, respectively and 4.6% in the IV group, $p < 0.05$), more often than elderly people. Obesity was least often observed in adolescents (9.3% in group II, in all other 16.3% -25.5%, $p < 0.05$).

50% of patients had symptoms of polyhypovitaminosis and mineral deficiencies. We consider poor nutrition of modern schoolchildren as the reason of trophological status disorders. Children and adolescents (69.8% and 79.2%) had more significant pain on palpation than patients of older age groups (41.8% and 23.4%; p1.3 <0.05; Pl, 4 <0.05; p2.3 <0.05; P2.4 <0.05), especially near the epigastrium, which facilitated the possibility of topical diagnosis. Pains in the pyloroduodenal are and in the right hypochondrium were decreasing significantly with age. Meanwhile, there were significant differences between patients with abdominal pain caused by intestines disorders (23.4% - 32.5%; $p > 0.05$).

Adults and the elderly patients the most frequently had no pain on palpation (III group - 34.5%, IV group - 50%) the younger groups had statistical different results (10.8% and 8.9%; p1.3 <0.05; 1.4 <0.05; p2.3 <0.05; p2.4 <0.05; p3.4 <0.05). The age-related dynamics of palpatory pain syndrome and subjective complaints on abdominal pain were similar. Hepatomegaly was equally common in all studied groups (9% -11.3%; $p > 0.05$). Tonsillar hypertrophy and micropoliadenia were more frequently observed in children and adolescents than in adults and elderly patients.

The presence of these symptoms did not have a correlation with herpes viruses' infection in all studied groups ($p > 0.05$). The frequency of endoscopically positive gastro esophageal reflux disease (GERD) did not differ in the studied groups with averaged 14.6%, since heartburn was more common in children and adolescents. The discrepancy between the frequency of heartburn and the GERD in patients of different age groups may be due to the peculiarities of acid formation in different age periods.

Hyperacidity prevails in children and adolescents (45.6 and 52%) and was not found among elderly patients (0%, $p < 0.05$). However, almost every fifth child or teenager was diagnosed with hypoacidity (18.1% and 20.3%, respectively, in groups I and II). With age, the frequency of hypoacidity increased (54.3% in group IV, $p < 0.05$) and antacid states appeared (4% in group III, 25% in group IV, $p < 0.05$). Normacidity was observed with the same frequency in all groups ($p > 0.05$). Children and adolescents reviled to have no significant correlation between the pH level and the presence of antibodies to H + / K + -ATPase of the parietal cells of the gastric mucosa.

Meanwhile, adults and elderly patients were identified with a negative correlation between the level of antibodies to H + / K + -ATPase and acid formation in the stomach: g = -0.36, $p < 0.05$. Indicators of pepsinogen I (PGI), pepsinogen II (PGII) in serum can be the cause of a decrease in enzyme formation in the gastric mucosa with age. Minimal levels of PGI and PGII were recorded in the elderly patients, while differences with groups of adolescents and adults were statistically significant (p1.4 <0.05; p2.4 <0.05). Fundamental studies explain this fact by the atrophic changes in the gastric mucosa of the stomach.

Endoscopic Features of Chronic Gastritis in the Examined Patients

Most often, gastritis with affections of the antrum was determined endoscopically in all groups (51% -80% without statistical difference between groups, $p > 0.05$). The next in frequency was gastritis with affections of both parts of the stomach (20% -49%, $p > 0.05$). No patients had an isolated affection of the stomach. Affection of the surface of the gastric mucosa was observed with the same

frequency between groups I (29.8%) and II (20%, p> 0.05). Only group III had significant differences caused by the presence of superficial gastritis of the fundal part of stomach - 49% (p <0.05). In group IV significantly more frequent than in all other groups, the range of surface changes decreased (9.2%), due to the presence of gastric mucosa atrophy-17%, where the atrophy of the fundus was not determined by endoscopic examination. The changes revealed in the fundus were associated with affections of the antrum and were determined as gastritis with affections of both parts of the stomach. With age, a significant decrease in the frequency of antral gastritis was observed (p <0.05 between the I and IV, II and IV, III and IV groups, Fig. 1).

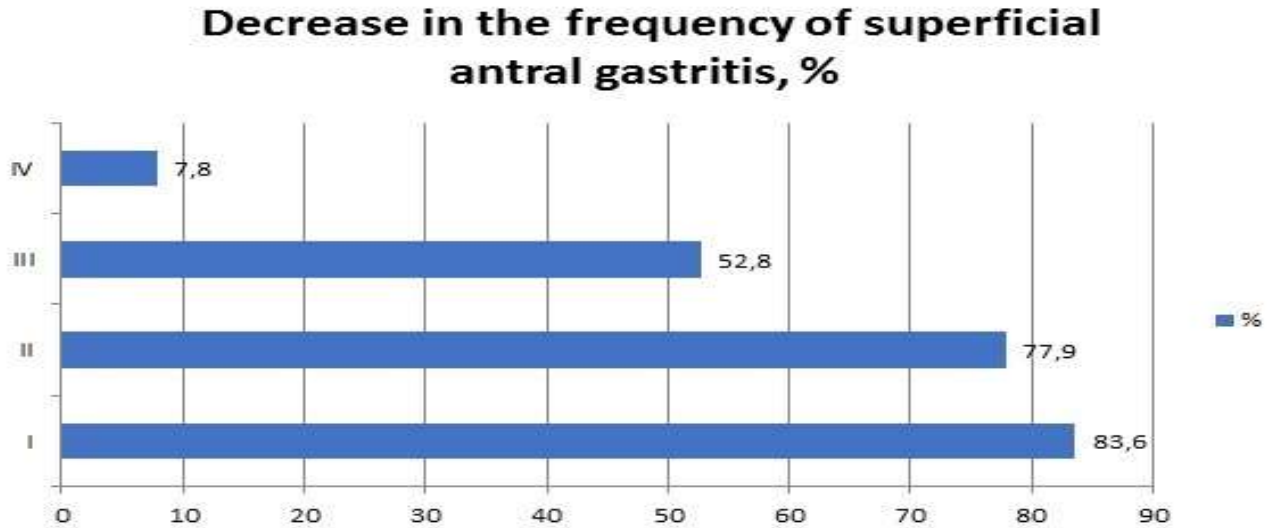

Figure 1: Indicators of the frequency of superficial antral gastritis in the four studied groups of patients of different age

The nodular lesion distinguishing for young people was significantly more frequently observed in groups I and II (16.4% and 16.6%) and was practically not observed in groups III and IV (0% and 1.5%). The frequency of atrophic antral gastritis increased significantly with age from 0.6% in adolescents to 70.7% in the elderly patients.

Erosive gastritis was equally often detected in the II (4.9%) and III (10.9%) groups and was practically not detected in children (p <0.05). The maximum frequency of erosive changes occurred in the elderly patients (20%).

No patients were observed with normal endoscopy of the antrum.

The high frequency of endoscopic changes of the duodenum in the examined patients (up to 70%) gains the most attention.

Histological Picture of the Gastric Mucosa and Duodenum Associated with Chronic Gastritis in Patients of different Age Groups

Morphologically, the most frequently detected were active gastritis (44.4% -73.6%, p> 0.05) and inactive gastritis (26.4% -51.8%, p> 0.05) with affections of both parts of the stomach (80% and 3.8% - in group II; 51% and 5.6% - in group III; 73.8% and 0% in group IV; (p <0.05)). Morphologically, CG was detected with endoscopically unchanged gastric mucosa of the fundus. The frequency of endoscopically and morphologically identified antral gastritis was 72% and 7% in group I; 80% and 3.8% in group II; - 51% and 5.6% in group III; -73.8% and 0 % in group IV;(p <0.05).

Patients of all age groups were frequently recorded with the inflammation of the fundus associated with severe lymphocytic infiltration (57.2% -75.5 %; p> 0.05). Children more often than in adolescents, along with lymphocytic were observed with plasmacytic infiltration (15.2% and 2.3%, p <0.05) which was not detected at all in the elderly patients (p <0.05 between groups I and II, I and III, I and IV). Eosinophilic infiltration had no differences between groups (p> 0.05). The studied groups were equally often observed with the lymphoid follicles (from 7.2% to 14%, p> 0.05). The significant activity of inflammation was maximum in group IV (22.8%).

The severe lymphocytic infiltration in the antrum was less often observed in adolescents (35.8%), the differences were significant compering with groups III and IV, p <0.05.

Meanwhile, lymphoid follicles were significantly more frequently found in children than adolescents and elderly patients, as well as plasmocytic infiltration (17.9% - group I; 3.8% - group II; 1.8% - group III and – 0% - group IV; p>0.05). Eosinophils were observed with equal frequency for all studied groups (1.7% -4.5%, p> 0.05). Moderate neutrophilic infiltration of the gastric mucosa was equally common for all age groups (37% -44.7%, p> 0.05), while severe neutrophilic infiltration was the most frequent in elderly patients (28.2%) with a significant difference compeering to the rest groups (4.5% -7.5%, p <0.05).

The group of adult patients the most frequently suffered from the lack of neutrophil infiltration of the gastric mucosa in the antrum (55.5), the difference is significant comparing to elderly patients. Microcirculation disorders increase in frequency in both parts of the gastric mucosa with age. Differences were significant 1) between groups I and II, I and III and I and IV in the frequency of severe edema of fundal gastric mucosa (I - 6.9 %, II - 21.9 %, III - 38.8 %, IV - 26.3 %) (p <0.05); 2) between groups I and II, I and III, I and IV, II and III, II and IV in the frequency of hemorrhages (I - 2.7%, II - 17.8 %, III - 53.7%, IV - 80, 7 %) and 3) micro thrombosis (I - 0%, II - 12.1%, III -31.4 %, IV - 26.3 %)(p <0.05) in the body of the stomach. Besides, in the fundal part of the stomach, there was a significant difference in the frequency of mucus hyper secretion between groups I and III and I and IV - (5.5% in group I, 12.1% in group II, 20.3% in group III, 19.3 % in group IV; p <0.05).

Severe edema in the antrum is less common for children, with a significant difference between the other groups (I - 5.8%, II - 21.9%, III - 38.8%, IV - 22.8%). As well as in the body of the stomach, significant differences were found between groups I and II, I and III, I and IV, II and III, II and IV in the frequency of hemorrhages (I - 2.9%, II - 12.1%, III - 53.7%, IV - 85.9%) and micro thrombosis (I - 1.5%, II - 5.1%, III - 31.4%, IV -38.6%) (p <0.05).

The frequency of hyper secretion in the antrum has no significant differences between the groups (I - 5.9%, II - 12.1%, III - 10.2%, IV - 8.8%, p> 0.05). There were significantly positive correlations between age and the presence of hemorrhages, micro thrombosis and severe edema in both parts of the gastric mucosa. Fibrosis in the body of the stomach was observed with a frequency of 40.2% in group I, 47.1% in group II, 83.6% in group III, 94.7% in group IV; (p <0.05 between groups I and III, II and III, II and IV).

Fibrosis in the antrum of the gastric mucosa was detected: 67.1% in group I, 64.6% in group II, 90.7% in group III, and 96.4% in group IV (p <0.05 between groups I and III, I and IV, II and III, II and IV). The frequency of local glands destruction of the gastric mucosa of the stomach body in children did not differ from adults and the elderly patients (18.7% -25.1%, p> 0.05). Atrophy of the glands was also detected in childhood and in adolescents, - 2.7% and 5.3%, respectively, in the gastric mucosa of the stomach body, 8.9% and 20.7% in the gastric mucosa of the antrum.

In adults and people over 65, the frequency of atrophic changes was 38.5% in the gastric mucosa of the stomach body and 82.4% % in the gastric mucosa of the antrum, which was significantly more frequent than in children and adolescents (p <0.05). Intestinal metaplasia was most significant for the III and IV age groups, but it was also observed in adolescents - 1.1% (p <0.05 between groups I and III, I and IV, II and III, II and IV).Dysplasia in the gastric mucosa of the antrum was not found in children or adolescents, and dysplasia in the body of the stomach wasn't found in any patients.

Histologically, duodenitis was detected in all patients, and was significantly more often than with endoscopic examinations (p <0.05)., The stage of duodenitis in children and adolescents was higher than in older patients (in group I, the duodenitis of the 2nd stage frequency was 37.1% - in group I, 20% - in group II, 35.2% - in group III, and 8% - in group IV (p <0.05 between groups I and IV, II and IV, III and IV).

Inflammation without exacerbation was significantly more often diagnosed in older people (p <0.05 between groups I and IV, II

and IV, III and IV). Meanwhile, the frequency of severe lymphoplasmacytic infiltration in the duodenal mucosa did not differ for the first three age groups from that in the body of the stomach and antrum ($p > 0.05$). The frequency of atrophy in duodenal mucosa increased with age, from 0% in children to 34.6% in the elderly patients ($p < 0.05$) and was similar to the frequency of atrophy in the body of the stomach, but was significantly less frequent ($p < 0.05$) than in antrum in children, adults and elderly patients. The frequency of stromal fibrosis in the duodenal mucosa was high in all groups and increased with age, from 40% in children to 84.6% in the elderly group ($p < 0.05$).

Meanwhile, the frequency of fibrosis in the duodenum, in the body of the stomach and in the antrum was similar for children, adolescents and elderly patients, $p > 0.05$. A morphometric study of duodenal mucosa revealed that the total thickness of the mucosa, height and width of the villi, the depth of the crypts and the height of the villi enterocytes in patients under 18 years are significantly different from those in other age groups ($p < 0.05$).

There is a decrease in the total thickness of the mucous; in height, width and depth of the villi, the coefficient of the villous/crypt; villi and crypts enterocytes' volume also decreases depending on age. More than half of the world's population suffers from H. pylori infection, and it continues to play a key role in the pathogenesis of a number of gastro duodenal diseases [8, 2]. Therefore, CG is classified as a Group 1 carcinogen according to World Health Organization classification. Epidemiological studies have determined that the predicable risk of gastric cancer caused by H. pylori infection is approximately 75% [9].

Although there is a fact that the prevalence of H. pylori decreases in all age groups, understanding of the spectrum of diseases caused by this bacterium continues to increase [11]. The study compared CG in different age groups among the Russian population.

The clinical picture of chronic gastritis (CG) depending on age is characterized by a decrease in the frequency of ulcerative and gastritis variants processes and an increase in indefinite pain syndrome in old age along with the progression of coexisting diseases of the digestive organs as well as other organs and systems; differences in HP genotypes found in both children and adults; different structure of coexisting chronic infections and the frequency of the parietal cells damages with auto antibodies.

The histological picture of chronic hepatitis usually shows an active gastritis with damages of both the antral and fundic mucosa of the stomach in all age groups. With age, the inflammation increases in the gastric mucosa (GM), microcirculatory disorders, stromal fibrosis, atrophy of glands and intestinal metaplasia are progressing. Atrophy of glands of the gastric mucosa starts at an early age. The study compares the frequency of Helicobacter pylori (H. pylori) infection in the presence of chronic gastritis in children and adults, 63.8% -80% respectively.

Meanwhile, children and adults have causative agents of different genotypes. 52% of children and 40% of adults have H. pylori infection combined with herpes virus infections, when H. pylorus as a single infectious agent is rare. The nature of gastrointestinal complaints in patients of different ages is similar with different H. pylori status and herpes virus infection.

Such differences occur due to presence of coexisting diseases. The functional and morphological characteristics of chronic gastritis depend on 1) the presence of H. pylori infection; 2) whether H. pylori infection is combined with herpetic infections; 3) whether H. pylori infection is combined with enterovirus infections, and 4) single-agent infection with herpes viruses. Among patients with chronic gastritis, 23.9% of children and 51.5% of adults were reviled to have an increased level of antibodies to H + / K + -ATPase of parietal cells and 3.8% of children and 93.7 % of adult were reviled to have antibodies of Castle factors.

The frequency and the level of auto antibodies to H + / K + -ATPase and to Castle factor increases with age and correlates with the increase of inflammation, microcirculatory disorders, stromal fibrosis, atrophy of glands, meanwhile in adult patients - with the progression of hypo and achlorhydria and the development of anemia.

The study analyzes the presence of H. pylori infection in patients of different ages. It was found that the frequency of H. pylori infection increases with age. Some studies have shown that the prevalence of H. pylori infection increases with age among the general population of Developing and Developed Countries [11, 12].

It was also found out that 92.33% of H. pylori-positive patients simultaneously had active inflammation, which demonstrated a statistically significant correlation between H. pylori infection and activation of the neutrophil. H. pylori infection can lead to activation of neutrophils and CG [13].

The loss of normal glandular tissue is the first stage of gastric cancer [14, 15]. Chronic inflammation caused by H. pylori may lead to a loss of the normal structure of the gastric mucosa, along with the destruction of the gastric glands and the replacement of fibrosis and epithelium of the stomach. Impaired regeneration and may contribute to the development of gastric cancer.

This process of CAG and IM occurs in about half of the H. pylori population in areas with the strongest inflammation. H. pylori infection of the gastric mucosa can persist for decades or throughout life if the patient does not receive the antimicrobial treatment. It is possible that elimination of H. pylori infection at the later stages is the cause for such a conclusion.

Meanwhile, there is some evidence that the prevalence of these infections is declining in Developing Countries, as a result of the associated increase in living standards [16]. ED is characterized by a neoplastic phenotype in terms of cell morphology and architectural organization. The current study presents that the prevalence of ED increased along with the progression of CG. All stages of dysplasia were recorded as the cause of gastric cancer and they significantly correlate with severe CG [6].

Conclusion

Intestinal metaplasia represents a phenotypic change compared to normal epithelial cells of the gastric mucosa. It is believed that with the presence of IM the stomach is at a late stage of atrophy, since the original glands are replaced by metaplastic, and chronologically, the metaplastic glands appear after the loss of gastric glands.

In the present study, most patients suffer from CG along with IM. Moreover, IM significantly correlate with the severity of CG. Meanwhile, the study shows that risk of CG disease increased with age and significantly correlates with active inflammation in patients with chronic gastritis. IM and positive ED significantly increased along with increasing degree of the stomach atrophy. Although important results were received by analyzing the clinical and pathological characteristics of 800 cases of chronic gastritis, there were some limitations in our study.

Only a histological examination of H. pylori infection was carried out, which could reduce the frequency of H. pylori occurrence. There is a need of further studies including larger number of population and including the usage of morphological analysis of changes with the OLGA-Operative Link for Gastritis Assessment system, for better understanding of the CAG progression.

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