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MORPHO-FUNCTIONAL STATE OF THE HEPATOBILIARY SYSTEM IN PATIENTS WITH STOMACH AND DUODENUM PEPTIC ULCER AT CHRONIC HELICOBACTERIOSIS

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The state of the liver was determined based on indices of liver enzyme activity and ultrasound diagnostics in patients with gastric and duodenal ulcers against the background of chronic helicobacteriosis. 127 patients (74 men and 53 women) with peptic ulcer disease of the stomach and duodenum were examined, in all cases *Helicobacter Pylori* was verified as an etiological factor. The diagnosis was confirmed endoscopically with further analysis of the biopsy material. Urease and microbiological tests were positive in all patients, transabdominal ultrasound was additionally performed. A probably higher degree of insemination of *Helicobacter Pylori* was found on the mucous membrane of the body of the stomach according to the small curvature ($p < 0.05$) in relation to the topographic zones of the antral area. In most patients, accompanying changes in the gallbladder, pancreas, and liver were observed. The own results of ultrasound diagnostics indicate a high frequency of pathological changes in the liver parenchyma, the structure of the gall bladder and pancreas in peptic ulcer disease of the stomach and duodenum when *Helicobacter Pylori* is detected. Signs of cytolysis are observed in patients with peptic ulcer disease of the duodenum during *Helicobacter Pylori*.

Key words: gastric ulcer disease, duodenal ulcer disease, chronic helicobacteriosis.

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МОРФО-ФУНКЦІОНАЛЬНИЙ СТАН ГЕПАТОБІЛІАРНОЇ СИСТЕМИ У ХВОРИХ НА ВИРАЗКОВУ ХВОРОБУ ШЛУНКА ТА ДВАНДЦЯТИПАЛОЇ КИШКИ ПРИ ХРОНІЧНОМУ ХЕЛІКОБАКТЕРІОЗІ

Стан печінки визначали за показниками активності печінкових ферментів та ультразвукової діагностики у хворих на виразкову хворобу шлунка та дванадцятипалої кишки на тлі хронічного хелікобактеріозу. Обстежено 127 хворих (74 чоловіки та 53 жінки) з виразковою хворобою шлунка та дванадцятипалої кишки, у всіх випадках як етіологічний фактор верифіковано *Helicobacter Pylori*. Діагноз підтверджено ендоскопічно з подальшим дослідженням біопсійного матеріалу. Уреазна та мікробіологічна проби були позитивними у всіх пацієнтів, додатково проводили трансабдомінальну УЗД. На слизовій оболонці тіла шлунка за малою кривизною ($p < 0.05$) виявлено вірогідно вищий ступінь обсеменіння *Helicobacter Pylori* по відношенню до топографічних зон антральної ділянки. У більшості хворих спостерігалися супутні зміни з боку жовчного міхура, підшлункової залози та печінки. Результати біохімічних досліджень та ультразвукової діагностики свідчать про високу частоту цитолітичного синдрому, патологічних змін паренхіми печінки, структури жовчного міхура та підшлункової залози при виразковій хворобі шлунка та дванадцятипалої кишки при виявленні *Helicobacter Pylori*.

Ключові слова: виразкова хвороба шлунка, виразкова хвороба дванадцятипалої кишки, хронічний хелікобактеріоз.

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Since 1994, authors have reported an association between *H. pylori* infection and other systemic manifestations. The list of potential effects of *H. pylori* outside the stomach includes a range of extragastric manifestations of neurological, dermatological, hematological, ocular, cardiovascular, metabolic, allergic and hepatobiliary diseases [6, 9]. According to literature the atypical course of gastric and duodenal ulcer in CH is determined in 8–25 % of patients, mainly in women, and half of them complain of a "cholecystic" variant of the ulcer disease course [2, 7, 11]. In 55 % of cases it is possible to detect signs of chronic non-calculous cholecystitis, and the combination of erosive-ulcerative lesions of the stomach and duodenum with gallstone disease occurs in 20–25 % of cases [12]. In 89 patients with cancer of the gallbladder and biliary tract, adenocarcinoma was found in 70 % of histologically confirmed cases, bile duct stones were detected in 53.9 % of cases, *Helicobacter pylori* was detected in 54 % of bile duct samples. A potential link has been established between *Helicobacter pylori* infection and the development of gallbladder cancer, including through the formation of stones in the bile ducts [5]. HP infection is a major risk factor for peptic ulcer disease, as well as gastric adenocarcinoma and gastric MALT lymphoma. Highlights the important connection between HP infection and a number of hepatobiliary diseases, such as biliary lithiasis, cholestatic syndromes (primary sclerosing cholangitis and primary biliary cholangitis) [8]. The patients with *H. pylori* infection in the blood must be properly identified. The iron level and vitamin B12 are used for the anemia. The results indicate the infection of *H. pylori* with the development of racial sclerosis, Alzheimer's disease, Parkinson's disease and Gien-Barre's syndrome. Infection *H. pylori* poses a risk of

development of cardiac and cardiac diseases, including: atherosclerosis. As a result, H. pylori-associated cancer can also be used to treat the lesion. The intent of insulin is to infect people with high-grade cancer. Risk of developing sugar diabetes. Advanced knowledge of dermatology and ophthalmology [10].

The purpose of the study was to determine the state of the liver based on indices of the hepatic enzymes activity and ultrasound diagnostics data in patients with gastric and duodenal ulcers at the background chronic helicobacteriosis.

Materials and methods. Gastroenterological patients with gastric and duodenal ulcer and confirmed, verified etiological factor, have been examined Helicobacter Pylori. In all the patients examined, the diagnosis of peptic ulcer disease due to chronic helicobacteriosis was confirmed endoscopically with subsequent sampling of biopsy material [4]. Urease and microbiological tests for Helicobacter Pylori were positive in all patients.

127 patients (74 men and 53 women) with peptic and duodenal ulcer disease at the background of CH and 20 persons (control group) were examined. The patients underwent biochemical blood tests at the initial stages of examination, before treatment. Patients who took biochemical blood tests did not receive anti-Helicobacter therapy for the previous 6 months [1].

The patients with peptic and duodenal ulcer disease and CH additionally underwent transabdominal ultrasonography. Ultrasound examination was performed according to the generally accepted method in the position of the patient on his back, on his left side, and after a change of position. Liver, pancreas, spleen, vessels of the abdominal cavity were examined. The condition of the liver, common bile duct and bladder duct, gallbladder wall, its shape and size (volume), motor activity, nature of contents (presence of sediment, polyps and concretions) were analyzed.

Statistical analysis was performed using the Statistica program (StatSoft, Inc. (2001). STATISTICA (data analysis software system) [3]. The Pearson correlation coefficient was used to assess the relationship between parametric indices. Comparison of parametric groups of data was performed using the Student's test.

The data we received were statistically processed using Student's t test. The mean square error of the results was used to determine the reliability of the differences in the mean values of the results.

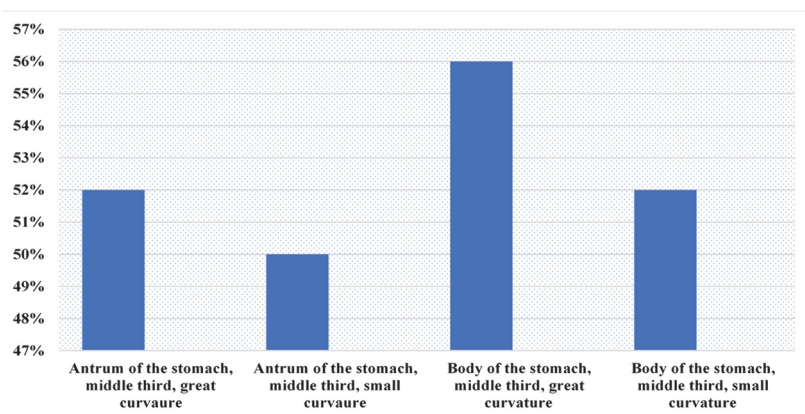


Fig. 1. Frequency of detection and degree of insemination of the gastric mucosa at active forms of HP – infections by topographic zones in patients with chronic helicobacteriosis (n=127). Note: n is the number of studies.

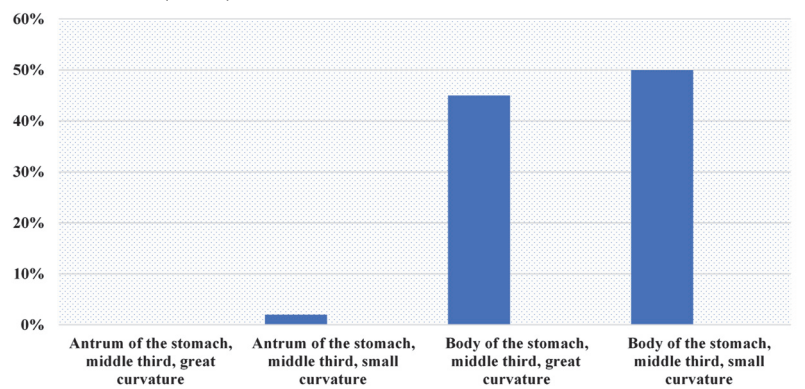


Fig. 2. Frequency of detection and degree of insemination of the gastric mucosa in the inactive form of HP – infection by topographic zones in CH patients (n=127). Note: n is the number of studies.

Results of the study and their discussion. 80 (72.1 %) patients under examination complained of heartburn, 76 (68.5 %) of sour eructation, pain; heaviness in the epigastric area noted 89 (80.1 %) patients, nausea was marked in 92 (82.9 %) patients, vomiting – in 3 (2.7 %), flatulence – in 12 (10.8 %), stomach upsets (constipation, diarrhea) were registered in 87 (78.4 %) persons, change in the taste qualities of the oral cavity (dryness, feeling of bitterness in the morning, metallic taste, hypersalivation) took place in 43 (38.7 %) persons, coated tongue (yellow, gray, white plaque) had 99 (89.2 %) patients, and manifestations of intoxication were marked by 110 (99.1 %) patients.

During a comprehensive examination of patients, the following concomitant pathology was revealed: chronic pancreatitis had 48 persons, chronic non-calculous cholecystitis – 53, post cholecystectomy syndrome – 8, arterial hypertension – 16, coronary heart disease – 9, chronic kidney diseases – 12, oncopathology – 2, lung diseases – 4 patients.

The above mentioned draws our attention to the need to study the state of the hepatobiliary system in CH. In connection with it, further functional and biochemical studies of the state of the hepatobiliary system were carried out.

Data on the detection and degree of insemination of the mucous membrane of the stomach different topographical zones in active and inactive forms of HP-infection are presented in Figs. 1–2. Microscopy of stained smears – prints in CH patients was performed.

A total of 73 (58 %) cases of intracellular "depot" of HP infection were detected in the gastric mucosa.

A significantly higher degree of insemination was found on the mucous membrane of the stomach body along the small curvature in relation to other zones ($p < 0.05$).

In the comparative analysis of the data obtained as to the mean degree of insemination of the gastric mucosa by inactive forms of HP by topographic zones, a significantly higher degree of insemination was detected in the stomach body along the small curvature in relation to the topographic zones of the antral area. In that while there were no significant differences between the zones of the antral department, as well as between the zones of the body of the stomach ($p > 0.05$).

When analyzing the results obtained, it was found that in CH patients the number of detected cases of precancerous changes of the gastric mucosa (atrophy, dysplasia, colonic metaplasia) in the antral part was 71 (56.2 %) cases; in the middle-upper third of the body of the stomach along the greater curvature – 39 (31.2 %) cases; in the middle-upper third of the body of the stomach along the lesser curvature – 37 (29.2 %) cases.

In the comparative analysis of the mean speed of a positive reaction onset during the urease test, no significant differences in the topographic zones of the stomach ($p > 0.05$) were registered.

The results of clinical and laboratory studies in CH patients, a number of features in the course of the disease were revealed, which indicate the presence of signs of hepatobiliary system pathology. Laboratory tests were confirmed by instrumental researches.

It is known that biochemical tests are basic in the diagnosis hepatobiliary system pathology.

To study pigment metabolism, the quantitative content of total bilirubin and its fractions in blood serum is determined.

As to the enzyme tests, the determination of the so-called "indicator enzymes" alanine aminotransferase and aspartate aminotransferase and are used most often. The increase in their activity indicates hepatocytes' damage. Excretory enzymes – alkaline phosphatase, gamma-glutamyltransferase, cholesterol, – activity increase with the development of cholestasis. Proteins and nitrogenous hepatic metabolism, i.e. total protein, thymol test, urea decrease indicate violation of the liver's protein-synthesizing function.

At the examination of 127 patients (74 men and 53 women) with peptic and duodenal ulcer disease and CH and 20 persons of a control group, a biochemical blood test was performed at the initial stage of the examination, before treatment. Patients referred for biochemical blood tests had not received anti-*Helicobacter pylori* therapy during the previous 6 months (Table 1).

Table 1

Data of biochemical tests in gastric and duodenal ulcer patients with CH before the appointment of anti-helicobacter therapy

Indices of biochemical tests	Control, n = 20	Before administration of anti- Hb therapy, n=127
Total protein, g/l	75.12±1.91	76.63±6.21
Cholesterol, mmol/l	4.98±0.95	5.08±1.92
Total bilirubin, μmol/l	13.55±2.15	17.01±3.84
Direct bilirubin, μmol/l	3.54±0.98	3.08±1.78
Indirect bilirubin, μmol/l	10.74±2.26	11.81±3.19
ALT, U/l	21.72±1.82	17.21±2.82 *
AST, U/l	19.91±3.09	23.74±2.21
Alkaline phosphatase, U/l	168.61±11.19	189.23±12.79
Thymol test, U	1.56±0.97	1.68±0.84
Urea, mmol/l	5.22±0.63	5.31±0.96

Note: n is the number of studies; *statistically significant change relative to the control group, $p < 0.05$

The data of biochemical tests presented in the Table. 1 are within the normal range compared to the control group and indicates the absence of signs of liver involvement in the pathological process in CH.

Biochemical parameters of the hepatobiliary system were studied at the stage of anti-*Helicobacter* therapy in patients with gastric and duodenal ulcer and CH.

The results presented in Table 2 show an increase of biochemical indices by 1.5–2 times, which indicates a violation of the hepatobiliary system functional state mainly by the mechanism of cytolysis – transaminase activity, especially alanine transaminase was increased by 5 times.

The results of the study also indicated the phenomenon of cholestasis, which is pointed by a threefold increase of direct bilirubin with a simultaneous increase in the activity of alkaline phosphatase.

Cholestasis and the phenomena of cytolysis reduce liver's functional capabilities, based on the increase in indirect bilirubin and the tendency to a positive thymol test.

Table 2

Data of a biochemical study of the hepatobiliary system in patients with gastric and duodenal ulcer and CH during anti-Helicobacter therapy on the 7th day and after anti-Helicobacter therapy, 15th days

Data of biochemical tests	Control, n=20	During anti-Helicobacter therapy, the 7 th day, n=127	After anti-Helicobacter therapy, the 15th days, n=127
Total protein, g/l	75.12±1.91	78.21±3.46	78.47±5.18
Cholesterol, mmol/l	4.98±0.95	5.51±1.09	5.49±1.33
Total bilirubin, μmol/l	13.55±2.15	30.41±3.42*	34.11±2.66*
Direct bilirubin, μmol/l	3.54±0.98	9.01±1.03 *	9.47±0.59 *
Indirect bilirubin, μmol/l	10.74±2.26	23.24±1.17 *	25.09±2.03*
ALT, U/l	21.72±1.28	97.00 ±4.93*	139.21±5.46*
AST, U/l	19.91±3.09	63.84±3.16*	71.37±4.81*
Alkaline phosphatase, unit/l	168.61±11.19	289.2±17.69*	318.21±15.02*
Thymol test, U	1.56±0.97	3.18±1.92	3.12±0.70
Urea, mmol/l	5.22±0.63	5.32±1.02	5.40±1.04
Glucose, mmol/l	5.14±0.86	5.24±0.74	5.21±0.62
GGT, U/l	32.57±1.91	391.47±9.87*	612.86±8.23*

Note: n is the number of studies. *statistically probable change relative to the control group, p<0.05

At the same time, the detected biochemical differences testify to the hepatotoxic effect of drugs included in the standard scheme of anti-Helicobacter therapy. Thus, the phenomenon of cytolysis is primarily evidenced by the increase in transaminases level, and with a predominant increase in alanine transferase, a liver enzyme which increased 9 times.

Cytolysis is the cause of hepatocytes functional activity decrease, judging by indirect bilirubin and thymol test indices increase. Hepatocytes' damage probably leads to a violation of bile passage due to increase of pressure in the bile ducts. The criteria of the latter are direct bilirubin and alkaline phosphatase activity increase.

These indices are combined with changes in the clinical manifestations of hepatobiliary system disorders, namely feeling of distension, heaviness in the right hypochondrium, gastrointestinal dyspepsia, appearance of nausea, vomiting, an unpleasant taste of bitterness or metal in the mouth, flatulence, bloating, indigestion, discomfort in the stomach and intestines, which can be a consequence of dysbiosis.

It is known that the imbalance of the intestinal microflora most often develops when macrolides (clarithromycin, azithromycin) and tetracycline are prescribed, which have the most detrimental effect on the intestinal flora, including *E. coli*. This can lead to a violation of the bacterial balance and the development of dysbacteriosis.

Indeed, our results showed that during and especially after anti-Helicobacter therapy, 50 patients (40 %) complained of meteorism, abdominal distension, and 59 patients (47.2 %) had pain along the bowel loops. Complaints of grumbling in the stomach after eating were present in 50 patients (40 %), constipation in 43 (34 %), diarrhea in 16 (13.2 %) patients, which indicates a disturbance in the balance of the intestinal microbiocenosis.

Therefore, the detected changes in the functional and biochemical state of the liver are most likely related to the hepatotoxic effect of the drugs used in anti-Helicobacter therapy, which can be combined with the etiotropic effect of *Helicobacter pylori*.

This can be confirmed by the data, which indicate that after effective anti-Helicobacter therapy, judging by clinical data and complete eradication, *Helicobacter pylori* was not detected in patients by any of the methods. At the same time, we received data indicating that the phenomena of cytolysis and cholestasis are almost completely preserved.

Thus, the indices of the hepatobiliary system study in patients with gastric and duodenal ulcer in CH received anti-helicobacter therapy, indicate additional liver's involvement in the pathological process.

Signs of cytolysis on account of alanine transferase and aspartate transferase are kept, the amount of which remains elevated.

Cholestasis is characterized by an increase in both direct and indirect bilirubin, but especially the first indicates a violation of the liver, an increase in indirect bilirubin indicates a decrease in the function of hepatocytes as a result of cytolysis. Additional confirmation of cholestasis development is evidenced by an increase in gamma-glutamyltransferase.

The data indicate that gamma-glutamyltransferase increases 10 times during anti-Helicobacter therapy on the 7th day and 20 times on the 15th day from the beginning of the eradication therapy in patients with gastric and duodenal ulcer in chronic Helicobacteriosis.

Thus, anti-helicobacter therapy in the patients under observation is accompanied by even more pronounced damage of hepatobiliary system. The latter may be a consequence of the direct hepatotropic effect of anti-Helicobacter drugs, but it may also be a result of the development of intestinal microflora disturbance, which was detected in our patients both clinically and by laboratory analysis data. The fact that the pathology of the hepatobiliary system can be the result of a violation of the microbiocytointestinal system was previously shown in our laboratory studies and experiments.

During the examination of 127 patients (74 men and 53 women) with peptic ulcer disease and duodenal ulcer disease with CH, transabdominal ultrasonography was additionally performed. Ultrasound examination was performed according to the generally accepted methodology in the position of the patient on his back, on his left side, and after a change of position.

They studied the condition of the liver, pancreas, spleen, vessels of the abdominal cavity, common bile duct and bladder duct, gall bladder wall, its shape and size (volume), motor activity, nature of contents (presence of sediment, polyps and concretions) were analyzed.

As the given data show, in patients with peptic ulcer disease and duodenal ulcer disease with CH, in most cases had accompanying changes in the gallbladder, pancreas, and liver, Fig. 3.

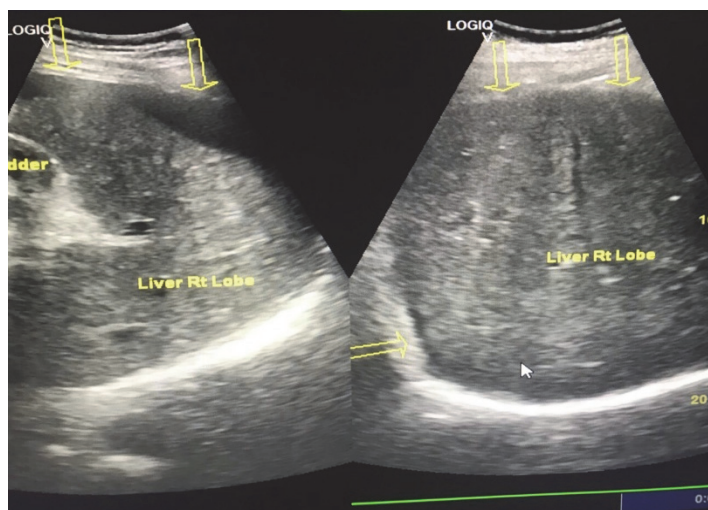


Fig. 3. Patient K. 51 years old., Diagnosis: gastric ulcer, Helicobacter pylori-associated (++), exacerbation, ulcer (0.9 cm) in the middle third of the stomach along the lesser curvature. Diffuse liver changes.

Ultrasound was performed according to the generally accepted methodology, before the appointment of anti-helicobacter therapy.

Ultrasound examination has revealed the following: thickening of the gallbladder wall had 58 patients (45.67 %), changes in the structure of the pancreas were in 59 patients (46.46 %) diffuse changes in the liver parenchyma – in 58 patients (45.67 %) and, accordingly, there were signs of gall bladder stones in 11 patients (8.66 %). Condensation, thickening of the gallbladder wall and its deformation were found more often in patients with peptic ulcer disease located in duodenum than in patients with gastric ulcers in CH (50.0 % and 42.8 % of patients, respectively).

Diffuse changes of the pancreas parenchyma were also more common in duodenal ulcers patients than in gastric ulcers, however, no significant differences were found (in 55.3 % and 42.8 % of patients, respectively). Diffuse changes in the hepatic parenchyma were observed in patients with duodenal ulcer disease more often than in those with gastric ulcer disease (42.1 % and 38.1 % of patients, respectively). Gallstone disease was diagnosed with the same frequency in patients with duodenal and gastric ulcers.

Recently, more and more authors, on the basis of documented studies, show that in patients with cholesterol lithiasis more frequent detection of HP and other species of Helicobacter (*H. bilis*, *H. hepaticus*) both at the level of the bile and at the level of the biliary tract. as at the level of calculation. On the basis of recent studies, it is possible to ascertain the presence of a number of data on the role of HP infection in the etiopathogenesis of the formation of cholesterol stones [8]. The own results of the study carried out indicate a high frequency of pathological changes in the ultrasound picture of the liver parenchyma, structure of the gallbladder and pancreas in gastric ulcer disease and duodenal ulcer disease in CH. This is fully consistent with literature data, except for some differences regarding the frequency of development of gallstone disease.

Higher levels of alkaline phosphatase and prothrombin time were established in patients in whom Helicobacter DNA was detected in gastric biopsies compared to patients in whom Helicobacter DNA was

not detected. In one patient from the group of non-cholestatic liver cirrhosis with detected *Helicobacter*, the highest value of alkaline phosphatase in this group was observed [5]. Our clinical and laboratory studies of the liver showed that in patients with gastric ulcer and duodenal ulcer in CH, there are signs of cytolysis – a significant increase in transaminases: alanine transaminase and aspartate transaminase, indirect bilirubin and a positive thymol test, as well as cholestasis – an increase in gamma-glutamyltransferase and bilirubin, both direct and indirect. During anti-helicobacter therapy, the above indices increase even more.

The choice of *H. pylori* eradication regimen should be based on the local prevalence of clarithromycin resistance and previous use of macrolides. Declining eradication rates due to antibiotic resistance have become a major clinical problem [12]. Our results showed that after anti-helicobacter therapy, 40 % of patients complained of flatulence, and 47.2 % of patients had pain along the course of intestinal loops, which indicates a violation of the balance of intestinal microbiocenosis.

Military servicemen with peptic ulcer disease had a higher prevalence of *Helicobacter pylori* infection and a lower prevalence of liver cirrhosis and malignant tumors, but the difference was not statistically different [11]. In view of our research, a transabdominal ultrasonography of the hepatobiliary system should be included in the list of comprehensive examinations for the patient with an exacerbation of gastric ulcer and duodenal ulcer in CH as liver disorders were detected.

The detected changes in the state of the liver parenchyma have been confirmed by liver ultrasound picture in the form of diffuse changes of the hepatic tissue and fatty infiltration.

The association of *Helicobacter*-positive patients with cholestatic liver disease is motivated by higher alkaline phosphatase and prothrombin complex factors (consisting of blood coagulation factors II, VII, IX, and X), as well as the absence of differences between serum bilirubin values in HP-positive and negative patients. Differences in the levels of prothrombin complex factor in *Helicobacter*-positive and *Helicobacter*-negative patients confirm the connection with cholestasis, but not with severe liver dysfunction [6].

Conclusion

Changes in biochemical indices (gamma-glutamyltransferase) characterizing the state of the liver and combined with the peculiarities of the structure of the organ revealed by ultrasound, it is possible to confirm the presence of pathological changes developing in the liver as a result of infection HP. The changes detected indicate a high frequency of pathological changes in the ultrasound characteristics of the liver in patients with stomach pathology and helicobacteriosis. Attention is drawn to the presence of diffuse changes in the liver tissue in the form of fatty infiltration.

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