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Ya. M. Vakhrushev[1], N. A. Khokhlacheva*[1], P. S. Mikheeva[2], E. V. Suchkova[1]

[1] – Izhevsk State Medical Academy, Izhevsk, Russia

[2] – City Clinical Hospital No. 8 n.a. I. B. Odnopozov, Izhevsk, Russia

THE MECHANISMS OF THE DISORDERS OF MOTOR-EVACUATION FUNCTION OF GALL BLADDER AND THEIR IMPORTANCE IN THE DEVELOPMENT OF CHOLELITHIASIS

Abstract

The objective was to study the role of gastrin in the gallbladder motor-evacuation function damage and the biochemical properties of bile in cholelithiasis. **Material and methods.** 230 patients with pathology of the biliary system were examined. In verification of the diagnosis, in addition to general clinical data, the results of ultrasound examination of hepatobiliary system were used. Cholecystometry and dynamic hepatobiliary scintigraphy were used to examine the functional state of the gallbladder. In different variants of the gallbladder motor-evacuation function disorder, biochemical properties of bile (cholesterol, bile acids, cholate-cholesterol coefficient) obtained as a result of multifractional duodenal drainage were studied. The level of the gastrointestinal hormone gastrin in the peripheral blood was determined by the enzyme-linked immunoassay. **Results.** According to US results, 78 % of the patients are diagnosed with signs of biliary sludge. In 75.4 % of cases crystals of cholesterol and calcium bilirubin were detected via microscopic examination of bile. The study of the biochemical composition revealed an increase in cholesterol, a decrease in bile acids and cholate-cholesterol ratio in B bile and C bile. Gallbladder motor-evacuation function disorders, which are one of the pathogenetic factors of cholelithiasis, were detected in 72 % of patients. In patients with the disorder, gastrin level was reduced, and to a greater extent — in patients with hypokinetic gallbladder dysfunction. The significant role of gastrin in the functional state of the gallbladder and, therefore, in the formation of lithogenic bile, is established by the method of correlation analysis. **The conclusion.** Studies of the parameters of the gallbladder motor function and the biochemical properties of bile on the one hand and the level of the gastrointestinal hormone gastrin on the other have shown the important role of hypogastrinemia in the formation of lithogenic bile by suppressing the emptying of the gallbladder.

Key words: *gallbladder, motor-evacuation function, lithogenic properties of bile, cholelithiasis, gastrin*

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CLT — cholelithiasis, GB — gallbladder, BAB — bile acids of bile B, BAC — bile acids of bile C, CBB — cholesterol of bile B, CCB — cholesterol of bile C, CCRB — cholate-cholesterol ratio of bile B, CCRC — cholate-cholesterol ratio of bile C

*Contacts. E-mail: stoxel@yandex.ru

Introduction

One of the most urgent problems faced by clinical medicine is cholelithiasis (CLT) [1, 2, 3, 5, 6], whose prevalence is high and increasing from year to year, and which has a pronounced negative impact on social activity and quality of life. According to statistics, in recent decades, the increase in the incidence of CLT is a steady trend; and if today it is registered in more than 10 % of the population [2, 3, 6, 7], and if the current rate of morbidity growth remains, 20 % of the world's population will be suffering from CLT by 2050 [8].

The formation of calculi in the gallbladder (GB) is a long multistage process. Debate is still going on over the pathogenetic factors of cholelithiasis. In addition to the formation of lithogenic bile [9, 10], a necessary condition for gallstone formation is a GB motor function disorder [11, 12]. Animal experiments have shown the involvement of gastrointestinal hormones in the processes of bile formation and bile secretion [13]. However, the mechanisms of changes in bile metabolism and GB contractile capacity have not been studied enough.

Study Objective

To study the role of gastrin in GB motor-evacuation function disorders and biochemical properties of bile in CLT.

Materials and methods

Two hundred and thirty patients with stage I CLT (classification of Central Research Institute of Gastroenterology (CRIG), 2001) [4], secondary to hepatobiliary diseases (functional disorders of the biliary system, chronic non-calculous cholecystitis, steatohepatitis and steatohepatitis of alimentary etiology) were examined. Mean age of the patients was 47±6 years, including 113 men and 117 women. Examination of patients was carried out with the compulsory signing of a voluntary informed consent in accordance with order No. 390n of the Ministry of Health and Social Development of the Russian Federation dated April 23, 2012 (registered by the Ministry of Justice of the RF on May 5, 2012 under No. 24082). This study was approved by the Ethical Committee of Izhevsk State Medical Academy. The scope of examination was justified statistically by the sampling frequency using the L. Zaks formula.

For verification of the diagnosis, along with the anamnestic and general clinical data, the results of ultrasound examination (ultrasound) of the hepatobiliary system using S-DN-500 (with two standard transducers (linear and convex) with a frequency of 3.5 MHz) were taken into account. For assessment of GB functional state, data on cholecystometry and dynamic hepatobiliary scintigraphy (HBS) were used. Cholecystometry was performed according to the standard technique, which consists of measurement of GB volume before and after choleretic breakfast with intervals of 10 minutes (for 1.5 hours) by ultrasound scanning. The choleretic breakfast consisted of 2 raw egg yolks. GB volume was calculated with the formula V=3.14 dH, where d is the diameter of GB; H is the longitudinal axis of the GB. The following parameters were evaluated: baseline GB volume; duration of GB contraction phase; degree of maximal contraction from baseline; rate of GB emptying (ratio of the maximum contraction to duration of contraction phase). HBS was performed using the MB-9200 gamma camera with a Super Segams processor after intravenous administration of the hepatotropic radiopharmaceutical agent (RPA) Bromesida-Tc99 with a total activity of 185–370 MBq using choleretic stimulation consisting of 2 raw egg yolks. In the analysis of hepatograms, GB deposit function based on the time of maximum accumulation of RPA in GB (GB Tmax), motor-evacuation function of the gallbladder according to RPA half-life from GB (GB T½) and according to the latent time with choleretic breakfast were evaluated.

Microscopic and biochemical examination of bile obtained by multifractional duodenal drainage was carried out. In B and C portions the total concentration of bile acids (BAB, BAC), and cholesterol (CBB, CCB) [14] was determined, and cholate-cholesterol ratio (CCRB, CCRC), which is a bile lithogenetic index, was calculated. In peripheral blood the level of the gastrointestinal hormone gastrin was studied by a two-step sandwich enzyme-linked immunoassay.

The control group comprised of 30 apparently healthy individuals aged from 20 to 25 years.

Statistical processing of the results was performed using a standard package in Microsoft Office Excel editor, version 2010. The data presented as mean values (M) with the definition of their errors (±m) were compared by correlation analysis with the calculation of the correlation coefficient (*r*) according to Pearson's formula. The reliability was evaluated by Student's test with normal distribution of the sample.

Results and discussion

All patients suffered from abdominal pain; in 84 % of cases the pain was localized in the right hypochondrium, and in 16 % — in the epigastrium. Constant, dull pain intensifying after eating (mainly after fatty foods) accompanied by sense of pressure, bursting, with irradiation in the back, under the right scapula, in the right shoulder was observed in 68 % of patients, and 32 % of patients noted a short-term, colic-like pain arising from deviations in the diet. In addition, symptoms of biliary dyspepsia, which were dominated by eructation, nausea and bitter taste in the mouth, were found in 76 % of the patients during history-taking. In physical examination 78 % of patients had excessive nutrition, 56 % of patients had yellow or gray-yellow tongue coating, teeth prints at tongue edges, 83 % had pain during palpation with localization in the right hypochondrium and positive gallbladder symptoms. During ultrasound scanning, induration and thickening of GB wall were observed in 62 % of patients, GB deformation — in 30 % of patients, the presence of biliary sludge (microlites, putty-like bile) — in 78 % of patients.

Based on the results of cholecystometry, patients were divided into three subgroups: 1 — with GB dysfunction of hypokinetic type, 2 — with normal contractile activity of GB, 3 — with GB dysfunction of hyperkinetic type. Subgroups were balanced in terms of age and sex. The 1st subgroup included 49 women and 40 men with mean age of 51±2 years; the 2nd subgroup included 36 women and 39 men with mean age of 44±4 years, and the 3rd subgroup included 32 women and 34 men with mean age of 49±4 years. According to *Table 1*, there are no significant differences between baseline GB volume at different motor options.

As shown in Figure 1, in patients with GB dysfunction of hyperkinetic type the rate of GB emptying increases after test breakfast, not only due to a higher degree of maximum contraction but also due to a shorter duration of the contraction phase. In case of GB dysfunction by hypokinetic type the decrease in the emptying rate was associated with a decrease in the degree of maximum contraction and a longer duration the of contraction phase.

Unidirectional changes in GB motor activity parameters according to cholecystometry and HBS (Table 2) suggest of their information value and equivalence in the early diagnosis of CLT.

Basal gastrin level in the examined patients was reduced (Table 3), with a greater extent in GB dysfunction of hypokinetic type. At present there are conflicting data about the involvement of gastrin in the process of choleresis and cholekinesis. It has been proven that GB muscle wall contains gastrin receptors. Gastrin has a stimulating effect on GB contraction and a relaxing effect on the sphincter of Oddi, causing decreased pressure in the biliary tract [15]. Some authors prove the increase of cholecystokinin secretion in the duodenum by gastrin [16] which has a stimulating effect on GB contractility. Others note the improvement of hepatic blood flow under the influence of gastrin, resulting in positive changes in hepatic metabolic processes and in increased choleresis [17].

Table 1. *Gallbladder motility data in different functional disorders*

Parameter	Control (n=30)	Subgroup 1 (n=89)	Subgroup 2 (n=66)	Subgroup 3 (n=75)
Contraction phase duration, min.	45.64±4.2	52.41±4.4 *	46.62±3.4 *	39.25±2.5 *
The degree of maximum contraction, %	46.43±3.8	29.24±2.7 *	47.01±5.8 *	63.63±6.2 *
The rate of the gallbladder emptying, %/min	1.02±0.4	0.85±0.04 *	1.03±0.09 *	1.87±0.2 *
The initial volume of the gallbladder, cm^3	16.75±1.8	17.1±2.0*	16.85±2.4*	16.23±2.1*

Note: * — P < 0.05 compared with the control.

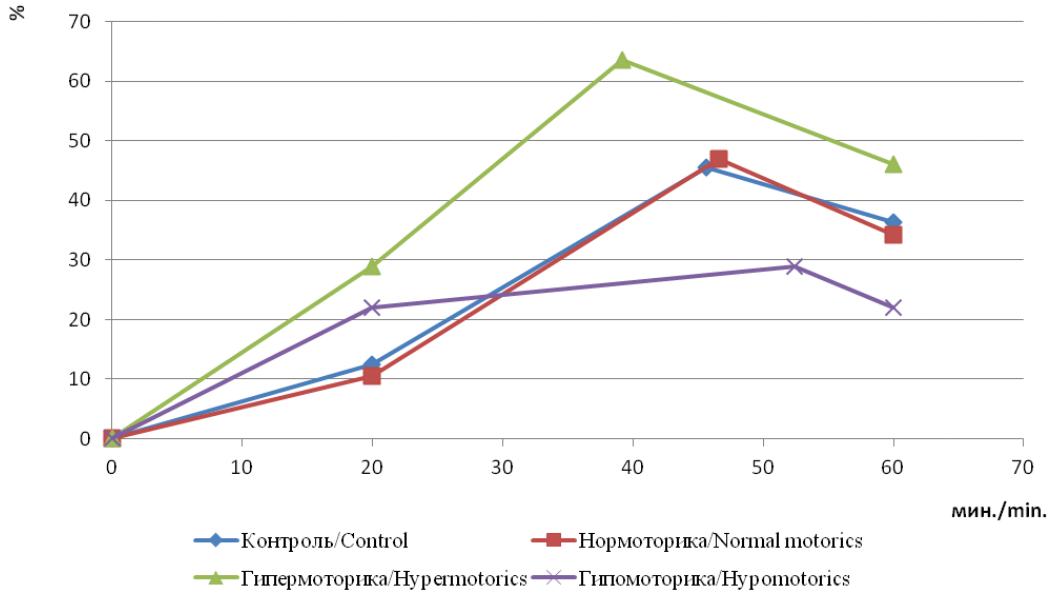

Figure 1. *Contractile function parameters of the GB after the test breakfast*

Table 2. *Correlation analysis of GB motor-evacuation function parameters in different examination methods*

Parameter	Half-life of RPA from GB according to HBS	Latent time of choleretic breakfast according to HBS
Duration of the contraction phase according to cholecystometry	r=0.49	r=0.36
The rate of emptying of the GB according to cholecystometry	r=–0.70	r=–0.60

Table 3. *Basal gastrin level in different GB functional disorder*

Parameter	Control (n=30)	Subgroup 1 (n=89)	Subgroup 2 (n=66)	Subgroup 3 (n=75)
Gastrin (pg/ml)	66.14±3.32	24.45±2.91*	27.06±3.02*	28.44±2.13*

Note: * — P < 0.05 compared with the control.

The results of the correlation analysis (Figure 2) indicating the existence of a relationship between gastrin level and GB functional state are evidence that hypogastrinemia leads to decreased GB emptying rate, maximum GB contraction degree by cholecystometry, as well as to increased RPA half-life and the latent time of choleretic breakfast during HBS.

In 75.4 % of patients crystals of cholesterol and calcium bilirubinate, which are typical for the first (pre-calculus) stage of CLT, were found by bile microscopy. Assessment of the biochemical composition of bile was carried out depending on the type of motor-evacuation function of the gallbladder. As shown in the *Table 4*, in the examined patients, the bile content of CL was elevated in both bile B and bile C compared to the control. In contrast, BA level was decreased in both bile B and bile C in comparison with the control. There was a significant decrease in CCR in both portions of bile in comparison with the control group. The highest degree of bile lithogenicity was observed in GB dysfunction of hypokinetic type.

According to Table 5, changes in the biochemical composition of bile are directly dependent on gastrin level. With decreased gastrin level, an increase in CL content and a decrease in BA levels in bile B and bile C are observed. A positive correlation between gastrin level and CCR was revealed, that is, CCR decreases with decrease in gastrin content.

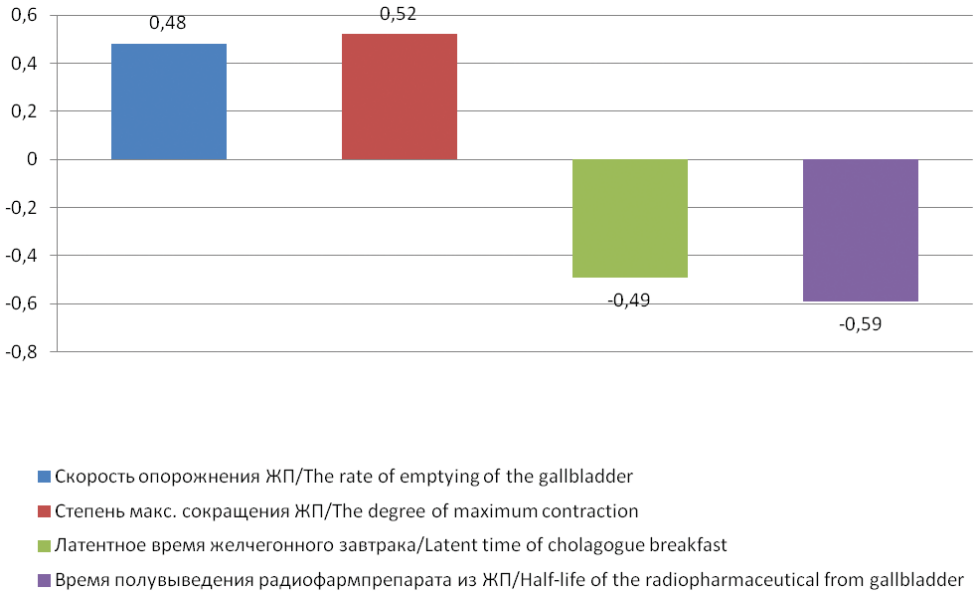

Figure 2. *The data of correlation analysis between the gastrin level and GB functional state parameters*

Table 4. *Biochemical parameters of bile in different GB motility disorders*

Parameter	Control (n=30)	Subgroup 1 (n=89)	Subgroup 2 (n=66)	Subgroup 3 (n=75)
CL (mmol/l)				
B bile	7.53±2.14	30.14±4.9*	19.91±4.6*	26.73±3.8*
C bile	3.45±0.9	21.28±3.6*	10.78±2.1	15.84±3.4*
BA (mmol/l)				
B bile	53.52±5.4	24.25±4.4	49.14±4.8*	37.24±3.1*
C bile	19.14±2.7	14.76±2.5*	17.37±1.4*	18.44±2.7*
CCR (U)				
B bile	9.53±1.1	0.84±0.04*	2.46±0.6	1.33±0.09
C bile	6.37±1.7	0.69±0.01*	1.61±0.4*	1.16±0.09*

Note: * — P < 0.05 compared with the control.

Table 5. *The data of correlation analysis between the gastrin level and biochemical properties of bile*

Parameter	CLв	CLc	BAв	BAc	CCRв	CCRc
Gastrin	r=–0.31	r=–0.31	r=0.47	r=0.35	r=0.38	r=0.31

Thus, hypogastrinemia, which correlates with the GB functional state disorder and altered biochemical composition of bile, indicates the significant role of gastrin in gallstone formation.

Conclusion

Disorders of GB motor-evacuation function were found in 72 % of patients with hepatobiliary system diseases. GB dysfunction of hypokinetic type has a more unfavorable prognosis in relation to possible gallstone formation. Studies of GB motor function parameters and biochemical properties of bile, on the one hand, and studies of gastrointestinal hormone gastrin levels on the other helped to show the important role of hypogastrinemia in the formation of lithogenic bile by inhibiting GB emptying.

Conflict of interests
The authors declare no conflict of interests.

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