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Case Study

Biliary Sludge. Analysis of a Clinical Case

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Abstract

The article presents the definition and frequency of detection of biliary sludge in patients with different pathologies of the gastrointestinal tract. Classifications of biliary sludge and laboratory and instrumental research methods in patients with biliary tract pathology are considered. Attention is drawn to functional disorders of the biliary tract, which lead to the formation of biliary sludge. Algorithms for the diagnosis of dysfunctions of the biliary tract are presented. Depending on the features of the clinical course of biliary sludge, a tactic of patient management with the use of drugs with choleretic and antispasmodic action is proposed.

Keywords: *Biliary sludge (BS); Gastrointestinal Tract; Algorithms; Drugs*

Introduction

Biliary sludge (BS) is an accumulation of cholesterol crystals, pigment crystals and calcium salts in one formation that occurs in the gallbladder and bile ducts. BS occurs when there is stagnation of bile, it is the stagnation that creates the conditions for its formation.

In most cases, BS is detected during instrumental studies carried out in the diagnosis of diseases of the gastrointestinal tract. The frequency of detection of biliary sludge in different populations varies widely and amounts to 1.7 - 4.0% in the general population among individuals without cholelithiasis (GSD); presenting complaints from the digestive system - 7.0 - 8.0%; typical for biliary dyspepsia - 24.4 - 74.0%. Most often, BS is detected in individuals with biliary pathology [1,2].

Like gallstones, biliary sludge is often asymptomatic in most patients. However, in addition to a predisposition to gallstones, biliary sludge can lead to biliary colic. More importantly, biliary sludge found in patients with abdominal pain can spontaneously disappear in 50% of cases and remain asymptomatic in 20% of cases within 3 years. During the same period, 10% to 15% of patients develop symptoms, and gallstones develop in 5% to 15% of patients. Biliary sludge is found in 31% of patients with non-alcoholic pancreatitis and up to 74% of patients with "idiopathic" pancreatitis. There is a provocative hypothesis: biliary pain and inflammation arising in cholelithiasis is mediated by the presence of BS. This is supported by the fact that patients with symptoms of gallbladder disease receiving treatment with ursodeoxycholic acid (UDCA) have symptom relief after three months, although the number and size of their gallstones does not change. It is likely that solid crystals of cholesterol in bile dissolve earlier than gallstones [3].

Most gallstones are cholesterol. In general, the formation of BS and cholesterol stones in the gallbladder can be divided into three phases: (1) oversaturation of bile with cholesterol; (2) crystallization and (3) gallbladder hypotonia, allowing calculus to grow (Figure 1).

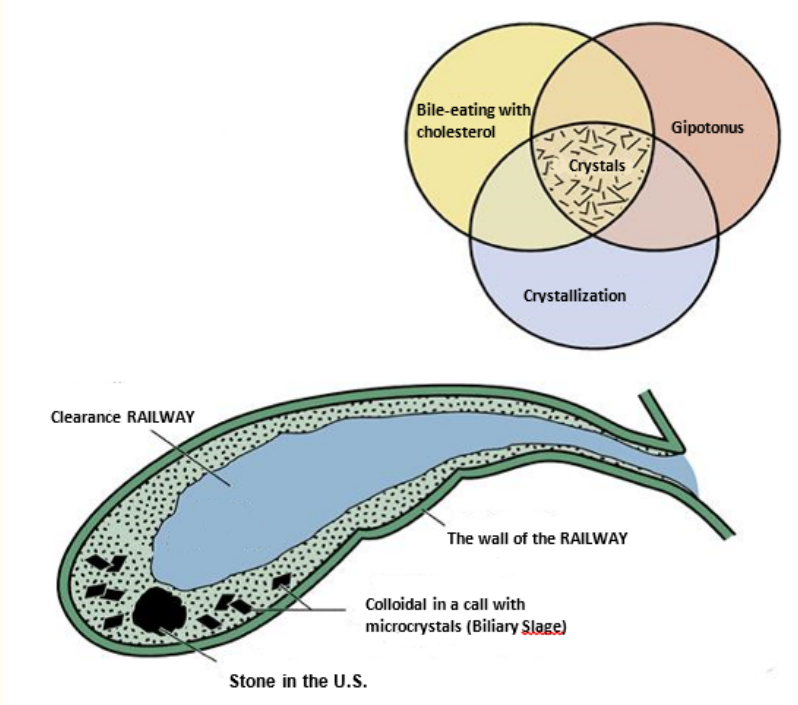

Figure 1: *The three main phases of gallstone formation are illustrated by a Venn diagram [4].*

The formation of BS occurs in several stages: oversaturation of bile with cholesterol; violation of the dynamic balance between pro- and antinuclear factors; nucleation and precipitation of cholesterol crystals; aggregation of crystals into microlites and their further growth [5]. The composition of BS includes: crystals of cholesterol in a composition with mucin, calcium salts and bilirubin containing pigments, which noticeably predominate.

There are three main types of BS, each of which has a clearly defined echographic picture [6,7]:

- BS-1: Microlithiasis - a suspension of hyperechoic particles in the form of point single or multiple displaced hyperechoic formations up to 4 - 5 mm in size, which do not give an acoustic shadow and are detected after changing the position of the patient's body (Figure 2).
- BS-2: Clots of putty bile - echo non-uniform bile with clots of different density, displaced and not giving an acoustic shadow or, in rare cases, with a weakening effect behind the clot;
- BS-3: Combination of putty bile with microliths - while microliths can be contained simultaneously both in the clot of putty bile and in the gallbladder cavity.

The main risk factors for the formation of BS are: diabetes mellitus; cholestasis of various origins; hemolytic anemias; operations on the stomach and intestines (postoperative period); complete parenteral nutrition of the patient; Taking drugs such as cyclosporine, ceftriaxone, octreotide, clofibrate and calcium supplements rapid weight loss; pregnancy [2].

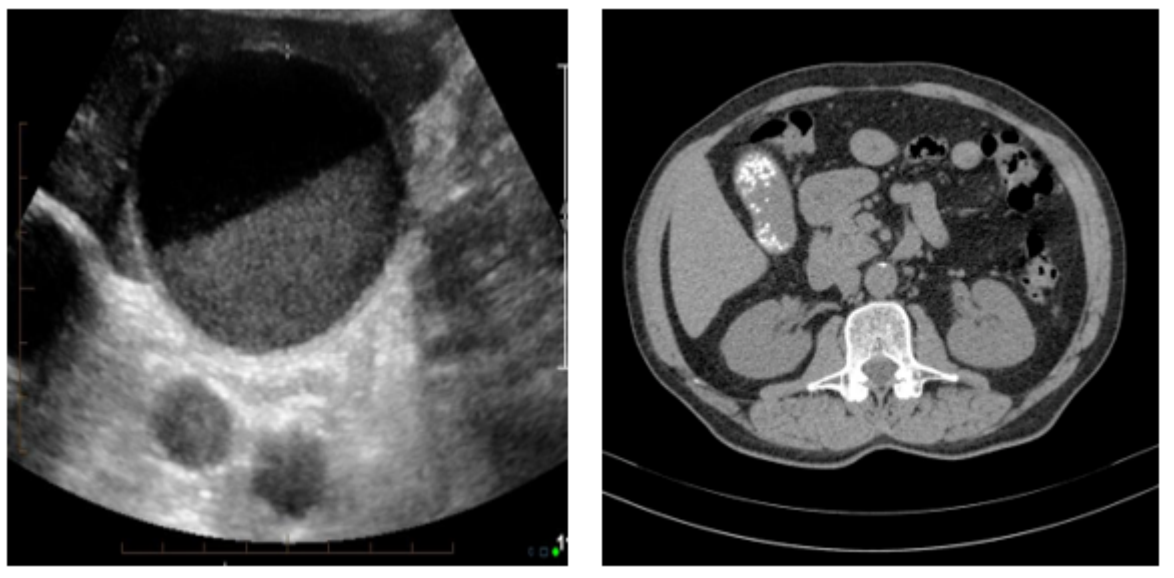

Figure 2: *An example of visualization of BS during studies of the abdominal organs using ultrasound (left) and MRI (right). BS-1 is presented (hyperechoic inclusions are visualized in the gallbladder cavity, which are detected when the patient's body position changes) [8].*

Classification of biliary sludge [9]:

- According to the ultrasound form of the biliary sludge: echo weight - its initial manifestations; biliary sludge - clots; special forms (microcholelithiasis, cholesterol polyps of the gallbladder, putty bile when the gallbladder is "off");
- According to the state of the contractile function of the gallbladder (assessed by dynamic scintigraphy): with preserved or reduced contractile function when the gallbladder is "off";
- In combination with cholelithiasis: without and with stones in the gallbladder.

Early diagnosis and treatment of BS pathology is of great clinical importance due to the possibility of BS transformation into chronic cholecystitis and gallstone disease.

Laboratory research

- Clinical blood test: Leukocytosis testifies to adherence to functional disorders of the inflammatory process, the severity of which correlates with the severity of complications of BS (cholecystitis, gallstone disease) and affects the outcome of the disease; coprogram (with cholepathies, droplets of neutral fat plus a moderate amount of fatty acids, the feces have a shiny color); biochemical blood test: total bilirubin and its fractions; total cholesterol;
- Alanine aminotransferase (ALT); aspartate aminotransferase (AST); alkaline phosphatase (ALP), with exacerbation of cholecystitis, a moderate increase in ALP, bilirubin, an increase in ALT; gammaglutamyl transpeptidase (GGTP); total protein and protein fractions;

- Serum pancreatic amylase; determination of the cholesterol index (the ratio between the content of bile acids and cholesterol in bile).

Instrumental research

Ultrasound of the liver, gallbladder, pancreas; fractional chromatic duodenal intubation with microscopic and biochemical examination of bile; oral and intravenous cholecystography; scintigraphy of the gallbladder and biliary tract; percutaneous transhepatic cholangiography (CCH) - using a Hiba needle under ultrasound control, the needle punctures the bile duct and then a water-soluble contrast is injected; endoscopic retrograde cholangiopancreatography (ERCP) with sphincter of Oddi manometry (CO) - allows to detect choledocholithiasis, CO strictures, primary sclerosing cholangitis; computed tomography - for the diagnosis of gallbladder tumors, metastases.

Functional disorders of the biliary tract, which lead to the formation of BS: primary dyskinesias, causing impaired outflow of bile and/or pancreatic secretion into the duodenum in the absence of organic obstructions; dysfunction of the gallbladder and CO; secondary dyskinesias of the biliary tract, combined with organic changes in the gallbladder and CO.

It should be borne in mind that long-term functional disorders in the biliary system can lead in the future to gallbladder hypokinesia with stagnation of bile, a violation of its colloidal stability, the formation of BS and the formation of gallstones. In addition, stagnation of bile against the background of dysfunction of the biliary tract can contribute to the addition of infection, i.e. contributes to the occurrence of cholecystitis.

An increase in the lithogenicity of bile is most often due to a violation of the ratio of cholesterol, bile acids and phospholipids. In the presence of an excess of cholesterol, bile cannot be maintained in a solubilized state, which means that it precipitates in the form of crystals of cholesterol monohydrate, creating the basis for the formation of BS. In the case of the preserved contractile activity of the gallbladder and CO, the agglomerated particles are evacuated into the duodenum through CO. Otherwise, cholesterol particles remain in the stomach.

Differential diagnostics

Differential diagnosis of gallbladder dysfunction is carried out with the exclusion of intestinal diseases, diseases of the musculoskeletal system, acid-dependent diseases, as well as with the exclusion of cholecystitis, pancreatitis and kidney diseases. A schematic generalized algorithm for differential diagnosis of patients with pain in the upper right quadrant of the abdomen is shown in figure 3.

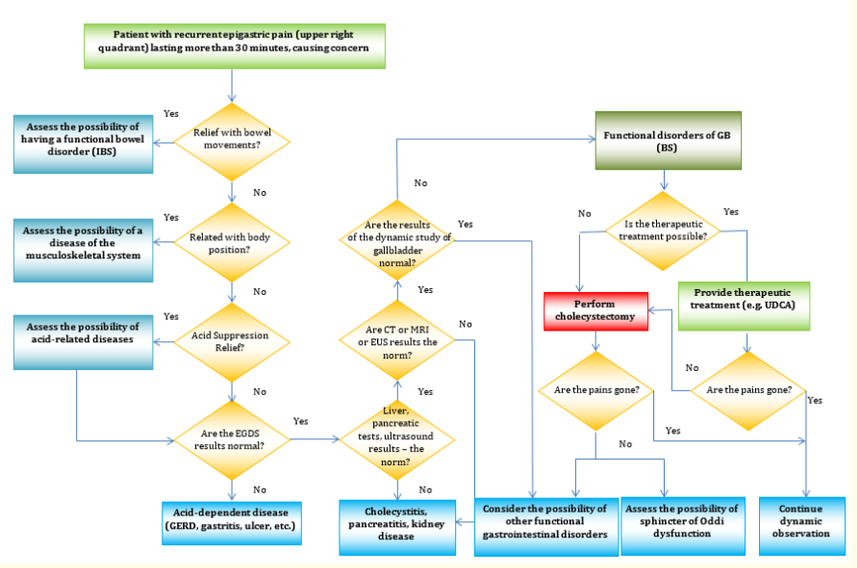

Figure 3: *Algorithm of differential diagnosis for pain in the right quadrant of the abdomen [11,12].*
Legend: IBS: Irritable Bowel Syndrome; GI: Gallbladder; EGDS: Esophagogastroduodenoscopy; GERD: Gastroesophageal Reflux Disease; CT: Computed Tomography; MRI: Magnetic Resonance Imaging; EUS: Endoscopic Ultrasound; UDCA: Ursodeoxycholic Acid.

In differential diagnosis in patients with abdominal pain, true biliary colic should be distinguished from nonspecific abdominal discomfort. Cholecystectomy usually relieves biliary colic, but symptoms of discomfort often persist if it was performed in patients with nonspecific abdominal pain, such as dyspepsia, stomach ulcer, duodenal ulcer, irritable bowel syndrome, dysmenorrhea, psychosomatic pain, constipation, viral, mesenteric adenitis or choledocholithiasis. However, while there are many imaging techniques that can be used to identify BS and gallstones, the diagnosis of biliary colic is ultimately based on clinical judgment. If biliary pathology (BS, gallstones, etc.) is suspected, the choice of the diagnostic method should be based on clinical symptoms, as well as on the sensitivity, specificity and availability of diagnostic tests available to the doctor.

In general, given its high availability and non-invasiveness, transabdominal ultrasonography should be the initial test. However, since the sensitivity of this test is only 60%, further diagnostic testing should be considered if the ultrasound result is negative and clinical suspicion remains high. For example, in a patient with recurrent attacks of idiopathic pancreatitis. If a diagnosis is needed, either endoscopic ultrasound (EUS) or biliary microscopy should be chosen. The sensitivity of EUS for visualization of BS is 96%. On CT, the biliary sludge has more attenuation than normal bile and layers in the gallbladder. Its manifestation on magnetic resonance imaging (MRI) is not always well visualized [3].

Treatment of biliary sludge

An indication for conducting courses of conservative therapy in BS, even without clinical symptoms, is its persistent detection according to ultrasound data for 3 months.

The tactics of managing patients with BS is determined depending on the characteristics of the clinical course of biliary sludge: I - not requiring treatment, since the elimination of the etiological factor leads to regression of BS; II - those in need of therapeutic treatment, because without appropriate treatment, BS is transformed into gallstones with the involvement of other organs and systems in the pathological process; III - in need of surgical treatment, without which complications are possible that require urgent surgical intervention, with a high risk of purulent complications and mortality [10].

However, the choice of tactics for treating patients with BS should be based not only on the features of the clinical course, but also on the variants of biliary sludge diagnosed using ultrasound. With BS in the form of a suspension of hyperechoic particles (microliths), surgical intervention is not advisable. The only exceptions can be cases when, due to long-term persistence of BS, a stricture of the terminal section of the common bile duct or stenosing papillitis is formed, which impede the outflow of bile. Clots of putty bile can block the bile ducts in the narrowest places. These are the cystic duct and the distal common bile duct.

The main areas of pathogenetic therapy for patients with BS are:

- Improvement of the rheological properties of bile (preparations of ursodeoxycholic acid - UDCA);
- Normalization of motor function of the gallbladder, CO, small intestine (cholekinetics, prokinetics, selective antispasmodics);
- Restoration of the normal composition of the intestinal microbiota (intestinal antiseptics, pro, pre, metabiotics).

All patients with BS should be advised to eat regularly every 3 - 4 hours, including a small amount before bedtime, excluding long periods fasting. It is necessary to reduce the energy value of the diet at the expense of saturated fats and easily digestible carbohydrates. It is important to limit the intake of cholesterol by reducing the intake of cholesterol-containing foods. The diet in patients with FD should be balanced in terms of protein and fat, mainly vegetable. You should limit the use of flour and cereal dishes. It is recommended to include a sufficient amount of fiber in the diet. Compliance with a diet improves the rheological properties of bile and enterohepatic circulation of

its constituent components, improves the transit of chyme through the intestine and reduces the likelihood of spastic contractions of the muscles of the gallbladder and CO, which can cause BS migration [7].

Currently, drugs that improve the rheological properties of bile include UDCA drugs. The mechanism of action of UDCA is associated with inhibition of cholesterol synthesis in the liver, a decrease in its secretion into bile, a decrease in absorption in the intestine and an increase in solubility in gallbladder bile. In addition, UDCA has choleretic and cholekinetic effects, participates in digestion processes, does not undergo microbial deconjugation, does not have a toxic effect on the intestinal epithelium, enhances the bactericidal effect of bile, and stimulates the motor function of the gallbladder.

Peculiarities of UDCA prescription: in BS-1, both UDCA drugs and cholekinetics in standard doses are prescribed for the course treatment. However, in the presence of BS-2 or BS-3 type, it is advisable to start treatment with UDCA drugs. This is due to the fact that in the presence of echo inhomogeneous and putty-like bile in the lumen of the bladder, small stones that are difficult to visualize can be found in it. When treated with cholekinetics, this situation can provoke the occurrence of pain in the right hypochondrium, and in some cases - mechanical obstruction of the bile ducts with a small calculus or a dense clot with the development of jaundice [2]. The duration of the course of treatment depends on the severity of the clinical picture and the form of BS. With BS-1, a 1 - 2-month course of therapy is usually sufficient. In other forms, a longer course of treatment is required, usually not exceeding 12 months. Ursodeoxycholic acid is prescribed in a dose of 10 - 15 mg/kg body weight once at night for 1 - 3 months. With a frequency of 1 every 3 months, ultrasound and biochemical blood tests are performed (the level of total cholesterol, ALT, AST, ALP for 3 months is 75 - 85%. If necessary, the dosage of UDCA can be increased from 10 to 15 mg/kg of body weight and therapy was continued until the complete disappearance of sludge from the GB [7].

UDCA is an orally administered bile acid that has been extensively studied to dissolve cholesterol gallstones and treat primary biliary cholangitis. The pathogenetic rationale for the use of UDCA in the treatment of biliary dysfunctions lies in a decrease in hepatic cholesterol secretion in bile and in an increase in the time of formation and crystallization of cholesterol. Several studies have examined the effect of UDCA on the treatment of BS. In patients who are rapidly losing weight, UDCA reduces the incidence of gallstones by 50% to 100% [3]. In patients with BS and idiopathic acute pancreatitis after initial treatment with UDCA to dissolve solid cholesterol crystals, maintenance therapy has successfully prevented recurrence of BS and pancreatitis. Notably, UDCA effectively prevents the recurrence of solid cholesterol crystals and significantly reduces the risk of recurrent pancreatitis. UDCA therapy may be a reasonable alternative for ineffective cholecystectomy candidates or very elderly people.

One of the UDCA drugs widely used in BS therapy is Grinterol® (JSC Grindeks, Latvia) [13,14]. Greenterol® is a full-cycle micronized UDCA of European production (from substance to finished form). The micronization process makes it possible to obtain homogeneous and pure microparticles, which improve the parameters of the drug's bioavailability.

The micronized active ingredient reduces the risk of side effects and provides a faster therapeutic effect.

Relief of pain, symptoms of dyspepsia, a decrease in the lithogenic properties of bile and elimination of BS occurs when drugs capable of restoring the contractile function of the gallbladder and arresting the CO spasm are included in the treatment regimen. In the presence of hypomotor dysfunction of the gallbladder, cholekinetics are traditionally prescribed, which stimulate the contractility of the gallbladder and promote the flow of bile into the duodenum. In the presence of a functional disorder of CO, relaxants of smooth muscles are currently used. In patients with BS, the appointment of the latter is also justified in case of gallbladder dysfunction of the hypomotor type, since it is often secondary in nature and is caused by the hypertonicity of the CO [7]. Recently, selective antispasmodics have been widely used to restore the functions of the gastrointestinal tract and CO. The advantages of selective antispasmodics are that they have practically no effect on other smooth muscles, in particular, the circulatory system and intestinal muscles [9,15].

To restore the normal composition of the intestinal microbiota, pro, pre, metabiotics can be used. The use of pro, pre-, metabiotics leads to the normalization of the intestinal microbiota, improvement of intestinal digestion, normalization of intestinal and stool motility.

Thus, the appointment of the UDCA drug in the presence of BS is pathogenetically justified, aimed at restoring the rheological properties of bile and normalizing the functional state of the mucous membrane and gallbladder.

Below is a clinical example of formulating the diagnosis and treatment of a patient with BS.

Clinical Example

Patient: B., 50 years old, complained of girdle pain and heaviness in the right hypochondrium after errors in diet, diarrhea 3 - 4 times a day, nausea, vomiting of food eaten, bitterness in the mouth in the morning.

Anamnesis:

- Past diseases: Cholecystitis.
- Bad habits: Drinking alcohol - sporadically.
- Physical examination data: The condition is satisfactory.
- The tongue is coated with a yellow-brown thick coating.
- The skin, visible mucous membranes are icteric.
- Height 182 cm weight 88 kg
- Abdomen: Regular, symmetrical.

The edge of the liver: on palpation, the edge of the liver is sharp, the contour is even, the consistency is soft, the surface is smooth, there is no pain, under the edge of the costal arch along the mid-clavicular line, smooth, soft. The spleen is not enlarged.

Gallbladder and pancreas: on palpation at the point of the gallbladder, moderate pain is determined, Symptoms of Shoffard and Mayo-Robson are positive.

Stool: Diarrhea BK-5, 3 - 4 times a day.

Ultrasound of the PD: GB: heterogeneous bile with clots of different contrast. Liver: fatty infiltration, moderate hepatomegaly.

EGDS and duodenography: In the lumen of the stomach and 12 sc. bile. The intestinal lumen is free. Vater nipple 5 - 6 mm. Its mucosa was unremarkable. The mouth is free.

Colonoscopy: Colon without pathology.

Serological blood test: *Shigella* spp., *Salmonella* spp., *Yersinia* spp. - neg. Antibodies to endomysium and tissue transglutaminase within normal limits. Markers HAV, HBV, HCV, EBV and CMV neg.

Stool analysis: Moderate steato-, creatorrhea, intestinal microbiota - a decrease in the level of Bifido and Lactobacilli (method of mass spectrometry of microbial markers). PCR tests for *Salmonella, Shigella, Yersinia*, Norvovirus, Rotovirus and Adenovirus were not detected.

BC 5-6 type, blood in the feces was not detected, Clostridium difficile A and B - neg. Verotoxin - neg. Calprotectin - 35 U Pancreatic elastase - 250 U.

Laboratory results (upon admission of the patient)

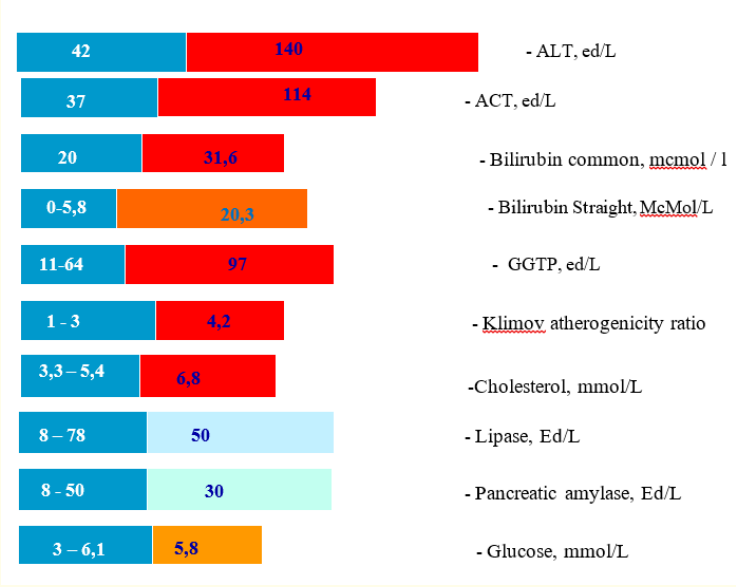

Figure 4

Diagnosis: Cholelithiasis, stage I. Biliary sludge type 2. Functional gallbladder disorder of the hypomotor type. Deformation of the gallbladder.

Dyspepsia. Duodeno-gastric reflux.

Functional diarrhea.

Treatment

Diet. Table 5.

Drug therapy: UDCA (Greenterol®) 250 mg 3 times a day after meals for 3 months; selective antispasmodic for 14 days; probiotic 1 month.

Monitoring of the hepatic profile, function of the gallbladder and pancreas 1 time at 2 and 3 weeks of therapy and then 1 time in 3 months.

Ultrasound of the abdominal cavity after 1 month and further on 3 months of treatment.

Against the background of the therapy, after 14 days, a positive trend was noted, manifested in the relief of discomfort and pain in the right hypochondrium; in reducing the size of the liver and gallbladder; in a tendency to normalize the indicators of the hepatic spectrum.

On the 21st day of treatment, normalization of hepatic spectrum indices was noted.

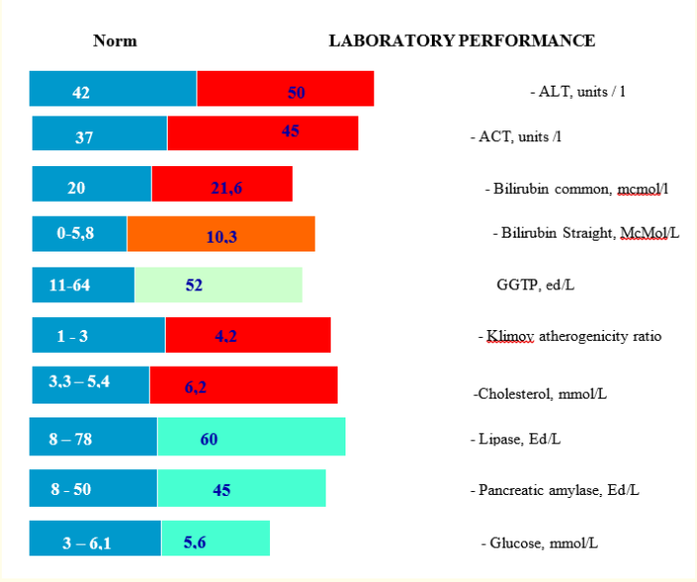

Figure 5

As a result of 1 month of treatment:

- Ultrasound showed the normalization of the size and contractile function of the gallbladder, as well as the consistency of bile.
- According to the results of biochemical tests, a stable positive dynamics of the pancreatic, hepatic, lipid spectrum and indicators of coprology was revealed.
- Relief of pain syndrome, dyspeptic symptoms and stool normalization.

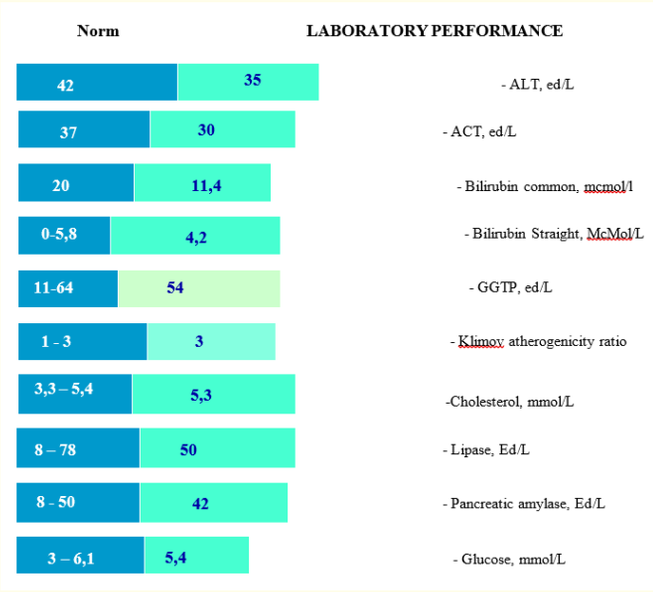

Figure 6

Conclusion

Early diagnosis and treatment of biliary sludge is of great clinical and prophylactic importance due to the possibility of disease progression with the transformation of biliary sludge into chronic cholecystitis and gallstone disease [5,10].

In some patients with biliary sludge during treatment with UDCA drugs, symptoms of biliary dyspepsia persist. This fact is associated with motor disorders of the biliary tract, which cannot be stopped by taking UDCA drugs.

The addition of selective antispasmodics to urso therapy, which has a selective antispasmodic effect on the sphincter apparatus and affects the motor function of the biliary tract, makes it possible to relieve pain and symptoms of biliary dyspepsia.

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