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Clinical Course and Diagnosis of Cholelithiasis in Children

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ANNOTATION

Gallstone disease (GSD) is one of the most common human diseases, which ranks third after diseases of the cardiovascular system and diabetes mellitus. In terms of the number of cholecystectomies performed for cholelithiasis, this disease is in second place in the world after appendicitis. If current rates of growth in the incidence of cholelithiasis are maintained, by 2050 every fifth person on the planet will suffer from it. In this regard, the problem of "well-being disease," as it has been figuratively called, is one of the most pressing for modern medicine.

Relevance and problems. The review is devoted to modern scientific data on the pathogenesis of cholelithiasis and the current opportunities for optimizing litholytic therapy. It has been shown that cholelithiasis should be considered as a local manifestation of systemic disorders of metabolic and inflammatory origin throughout the body. A key role in its development of insulin resistance, metabolic disorders of cholesterol, bile acids, biliary dyskinesia and the production of inflammatory mediators has been demonstrated. Factors that determine the comorbidity of cholelithiasis with cardiovascular diseases, cerebrovascular diseases, cancer of the gastrointestinal tract of various localizations and liver diseases have been identified; the role of cholelithiasis as a risk factor and criterion for poor prognosis is substantiated. A pathogenetically justified approach to improving oral litholysis, providing a complex effect of therapy, is considered; the rationality of using a fixed combination of ursodeoxycholic acid and glycyrrhizic acid has been substantiated [1, 15].

According to statistics, in Europe and the USA, 15–20% of residents suffer from cholelithiasis [3.4, 5, 6]. These figures can be extrapolated to Russia. At the same time, it is fair to note that the prevalence of cholelithiasis in different countries is characterized by significant variability, which is determined by genetic and external factors [5¸23]. Being the cause of the largest number of hospitalizations among all diseases of the gastrointestinal tract, cholelithiasis also occupies the position of one of the most costly diseases of the digestive system for healthcare [3, 4, 5, 6, and 7]. The main risk factors for cholelithiasis include: old age; female; pregnancy; taking estrogen during postmenopause; high-calorie diet, rich in easily digestible carbohydrates and low in fiber; overweight or obesity; hereditary predisposition [7, 8]. Despite, that the disease occurs predominantly over the age of 40 years, there is a widespread tendency towards its rejuvenation. Increasingly, this diagnosis is made in childhood and adolescence. This fact is associated primarily with an increase in the prevalence of obesity, physical inactivity, diabetes mellitus, and early pregnancy in this category of patients [4, 11, 19]. Based on their composition,

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stones are divided into cholesterol and pigment stones. They can be localized in the gallbladder, less often in the common bile duct and intrahepatic bile ducts. In 80% of cases, the disease is asymptomatic and stones are discovered accidentally during ultrasound examination [9]. Of these, 80–90% consist primarily of cholesterol [7, 8,14,17]. Increasingly, this diagnosis is made in childhood and adolescence. This fact is associated primarily with an increase in the prevalence of obesity, physical inactivity, diabetes mellitus, and early pregnancy in this category of patients [4,11,19]. Based on their composition, stones are divided into cholesterol and pigment stones. They can be localized in the gallbladder, less often in the common bile duct and intrahepatic bile ducts. In 80% of cases, the disease is asymptomatic and stones are discovered accidentally during ultrasound examination [9]. Of these, 80–90% consist primarily of cholesterol [7, 8,14,17]. Increasingly, this diagnosis is made in childhood and adolescence. This fact is associated primarily with an increase in the prevalence of obesity, physical inactivity, diabetes mellitus, and early pregnancy in this category of patients [4,11,19]. Based on their composition, stones are divided into cholesterol and pigment stones. They can be localized in the gallbladder, less often in the common bile duct and intrahepatic bile ducts. In 80% of cases, the disease is asymptomatic and stones are discovered accidentally during ultrasound examination [9]. Of these, 80–90% consist primarily of cholesterol [7, 8,14,17]. Based on their composition, stones are divided into cholesterol and pigment stones. They can be localized in the gallbladder, less often in the common bile duct and intrahepatic bile ducts. In 80% of cases, the disease is asymptomatic and stones are discovered accidentally during ultrasound examination [9]. Of these, 80–90% consist primarily of cholesterol [7, 8,14,17]. Based on their composition, stones are divided into cholesterol and pigment stones. They can be localized in the gallbladder, less often in the common bile duct and intrahepatic bile ducts. In 80% of cases, the disease is asymptomatic and stones are discovered accidentally during ultrasound examination [9]. Of these, 80–90% consist primarily of cholesterol [7, 8,14,17].

Gallstone disease (GSD) has long been considered a pathology of adults; in childhood, the disease was rarely encountered [1,2,3,4]. However, over the past 20 years, the frequency of this pathology in young patients has increased significantly, from 0.13 to 2.00% [5,6,16]. The incidence ratio among boys and girls is 2:1 at the age of under 7 years, 1:1 at the age of 7 to 9 years, 1:2 - from 10 to 12 years, 1:3 - over 13 years [1,3]. The predominance of girls over 10 years old in the structure of patients is explained by endocrine changes in the body and, in connection with this, increased levels of progesterone [1,18,20]. A feature of cholelithiasis in childhood is the high frequency of burdened heredity among first-degree relatives (75–95%) [6]. At the present stage, predictors of the disease include ante- and postnatal pathologies, congenital variants of hypercholesterolemia, abnormalities in the development of the biliary system, artificial feeding, nutritional status characterized by a low amount of fiber, high content of carbohydrates and fats, long-term parenteral nutrition, obesity, type 2 diabetes mellitus, physical inactivity, stress [1, 6,7,8,9,10,11]. There is evidence that this pathology is associated with hemolytic disease and prematurity [1213,14]. Medicines, in particular antibiotics, can also be predictors of cholelithiasis. 14]. Medicines, in particular antibiotics, can also be predictors of cholelithiasis. 14]. Medicines, in particular antibiotics, can also be predictors of cholelithiasis.

More and more data are emerging characterizing cholelithiasis not only as an independent disease, but also as a comorbid pathology that has a close etiological and pathogenetic connection with other diseases. It can contribute to their development and progression, and influence outcomes. An inverse relationship is also possible: certain diseases and conditions may serve as an additional risk factor for stone formation. It has been proven that patients with cholelithiasis, especially females and young people, have a higher risk of developing cardiovascular and cerebrovascular diseases [4, 10, 11] . A direct connection has been identified between cholelithiasis and gallbladder cancer, as well as stomach cancer, hepatocellular

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carcinoma, cholangiocarcinoma, pancreatic cancer, and colorectal cancer [12]. Installed that in the presence of cholelithiasis, the risk of death from all causes and from cancer increases by 30%, and death from cardiovascular diseases by 40% [13]. In view of the anatomical and physiological unity of the hepatobiliary system, the combination of cholelithiasis with liver diseases deserves special attention. According to available data, the presence of chronic liver disease increases the likelihood of developing cholelithiasis by 1.2–5 times. At the same time, the prevalence of cholelithiasis increases in proportion to the increase in the Child-Pugh class of liver failure [6]. A correlation has been established for viral hepatitis B and C, which is likely due to the direct damaging effect of the virus on the cells of the gallbladder wall. With regard to alcoholic liver disease, it is difficult to draw clear conclusions due to contradictory data, indicating either the absence of the influence of alcohol on lithogenesis, or its preventive potential in moderate doses [14,15,16,17]. The strongest relationship was identified for cholelithiasis and non-alcoholic fatty liver disease, especially in female patients. In the presence of cholelithiasis, the prevalence of non-alcoholic fatty liver disease is 2 times higher than in the general population [18], as well as the higher prevalence of the inflammatory form of the disease - non-alcoholic steatohepatitis [19]. It is noteworthy that cholecystectomy does not solve the problem, but is an independent risk factor for non-alcoholic fatty liver disease. In turn, non-alcoholic fatty liver disease is an independent risk factor for cholelithiasis, which increases the likelihood of the disease by more than 50%. Additional factors contributing to stone formation in these patients include: are older age, high body mass index and female gender [10]. At the same time, the prevalence of cholelithiasis progressively increases with increasing stage of non-alcoholic fatty liver disease [12] and the stage of fibrosis: at stage 0–II it is 15%, at stage III - 29%, and at stage IV (cirrhosis) - 56% [13, 19].

The incidence of cholelithiasis in the pediatric population has increased significantly over the past 8-10 years [22]. Stones in the gall bladder and bile ducts are detected in children of school, preschool and even early ages. There is no clear reason for the increase in morbidity in children. Along with improved diagnosis, an increase in the number of cases of cholelithiasis starting from an early age should be noted [1]. Cholelithiasis in children, previously considered a casuistry, is today an actively discussed problem.

Diseases of the gallbladder, biliary tract and pancreas in ICD-10 are included in headings K80–K87, cholelithiasis itself is included in heading K80. According to extensive epidemiological studies conducted in recent years, the incidence of cholelithiasis in developed countries is 10–15% among the adult population [9, 20, 24]. Separate cohort studies conducted in Russia showed that the prevalence of cholelithiasis varies widely - from 6 to 12% [30]. The wide prevalence and continuing trend of its growth allows us to classify cholelithiasis as a disease that has not only medical, but also important socio-economic significance [19]. Detection of cholelithiasis at an early, pre-stone stage is difficult to overestimate, since it is possible to carry out primary and secondary prevention of the disease [3, 5, 11, 13].

GSD is characterized by a fairly high prevalence in countries with a Western lifestyle (Europe, North America, and Russia): this disease is registered with a frequency of 10-15%. Such a high frequency, in addition to the contribution of genetic factors, is explained by dietary patterns and consumption of increased amounts of simple carbohydrates. In Africa, Asian countries and Japan, the prevalence of cholelithiasis is lower - 3.5-5%.

The NANESH III epidemiological study noted significant racial differences in the incidence of cholelithiasis, highlighting the important contribution of genetic factors to the pathogenesis of the disease. Among some nationalities, the incidence of gallstones is extremely high: among Mexicans and Chilean Indians, the probability of developing gallstones during their lifetime reaches 45-80%.

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The risk factor for the development of gallstone disease is: 1) age; 2) floor; 3) pregnancy; 4) hormonal therapy; 5) taking estrogens; 6) heredity; 7) obesity, hypertriglyceridemia; 8) diabetes mellitus; 9) cirrhosis of the liver; 10) use of medicines; 11) rapid weight loss; 12) damage to the terminal ileum. 13) Total parenteral nutrition.

1) The incidence of cholelithiasis clearly correlates with age. In Western countries, the detection rate of cholelithiasis in old age reaches 30%. However, the maximum frequency of clinical manifestations of cholelithiasis is recorded at the age of 40-69 years. 2) The risk of developing cholelithiasis in women is approximately 2-3 times higher than in men, which is associated with the influence of estrogens on lithogenic potentials. However, differences in the incidence of men and women are smoothed out with age: in the age group of 30-39 years, the ratio of the risk of developing cholelithiasis in women and men is 2.9:1, at the age of 40-49 years - the ratio is 1.6:1, in aged 50-59 years – the ratio is 1.2:1. 3) The risk of developing cholelithiasis increases during pregnancy, especially with repeated pregnancies (the likelihood of stone formation increases 10-11 times). During pregnancy, biliary sludge develops in 20-30% of patients, stones - in 5-12% of cases. However, cases of spontaneous dissolution of stones after childbirth have been reported. 4) hormone replacement therapy in postmenopause (the risk of cholelithiasis increases 3.7 times). 5) taking estrogen - in both sexes. 6) family history of cholelithiasis (the risk is increased by 4-5 times). 7) obesity, hypertriglyceridemia. Among people with metabolic syndrome, cholelithiasis is detected in ≈ 20% of cases. 8) diabetes mellitus (the risk is increased by 3 times). 9) cirrhosis of the liver (the risk is increased by 10 times). 10) the use of drugs that affect the concentration of cholesterol in bile, motility of the biliary tract or are capable of crystallization in bile (somatostatin, fibrates, ceftriaxone). 11) rapid weight loss, bariatric interventions (probability of developing cholelithiasis >30%). 12) damage to the terminal ileum. 13) sufficiently long total parenteral nutrition.

In recent decades, there has been an increase in the incidence of cholelithiasis in children and adolescents; the most likely reason for this is the "overweight epidemic."

GSD is a local manifestation of systemic metabolic disorders and inflammation in the body. As comorbid pathology, it influences the development, progression and outcomes of cardiovascular, cerebrovascular diseases, liver diseases and cancer. Surgical treatment, despite its availability and effectiveness, does not solve all problems. Oral litholysis remains relevant and needs to be optimized, the main focus of which is to ensure a comprehensive effect. One of the solutions may be a fixed combination of UDCA and HA, recently registered in the Russian Federation. The drug can be used: in patients with biliary sludge; patients with cholesterol stones less than 20 mm in size and a functioning gallbladder - asymptomatic and with clinical symptoms, if surgical treatment is not possible; in the postoperative period after cholecystectomy to reduce the risk of stone formation in the bile ducts; in patients at increased risk of stone formation for primary prevention. Currently, in real clinical practice, the long-term effectiveness and safety of the drug is being studied, including in various groups of patients, as well as in comorbid diseases.

To date, a large number of hemodynamic, rheological, immune and other risk factors for stone formation have been described in the medical literature. New methods for assessing a patient's readiness for surgery are constantly being presented, and the interpretation of the results of old tests is being revised. In this regard, it seems promising to create an integrated system for assessing the risk of early stone formation, which includes the results of a number of the most reliable methods, capable of adapting to the emergence of new diagnostic methods and harmoniously integrating them into the existing prognostic algorithm.

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