ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 02, February-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

Axmamadaliyev M. A. ,Usmonov E.I.

Andijan State Medical Institute.

ASSESSMENT OF MOLECULAR GENETIC RISK FACTORS FOR CHOLELITHIASIS

Abstract: The prevalence of cholelithiasis, its close pathogenetic relationship with metabolic syndrome, the high frequency of surgical intervention, and significant economic losses put this comorbid pathology among the leading problems of modern clinical medicine. Factors associated with metabolic syndrome not only increase the risk of cholelithiasis, but also form the basis of non-drug and drug therapy. Metabolic syndrome often determines the occurrence of three common and potentially life-threatening complications of cholelithiasis: acute cholecystitis, acute cholangitis, and biliary pancreatitis. Therefore, the solution of this problem is associated with the need for early detection of additional risk factors for cholelithiasis, optimization of the early diagnostic and prognostic model of the existing multi-organ pathology in order to reduce the progression of the disease and its complications. The data obtained in recent years on the genome of a person with metabolic syndrome and cholelithiasis make it possible to predict the development of comorbid pathology and fully ensure the effectiveness of primary prevention.

Key words: cholelithiasis, surgical intervention, inheritance of anomalies, pathogenesis

To understand the essence of the problem, it is first worth considering the normal anatomy of the gallbladder. The gallbladder (vesical fellea) is a hollow, pear-shaped organ 8–12 cm long and 403 cm in volume, consisting of a bottom (fundus vesicae fellea) (1), a body (corpus vesicae fellea) (2) and a neck (collum vesicae fellea) (3), which passes into the cystic duct (ductus cysticus) (Fig. 1) [3] The gallbladder is laid before the 12th week of embryo development from the endodermal layer, along with the digestive tract. Now let's consider the concept of cholelithiasis (cholelithiasis). Cholelithiasis (cholelithiasis) is a chronic disease with a genetic predisposition, in which the formation of stones in the bile ducts is observed [2]. In recent decades, the prevalence of cholelithiasis has doubled every 10 years, which is why its early diagnosis and treatment are of great clinical importance. The gallbladder is part of the extrahepatic biliary tract and is designed to accumulate and concentrate bile, which is secreted by the liver and periodically excreted into the duodenum. The contraction of the gallbladder is regulated by nervous reflex mechanisms that lead to the release of bile into the lumen of the duodenum [4]. Regular release of bile into the duodenum is necessary for the full functioning of the liver and bile system. In the gallbladder, bile is concentrated due to the absorption of water by the mucous membrane of the organ, which leads to an increase in its density. Any decrease in the concentration function of the gallbladder is accompanied by a decrease in its elasticity and the formation of lithogenic bile. The pathogenesis of cholelithiasis is based on the formation of gallstones in the presence of certain risk factors and the formation of biliary sludge. In conditions of cholesterol oversaturation, the contractility of muscle fibers is impaired [2]. In addition, the passage of bile crystals and stones can cause re-traumatization of the sphincters, prolonged spasm and the development of chronic inflammation and dyskinesias of the biliary tract. determines the presence of a significant number of risk factors for the development of the disease, such as age, female sex, pregnancy, obesity, diabetes mellitus, metabolic disorders and others. Genetic factors also make an important contribution to the pathogenesis of this disease [2], which emphasizes the high frequency of gallstone formation in first-degree relatives of patients with cholelithiasis and a significant percentage (25%) of the development of cholelithiasis in monozygotic twins. Also, the epidemiological study

eISSN: 2349-5715 pISSN: 2349-5707

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NANESH III noted significant racial differences in the incidence of cholelithiasis, when among some peoples of Northern Europe and North America, the probability of gallstone formation during life reaches 45-80%. Scientists attribute this fact to the peculiarities of mitochondrial DNA, in which the rate of conversion of cholesterol into bile acids is reduced, which leads to an increase in the ratio of "cholesterol / bile acids" in bile. Probably, in most cases, cholecystitis is of polygenic origin, but cases of monogenic inheritance are possible. Thus, the polymorphism of the gene encoding the structure of the intrahepatic cholesterol transporter, in which its secretion into the bile is increased, is described. In addition, with a mutation of the gene that catalyzes the first stage of the conversion of cholesterol into bile acids, there is a deficiency of bile acids, which in homozygous carriers always leads to hypercholesterolemia and cholelithiasis, in heterozygotes there is only a predisposition to them. In addition, birth defects and malformations of the biliary tract (abnormalities) are often the cause of functional disorders of the biliary tract with the subsequent development of inflammatory changes and the formation of stones. The mechanism of their development is laid down genetically. There are different points of view on the inheritance of anomalies, but assumptions are made about the dominant inheritance of genes in two generations [5]. Abnormalities in the development of the gallbladder are subdivided: 1) into anomalies of size (hypogenesis, giant gallbladder); 2) anomalies of position (intrahepatic, interposition, inversion, dystopia, rotation); 3) abnormalities in quantity (agenesis, doubling of the gallbladder); 4) anomalies of shape (gallbladder in the form of a bull's horn, in the shape of a Phrygian cap, mouth-shaped, S-shaped) [5]. With developmental anomalies, the passage of bile is disrupted, which leads to the development of dystrophic processes in the wall of the gallbladder and, as a result, to a violation of its contractile function up to atonia. Anomalies in the shape of the gallbladder often lead to its deformation [1]. The presence of these changes may indicate dystrophic processes of the walls of the gallbladder, due to which the organ is not able to contract normally – the wall becomes atonic [3] cholelithiasis. A hereditary predisposition has been found to be responsible for 25% of the overall risk of gallstone formation [2]. Lithogen genes 1 and 2 (Lith1 and Lith2), which play a role in liver cholesterol secretion and regulate bile flow, have been described in mouse models. Their human counterparts are the ABCG5 and ABCG8 genes [4]. The presence of the ABCG8 p.D19H lithogenic allele was detected in 14.9% of children, which is more common than in children and adults without gallstones. carriers of one copy of the lithogenic variant of p.D19H were also at higher risk of developing gallstones. An increased predisposition to the formation of cholesterol stones is associated with impaired cholesterol metabolism as a result of its accelerated transport or reduced absorption in the intestine in combination with increased cholesterol synthesis [10]. Regulate the expression of microRNA (miRNA) genes. miRNA-223 has been shown to prevent the development of gallstones in mice fed a lithogenic diet by directly affecting the transporter proteins ABCG5 and ABCG8 [4]. We did not find published descriptions of studies on the assessment of the effect of miRNA-223 on the development of cholecystitis in humans.

The NPC1L1 rs217434 polymorphism and the lower campesterol/desmosterol ratio were also associated with the occurrence of gallstones in children (compared to healthy adults). However, the UGT1A1 genotype did not differ in children with and without cholecystitis [3].

Polymorphism D19H of the ABCG8 gene, serum cholesterol, non-cholesterol sterols, and lipids were studied in 66 children with cholecystitis later in life and in 126 children in the control group. The ABCG8 19H allele was detected in 22.7% of patients in Group 1, and in the control group, this figure was 19.0%. In patients with the lithogenic variant, a decrease in phytosterol levels was observed. According to this study, low levels of phytosterols in childhood contributed to the onset of cholecystitis in adults who carry the 19H risk variant of the ABCG8 gene. Moreover, the NPC1L1

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variants: -18C>A (rs41279633) and V1296V T>C (rs2174340) had a negligible effect on non-cholesterol sterols [5].

In a study of the genetic aspects of the pathogenesis of idiopathic gallstones, the ABCB4 gene encoding multidrug-resistant protein 3 (MDR3) was evaluated. The ABCB4 mutation can lead to low-phospholipid associated cholelithiasis (LPAC), a hypophospholipid-associated cholelithiasis with symptoms, ultrasound signs, and recurrence in young patients, as well as to progressive familial intrahepatic cholestasis (PFIC) type 3, cholelithiasis caused by intrahepatic cholestasis during pregnancy [6]. In a retrospective analysis of 26 children with genetically proven mutations in the ABCB4 gene, cholecystitis was diagnosed in 15% of patients, while in adults this level was higher (67% of patients) [7].

In a study involving 35 children with idiopathic cholelithiasis who met the clinical criteria for LPAC, only one case revealed a potentially pathogenic variant of the c.2318G>T gene ABCB4. This phenomenon can be explained by sexual immaturity, which can affect the course of LPAC [8].

The etiology of gallstones may include NTCP deficiency, which is encoded by the SLC10A1 gene, and disorders of bile acid metabolism caused by NTCP deficiency predispose to gallstone formation [9]. Genetic assays have also identified pathogenic mutations in the ATP8B1 and ABCB11 genes in young adults. However, multivariate analysis did not show that cholelithiasis was an independent factor associated with mutations that cause cholestasis.

In children with cholesterol and pigmented gallstones, a study of the expression of ABCG5 and ABCG8 RNA showed higher levels in patients with cholelithiasis (both cholesterol and pigmented gallstones) than in healthy controls. However, the RNA expression of the FXR transporters, ATP-binding C2 cassette (ABCC2) and ABCB4 did not differ significantly in the study and control groups. Moreover, patients with cholesterol stones had reduced levels of plant sterols (campesterol and sitosterol) and increased levels of cholesterol precursors compared not only to healthy people, but also to children with pigment stones. Both results explain the higher cholesterol content in cholelithiasis [11].

Similarly, in another study, the level of phytosterols, a marker of cholesterol absorption, was lower than in patients with black pigment stones [11]. Comparatively low levels of phytosterols and cholestanol have been observed in children who developed gallstones in adulthood; these signs can be used as a prognostic marker for the development of cholelithiasis [12].

Proteins and lipids. There is evidence that adipokines and hepatokines are involved in the development of cholecystitis in children. Children with cholecystitis have higher levels of chemerin, retinol-binding protein 4 (RBP-4), and fibroblast growth factor 21 (FGF21). Chemerin levels are significantly elevated only in lean children with cholecystitis, and chemerin can be both a pro-inflammatory and anti-inflammatory factor , increased expression of interleukins (IL)-1, IL-4, IL-6, IL-7, IL-8, and IL-17A was revealed [13].

Serum lipid total cholesterol (TC), sphinganin (SPA), ceramides (C14:0-Cer, C16:0-Cer, C18:1-Cer, C18:0-Cer, C20:0-Cer, C24:1-Cer) and lactosylceramides (C16:0-LacCer, C18:0-LacCer, C18:1-LacCer, C24:0-LacCer, C24:1-LacCer) differed significantly in patients with and without gallstones. In a generalized multifactorial linear model, after accounting for age, sex, obesity, total cholesterol, and triglyceride levels, the best differentiating sphingolipids for cholecystis were reduced levels of SPA, C14:0-Cer, C16:0-Cer, C24:1-LacCer, C24:0-LacCer, and increased concentrations of C20:0-

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Cer, C24:1-Cer, C16:0-LacCer, and C18:1-LacCer [38]. These results suggest that serum sphingolipids may be potential biomarkers in patients with cholelithiasis.

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