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The Cholelithiasis Pathogenesis

The paper is dedicated to the memory of my teacher, MD, Professor, Honored Scientist of Russia, and Honorary Professor of the Sechenov First Moscow State Medical University

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ABSTRACT

The author reports his search for scientific papers in the open databases Pubmed, Europa Pubmed Central, eLIBRARY using the search terms «gallstones and pathogenesis», as well as Russian equivalents for "cholelithiasis". For the analysis articles on the cholelithiasis pathogenesis with a high citation level were selected.

So far, the mechanisms of formation of stable nuclei of crystallization of cholesterol stones are not fully elucidated. Recently, there are many facts proving essential Galkin - Chechulin effect in the formation of cholesterol stones crystal nuclei and the role of the bacteria and inflammation.

Thus, in the pathogenesis of gallstone disease, the Galkin-Chechulin effect plays a significant role in the formation of stable crystallization nuclei (embryos). Such bilirubin containing microlites do not spontaneously dissolve and there may be no symptoms for decades, and in the event of the conditions, described by W.H. Admirand and D.M. Small they become nuclei of crystallization of cholesterol stones of macroscopic dimensions.

Keywords: cholelithiasis, pathogenesis, lithogenesis, cholesterol stones, biliary sludge, the Galkin - Chechulin effect.

INTRODUCTION

Cholelithiasis (CL) in recent years has become one of the most common diseases of the digestive system in the world. Outstanding domestic gastroenterologist, author of the discovery of the phenomenon of bilirubin crystallization in the unsaturated solution of bile, MD, professor, honored scientist of Russia, V.A. Galkin writes about CL: "Like a cloud of locusts, cholelithiasis is coming upon the mankind - this is truly a scourge hanging over people. By the simplest estimations, every tenth inhabitant of the Earth is experiencing suffering from gallstones "[4]. The highest prevalence of gallstone disease is observed among American Indians - from 59.5 to

68.2% among women and to 45% among men [40, 35, 45]. The lowest morbidity is observed among the Masai of East Africa, until recently they have not been detected with cholelithiasis [44]. In the world the CL prevalence among the adult population is 10% on average. In recent years, its incidence is increasing rapidly, including in our country.

It should be noted that so far the CL pathogenesis is not fully studied out. Every year in the world hundreds of articles dealing with different aspects of cholelithiasis are published. Knowledge of the disease pathogenesis intricacies is the key to the development of effective prevention and treatment.

The current stage of the CL pathogenesis study begins in the second half of the last century. To the beginning of XX century for 300 years of CL studying two concepts of the pathogenesis of gallstones formation have been formed [5]. They were presented by German scientists: inflammatory - B. Naunyn [34], and metabolic - L. Aschoff [11]. Microbial nature of the gallstone formation the well - known Russian therapist S.P. Botkin suspected, long before the appearance of B. Naunin famous work he assumed that "... life [of the microorganisms] gives in a result such chemical compounds which make substances that are usually in the bile in solution - insoluble, and because of this shortfall ... [precipitate]" [1]. In the first half of XX century good results were achieved in the study of chemical compounds that are the part of gallstones: cholesterol, bile acids [25, 33]. Up to the 50-ies of the last century, the major lipoproteins were identified; their plasma concentration and the role in the metabolism and transport of lipids were also defined [36]. These achievements became the basis for the further development of the scientific study of the pathogenesis of gallstone disease and the search for new effective methods of disease prevention and treatment.

The discovery of the laws of crystallization of bilirubin and bile cholesterol is an important milestone in the study of the pathogenesis of stone formation in the gall bladder. V.A. Galkin and A.S. Chechulin in 1957 experimentally established previously unknown phenomenon of bilirubin crystallization in the bile unsaturated solution in terms of bacterial catarrh inflammation of the gall bladder, which was associated with a decrease in the pH of the colloidal solution of bile [6]. In 1968, an article of W.H. Admirand and D.M. Small (Boston University) about the laws of crystallization of cholesterol and bile was published; for the first time built a model schedule of cholesterol crystallization, depending on the concentration of cholesterol, lecithin and bile acids

in the triangular coordinate system [10]. The current stage of the study of the gallstone disease pathogenesis began with in-depth research around these two scientific problems.

Composition of gallstones. At studying the composition of gallstones and its crystal structure as a result of use of X-ray analysis in the 60-s of the last century new data were obtained. Thus, it was found out, that the in vivo cholesterol is crystallized into monohydrate crystals of cholesterol, bilirubin into - biliribunate crystals of calcium, and calcium carbonate - vaterite, aragonite and calcite [29]. Later, it was noted that gallstones were distinguished for their diversity. As part of the stones such minerals as apatite, struvite, whitlokite and et al were discovered. Most of the researchers have identified two large groups of stones: cholesterol and pigment. In turn, pigment stones are divided into black and brown [51]. Subdivision of gallstones into types is very conditional because in clinical practice there are no absolutely "pure" stones. The stones are composed of a main component and impurities. Stones, in the dry residue of which, cholesterol is more than 50% are Cholesterol ones [20, 37]. Cholesterol stones are the most common in Western countries; they make up to 75-80% of gallstones. It should be noted that the frequency of the stones with cholesterol content in dry residue 90% (the so-called "pure" cholesterol stones) is not so high, only up to 10% of the gallstones' structure.

Scientists at the head of T. Qiao from the laboratory for the study of cholelithiasis (Guangzhou, China), based on the analysis of cholelitomy 807 cases identified 8 types of gallstones: cholesterol, pigment, calcium carbonate, phosphate, calcium stearate, protein, cystine and mixed [50]. In turn mixed stones were divided into more than 10 subtypes. Earlier, German researchers based on analysis of 1025 gallstones identified 6 types of stones: cholesterol, bilirubin, calcium, magnesium, palmitate-stearate, and polysaccharide. Calcium stones are composed of apatite, aragonite, calcite and uncertain calcium minerals, and magnesium – of struvite [39]. The mineral composition of gallstones has wide variability not only among the inhabitants of different countries, ethnic, age and gender groups, but also in one and the same patient. Type of the postponed for gallstone crystal layers may vary throughout one's life.

The microstructure of gallstones by scanning electron microscope allows understanding some aspects of lithogenesis [50]. Thus, it was found that the cholesterol monohydrate crystals in the form of rhomboid blocks are packaged as packs of a linear or radial character [28], and the crystals of calcium salts bilirubinate, often in the form of bizarre and globular formations, - chaotic. Primary elements of cholesterol monogidrite crystals and bilirubinate calcium in the

form of a separate rhomboid and globular crystals scientists find at microscopic examination of bile in patients with biliary sludge [31].

Biliary sludge. The term "biliary sludge" was introduced in the 70 -s of the last century in connection with the broad introduction of ultrasound [27]. It should be noted that in 1957, V.A. Galkin and A.S. Chechulin determined the conversion of bile into the gel state [6], but only in the late 60-s American scientists have found out the conditions of the crystallization of cholesterol and its precipitation [10] .

Biliary sludge - a state of bile with increased echogenicity with or without microcrystalline suspended or precipitated particles, diagnosed by transabdominal ultrasonography and clinical research methods. In 2002, the Russian Gastroenterological Association adopted a classification of gallstones, in which biliary sludge has been recognized as its initial or pre-stone stage [7]. Some researchers abroad have come to this conclusion earlier. [19, 43]. In Russia, V.A. Galkin, professor at the Setchenov Moscow Medical Academy was the first to study CL pre-stone stage [2 - 4].

The mechanism of formation of pigment stones is studied in detail enough. Black and brown pigment stones mainly consist of dicalcium bilirubinate (Ca (HUCB) 2), which polymerized and oxidized, turns into black stones, and those that remain unpolymerized, turn into brown ones. The formation of brown stones is caused by a bacterial infection, and black stones are formed by the crystallization of calcium bilirubinate at relatively sterile bile [53].

The formation of cholesterol stones. Some stages of crystallization of cholesterol gallstones are not entirely clear. Cholesterol in the bile because of its insolubility in water forms mixed micelles with phospholipids and cholate, which merging form vesicles at the fullness of bile with cholesterol and changes of cholates and phospholipids ratio. Subsequently unilamellar vesicles fuse to multilamellar forming liquid crystals, and then, through the intermediate forms, - into rhomboid crystals of monohydrate cholesterol [54]. These crystals merging must form embryos (tiny crystalline particles), which growing, must reach macroscopic dimensions. That embryo formation of cholesterol stones until now has not been sufficiently studied. This initial stage of formation of gallstones is indicated by a number of authors as nucleation stage or nucleation followed by growth stage or crystallization. The generation stage begins with the appearance of the first crystals, and ends with the formation of the embryo. According to some authors, the formation of "pure" cholesterol nucleation is impossible. Spontaneous crystals

nucleation requires highly supersaturated solutions. It is considered that cholesterol may spontaneously crystallize in a solution, supersaturated with cholesterol on 300%. For a human such a concentration of cholesterol in bile is not possible. Therefore, the formation of nuclei of cholesterol crystalline stones occurs in a result of heterogeneous crystallization [41] with participation of salts of calcium, phosphate, bilirubin, etc.

The nucleus or embryo of gallstones' crystallization is detected as small stones smaller than 3 mm. In current clinical practice, the detection of stones with a diameter of less than 3 mm is treated as a diagnostic criterion for gallbladder microlithiasis [42]. It should be noted that so far there is no clear definition of the terms: microcrystals, biliary sludge and microlithiasis. However, for a number of publications microcrystals can be determined as microscopically detected crystals of cholesterol monohydrate, calcium bilirubinate and calcium microsferolits [9], they do not cause any signs of clinical manifestations. Judging on the growth rate of gall stones in the average 1.5 mm per year, the size of the nucleus (embryo) of crystallization may be equal to 1-2 mm in diameter [21]. This position is confirmed by the fact that the study of the structure of small size cholesterol gallstones, referred as microlithiasis, scientists from Italy in the vast majority of cases have not detected the presence of the nucleus. So, out of 10 studied microstones only in two of them the nucleus was determined [16]. It should be noted that cholesterol microstones are unstable; they spontaneously dissolve and respond well to treatment.

It is known that most of the cholesterol stones have a nucleus of dark color. The study of chemical composition of cholesterol stones nuclei has shown that they are heterogeneous and contain cholesterol, bilirubin and high calcium compound [13]. Based on the fact that in the nucleus of cholesterol stones calcium is almost always detected, an American scholar E.W. Moor et al hypothesized the formation of cholesterol stones from calcium embryo. According to the authors of the hypothesis, perhaps, first the calcium nucleus forms, which then begins to grow thick with cholesterol crystals [38]. It should be noted that, according to modern concepts, the surfeit of bile by cholesterol is the main condition for the formation of cholesterol stones [52]. This formation can be accelerated or decelerated with the so-called protein-promoters and inhibitors of nucleation (stone nucleation). Nevertheless, a number of researchers have not confirmed the catalytic role of many proteins candidates for promoters [52]. Controversial is the inhibitory role of apolipoprotein A-I and A-II, as both lipoproteins were found in the bile not only

in patients with gallstone disease, but also in healthy individuals [30]. Mucin remains one of the few protein - candidates with potential role in the formation of gallstones in a human [52].

According to modern concepts, in the pathogenesis of formation of cholesterol stones there are several links:

- Cholesterol-supersaturated bile;

- Crystallization of cholesterol and the formation of the nucleus;

- Factors of the gallbladder, including its hypomotor dysfunction.

Genes - candidates of predisposition to cholelithiasis are identified on all of these links in the pathogenesis [18, 46, 52]. Genetic predisposition to cholelithiasis is oligogene and polygenic. Mutations in the genes: *CYP7A1, ABC1, ADCB4, CCK-1R, ATB7B, ATP8B1, ABCB11* and *ABCB4* cause oligogene cholelithiasis [17]. Polygenic is caused by multiple genes mutation responsible for synthesis, excretion and transport of cholesterol, bile acids and phospholipids, and mucin gene mutation, various receptors [17]. In experiments in mice over 80 the so-called *LITH* genes are identified. In humans, there are appearing more and more cholelithiasis genes - candidates.

Factors in the development of gallbladder gallstones. Gallbladder dysmotility, probably, is the "trigger" in the pathogenesis of cholesterol gallstones, providing the time, required for the precipitation of microcrystals of cholesterol from supersaturated bile. Polish scientists have revealed that in the patients with gallstones in the gallbladder the amount of interstitial telocytes (Cajal-like cells) significantly reduces [32]. Cajal interstitial cells are neural cells, playing a key role in regulating the motility of smooth muscle of the gastrointestinal tract, being a pacemaker for generating electrical pulses of the slow waves.

Besides a hypomotor dysfunction of gallbladder in the etiopathogenesis of stones' formation recently a number of new local factors of the gallbladder has been identified. Thus, not long ago American and Chinese scientists first identified the role of two single nucleotide gene polymorphisms of vascular endothelial growth factor A (VEGFA) in susceptibility to the development of gallstones. VEGFA gene encodes a protein that regulates vascular permeability and angiogenesis [26]. It is known that bile concentrates several times in the gallbladder (Table).

Table

The composition of the liver and gallbladder bile [48, 49]

Indicator	Hepatic bile	Gallbladder bile
pH	7.0 - 8.2	6.0 - 7.0
Specific gravity	1.010	1.040
Water,%	97.2	88.0
Dry residue	2.7	12.0
Bile acids, g / dl	1.1	6
Bilirubin, g / dl	0.04	0.3
Cholesterol, g / dL	0.1	0.3 - 0.9
Fatty acids, g / dl	0.12	0.3 - 1.2
Lecithin g / dl	0.04	0.3
Ca ++, mg-Eq / l	5	23

In the light of new data the gallbladder bile regulatory indicators can significantly be adjusted depending on the genetic characteristics of the vascular system and its permeability. Even in a healthy human gallbladder bile becomes potentially lithogenic due to the accumulation of lithogenesis activators: cholesterol, bilirubin, calcium and pH acidification. It should be noted that the optimum activity of bacterial ß-glucuronidase is observed at pH 5.2. Bilirubin goes to the gallbladder usually in a conjugated form; at bile acidification endogenous ß-glucuronidase can hydrolyze conjugated bilirubin into unconjugated one. The last is connected with Ca, forming insoluble calcium bilirubinate, and precipitates. With increasing bile alkalinity (pH ~ 7.8) and bile fullness with calcium carbonate precipitated [15]. British scientists led by R.P. Thompson found that the gallstones were more closely associated with the level of unconjugated bilirubin than the degree of saturation of bile with cholesterol. Based on these data, the authors concluded that bilirubin and its metabolites are likely to play an important role in formation of cholesterol gallstones [22]. The phenomenon of crystallization of bilirubin in bile unsaturated solution with pH and the presence of inflammatory changes observed in 1957 by V.A. Galkin and A.S. Chechulin

gets more evidence of the important role of this phenomenon in the pathogenesis of cholesterol stones.

The role of bacteria and inflammation.

After the discovery of the Galkin-Chechulin effect more than 50 years have passed, but recently there is increasing evidence to support the role of bacteria and inflammation in the development of gallstone disease, including the formation of cholesterol stones. According to surveys on this issue by A. Swidsinski, S.P. Lee [47] and T.V. Rukosueva [8], the bacteria are found in the bile, gallbladder mucosa and stones, including at their center. Often it is very difficult to set a time when bacterial infection joined CL: before stone formation or after. Perhaps in the development of cholelithiasis bacterial and non-bacterial mechanisms of disease pathogenesis are working closely, replacing each other for years and decades, creating unique personalized microstructure of gallstones. It should be marked that in the patients with cholesterol stones in 24% of cases in bile the presence of bacteria is detected, and at the use of quantitative PCR with primer, universal for bacteria, positive result is recorded in almost all cholesterol stones, even at a negative result of seeding. M. Kawaguchi et al in 1996 first discovered in the mucosa of the gallbladder in a patient with cholelithiasis Helicobacter Pylori [12]. Since there is increasing evidence of participation of the family of Helicobacter spp. bacteria in the pathogenesis of gallstone disease, including the formation of cholesterol stones.

Mechanism of bacterial lithogenesis is associated with activation of the bacterial enzyme systems: beta-glucuronidase, phospholipase, hydrolases and urease. It was established that bacterial phospholipase played an important role in brown gallstones lithogenesis. It frees palmitic and fatty acids from phosphatidylcholine which can form with ionized calcium insoluble compound of calcium palmitate, subsequently precipitating [47]. As for the urease Helicobacter spp., it hydrolyzes urea to ammonia and bicarbonate. The ammonia increases the pH in the bile; it promotes the formation of insoluble calcium salts and their subsequent precipitation [14]. Recently published studies, conducted with flawlessly chosen methods and extensive material, confirm that the bacteria may be one of the main factors that play an important role in the pathogenesis of gallstone disease [24, 23].

CONCLUSION

Thus, in the pathogenesis of gallstone disease, the Galkin-Chechulin effect plays a significant role in the formation of stable crystallization nuclei (embryos). Such bilirubin containing microlites do not spontaneously dissolve and there may be no symptoms for decades, and in the event of the conditions described by W.H. Admirand and D.M. Small [10] they become nuclei of crystallization of cholesterol stones of macroscopic dimensions.

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