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ORIGINAL ARTICLE

Risk factors in the occurrence of cholelithiasis in children and adolescents: a single-center experience

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Summary

Introduction: Cholelithiasis is etiopathogenetically very heterogeneous and, in terms of frequency, a rare disease in the period of growth and development. The aim of the study was to analyze risk factors for the occurrence of cholelithiasis in that period of life.

Material and Methods: This retrospective study included 80 children and adolescents, 50 females and 30 males, aged 4-18 (14±5.55) years, with symptomatic cholelithiasis who were operated on at the University Children's Hospital in Belgrade in the period from 2000 to 2016. The diagnosis of the disease was based on ultrasound findings. Data on risk factors for the development of biliary calculosis were obtained from medical history.

Results: Predisposing risk factors for cholelithiasis were verified in 46 (57.5 %) patients. One risk factor was identified in 34 patients, two risk factors were identified in 10 patients, three risk factors were found in two patients, while in others risk factors were not identified. Family predisposition to cholelithiasis was registered in 28 (35%) patients, obesity in 10 (12.5%), pre-obesity in nine, rapid weight loss in four, hereditary hemolytic disease in two, and premature birth combined with parenteral nutrition and sepsis as a complication were found in two patients. Apart from those who were born prematurely, another 10 patients had combined risk factors for cholelithiasis, six patients had family predisposition and obesity, and four patients had obesity and self-initiated rapid weight loss program.

Conclusion: According to our research, the most common risk factors for cholelithiasis in children and adolescents are family predisposition and excess body weight. Most of the patients were adolescents and females.

Keywords: cholelithiasis, risk factors, children, adolescents

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INTRODUCTION

Cholelithiasis is a rare disease in children and adolescents. According to literature data, it occurs in 0.13 to 0.22% of members of this age group (1-4). It occurs as a consequence of various etiopathogenetically clear pathological conditions or in idiopathic form (1). This condition is extremely rare prenatally and it can be revealed in the first years after birth, but it is usually diagnosed in late childhood and adolescence (2, 5, 6). With the onset of puberty, cholelithiasis is more common in girls than in boys (2). From a clinical point of view, it can be symptomatic and asymptomatic (1, 6, 7). Possible complications of the disease are cholecystitis, acute cholangitis, and pancreatitis (1, 6-12). Symptomatic cholelithiasis requires treatment, most often and most reliably cholecystectomy, while asymptomatic cholelithiasis, due to the possibility of spontaneous resolution, especially in infants, requires an appropriate follow-up (1, 6, 9). All modern guidelines recommend laparoscopic cholecystectomy as the treatment of symptomatic uncomplicated cholelithiasis (6, 13).

The aim of this study was to analyze risk factors for the occurrence of cholelithiasis in children and adolescents.

MATERIAL AND METHODS

This retrospective study included a group of 80 children and adolescents, 50 females and 30 males, aged 4-18 (14±5.55) years, with symptomatic cholelithiasis who had undergone cholecystectomy at the University Children's Hospital in Belgrade in the period from 2000 to 2016. Cholecystectomy was performed laparoscopically in 77 patients while three patients required open approach due to choledocholithiasis. The approval for conducting the study was obtained from the Institutional Review Board of the University Children's Hospital in Belgrade (the approval number: 017 16/48).

Diagnosis of the disease was based on the association of recurrent abdominal pain, characteristic for biliary colic, and ultrasound findings of echogenic foci in the gallbladder lumen or choledochus with acoustic shadowing.

Data related to risk factors in all patients concerning the occurrence of cholelithiasis were obtained from the available medical documentation, according to the objectives. Beside the anamnestic data of the presence of cholelithiasis in first and second degree relatives, personal medical history and clinical and laboratory findings of each patient were analyzed for the existence of additional factors that could cause this pathological condition. Those factors included being overweight (obesity and pre-obesity), a rapid loss of body weight, parenteral nutrition, congenital or acquired hemolytic disease, hepatobiliary diseases, premature birth, etc. The criteria for obesity, pre-obesity and rapid weight loss were determined. For obesity, it was body mass index (BMI) ≥95th percentile for age and sex, for pre-obesity the BMI ≥85th percentile but <95th percentile on the Centers for Disease Control and Prevention's (CDC) specific growth charts. The criterion for excessively fast weight loss was the loss of >1 kg per week (14, 15). In addition to adequate clinical indications and ultrasound findings, complete preoperative evaluation of the patients was done by using corresponding laboratory blood parameters, such as complete blood count, sedimentation rate, C-reactive protein, liver function tests, the level of amylase, lipase, as well as the levels of amylase and bile pigments in the urine. In the absence of hepatocellular damage in patients with unconjugated hyperbilirubinemia, the additional tests to verify or rule out a hemolytic state were the determination of the number of reticulocytes, the analysis of morphology of erythrocytes, Coombs's test and the measurement of osmotic resistance of erythrocytes.

RESULTS

Most patients were older than 10 years (90%) and females (62.5%). In 46 (57.50%) cases, cholelithiasis-predisposing risk factors were identified. In 34 (42.5%) patients there was one risk factor, in 10 patients (12.5%) there were two risk factors and in two patients there were three risk factors, while in the rest of the patients no risk factors were found **(Table 1)**. In the group of patients with more than one cholelithiasis-predisposing risk factor, six of them had an association of obesity and familial predisposition, four patients were obese and experienced too rapid weight loss, and two patients had premature birth (31 and 32 weeks of gestation), parenteral nutrition and sepsis. Four patients with rapid weight loss were adolescent girls who underwent an excessive hypocaloric diet on their own and without any professional supervision, while two patients had required parenteral nutrition due to prematurity, which had been complicated by sepsis as an additional cholelithiasis-risk factor.

Table 1. Frequency of risk factors for the occurrence of cholelithiasis in our group of patients (n= 80)

Risk factors	Frequency
Familial predisposition*	28 (35,0%)
Obesity and pre-obesity**	19 (23,75%)
Rapid loss of body weight	4
Hereditary hemolytic disease***	2
Premature birth	1
Parenteral nutrition	1
Sepsis	1

Notes: *First degree relatives 12, second degree relatives 16; **Obesity 10, pre-obesity 9;
***Spherocytosis 1, elliptocytosis 1

DISCUSSION

Cholelithiasis, a mixture of cholesterol, calcium salts of bilirubinate or palmitate, proteins, and mucin, is etiopathogenetically a very heterogeneous disease that occurs with varying frequency in all population groups and ages. It is much less common in children and adolescents than in adults (1-4, 16). Based on their composition, gallstones are classified into pigment stones, cholesterol stones, and mixed stones. Both in adults and in pediatric patients, their prevalence increases throughout life (2, 6, 8, 17, 18). Due to the cholelithiasis-favoring effect of estrogens, from puberty to the end of the reproductive period, it is significantly more common in women than in men (2, 4, 6, 17). According to some studies in humans and animals, the basis of this phenomenon lies in the fact that estrogens have such an effect on the liver that it produces supersaturation of bile with cholesterol. This is due to simultaneous increase in its secretion while the synthesis of bile acids is decreased (7, 19, 20, 21). These facts are also true for the group of our respondents, in which the ratio of representation of children over and under ten years of age was 9 vs 1, and the representation of girls compared to boys was 1.7 vs 1.

Apart from the mentioned factors, important risk factors for the occurrence of cholelithiasis are family predisposition and various diseases accompanied by destabilization of the solubility of biliary contents, such as obesity, hemolytic diseases, Crohn's disease, ileal resection, cystic fibrosis, hepatobiliary diseases, hyperlipidemia, insulin resistance and others (2, 6, 7, 19, 23, 24, 25). Additional risk factors for biliary stone formation are excessively fast weight loss, prolonged parenteral nutrition, and systemic infections (2, 6, 8, 19, 23). In a significant number of cases, several factors are involved in the etiopathogenesis of cholelithiasis (8). Also, in many cases, the cause of the occurrence of cholelithiasis remains unknown (8, 9). Some of the risk factors for the occurrence of cholelithiasis were registered in slightly more than half of our respondents, out of which a quarter had two or three risk factors. One third of the patients had first or second degree relatives with cholelithiasis, a quarter were obese or pre-obese, while in a smaller number of them cholelithiasis-predisposing factors included too rapid weight loss, hereditary hemolytic disease and association of premature birth, parenteral nutrition and sepsis. Family history and obesity play a critical role in the incidence of gallstone disease (4, 20). Genetic factors account for the occurrence of approximately 25%–30% of symptomatic gallstones (4, 19). Familial predisposition to gallstone disease is linked to variations (polymorphism) or mutations of genes that encode regulatory proteins responsible for biliary cholesterol solubility, such as ATP-binding cassette transporters ABCG5, ABCG8 and ABCB4 and farnesoid X receptor (19). Coding genes for ABCG5 and ABCG8 transporters, responsible for hepatobiliary cholesterol secretion, are located on chromosome 2p21, for ABCB4 transporter, the regulator of hepatic phospholipid secretion, on chromosome 7q21.12 and for farnesoid X receptor, the inducer of reabsorption of bile acids, on chromosome 12q23.1. (7, 19, 20, 21, 26-29). Also, it is thought that alteration of mucin gene expression (11p15.5) is involved in the pathogenesis of gallstone formation (30). Being overweight (obesity and pre-obesity), as a highly prevalent and continuously growing health problem of modern man, is also a frequent risk factor for biliary lithogenesis (7, 13, 21). The disturbance of the solubility of biliary content in obese and pre-obese patients is a consequence of hypersaturation of bile caused by either increased hepatic cholesterol uptake or increased de novo cholesterol synthesis (4, 7). This especially applies to the central (abdominal or visceral) type of obesity, which is characterized by pronounced insulin resistance and the consequent high hepatic cholesterol secretion (21). The basis of biliary lithogenesis during rapid weight loss on very low-calorie diets is cholesterol supersaturation of bile due to its mobilization from adipose tissue and cholecystic hypomotility as a consequence of reduced cholecystokinin stimulation (7, 13, 21, 24). Cholestasis due to insufficient cholecystokinin induced gallbladder contraction and accompanying hyperconcentration of bile is the cause of biliary lithiasis as a complication of prolonged total or subtotal parenteral nutrition (5, 24). The pathogenesis of gallstone formation in premature infants is of a multifactorial nature and is a consequence, not only of the necessity of prolonged parenteral nutrition, as well as often accompanying catheter related recurrent sepsis, i.e. hemolysis and bacterial translocation and cholangitis, but also of immaturity, reduced gallbladder motility and the bile acid enterohepatic circulation (5, 6, 23, 31-35). Gallstones in hemolytic diseases are the result of an excess of unconjugated bilirubin in the bile, which binds with calcium and builds up insoluble calcium bilirubinate (6, 23, 24).

CONCLUSION

Slightly more than half of children and adolescents with cholelithiasis have some of the known risk factors for its occurrence, and of those two thirds have one risk factor whereas one third have two or three risk factors. The most common cholelithiasis risk factors, which are found in around half of the patients, are family predisposition and/or excess body weight. Nine tenths of the patients are adolescents and two thirds of them are females.

Conflicts of interest

The authors declare that they do not have any conflicts of interest.

Ethical approval

This research and publication were approved by the Ethical Committee of the University Children's Hospital, Belgrade, Serbia (approval number: 017 16/48).

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FAKTORI RIZIKA ZA POJAVU KAMENA U ŽUČNOJ KESI KOD DECE I ADOLESCENATA: ISKUSTVO JEDNOG CENTRA

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Sažetak

Uvod: Holelitijaza je etiopatogenetski veoma heterogena i po učestalosti retka bolest u periodu rasta i razvoja. Cilj rada bio je da se analiziraju faktori rizika za nastanak holelitijaze u tom životnom dobu.

Materijal i metode: Ovom retrospektivnom studijom obuhvaćeno je 80 dece i adolescenata, 50 ženskog i 30 muškog pola, uzrasta 4-18 (14±5,55) godina, sa simptomatskom holelitijazom operisanih u Univerzitetskoj dečjoj klinici u Beogradu u periodu od 2000. do 2016. godine. Dijagnoza bolesti postavljana je na osnovu ultrazvučnog nalaza. Podaci o faktorima rizika za nastanak bilijarne kalkuloze dobijeni su iz istorije bolesti.

Rezultati: Kod 46 (57,5%) bolesnika verifikovani su faktori rizika koji predisponiraju pojavu holelitijaze. Kod 34 pacijenta je identifikovan jedan faktor rizika, kod 10 pacijenata dva faktora rizika, kod dva pacijenta su identifikovana tri faktora rizika, dok kod ostalih nisu pronađeni faktori rizika. Porodična sklonost holelitijazi registrovana je kod 28 (35%) pacijenta, gojaznost kod 10 (12,5%), predgojaznost kod devet, prebrzo mršavljenje kod četiri, nasledna hemolizna bolest kod dva, i prevremeno rođenje kombinovano sa parenteralnom ishranom i sepsom kao komplikacijom kod dva. Osim prevremeno rođenih, još 10 pacijenata je imalo udružene faktore rizika za holelitijazu, šest pacijenata je imalo porodičnu predispoziciju i obezitet, a četiri pacijenta obezitet i samoinicijativno započet program brzog gubitka telesne težine.

Zaključak: Prema našim istraživanjima, najčešći faktori rizika za pojavu holelitijaze kod dece i adolescenata su porodična predispozicija i povišena telesna težina. Većina pacijenata pripadala je adolescentnom uzrastu i bila je ženskog pola.

Ključne reči: holelitijaza, faktori rizika, deca, adolescenti

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