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REVIEW PAPER

Management of gallstone disease in children

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ABSTRACT

In recent years an increase in incidence of cholelithiasis in children has been observed. Among the various factors predisposing to the occurrence of cholelithiasis, some are modifiable and some are non-modifiable (including 25% of gallstones caused by genetic factors). One of the factors predisposing to the occurrence of cholelithiasis is obesity. The article describes the methods of prevention, diagnosis and treatment of uncomplicated and complicated cholelithiasis in children. Attention was paid to the new guidelines for the use of ursodeoxycholic acid in gallstone disease, as well as the molecular basis and research progress that has been made in this field.

KEY WORDS:

cholelithiasis, children, ursodeoxycholic acid, prevention, diagnosis, management, gallstone disease.

INTRODUCTION

Cholelithiasis rarely occurs in children. In recent years an increase in the incidence of this disease in the pediatric population has been observed, but data on the epidemiology of gallstone disease in children are discrepant. A significant relationship between gallstone disease and numerous metabolic and environmental factors has been identified. In England the incidence of cholecystectomy in children under 16 years old increased from 0.78 in 1997 to 2.7 per 100,000 in 2012. In Canada, the incidence of cholecystectomy in patients under 18 years old increased from 8.8 in 1993 to 13.0 per 100,000 in 2012. In the United States, the number of cholecystectomies performed for cholesterol stones increased by 216% from 2003 to 2012 [1]. There are no precise data on the incidence of gallstone disease in children in Poland.

According to some authors, the reason for the more frequent diagnosis of gallstone disease is the increasing availability of ultrasound imaging and, therefore, accidental detection of gallstones during a differential diagnostic of other diseases, e.g., abdominal pain or urinary tract infection [2]. Another reason for the increased incidence of cholelithiasis reported in the literature is the increase in the percentage of overweight and obese children and adolescents, which is a known risk factor for the development of gallstone disease [3, 4].

In the group of pediatric patients, cholelithiasis is most often found in children over 3 years of age (81%) [5]. There are various predisposing factors for gallstone disease, such as obesity, insulin resistance [6], dyslipidemia and type 2 diabetes, which are all independent factors contributing to the formation of gallstones [7, 8]. Most pediatric sources report a higher incidence of cholelithiasis in girls than in boys [2, 3], although a higher incidence in females has only been reported in adolescents [9]. This is probably related to the increased production of estrogens, which, after binding to the receptors, cause increased secretion of cholesterol into the bile. Additional factors predisposing to the development of gallstones in children are: chronic hemolytic anemia (most often spherocytosis and sickle cell anemia), parenteral nutrition, prematurity, rapid weight loss, certain medications (including e.g., antibiotic therapy or chemotherapy), genetically determined diseases (progressive familial intrahepatic cholestasis, Gilbert's disease, Wilson's disease [10],

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TABLE 1. Risk factors for cholelithiasis

Risk factors for cholelithiasis
Family history (25% of gallstones are caused by genetic factors)
Prematurity
Total parenteral nutrition
Medicines (furosemide, ceftriaxone, somatostatin)
Previous chemotherapy
Chronic hemolytic anemias (mainly congenital)
Diseases of the bile ducts (for example choledochal cyst)
Genetic disorders (most often: cystic fibrosis, progressive familial intrahepatic cholestasis, Wilson's disease, Gilbert's disease, trisomy of chromosome 21)
Obesity
Rapid weight loss
Congenital enteropathies
Dehydration and urinary tract infections
Crohn's disease
Surgical procedures (state after resection of the ileum, abdominal surgery in the neonatal period)

trisomy of chromosome 21), sepsis, cirrhosis, chronic cholestasis, and history of abdominal surgery in the neonatal period. An additional risk factor for gallstones is biliary tract defects such as a choledochal cyst or primary sclerosing cholangitis [11] (Table 1).

Based on a study of 43,141 pairs of Swedish twins with gallstones, approximately 25% of cases are believed to have a genetic background [12].

Among many genes responsible for the pathogenesis of cholelithiasis, a significant relationship between polymorphisms of the *ABCG8* rs11887534 and *NPC1L1* rs217434 genes and the occurrence of gallstones in children was found [13]. Based on analyses, it seems that the presence of lithogenic gene polymorphisms known so far increases the likelihood of gallstone disease, but metabolic and environmental factors also contribute to the occurrence of the disease.

Gallstones are divided (depending on their structure) into cholesterol, pigment and mixed deposits. Because of the increasing incidence of obesity among children, the incidence of cholesterol gallstones is increasing [14]. Occurrence of cholesterol deposits is also the result of impaired intestinal absorption of bile acids, e.g., in patients after ileal resection, diagnosed with Crohn's disease or cystic fibrosis [15].

A common complication of hemolytic anemia and other hemolytic disorders is pigmented deposits consisting of calcium bilirubinate and a glycoprotein matrix [16].

GENETIC FACTORS

The influence of genetic factors on the development of gallstones is not fully understood. Thanks to genome-wide association scans (GWAS) performed in adult patients, a relationship between the occurrence of *ABCG8* and *UGTA1* gene polymorphisms and the occurrence of gallstones was demonstrated [17]. To date, GWAS analysis has not been performed in pediatric patients with gallstones. In a study targeting the polymorphisms *ABCG8* rs11887534, *ABCB4* rs1202283, *ABCB4* rs2109505, *NPC1L1* rs217434, *NPC1L1* rs41279633, *UGT1A1**28, conducted in 214 children with gallstones, the presence of the lithogenic variant *ABCG8* rs11887534 was detected in 15% of patients; it was significantly higher than in the children and adults without gallstones. An increased risk of developing cholelithiasis was also found in carriers of only one copy of the lithogenic variant. An association between the *NPC1L1* (Niemann-Pick C1-Like 1) rs217434 polymorphism and the occurrence of gallstone disease in children has also been demonstrated [13]. In carriers of the *NPC1L1* rs217434 polymorphism, a lower ratio of campesterol (natural phytosterol) to desmosterol (cholesterol precursor allowing indirect assessment of *de novo* cholesterol synthesis) was found in the serum. In addition, patients with cholesterol deposits had decreased serum plant sterol levels (campesterol and sitosterol) and increased cholesterol precursor levels compared to patients without gallstones and with pigmented deposits [18].

In humans, intestinal cholesterol absorption, *de novo* synthesis, hepatic secretion, and fecal excretion play a key role in cholesterol metabolism. In the intestine, two proteins – NPC1L1 (Niemann-Pick C1 like 1) and ABCG5/8 (adenosine triphosphate – ATP, binding cassette transporters G5/G8) – are responsible for cholesterol absorption. The presence of the NPC1L1 protein is restricted to epithelial cells of the duodenum and the proximal jejunum, where most of the absorption of cholesterol from the gastrointestinal tract takes place [19]. The ABCG5/G8 transporter belongs to the ABC transporters (ATP binding cassette transporter) from the G family; it is responsible for the transport of cholesterol to the lumen of the gastrointestinal tract [20]. In addition, NPC1L1 and ABCG5/8 are also expressed in the tubular membrane of hepatocytes. NPC1L1 and ABCG5/8 in the intestine and in hepatocytes, in addition to cholesterol, also transport phytosterols (sitosterol, campesterol). In the case of impaired NPC1L1 function, serum phytosterols are reduced [21], while in the case of ABCG5/8 dysfunction, bile cholesterol is decreased and serum phytosterols are increased [22]. A gain of function mutation in the ABCG5/8 gene leads to an increase in cholesterol in the bile, which contributes to the formation of gallstones.

Another study investigated the role of the *ABCB4* gene encoding the multi-drug resistance protein 3 (MDR3) as a transporter for phospholipids. As a result of the *ABCB4* gene mutation, low phospholipid-associated cholelithiasis (LPAC) is developed, associated with recurrent gallstones and biliary tract stones in people under 40 years of age. It has been found that mutations in the *ABCB4* gene may lead to recurrent gallstones in children with progressive familial intrahepatic cholestasis type 3 and in patients with intrahepatic cholestasis of pregnancy [23]. In a retrospective analysis of 26 patients with a confirmed

mutation in the *ABCB4* gene, cholelithiasis was found in 15% of pediatric patients and 67% of adult patients [24]. In another study, the association of *ABCB4* rs1202283 and *ABCB4* rs2109505 polymorphisms with the occurrence of gallstones was not confirmed [13].

Genes that are also probably involved in the pathogenesis of gallstones are genes encoding membrane lipid transport (solute carrier family – SLC) responsible for reduced intestinal absorption of bile salts, e.g., *SLC10A2*. This gene encodes apical sodium-dependent bile acid transporter (ASBT). Decreased ASBT expression leads to increased excretion of bile acids in the stool and a decrease in the bile acid pool in the body, increasing the risk of bile deposits [25].

Dixit *et al.* describe the role of receptor genes for: apolipoprotein A1 (ApoA1), which is the main component of HDL and plays an important role in the elimination of excess cholesterol by interacting with various receptors and transporters, including ATP binding cassette transporter A1 (ABCA1), lecithin-cholesterol acyltransferase (LCAT) and scavenger class B receptor type 1 (SR-B1); and apolipoprotein B (ApoB) – increasing cholesterol excretion into bile secondary to reduced very-low-density lipoprotein (VLDL) synthesis in the liver and increasing cholesterol absorption in the intestine [26]. Apolipoproteins are protein components of lipoproteins, responsible for binding lipids, thanks to which they participate in their metabolism. The *APOA1 −75 G* polymorphism is associated with an increased risk of gallstone disease in men; the difference is probably related to the hormonal balance. Carriers of the *APOA1-75A* allele appear to have higher levels of the APOA1 protein, which prevents the formation of crystal nuclei. Apolipoprotein B-48 is produced in the intestine and is an integral part of the structure of chylomicrons. In mice with reduced expression of *Apob48*, significantly reduced cholesterol absorption was found, leading to reduced secretion of cholesterol into the bile and thus reducing the risk of cholelithiasis [27].

Apolipoprotein E (ApoE) is the protein component of triglyceride-rich lipoproteins (VLDL, LDL). It is a ligand for the hepatic LDL receptor. There are three main ApoE alleles (e2, e3 and e4). The presence of the e4 allele is associated with an increased risk of gallstone disease, more frequent recurrence of cholelithiasis [28], more cholesterol-rich deposits due to increased intestinal absorption of cholesterol [29], decreased secretion of bile acids into the bile, and shortened crystallization time of deposits. On the other hand, Mella *et al.* did not detect the influence of polymorphisms of ApoE4 on the development of gallstones [30].

The *CYP7A1* gene encodes an enzyme involved in the synthesis of bile acids. A *CYP7A1* 5′terminus variant has been shown to be associated with gallstones in the Mexican American population [31]. In mice, overexpression of the orthologous *Cyp7a1* gene inhibits the formation of bile deposits by affecting the concentration of bile acids and cholesterol [32].

Genes affecting the motility of the gallbladder also influence the development of gallstones. Retention of bile in the gallbladder promotes formation of bile deposits. In mice, loss of function of the *Cckar* gene, which encodes the cholecystokinin receptor, results in impaired gallbladder motility and the formation of an increased amount of bile deposits [33].

Polymorphism of the gene encoding the LDL receptor (LDLR) has also been found to influence the development of gallstones [34]. Impaired LDL receptor function is associated with increased levels of circulating LDL, triglycerides and total cholesterol as well as pro-inflammatory cytokines including TNF-α, IL-1 and IL-6.

CLINICAL PRESENTATION

Data on the pediatric population vary widely. Most often the literature on this problem states that the course of the disease in children is asymptomatic in 17–57% of cases [2, 9, 16, 18]. The disease is then diagnosed incidentally during an ultrasound examination performed for other reasons. The most common symptom of gallstone disease is recurrent colic abdominal pain located in the right upper quadrant of the abdomen, which may be accompanied by nausea and vomiting. The pain may radiate to the right shoulder blade and appear after eating fatty food. Pain episodes have an acute onset and last a minimum of 15–30 minutes [35]. In young children, symptoms of cholelithiasis are non-specific – in most cases, poorly localized abdominal pain, abdominal distension, crying, restlessness, nausea and vomiting. In infants, symptoms resemble intestinal colic. The results of laboratory tests do not show any deviations from the norm [35].

In approximately 25% of children, the diagnosis of gallstone disease is made when complications such as pancreatitis, choledocholithiasis, acute cholecystitis and chronic cholecystitis [36] are present (Table 2). Symptoms suggestive of acute cholecystitis include: fever, prolonged pain in the right upper quadrant of the abdomen (often lasting more than 5 hours), palpable resistance in this area, positive Murphy's sign and Chelmonski's sign. Results of laboratory tests show elevated parameters of inflammation (C-reactive protein, procalcitonin, leukocytosis with a predominance of granulocytes). Ultrasound imaging of calculi and a positive sonographic Murphy's sign (pain during the application of the ultrasound transducer in the projection of the gallbladder) or thickening of the gallbladder indicate acute cholecystitis. Another possible complication of cholelithiasis is cholangitis with the occurrence (not in all patients) of the so-called Charcot's triad: pain in the right subcostal area, fever and jaundice. Clinical presentation is most often accompanied by abnormal test results – increased inflammatory parameters, increased activity

TABLE 2. Clinical symptoms of uncomplicated and complicated gallstone disease

Clinical symptoms of gallstone disease (asymptomatic course in 80% of cases)	
Uncomplicated cholelithiasis	
Uncomplicated cholelithiasis	Paroxysmal colic pain in the right subcostal area or in the middle epigastrium, often occurring after eating fatty food, radiating to the right shoulder blade Nausea and vomiting Abdominal bloating Constipation
Complicated cholelithiasis	
Acute cholecystitis	Positive Chelmonski's sign – pain when shaking the right subcostal region Positive Murphy's sign – pain when the patient inhales while the examiner's hand is placed in the projection of the gallbladder – a symptom suggesting acute cholecystitis
Gallbladder hydrops	Usually asymptomatic (or constant, mild pain) Palpable mass under the right costal arch No fever and peritoneal symptoms
Empyema of the gallbladder	Pain in the right subcostal area Fever In some cases peritoneal symptoms
Choledocholithiasis	
Uncomplicated choledocholithiasis	Pain in the right subcostal area Jaundice Nausea and vomiting Over time, increasing bilirubin levels, pruritus, discolored stools and dark urine are observed In 5–15% of patients choledocholithiasis may be asymptomatic
Complicated choledocholithiasis	
Cholangitis	Charcot's triad – biliary colic pain, fever and jaundice Reynolds' pentad – additionally shock and an altered mental status
Biliary pancreatitis	Presence of bile deposits found in imaging and meeting 2 of the following criteria: – abdominal pain starting in the upper abdomen or upper left quadrant of the abdomen, sometimes radiating to the spine – blood amylase and/or lipase increased to $> 3 \times$ ULN – imaging test showing pancreatitis (pancreatic edema, perfusion disorders, acute pancreatitis complications – e.g., fluid collections)

ULN – upper limit of normal

of aminotransferases and γ-glutamyl transferase, and an increase in bilirubin concentration, with a predominance of conjugated bilirubin. Abdominal ultrasonography reveals dilation of bile ducts [36]. In 12–37% of cases, gallstones may be the cause of acute pancreatitis in children [37–40]. Mechanical irritation caused by the presence of gallstones leads to fibrosis and thickening of the gallbladder wall, i.e. chronic cholecystitis.

PREVENTION

Methods of preventing the development of gallstone disease are maintaining a proper body weight through a balanced diet and regular exercise. Regularly consumed meals that contribute to the systematic emptying of the gallbladder and a diet rich in fiber, calcium and vitamin C reduce the risk of gallstone formation [41, 42]. Pharmacological prevention of gallstone formation in the general population is not recommended. Prophylactic administration of ursodeoxycholic acid (UDCA) may be considered in the group at high risk of cholelithiasis, i.e.:

1) During rapid weight loss when following a very restrictive diet (< 800 kcal/day) or after bariatric surgery. After surgery, there is rapid weight loss, which promotes crystallization of gallstones and increases the risk of gallstone disease three-fold compared to the general population. The mechanism of action of UDCA consists in reducing the secretion of cholesterol into the bile and inhibiting the formation of nuclei of crystallization. It was found that among patients undergoing band gastroplasty taking 500 mg of UDCA prophylactically daily, the risk of developing gallstones at 12 and 24 months was 3% and 8%, respectively, while in those not taking the drug it was 22% and 30%, respectively [43].
2) In patients with LPAC gallstone syndrome due to a mutation in the *ABCB4* gene. The development of cholelithiasis is associated with a low concentration of phospholipids in the bile, and the symptoms recur after cholecystectomy [44]. In this case, according to the European Association for the Study of the Liver 2016 recommendations, the use of UDCA at a dose of 15 mg/kg

b.w. seems to be effective in reducing the risk of recurrent urolithiasis and its complications [35].

DIAGNOSIS

The diagnosis of cholelithiasis is made on the basis of the characteristic image of deposits in an ultrasound examination. The diagnostic effectiveness of this method exceeds 95% [15]. The examination also allows one to determine the width of the intra- and extrahepatic bile ducts and to assess the remaining organs of the abdominal cavity. Endoultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP) is performed in patients with suspected choledocholithiasis, in whom the US result is doubtful or negative, but the patient has typical symptoms of gallstone disease. Endoscopic retrograde cholangiopancreatography (ERCP) is a diagnostic and therapeutic method in choledocholithiasis. Computed tomography of the abdominal cavity is the method recommended in diagnosing complications of gallstone disease.

Currently, abdominal radiography is not recommended for the diagnosis of gallstone disease; this examination performed for other reasons can visualize calcified deposits.

TREATMENT

ASYMPTOMATIC CHOLELITHIASIS

There are no guidelines for the management in children, while there are guidelines for adults [35]. Currently, further observation of the patient with periodic abdominal ultrasound examinations is recommended. Treatment of asymptomatic cholelithiasis with UDCA is not recommended [35]. Although therapy was successful in most adult patients with small, non-calcified stones, the disease was often recurrent (25–64% recurrence after 5 years, 49–80% after 10 years) [45, 46]. Data on children are scarce. In a study of 180 Italian children with gallstone disease treated with UDCA, dissolution of gallstones was observed in 8 children, but the cholelithiasis recurred in 3 of them [47].

Cholecystectomy is not indicated in children with asymptomatic gallstone disease. Exceptions are patients at increased risk of gallbladder cancer, i.e.: with a porcelain gallbladder, in the case of gallbladder polyps larger than 1 cm or polyps 6–10 mm in size and documented increase in polyp size. Such cases are extremely rare in the pediatric population. In patients with primary sclerosing cholangitis in the presence of gallstones and the presence of gallbladder polyps, cholecystectomy should be considered regardless of the size of the polyps due to the high risk of malignancy [35]. Cholecystectomy in patients with asymptomatic gallstone disease in conjunction with other abdominal procedures is not routinely recommended. The exception is patients with hemolytic anemia undergoing splenectomy, in whom simultaneous cholecystectomy should be considered [35].

Despite the high prevalence of gallstone disease, there are limited data on its natural history. According to a clinical prediction model developed for adult patients with asymptomatic cholelithiasis [48], 14.5% developed symptoms with a median follow-up period of 4.6 years. The cumulative incidence was 10% at 5 years, 21.5% at 10 years and 33% at 15 years.

SYMPTOMATIC CHOLELITHIASIS

In a child with biliary colic, antispasmodics, analgesics and anti-inflammatory drugs [49] should be used. Fluid therapy may be used in severe cases. Dosing of the medications is age and dose dependent.

Excision of the gallbladder is recommended in all patients with symptomatic gallstone disease. The method of choice is laparoscopic cholecystectomy. Elective surgery is recommended soon after the onset of symptoms due to the risk of complications and recurrence [35]. The use of UDCA in patients with symptoms of cholelithiasis does not reduce the severity of symptoms [50].

TREATMENT OF GALLSTONE DISEASE COMPLICATIONS

Conservative treatment of acute cholecystitis is identical to that of biliary colic. Approximately 30% of patients treated in this way will require cholecystectomy at a later time. Antibiotic therapy is not routinely indicated for mild to moderate cholecystitis. Antibiotic therapy targeting Enterobacteriaceae, especially *Escherichia coli*, is indicated in patients who are not immunocompetent or have complications of the disease, such as cholangitis, bacteremia, or abscesses. In severely ill patients, antibiotics covering the spectrum of anaerobic bacteria, mainly the genus *Bacteroides*, should be introduced – e.g., metronidazole 20–30 mg/kg body weight per day [51].

In patients with acute cholecystitis, cholecystectomy should be performed within 72 hours of diagnosis [35]. In the case of choledocholithiasis, the diagnostic and therapeutic method of choice is ERCP. For patients with simultaneous cholelithiasis and choledocholithiasis, cholecystectomy should be performed within 72 hours of ERCP with sphincterotomy and gallstone evacuation.

Treatment of cholangitis in the course of cholelithiasis consists in broad-spectrum antibiotic therapy, including Gram-negative and anaerobic bacteria, and intensive analgesic treatment. Endoscopic retrograde cholangiopancreatography should then be performed within 24 hours of symptom onset, and promptly in septic patients unresponsive to antibiotics and fluids.

Patients with biliary pancreatitis with cholangitis require pain relief, antibiotics and ERCP (preferably within 24 hours of the onset of symptoms). In this case, cho-

TABLE 3. Management of uncomplicated and complicated gallstone disease

Treatment	Observation
Asymptomatic cholelithiasis	Cholecystectomy: in patients with increased risk of gallbladder cancer in patients with hemolytic anemia undergoing splenectomy
Symptomatic cholelithiasis	Elective surgery within a short period of time after the onset of symptoms
Acute cholecystitis	Cholecystectomy within 72 h
Choledocholithiasis	ERCP
Choledocholithiasis with cholelithiasis	ERCP and cholecystectomy within 72 h
Cholangitis in the course of choledocholithiasis	Broad spectrum antibiotic therapy ERCP within 24 h
Biliary pancreatitis with concomitant cholangitis	ERCP within 24 h Cholecystectomy during the same hospitalization

ERCP – endoscopic retrograde cholangiopancreatography

lecystectomy should, if possible, be performed during the same hospitalization. Indications for surgical procedures and antibiotic therapy are summarized in Table 3.

CONCLUSIONS

In recent years, the incidence of gallstone disease in children has been increasing. Among the various factors predisposing to the occurrence of cholelithiasis, some are modifiable and some are non-modifiable (including 25% of gallstones caused by genetic factors). The role of the pediatrician is to control and modify the modifiable risk factors, as well as health education of parents and guardians in this regard. Attention should be paid to the growing risk of obesity in children (obesity is one of the factors predisposing to the occurrence of cholelithiasis). On the other hand, significant caloric restrictions, so recently fashionable among teenagers, may also be a risk factor for gallstone formation. Therefore, it is important to know the risk factors for developing gallstones and take appropriate preventive measures.

DISCLOSURE

The authors declare no conflict of interest.

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