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Cholelithiasis in Children: A Diagnostic and Therapeutic Approach

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Abstract

Context: Although cholelithiasis is not a common condition in children, recent studies have documented an increasing incidence rate, owing to the development of diagnostic tools. The prevalence of cholelithiasis in children has been reported to be 0.13% - 0.3%, whereas in obese children and adolescents, the prevalence rate has been estimated at 2% - 6.1%. In this study, we aimed to review cholelithiasis in children. The gathered results could be useful in finding a suitable method and proper clinical practice for this complication.

Evidence Acquisition: For literature review, international databases, including PubMed and Google Scholar, were searched, using keyword combinations, e.g., "cholelithiasis in children", "gallstone in children", and "childhood cholelithiasis", to review diagnostic and therapeutic approaches for cholelithiasis in children from 2006 to 2016. Also, some articles were retrieved through hand searching and reviewing the reference lists of papers, regardless of the date of publication. Abstracts, duplicates, and articles irrelevant to childhood cholelithiasis were excluded.

Results: A total of 36 out of 93 articles were reviewed. The results showed that the prevalence of childhood cholelithiasis varies in different communities, with a global rate of 1.9%. Most cases of cholelithiasis in children were associated with underlying diseases. Hemolytic diseases, hereditary blood disorders, and cirrhosis were among the main causes of cholelithiasis in children. Cholelithiasis was detected incidentally or via diagnostic evaluations due to the presentation of symptoms.

Conclusions: Although evaluation of the underlying causes of gallstone formation and appropriate diagnostic/therapeutic implications is still a challenging issue in the management of childhood cholelithiasis, in asymptomatic cases or those with gallstones of certain sizes, it is only recommended to monitor the disease or rule out the underlying causes. It should be noted that long periods of diagnostic and therapeutic approaches can impose stress and tension on families.

Keywords: Cholelithiasis, Childhood, Diagnosis, Therapy

1. Context

With the development of diagnostic methods such as ultrasonography, cholelithiasis in children is being frequently reported. This disease may be either symptomatic or asymptomatic, even though the asymptomatic presentation is less likely in children (17% - 50%) (1-5). Although both genders are equally affected in early childhood, most previous studies have demonstrated a female predominance in pediatric gallbladder disease, starting from puberty. In fact, most cases of cholelithiasis at young age are diagnosed in the second decade of life (1, 6-8).

Cholelithiasis is sometimes diagnosed in patients incidentally or as silent stones. In some other cases, they are reported in association with clinical symptoms such as cholecystitis and cholangitis (9-11). Although hemolytic diseases are the most common causes of cholelithiasis in children, some other factors such as obesity, metabolic syndrome, prematurity, necrotizing enterocolitis (NEC), congenital heart diseases, cystic fibrosis, parenteral nutrition, use of certain medicines, and anatomic stenosis of bile ducts should be also considered.

Information about cholelithiasis and bile duct stones causes stress and anxiety in parents and sometimes leads to the use of improper diagnostic and therapeutic approaches by physicians (9, 10, 12). Evaluation of the causes of cholelithiasis and utilization of a proper therapeutic method are among the challenges of cholelithiasis management in children. Considering the use of gallbladder lithotripsy procedures in certain cases and status of pharmacological treatments in gallbladder stone management, we aimed to review different types of cholelithiasis, clinical symptoms, underlying causes, and pharmacological/non-pharmacological therapies in children.

2. Evidence Acquisition

For the purpose of literature review, international databases, including PubMed and Google Scholar, were searched, using keyword combinations, e.g., "cholelithiasis in children", "gallstone in children", and "childhood cholelithiasis", to review diagnostic and therapeutic approaches for cholelithiasis in children from 2006 to 2016. Also, some articles were retrieved by hand searching and reviewing the articles' references, regardless of the date of publication. After removing duplicates, abstracts, and articles irrelevant to cholelithiasis in children, 36 eligible ar-

ticles were obtained and reviewed. The qualitative results are presented in this article.

3. Results

3.1. Epidemiological Review

Generally, the incidence and prevalence of cholelithiasis are influenced by age, gender, genetics, race, and geographical factors (9-12). Epidemiological studies have indicated the involvement of genetic factors in the formation of cholelithiasis. The effect of a gene on incontinentia pigmenti chromosome has been confirmed in the formation of cholelithiasis. In fact, patients with ABCB11 mutations are at a higher risk of cholelithiasis.

The first report of cholelithiasis in children was presented by Gibson in 1737. The prevalence of cholelithiasis in children is variable, with a global rate of 1.9% in different communities. Children under 26 months of age constitute 10% of cholelithiasis cases. Sometimes, cases of fetal cholelithiasis are reported, most of which are asymptomatic and gradually resolve following the postnatal monitoring of newborns (9, 10, 13, 14).

Most cases of cholelithiasis in children are associated with underlying factors, such as hemolytic diseases, history of treatment with total prenatal nutrition (TPN), Wilson's disease, and cystic fibrosis; also, use of some medicines should be always considered. Hemolytic causes appear mostly in one- to five-year-old children. On the other hand, cholelithiasis in adolescents is usually associated with obesity, pregnancy, and medication use (10, 11, 15).

3.2. Pathophysiology

The five main constituents of bile include water, bilirubin, cholesterol, bile pigments, and phospholipids; also, lecithin is the precursor of bile phospholipids. The early stage of gallstone formation initiates from the sedimentation of insoluble primary components of bile, which mainly include cholesterol, bile pigments, and calcium salts (10). Gallstones are mainly categorized in three groups of cholesterol, pigment, and mixture, among which the mixture is more common. Imbalance in bile constituents, such as cholesterol, lecithin, and bile salts, is the main cause of gallstone formation. As the concentration of cholesterol increases, the rate of crystallization also elevates, which gives rise to underlying conditions for gallstone formation (15, 16).

3.3. Cholesterol Stones

When the bile includes higher levels of cholesterol and bilirubin, along with lower levels of bile salts, cholesterol stones are formed. Generally, three factors are involved in the formation of cholesterol stones: 1) Bile saturates with cholesterol which creates solid cholesterol; 2) bile kinetics majorly contribute to cholesterol crystal formation; and 3) cholesterol crystals bind to the central core. It should be noted that most cholesterol stones are yellow-white in color (16).

3.4. Pigment Stones

These stones are mostly reported in cases with hemolytic disease, cirrhosis, bile tract infection, and hereditary blood disorders, such as spherocytosis and sickle cell anemia. These stones are black-brown in color and are more common in adolescents (10, 12, 16).

3.5. Cholelithiasis in Infants

Bile is more diluted in infants than older children. Lower concentrations of bile salts, short period of core formation, and higher levels of cholesterol saturation may predispose infants to bile deposition and gallbladder sludge. According to different studies, more than half of gallstone cases in infancy are resolved spontaneously following the postnatal monitoring of newborns; therefore, surgical interventions or symptomatic treatments are necessary only in some certain cases (13, 16-18). The features of cholesterol and pigment stones are presented in Table 1 (16, 19-22).

3.6. Clinical Symptoms of Cholelithiasis

In most cases, cholelithiasis is asymptomatic in children and is incidentally diagnosed in abdominal sonography assessments. Cholelithiasis can be symptomatic if leading to cholestasis, cholecystitis, and cholangitis. The main clinical symptoms include icterus, abdominal pain, nausea, vomiting, and Murphy's sign. In case of any underlying factors, the clinical symptoms of the causes of stone formation should be also included (12, 13, 16).

3.7. Diagnosis of Cholelithiasis

Diagnostic interventions for cholelithiasis should be performed to identify the stones and to determine the underlying causes. Liver, gallbladder, and biliary tract ultrasonography is the optimal diagnostic method with high sensitivity and specificity. Deposition of biles due to different pharmacological therapies, fasting of the patients, and reduced physical activity lead to no posterior opacity in ultrasonography; however, opacity can appear in cases of cholelithiasis.

Abdominal plain sonography can be helpful in cases of pigmented stones, considering the sedimentation of calcium bilirubinate, whereas it is not effective in cases with cholesterol or radiolucent stones (12, 13, 16, 23). Along

Table 1. The Features of Cholesterol and Pigment Stones

Characteristics	Cholesterol Stones	Pigment Stones	
		Black	Brown
Color	Yellow-white (often with a dark core)	Black to brown	Brown to orange
Consistency	Hard, crystalline, and layered	Hard, shiny, and crystalline	Soft, greasy, 50% amorphous, and crystalline at rest with inorganic salts
Number and morphology	Multiple: 2 - 25 mm, faceted, and smooth, Solitary: 2 - 4 cm (~10%), round, and smooth	Multiple: < 5 mm, irregular, or smooth	Multiple: 10 - 30 mm, round, and smooth
Composition	Cholesterol monohydrate > 50% ,glycoprotein, Calcium salts	Bile pigment polymer ~ 40%, Calcium carbonate or phosphate, salts~ 15%, Cholesterol ~ 5%, Mucin glycoprotein ~ 20%	Calcium bilrubinate ~ 60%, Calcium palmitate and ,stearate soaps ~ 15%, Cholesterol ~ 15%, Mucin glycoprotein ~ 10%
Radiopaque	No	Yes, ~ 50%	No
Location	Gallbladder ± common bile duct	Gallbladder ± common bile duct	Common bile duct, Intrahepatic bile duct
Clinical associations	Hyperlipidemia, Obesity, Clofibrate use, Pregnancy, Cystic fibrosis, Octreotide use	Hemolytic anemia, Cirrhosis, Total parenteral nutrition (TPN) ,Ileal disease (after puberty), Ceftriaxone use	Bacterial infection, (*Escherichia coli*), Parasitic infection, Bile duct anomaly, Use of birth control pills
Recurrence	Yes	No	Yes
Sex	Female > Male	No difference	No difference
Age	Puberty (increasing with age)	Any age (increasing with age)	Any age (increasing with age)
Bacteria	No	No	Yes (consistently found at the core)
Soluble	Yes	No	No (minimally)

with the diagnosis of cholelithiasis, the underlying etiology should be also evaluated through medical history taking and patient examination, as gallstone is a sign indicating an underlying pathophysiological cause.

The evaluations should include positive history of hemolytic diseases in the child or his/her family members, metabolic syndrome in the child, history of recurrent icterus in the child or his/her family members, history of splenectomy in relatives, anemia, clinical symptoms of liver dysfunction, symptoms of chronic liver disease in the child, family history of mortality possibly due to liver disorders (e.g., Wilson's disease), chronic diarrhea, steatorrhea, weight loss, severe skin itching in the child (Bayler disease), obesity, and the underlying causes of gallstone formation (12, 16, 19).

Use of ceftriaxone, as a routine prescribed medicine, as well as clofibrate, is the main pharmacological cause of stone formation. The results of laboratory tests such as complete blood count, differential tests, Coombs test, reticulocyte count, hemoglobin electrophoresis, glucose-6-phosphate dehydrogenase (G6PD) test, liver functional tests, evaluation of amylase, lipase, and copper serum levels, Wilson's disease diagnostic tests, as well as sweat and stool exams can be helpful in the diagnosis of cholelithiasis. Evaluation of patients' medical history, contributing factors for gallstone formation, and clinical symptoms of systemic diseases, along with laboratory findings, can help determine the etiology of stone formation (12, 13, 16).

The most common causes of cholelithiasis in children include idiopathic diseases, TPN, hemolytic disease, malabsorption, NEC, hepatobiliary diseases, obesity, abdominal surgery, epilepsy medications, and acute leukemia (1, 5, 24-26). A review of 382 Canadian children with cholelithiasis reported complications attributable to gallstone disease in less than 5% of asymptomatic children. Also, about 20% of the asymptomatic children revealed eventual resolution of the gallstones. There was a similarly low rate of complication (8.6%) among infants in this study, and a high rate of spontaneous resolution of gallstones (34.1%) was reported among infants who were followed-up via ultrasound.

With this background in mind, expectant management seems appropriate, particularly for otherwise healthy infants and children with stones less than 2 cm in size. For patients with smaller stones, serial ultrasound examinations appear warranted to monitor spontaneous disappearance of stones. Larger stones are more problematic. Gallstones may play a role in the development of gallbladder carcinoma, with larger stones (> 2 cm) carrying a greater risk than smaller ones. As larger stones are unlikely to disappear spontaneously, there is a reasonable argument for removing the gallbladder in an otherwise asymptomatic child, given the inherent enhanced risk of

gallbladder carcinoma, caused by the presence of a stone in the gallbladder over several decades (5) (Table 2) Friesen and Roberts, 1989 (12).

Table 2. Diagnosis of Cholelithiasis

Age	Percentage of Total Cases
0 - 12 months	
None	36.4
Total parenteral nutrition (TPN)	29.1
Abdominal surgery	29.1
Sepsis	14.8
Bronchopulmonary dysplasia	12.7
Hemolytic disease	5.5
Malabsorption	5.5
Necrotizing enterocolitis (NEC)	5.5
Hepatobiliary disease	3.6
1 - 5 years	
Hepatobiliary disease	28.6
Abdominal surgery	21.4
Artificial heart valve implantation	14.3
None	14.3
Malabsorption	7.1
6 - 11 years	
Pregnancy	37.2
Hemolytic disease	22.5
Obesity	8.1
Abdominal surgery	5.1
None	3.4
Hepatobiliary disease	2.7
Total parenteral nutrition (TPN)	2.7
Malabsorption	2.8

3.8. Treatment of Cholelithiasis

Treatment of cholelithiasis is affected by several contributing factors, such as the anatomical status of gallstone, rate of symptoms in the child, underlying anatomic disorders, other underlying causes of stone formation, inflammatory changes of the biliary system, and age of the child. While the gallstone is located in the common bile duct or around the pupillary sphincter, it can cause cholangitis, obstruction of bile flow, and icterus in the child, which definitely require stone removal.

Gallstones with diameters less than 10 mm, which float in the gallbladder and are diagnosed incidentally in asymptomatic children, should be investigated for hemolytic diseases and underlying disorders and need to be treated after diagnosis. On the other hand, one or more gallstones, a few millimeters in size, floating in the gallbladder, are mostly asymptomatic and should be only monitored once every few months (11, 17). In case of the occurrence of cholecystitis and cholangitis after the administration of antibiotics, serum therapy, and vital sign monitoring, it is recommended to remove the gallstone (preferably by laparoscopy) as soon as possible.

In cases receiving TPN, the child should be monitored due to time limitations on the use of TPN regimens; also, asymptomatic patients should be assessed (13, 27). By discontinuation of TPN regimen, onset of an oral nutritional regimen, and establishment of bile flow, bile sedimentation and cholelithiasis development would gradually resolve. In cases with more severe underlying diseases such as intestinal pseudo-obstruction or short bowel syndrome, TPN regimen should be continued and repeated, as there is no chance for enteral feeding; in these patients, cholecystectomy is a preferable therapeutic approach.

Patients should be monitored to receive ceftriaxone and clofibrate after completing the therapeutic period. In most cases, cholelithiasis resolves after several months of monitoring. However, cholelithiasis is not usually resolved spontaneously in older children and should be removed in symptomatic cases. Cholecystectomy is applicable in cases requiring acute drainage of gallbladder and also severe cases of the disease. Removal of cholelithiasis through performing cholecystectomy (via laparoscopy) in children is an alternative, as adopted in adult cases. Non-surgical, therapeutic approaches for cholelithiasis in children are increasing, although there are still some controversies in this context (9, 11, 15).

3.9. Oral Medications

Ursodeoxycholic acid (Ursobil®) and chenodeoxycholic acid (chenodiol) can be only effective in cholesterol stones and therapy-resistant cases. However, their administration is restricted due to the long course of treatment, different efficacies, and side-effects such as diarrhea and liver consequences. Administration of hydroxyurea has been shown to be useful in reducing the frequency of cholelithiasis in some hemolytic diseases, such as thalassemia intermedia or major (10, 28, 29).

Extracorporeal shock-wave lithotripsy is another therapeutic method, which can be applied whenever the patient is asymptomatic or the gallstone is radiolucent (1, 30); consequently, the best result is obtained in single cholelithiasis. The most common complications of cholelithiasis include cholecystitis and pancreatitis. In cases with cholesterol stones, methyl tert-butyl ether

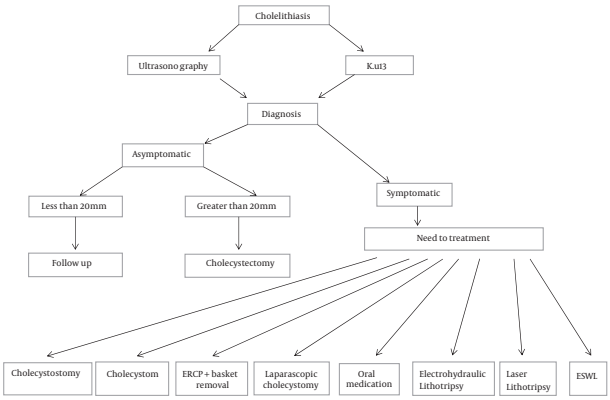

Figure 1. Recommended Therapeutic Methods for Childhood Cholelithiasis

should be injected into the gallbladder by a catheter. Although the results in adults seem to be satisfactory, implementation of this method in children is faced with some limitations due to its numerous side-effects, such as intravenous hemolysis, duodenitis, nausea, and vomiting.

Partial internal biliary diversion can be helpful in cases with progressive familial cholestasis (Bayler disease). Weight control in children with obesity, use of hypolipidemic drugs in high-risk populations, exercise, early return to oral nutrition in hospitalized children, and prevention of drug-induced calculi by prescription of proper medications are suggested. The recommended therapeutic methods are presented in Figure 1 (9, 13, 31) and Table 3 (24, 32-36).

4. Conclusions

Children with gallbladder disease may be either symptomatic or asymptomatic, although the asymptomatic presentation is less likely in children. The risk factors in children vary according to age, geographical localization, ethnicity, referral status, and medical facilities. Hemolytic anemia, family history, oncologic diseases, and ceftriaxone use were the most frequent risk factors in the asymptomatic group. Non-specific abdominal symptoms, especially in younger children, may mimic the gallstones; therefore, more children might have been factitiously classified in the symptomatic group. Although both genders are equally affected in early childhood, most previous studies have demonstrated a female predominance in pediatric gallbladder disease, starting from puberty. The results have shown that most gallstones at young age are diagnosed in the second decade of life. It seems that evaluation of the underlying causes of gallstone formation and appropriate diagnostic and therapeutic implications is still challenging in the management of childhood cholelithiasis. In asymptomatic cases or those with gallstones of certain sizes, only surveillance of the disease or ruling out the underlying causes is recommended. It should be noted that long periods of diagnostic and therapeutic approaches can impose stress and tension on the patients' families.

Table 3. Therapeutic Approaches for Childhood Cholelithiasis

Type	Comments
Cholecystectomy	Method of choice in most cases
Cholecystostomy	Effective for acute gallbladder drainage (i.e., acalculous cholecystitis)
Laparoscopic cholecystectomy	Effective for severely ill patients (e.g., cystic fibrosis), shortening the length of hospital stay
Endoscopic retrograde cholangio-pancreatography	
Basket removal	Bile duct stone removal
Mechanical basket lithotripsy	Stone crushing within the bile ducts
Electrohydraulic lithotripsy	Stone destruction within the bile ducts
Laser lithotripsy	Stone destruction within the bile ducts
Extracorporeal shock-wave lithotripsy	Limited experience (unpublished) only for cholesterol stones currently
Dissolution	
Oral medicine	Ursodeoxycholic acid and chenodeoxycholic acid
	Blockage of HMG-CoA reductase and reduction of cholesterol synthesis
Contact	Methyl tert-butyl-ether (for cholesterol stones only)
	Bile acid-EDTA solution for pigment stones (IfRr, experimental)
Preventive measures	
Enteral feeding	Even small amounts during total parenteral nutrition (TPN) can decrease the risk of stone formation
Weight loss	For obesity or gradual weight loss
Lovastatin and simvastatin	Blockage of HMG-CoA reductase and reduction of cholesterol synthesis (experimental)
Cholecystokinin	Stimulation of gallbladder contraction while NPO (experimental)

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