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Pediatric biliary calculus disease: clinical spectrum, predisposing factors, and management outcome revisited

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Abstract

Background: Biliary calculus disease (BCD) is one of the most prevalent diseases and poses a significant burden to the health care system in adults. The prevalence of BCD in children and adolescents is about 0.1% and 0.6%, respectively. Although many factors have been attributed to BCD in children, exact etiopathogenesis is not clear. BCD has been extensively studied in adults, but not much literature is available in children. The current review was undertaken to study BCD in children focusing on the objectives like predisposing factors, various modes of presentation, and management outcome of BCD in children in the northern part of India.

Results: Out of 42 children, two children had a history of ceftriaxone therapy. Two underwent ileal resection. The mean reticulocyte count was 1.79%. None had G6PD deficiency or abnormal osmotic fragility test. Clinical presentation was right upper quadrant pain ($n = 42$, 100%), calculous cholecystitis ($n = 8$, 19.0%), and jaundice ($n = 3$, 7.14%). The majority ($n = 26$, 61.92%) were overweight. Only 16.6% ($n = 7$) children had normal body mass index (BMI), and 9.3% ($n = 4$) were obese. The mean BMI was 26.3 kg/m^2. 85.5% of children frequently consume junk foods. The majority of calculi were GB calculi accounting for 92.8% ($n = 39$) whereas 7.1% ($n = 3$) children had CBD calculi. Thirty-five were managed by laparoscopic cholecystectomy, three were managed by non-operative management, and one was managed by open cholecystectomy; among the three cases of CBD calculi, two were managed by endoscopic retrograde cholangiopancreatography (ERCP), stenting, and CBD exploration and one was managed by ERCP sphincterotomy.

Conclusion: Diet and overweight both appear to be important risk factors for pediatric BCD. Drug-induced calculi can be safely observed.

Keywords: Biliary calculus, Gallstones, Choledocholithiasis, Laparoscopic cholecystectomy

Background

Biliary calculus is "a small hard concretion of cholesterol, bile pigments, and lime salts, which are formed in the gallbladder or its ducts." Biliary calculus disease (BCD) is one of the most prevalent diseases and poses a significant burden to the health care system in adults. The prevalence of BCD in children, adolescents, and adults is about 0.1%, 0.6% [1], and 6–21% [2], respectively.

The exact etiopathogenesis of pediatric BCD is not clear though many factors have been attributed which can be either hemolytic causes or non-hemolytic causes, although recently there is a decent rise in non-hemolytic causes; however hemolytic causes remain the most common cause for biliary calculus in children [3]. Hemolytic diseases account for about 60% of biliary calculus disease in children aged between 6 and 12 years [4]. About 30–40% of all BCD in the pediatric population is due to

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hemolytic diseases such as sickle cell disease, hereditary spherocytosis, and thalassemia [4, 5] and which may be attributed to chronic hemolysis. As a consequence, hemoglobin is broken down into its components, the globin and heme, the latter contributes to the formation of bilirubin. This excess bilirubin combines with calcium salts and leads to the formation of calcium bilirubinate crystals which are called pigment stones which contain < 20% cholesterol [5]. Non-hemolytic causes that are associated with BCD are total parenteral nutrition (TPN), prolonged fasting, ileal disease or resection, prematurity, diuretic therapy, congenital biliary malformations, chronic liver disease, and cystic fibrosis [4, 6]. It has been reported that obesity and its severity are risk factors for gallstones in children [7, 8]. Incidence of gallstones in obese children and adolescents is about 5.9%; moreover, it was also observed among those who lost more than 10% of initial body weight [9]. Ceftriaxone therapy is also considered to cause biliary sludge and BCD in children [10].

Most of the children with BCD are asymptomatic and are incidentally detected when evaluated for other causes. Classic symptoms for cholelithiasis include right upper quadrant (RUQ) pain following a fatty meal associated with nausea and vomiting [11]. BCD has been extensively studied in adults, but not much literature is available in children. The current review was undertaken to study BCD in children focusing on the objectives like predisposing factors, various modes of presentation, and management outcome of BCD in children in the northern part of India.

Objectives

The objective is to study the predisposing factors, various modes of presentation, and management outcome of BCD in children in the northern part of India.

Methods

It is a prospective observational study conducted at our institute from 1 February 2017 to 31 January 2020, comprising 42 children, all new cases of BCD [including both gallbladder (GB) and common bile duct (CBD) stones] with age varying from birth to 14 years. Cases with calculi in the intrahepatic ducts and biliary tracts which had been intervened previously (by endoscopy or stenting) and with a previous history of hepatobiliary surgery were excluded.

Children with BCD attending the outpatient department were enrolled in our study; a detailed history was taken regarding the age at presentation, gender, diet, past history of jaundice, TPN infusion, multiple transfusions, drug intake (ceftriaxone, frusemide therapy), rapid weight loss, and previous surgery (intestinal resection) along with documentation of height and weight and calculation of body mass index (BMI). Ultrasonogram (USG) was performed; findings related to the number of calculi (single or multiple) site (GB or CBD), GB wall thickness, and intrahepatic biliary dilatation (IHBD) were observed. Magnetic resonance cholangiopancreatography (MRCP) was done in cases with CBD stones and in the presence of CBD dilatation and IHBD.

All children were screened for hemolytic diseases by doing an osmotic fragility test (OFT) and measuring the reticulocyte count (RC) and G_6PD levels. Asymptomatic gallbladder calculi and drug-induced calculi were kept under observation (non-operative management) with regular follow-ups with serial USG 4 to 6 weekly. Symptomatic cases were managed by laparoscopic cholecystectomy procedure. In cases of CBD stones, cholecystectomy, CBD exploration, and stone extraction were done. Thereafter, patients were reviewed after 2 weeks and after 1 month postoperatively.

Results

A total of 42 children with BCD were included with ages ranging from 2.5 to 13 years with a mean age of 9.2 years (Fig. 1). Fifteen (35.7%) were female, and 27 (64.3%) were males.

Two children had a history of ceftriaxone therapy for 2 weeks for enteric fever. While two others underwent ileal resection for ileocecal intussusception. The mean reticulocyte count was 1.79%; however, one child with ideopathic thrombocytopenic purpura (ITP) had a high reticulocyte count (3.5%). None of the children had G6PD deficiency or abnormal osmotic fragility. The most common symptom in our group was right upper quadrant pain ($n = 42$, 100%). The second most common presentation is calculous cholecystitis ($n = 8$, 19.0%). Jaundice was

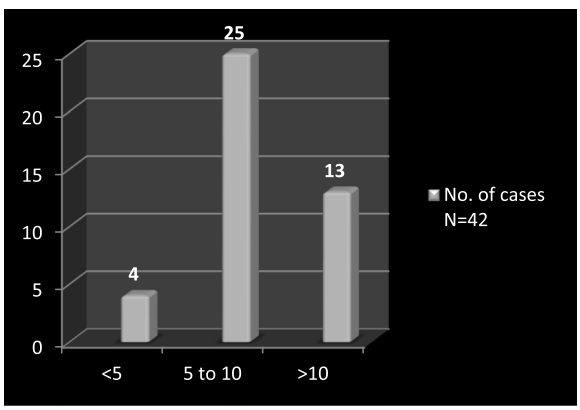

Fig. 1 Age distribution. The majority of children in our study are falling under the age group 5 to 10 years

Table 1 Predisposing factors for BCD in children

Sl. no.	Predisposing factors for BCD	No. of patients with risk factors ($n = 42$)	Percentage of patients with predisposing factors
1.	Drugs (ceftriaxone)	2	4.7%
2.	Ileal resection	2	4.7%
3.	Increased reticulocyte count	1	2.3%
4.	BMI:		
	i) Obese (> 95th percentile)[a]	4	9.3%
	ii) Overweight (85th to 95th percentile)	26	61.9%
	iii) Normal (5th to 85th percentile)	7	16.6%
	iv) Underweight (< 5th percentile)	5	11.9%
5	Dietary pattern		
	i) Frequent junk food consumers (once or twice daily)[b]	36	85.5%
	ii) Only traditional food consumers	6	14.5%

[a] Based on BMI for age-matched growth charts

[b] Junk food includes chocolates, biscuits, puffed corn (e.g., kurkure), potato chips, deep-fried food, momos, noodles, fried rice, and local savory food like chaat, etc.

Table 2 Type of management

Type of management	No. of cases ($n = 42$)
Laparoscopic cholecystectomy	**35**
ERCP + stenting + CBD exploration and stone extraction	**2**
Non-operative	**3**
Open cholecystectomy	**1**
ERCP + sphincterotomy + stone extraction	**1**

The majority were managed by laparoscopic cholecystectomy

seen in 3 children (7.14%). The majority ($n = 26$, 61.92%) were overweight (85th to 95th percentile) in our group. Only 16.6% ($n = 7$) of the children had normal BMI, and 9.3% ($n = 4$) were obese (Table 1). The mean BMI was 26.3 kg/m^2 (range 17.1 to 31.8 kg/m^2). 85.5% of children frequently consume junk foods (Table 1). The majority of calculi were GB calculi accounting for 92.8% ($n = 39$) whereas 7.1% ($n = 3$) of the children had CBD calculi. Out of 39 GB calculus cases, 35 were managed by laparoscopic cholecystectomy (Table 3), three were managed by non-operative management (Table 2), and one was managed by open cholecystectomy; among three cases of CBD calculi, two were managed by ERCP, stenting, and CBD exploration and one was managed by ERCP sphincterotomy. The mean follow-up period was 21.3 days.

Discussion

The patient's age group in our study ranged from 2.5 to 13 years with a mean age of 9.2 years. The majority [61.5% ($n = 16$)] were between 5 and 10 years. Though it was reported that BCD is slightly more common in females, we report a higher male preponderance of about

Table 3 Observation of outcome of laparoscopic cholecystectomy

Sl. no	Parameter	Zeidan et al. [29] ($n = 202$)	Present study (total $n = 42$) laparoscopy ($n = 35$)
1	Males	56 (27.7%)	27 (64.3%)
2	Females	146 (72.3%)	15 (35.7%)
3	Concomitant splenectomy	16 (7.9%)	1 (2.3%)
4	CBD injury	0	0%
5	Bile spillage	12 (5.9%)	3 (7.1%)
6	Converting to open technique	8 (4%)	2 (5.7%)
7	Wound infection	4 (1.98%)	0%
8	Postoperative recurrent abdominal pain	19 (9.4%)	2 (5.7%)
9	Mean operative time	117.5 min	105 min

Our observations are similar to Zeidan et al. [29] though the sample size is very less

64.3% ($n = 27$). It has shown that obesity and severity of obesity elevate the risk of gallstones in children [7, 8]. Incidence of gallstones in obese children and adolescents is about 5.9%, and it is related to the severity of obesity and degree and rate of weight loss as well [12]. Gallstones were observed in children losing > 10% of the initial body weight, and the prevalence was highest in those losing > 25% [9]. No child had lost significant weight rapidly. Kaechele et al. reported that the prevalence of cholelithiasis in obese children is about 1.6%. They had also documented a mean BMI of 39.2 kg/m^2 in children with cholelithiasis and obesity [1]. The mean BMI in our study was 26.3 kg/m^2, and 61.9% ($n = 26$) were overweight, indicating that a higher BMI percentile for age does seem to be a risk factor for BCD in our study group. Only 16.6% ($n = 7$) had a normal BMI, while 9.3% ($n = 4$) were obese.

Hemolytic diseases account for nearly 60% of biliary calculus disease in children aged between 6 and 12 years [11]. Screening tests for intravascular hemolysis include complete blood cell count (CBC), reticulocyte counts, peripheral blood smear, total and unconjugated bilirubin, lactate dehydrogenase, haptoglobin, ferritin, and urinalysis. The other second-line tests include Coomb's test, serological testing, enzymatic testing, osmotic fragility test, hemoglobin analysis, and genetic testing [13]. We used G6PD levels, osmotic fragility, unconjugated bilirubin levels, CBC, and reticulocyte count. G6PD deficiency as a cause for hemolytic anemia has a global prevalence of about 4.9%, the highest being in sub-Saharan Africa (7.2%) [14].

None of the children in our study was positive for G6PD screening.

The osmotic fragility test used to screen hereditary spherocytosis and hemoglobinopathies like α-thalassemia carriers, β thalassemia carriers, and sickle cell carriers. Increased osmotic fragility is seen in hereditary spherocytosis, certain autoimmune hemolytic anemias, and ABO hemolytic disease of newborns. Decreased osmotic fragility is seen in sickle cell anemia and thalassemia [15]. None of the children had an abnormal osmotic fragility test in our study.

Normal reticulocyte count is between 0.5 and 2.5% in healthy individuals [16]. A count of more than 3% with anemia indicates red blood cell destruction [17]. Only one child in our study had a high reticulocyte index (3.5%) who was a known case of idiopathic thrombocytopenic purpura (ITP).

Non-hemolytic factors that are associated with BCD are TPN, prolonged fasting, ileal disease or resection, prematurity, drugs like ceftriaxone and frusemide therapy, cardiopulmonary bypass, congenital biliary malformations, chronic liver disease, cystic fibrosis, and oral contraceptive pills [4, 6]. Among all these factors, we encountered only two, namely ileal resection ($n = 2$) for ileocecal intussusceptions and previous cases of enteric fever ($n = 2$) treated with ceftriaxone for 2 weeks. Poddar in 2010, after reviewing about 61 articles, published that 30 to 40% are idiopathic pediatric gallstones [18].

Dietary factors and their association with BCD have been studied well in adults. Diet with less protein and fiber and high simple carbohydrates, cholesterol, and saturated fats is associated with BCD in adults [19, 20]; however, not many studies are available in children. In our study, > 85% of the children had either chocolates, biscuits, crunchy snacks like puffed corn and potato chips, and fast food like noodles, momos, fried rice, or chaat (local savory food) at least once or twice a day in their diet. We have not studied in detail the dietary components and not correlated with blood lipid panel and sugar levels; hence, we need further studies to establish the relationship between junk diet and BCD in children.

Ceftriaxone is a third-generation cephalosporin most frequently used in the pediatric population. With the normal kidney function, it is excreted unchanged in urine as well as in bile approximately 60% and 40%, respectively [21]. Concentration of ceftriaxone combines with calcium to become insoluble calcium-ceftriaxone salt in bile, which results in the formation of sludge and eventually calculus [22]. Ceftriaxone-induced biliary calculus is more commonly associated with pre-existing renal disease, hypercalcemia, prolonged therapy, or higher dosage of ceftriaxone (> 2 g or > 200 mg/kg/day) [23]. The reported incidence of ceftriaxone-induced gallbladder calculi is about 15–46% [24, 25]. Very rarely, they cause symptoms and are seen to disappear with discontinuation of the drug by 2 weeks [26]. In our study, two children were treated by a pediatrician for enteric fever with ceftriaxone at 50 mg/kg/day for 2 weeks, and USG was normal at that time; however, repeat USG after 2 weeks revealed cholelithiasis. We assumed it to be drug-induced BCD and kept under close surveillance until it resolved in 4 weeks.

The most common symptom in our study was right upper quadrant (RUQ) pain ($n = 42$, 100%), though one child aged 2.5 years presented with a frequent unexplained cry. Upon evaluation, cholelithiasis was detected; hence, we assumed it to be a symptomatic case. Wesdorp et al. [4] reported that children with gallstones can present with biliary colic (52%), acute abdomen (7%), nonspecific abdominal pain (24%), or with no symptoms (17%). Nineteen percent ($n = 8$) of the children presented with acute cholecystitis which were initially managed conservatively and then with laparoscopic cholecystectomy after 4 to 6 weeks. Jaundice was observed in 3 children (7.14%) who had CBD calculus.

The majority of calculi were GB calculi accounting for 39 patients (92.8%). 7.7% had CBD calculi ($n = 3$). CBD calculi in children account for up to 10% of all bile stones [27]. Out of the 3 children with CBD calculus, one child aged 11 was already a known case of GB calculi (multiple stones, largest measuring 5.1 mm) and had been under workup for surgery, stone had slipped into CBD and caused symptoms. Hence, there is always a potential danger for GB calculi being slipped into CBD especially if they are tiny or multiple. Surgery was not required in 3 cases (ceftriaxone induced stone, $n = 2$; spontaneous resolution of stone, $n = 1$). Non-operative management protocol includes close follow-up with serial USG every 4 to 6 weeks till the spontaneous resolution occurs. Thirty-five children underwent laparoscopic cholecystectomy. One was planned for open cholecystectomy as part of open splenectomy for the treatment of ITP. This child was a 12-year-old girl, a known case of ITP with severe thrombocytopenia which was not responding to medical therapy, and complains of recurrent RUQ pain due to an 8.3-mm GB calculus. She was planned for open splenectomy simultaneously. We had witnessed the rise of platelets on the 2nd postoperative day. Laparoscopic technique to open conversion rate in children with cholelithiasis is about 1.9 to 11.11% [28]. Conversion rate in our study was 5.71% ($n = 2$); it was due to the dense adhesions. Intra-operatively, GB rupture and bile spillage were noted in 2 children. Later, the postoperative course was uneventful. Moiz et al. [29] performed laparoscopic cholecystectomy in 202 children (Table 3) and reported female preponderance of 72.3%, median BMI of 23.4 kg/m^2, concomitant splenectomy in 16 (7.9%), intraoperative bile spillage 12 (5.9%), open conversion rate 8 (4%), median operative time of 117.5 min, and postoperative recurrent abdominal pain in 19 (9.4%). Postoperatively, all children were reviewed after 2 weeks of follow-up visit.

There is a limited role of ERCP in children less than 1 year as a therapeutic tool because papillary sphincterotomy cannot be done [30]. In our study, 2 children (aged 9 and 11 years) who presented with pancreatitis due to distal CBD calculus required ERCP and stenting followed by laparotomy, CBD exploration, and cholecystectomy (Table 2). In one child with distal CBD calculus ERCP, sphincterotomy and stone extraction were required.

Complications encountered were gastritis ($n = 2$) and pancreatitis ($n = 2$). Two children presented postoperatively with gastritis managed by pantoprazole. Two children who developed pancreatitis were initially managed conservatively followed by ERCP and stenting followed by CBD exploration and cholecystectomy.

Biochemical analysis of stones revealed that the majority were pigment stones ($n = 21$) followed by cholesterol stones ($n = 10$) and mixed stones ($n = 8$) (Fig. 2).

To conclude, the prevalence of pediatric BCD is very low; the exact etiopathogenesis of pediatric BCD is

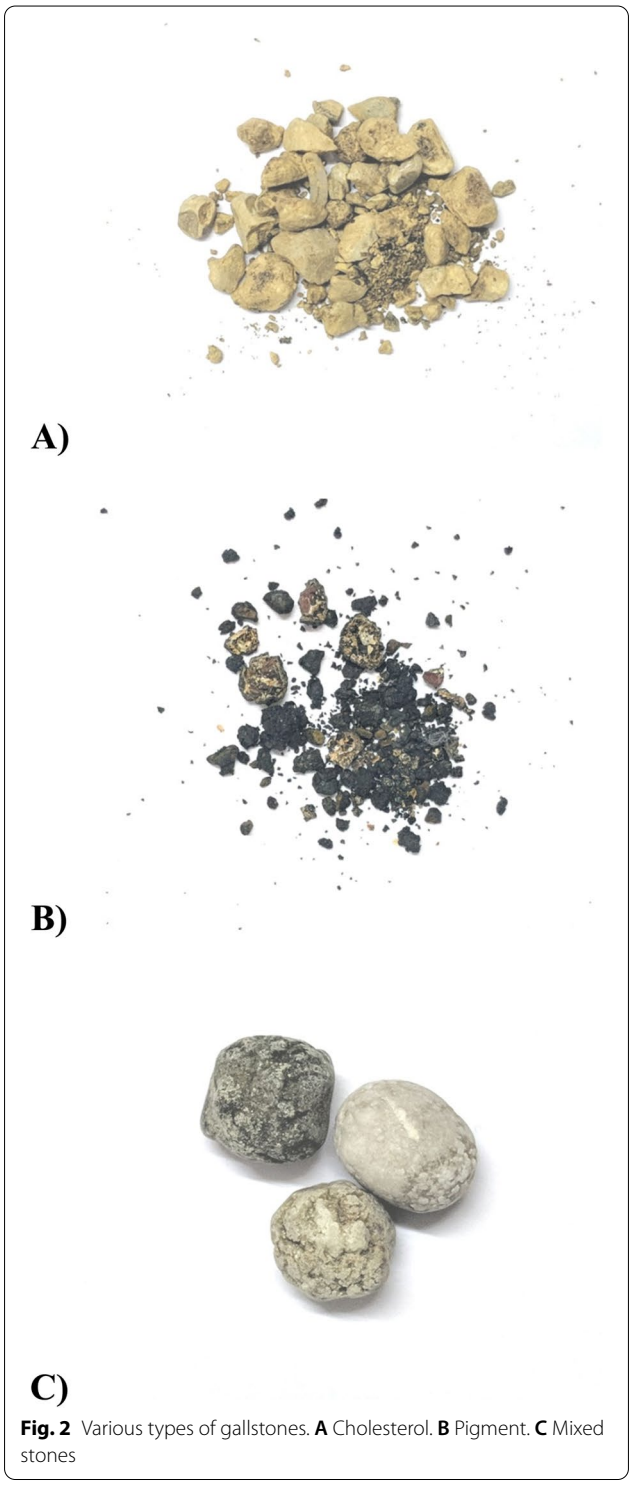

Fig. 2 Various types of gallstones. **A** Cholesterol. **B** Pigment. **C** Mixed stones

not clear though many predisposing factors have been attributed. Diet and overweight appear to be important risk factors for pediatric BCD in our study. More than 85% of children consume junk foods at least once a day apart from traditional Indian food. We need further studies to establish the relationship between diet, BMI, and BCD especially in Indian children. Drug-induced calculi can be safely observed without surgical intervention. Symptomatic cases of BCD should be operated because there is a potential danger of GB calculi moving into CBD. Laparoscopic cholecystectomy can be performed safely and effectively in children. Previous surgery with dense adhesions seems to be a risk factor for conversion to open technique.

Because of the very small sample size and limited study period, only a few predisposing factors were included and studied. Hence, to relate our study to the general population, we need to have a bigger sample size and longer duration of the study.

Abbreviations

BCD: Biliary calculus disease; TPN: Total parenteral nutrition; RUQ: Right upper quadrant; GB: Gall bladder; CBD: Common bile duct; BMI: Body mass index; USG: Ultrasonogram; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography; ITP: Ideopathic thrombocytopenic purpura.

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Authors' contributions

RA had collected and analyzed the data. VK had given the idea and proposed various predisposing factors to keep in the study. GD had helped in collecting the postoperative follow-up data. The author(s) read and approved the final manuscript.

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Availability of data and materials

The authors confirm the availability of, and access to, all original data reported in this study.

Declarations

Ethics approval and consent to participate

This study was approved by the "Institutional Review Board" of "ABVIMS (formerly PGIMER) and Dr. Ram Manohar Lohia Hospital, New Delhi. Informed consent for participation in the study was given by the patients' parents or their legal guardians.

Consent for publication

Written informed consent for the publication of this data was given by the patients' parents or their legal guardians.

Competing interests

The authors declare that they have no competing interests.

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