Section: Miscellaneous

Original Research Article

CHANGING PATTERN OF PEDIATRIC GALLSTONE ETIOPATHOGENESIS: A SINGLE-CENTER RETROSPECTIVE STUDY

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ABSTRACT

Background: To revisit etiopathogenesis of children who had undergone cholecystectomy for gall stone disease.

Materials and Methods: Retrospective observational study involving thirty-seven children upto 12 years of age with radiologically and clinically confirmed symptomatic gall stone disease between period of January 2017 to February 2020 in our centre were included. Children with complicated gallstone disease were excluded. Pre and post-surgical variables and outcomes were tabulated.

Results: Mean age was 9 $\pm$ 0.8 years with range of 3-12years. Most of them (67%) presented with complaints of right upper quadrant pain and vomiting for 3-4 days with M:F ratio of 1.3:1. Dietary history was not significant and no child had hemolytic disease. Risk factors were present in 2 patients, i.e., 1 with cardiac surgery and 1 with obesity. Single stone was present in 54% subjects and 20 had pigmented stones and 17 had yellow stones. Except for 2 subjects with acute cholecystitis and one with follicular cholecystitis all other patients had chronic cholecystitis on histopathology.

Conclusion: In our retrospective study of 37 children, we found that 94.6% of symptomatic gallstone cases were idiopathic which was contradicting the traditional understanding that pediatric cholelithiasis is primarily secondary to underlying pathology mentioned in literature. These findings necessitate a re-evaluation of current pediatric gallstone etiopathogenesis. Further large prospective study is required to evaluate etiopathogenesis of cholelithiasis in pediatric population.

Keywords: Cholelithiasis, Laparoscopic cholecystectomy, cholecystitis.

INTRODUCTION

Cholelithiasis is common in adults but relatively uncommon in the pediatric population. However, the incidence of symptomatic cholelithiasis in children has increased in recent years, with an overall reported prevalence of approximately 1.9% in the literature.[1,2] The etiopathogenesis of gallstone disease differs between adults and children. While cholesterol stones predominate in adults, pigment stones are more frequently encountered in the pediatric population. Traditionally, pediatric gallstones have been associated with hemolytic disorders, hereditary spherocytosis, Gilbert syndrome, prematurity requiring prolonged parenteral nutrition, cystic fibrosis, terminal ileal resection, previous cardiac surgery, and obesity.[3]

Recent studies have expanded our understanding of the pathogenesis of pediatric cholelithiasis by highlighting the roles of genetic susceptibility, dietary factors, medications, environmental toxins, and alterations in the gut microbiome. Genetic variants in ABCG5 and ABCG8 have been associated with an increased susceptibility to cholesterol

gallstone formation through abnormalities in cholesterol metabolism, including enhanced biliary cholesterol transport, reduced intestinal cholesterol absorption, and increased cholesterol synthesis. Quantitative real-time reverse transcription polymerase chain reaction studies have demonstrated increased expression of ABCG5 and ABCG8 in patients with cholelithiasis compared with healthy controls, suggesting their involvement in the formation of both cholesterol and pigment stones. Another important gene, ABCB4, has been implicated in low-phospholipid-associated cholelithiasis.[4]

Parenteral nutrition administered during the neonatal period, particularly in infants with intestinal pathology requiring ileostomy, has also been identified as a risk factor for gallstone formation. Lipid emulsions used in parenteral nutrition contribute significantly to this risk. Modification of these formulations to include soy-based lipids enriched with medium-chain triglycerides and fish oil has been shown to reduce the incidence of cholelithiasis.[3,4]

Dietary factors also play an important role in the development of pediatric cholelithiasis. Diets rich in fats, refined sugars, and fructose, along with low dietary fiber intake, predispose children to gallstone formation by increasing biliary cholesterol concentrations and promoting hypertriglyceridemia-induced gallbladder mucin secretion.[4]

More recently, the gut microbiome has emerged as a potential contributor to gallstone formation. According to the microbiome hypothesis, ascending migration of intestinal bacteria into the biliary system results in dysbiosis and alterations in bacterial colonization, thereby promoting gallstone formation. Metagenomic studies have demonstrated bacterial involvement in approximately 77% of pigment stones, 20% of cholesterol stones, and 76% of mixed stones. Beta-glucuronidase-producing gram-negative bacteria have been particularly implicated in this process. Mixed stones typically harbor gram-negative bacteria within both their core and surface, whereas cholesterol stones predominantly contain gram-positive bacteria within their core.[5]

Certain medications have also been associated with gallstone formation. Ceftriaxone, a third-generation cephalosporin, is excreted primarily in the urine and partially in the bile. Because its concentration in bile is substantially higher than in serum, it readily forms insoluble calcium-ceftriaxone complexes, resulting in ceftriaxone-associated pseudolithiasis.[6]

Obesity is another well-recognized risk factor for pediatric cholelithiasis because of impaired gallbladder motility, increased hepatic cholesterol secretion, and cholesterol supersaturation of bile. Children aged 2–18 years are considered obese when their body mass index (BMI) is at or above the 95th percentile for age and sex according to World Health Organization growth standards. Conversely, rapid weight loss (>1.5 kg/week) and prolonged low-calorie diets may also predispose to gallstone formation by accelerating cholesterol mobilization and causing biliary cholesterol supersaturation.

Despite these recognized risk factors, recent studies have reported an increasing proportion of idiopathic gallstones in children without any identifiable predisposing condition.[7,8] Furthermore, the widespread use of ultrasonography for the evaluation of unrelated abdominal complaints has led to an increased detection of asymptomatic gallstones, most of which are managed conservatively with regular follow-up.[8,9]

Laparoscopic cholecystectomy is currently the gold standard treatment for symptomatic gallstones because it is associated with lower morbidity, faster recovery, and superior cosmetic outcomes compared with open cholecystectomy.[10–13]

During our retrospective review of children who underwent cholecystectomy for symptomatic gallstone disease at our institution, we observed that only a small proportion had the traditionally recognized predisposing factors. This observation prompted us to question whether the etiopathogenesis of symptomatic pediatric gallstone disease is evolving. Therefore, the present study aimed to evaluate the etiological profile of pediatric gallstone disease at our center and to determine whether the current pattern differs from that described in earlier literature.

MATERIALS AND METHODS

A retrospective observational study was conducted at a tertiary care government hospital in Delhi. Thirty-seven children aged ≤12 years with clinically and radiologically confirmed symptomatic gallstone disease who underwent treatment between January 2017 and February 2020 were included. Children with complicated gallstone disease were excluded from the study.

The medical records of all eligible children were reviewed. Data collected included demographic characteristics, clinical presentation, reticulocyte count, lactate dehydrogenase (LDH) levels, lipid profile, liver function tests, bilirubin profile, drug history, family history, nutritional history, history of weight loss or weight gain, hemoglobin electrophoresis to exclude hemolytic disorders, operative findings, surgical technique, postoperative complications and recovery, and final histopathological diagnosis.

Laparoscopic cholecystectomy was performed by different surgeons using the standard four-port technique, with port placement modified according to the child's size. Open cholecystectomy was performed through a standard right subcostal incision.

Statistical Analysis

Data were analyzed using SPSS version 25. Descriptive statistics were used to summarize the study findings. Continuous variables were assessed for normality and are presented as mean ± standard

deviation (SD). Categorical variables, including gender, age group, clinical presentation, surgical approach, postoperative complications, gallstone characteristics, and histopathological findings, are presented as frequencies and percentages (n, %). Owing to the single-arm descriptive design of the study, comparative inferential statistical analyses and so, p-value calculations were not performed.

RESULTS

A total of 37 children were included in the study. The mean age was 9 years. Four children (10.81%) were aged 1–4 years, 10 (27.02%) were 5–8 years, and 23 (62.17%) were 9–12 years. The male-to-female ratio was 1.3:1, comprising 21 (56.76%) boys and 16 (43.24%) girls. Thirty-five children (94.60%) had idiopathic symptomatic gallstone disease, whereas one child had a history of previous cardiac surgery and one child was obese for age. The most common presenting symptom was right upper quadrant (RUQ) pain, observed in 13 children (35.13%), followed by RUQ pain associated with vomiting in 12 (32.43%). Eight children (21.62%) presented with isolated epigastric pain, while four (10.81%) had epigastric pain accompanied by vomiting. Ultrasonography confirmed the diagnosis in all children.

Laparoscopic cholecystectomy was performed in 33 children (89.19%), whereas four children (10.81%) underwent open cholecystectomy because of technical limitations related to the laparoscopic equipment. Intraoperatively, adhesions were identified and released in 11 children (29.73%). The mean operative time for laparoscopic cholecystectomy was 95.39 ± 5.23 minutes.

Postoperative recovery was uneventful in 25 children (67.57%). The remaining 12 children (32.43%) developed minor postoperative complications, including nausea, vomiting, and pain at the operative site, all of which were managed conservatively. Gross examination of the excised gallstones demonstrated pigment stones in 20 children (54.05%) and yellow-colored stones in 17 children (45.95%). Histopathological examination of the gallbladder specimens revealed chronic cholecystitis in 34 children (91.89%), acute-on-chronic cholecystitis in two children (5.41%), and follicular cholecystitis in one child (2.70%).

None of the children had hemolytic anemia, hereditary spherocytosis, Gilbert syndrome, cystic fibrosis, prematurity requiring prolonged parenteral nutrition, or a history of prolonged parenteral nutrition.

Table 1: Demographic, Clinical, and Operative Characteristics of the Study Cohort (N = 37)

Parameter	Frequency (n)	Percentage (%) / Value
Age (years)		
Mean ± SD	—	9.0 ± 0.8
1–4 years	4	10.81%
5–8 years	10	27.02%
9–12 years	23	62.17%
Gender		
Male	21	56.76%
Female	16	43.24%
Male-to-Female Ratio	—	1.3:1
Etiology		
Idiopathic	35	94.60%
Secondary (Previous Cardiac Surgery)	1	2.70%
Secondary (Obesity)	1	2.70%
Symptomatology		
Right Upper Quadrant (RUQ) Pain	13	35.13%
RUQ Pain with Vomiting	12	32.43%
Epigastric Pain Only	8	21.62%
Epigastric Pain with Vomiting	4	10.81%
Surgical Approach		
Laparoscopic Cholecystectomy	33	89.19%
Open Cholecystectomy	4	10.81%
Intraoperative Adhesions Released	11	29.73%
Operative Time (Laparoscopic) (mins)		
Mean ± SD	—	95.39 ± 5.23
Postoperative Outcome		
Smooth Recovery (No Complications)	25	67.57%
Minor Complications (Nausea/Vomiting/Pain)	12	32.43%
Intraoperative Gallstone Analysis		
Pigment Stones	20	54.05%
Yellow/Cholesterol-coloured Stones	17	45.95%
Histopathological Findings		
Chronic Cholecystitis	34	91.89%
Acute on Chronic Cholecystitis	2	5.41%
Follicular Cholecystitis	1	2.70%

DISCUSSION

The etiopathogenesis of pediatric gallstone disease has evolved significantly over the last two decades. Recent studies indicate that beyond classic causes, such as hemolytic anemia, spherocytosis, G6PD deficiency, IgA deficiency, cystic fibrosis, and neonatal parenteral nutrition for ileal pathologies, emerging risk factors require further evaluation. These include ceftriaxone use, obesity, dietary patterns, the gut microbiome hypothesis, and genetic variations in the ABCG5, ABCG8, and ABCB4 genes that alter cholesterol metabolism and phospholipid synthesis.[3,4] Specifically, dietary habits rich in junk food, high fat intake, and refined sugars, but low in fiber, have become leading causes of elevated systemic cholesterol, resulting in the supersaturation of bile. Additionally, obesity impairs gallbladder motility and triggers cholesterol hypersecretion, further contributing to bile saturation and subsequent stone formation.[3,4] Consequently, integrating these modern investigations is essential for accurately diagnosing the etiopathogenesis of gallstones in the pediatric population. Furthermore, asymptomatic or silent gallstone disease is increasingly diagnosed in children, primarily due to the expanded use of ultrasonography for non-specific abdominal complaints.[1,2]

In our study we included children from 1 to 12 years of age who presented with complaints of RUQ/epigastric pain and vomiting. They were evaluated clinically and with USG and then posted for elective cholecystectomy. The mean age of the children in our study was 9 years, which is comparable to that reported in previous studies, where the mean age ranged from 8 to 12 years. We observed that the majority of cases (62.17%) occurred in the 9–12-year age group.

Most published studies have reported a female predominance in pediatric gallstone disease. However, our study demonstrated a slight male predominance, with 21 (56.76%) boys and 16 (43.24%) girls. Similar findings have been reported by Sarrami et al. in children aged 0–11 years and by Wesdorp et al. in the 9–13-year age group. Owing to the descriptive design of our study, statistical significance was not assessed.[9–11]

Previously reported risk factors for pediatric cholelithiasis include idiopathic disease, familial predisposition, hemolytic disorders, obesity, previous abdominal or cardiac surgery, cystic fibrosis, IgA deficiency, recent ceftriaxone use, and liver disease. All children in our study were evaluated for hemolytic disorders using peripheral smear, complete blood count, and relevant investigations, but none had evidence of hemolytic disease. We found that 35 children (94.6%) had idiopathic gallstone disease, while one child (2.7%) was obese and one (2.7%) had undergone previous cardiac surgery. Since previous studies have reported idiopathic cholelithiasis in only 23–52.5% of cases, our findings suggest an increasing trend toward idiopathic pediatric cholelithiasis.[2,3,7–9]

All symptomatic children underwent ultrasonography before surgery. Gross examination of the excised gallstones demonstrated pigment stones in 20 children (54.05%) and yellow-colored stones in 17 children (45.95%). These findings are consistent with previous reports showing that pigment stones account for approximately 48–50% of pediatric gallstones. Similar observations have been reported by Serdaroglu et al. and Svensson et al.

Laparoscopic cholecystectomy is currently the preferred treatment for symptomatic gallstones because it provides excellent visualization of Calot's triangle, is associated with lower postoperative morbidity, and facilitates earlier recovery. In our series, 33 children (89.19%) underwent laparoscopic cholecystectomy, whereas four underwent open cholecystectomy because of technical limitations related to the laparoscopic equipment. The mean operative time for laparoscopic cholecystectomy was 95.39 minutes, which was longer than that reported in some published series, possibly reflecting the learning curve associated with pediatric laparoscopy. The mean operative time for open cholecystectomy was 79.25 minutes. Intraoperatively, adhesions involving Calot's triangle, bowel, or peritoneum were identified in 11 children (29.73%), which may have contributed to the longer operative time.[10–18]

Postoperative recovery was uneventful in most children. Minor complications occurred in 12 children (32.43%), including nausea, vomiting, and pain at the operative site, all of which were managed conservatively. One child developed transient hyperbilirubinemia (total bilirubin 2.6 mg/dL), prompting magnetic resonance cholangiopancreatography to exclude retained common bile duct stones; the examination was normal, and a positive sepsis screen explained the clinical findings. Another child developed postoperative ileus with bilious vomiting, which resolved with conservative management. These findings are consistent with previous studies reporting minor complications as the most common postoperative adverse events.[10–18]

Histopathological examination revealed chronic cholecystitis in 34 children (91.89%), acute-on-chronic cholecystitis in two (5.41%), and follicular cholecystitis in one (2.70%). These findings are in agreement with previous studies identifying chronic cholecystitis as the predominant histopathological diagnosis.

Most children who underwent laparoscopic cholecystectomy had an uneventful recovery and were discharged early. Compared with open surgery, laparoscopic cholecystectomy was associated with less postoperative pain, earlier mobilization, and shorter hospital stay. Therefore, it remains the preferred treatment for symptomatic pediatric gallstones in experienced hands, whereas the management of asymptomatic gallstones continues to be debated.

Limitation of Study

This study has several limitations. It was a retrospective, single-center study with a relatively small sample size. Biochemical analysis of gallstones was not performed, and genetic evaluation for susceptibility to cholelithiasis was not undertaken.

CONCLUSION

In this retrospective study of 37 children, 94.6% of symptomatic gallstone cases were idiopathic despite evaluation for recognized secondary causes. These findings suggest that idiopathic gallstones may now account for a greater proportion of symptomatic pediatric cholelithiasis than previously reported and support reconsideration of the evolving etiopathogenesis of pediatric gallstone disease. Larger prospective multicenter studies are needed to validate these observations and better define the changing etiopathogenesis of pediatric gallstone disease.

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