



RAPID COMMUNICATION

## High rate of complicated idiopathic gallstone disease in pediatric patients of a North American tertiary care center

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### Abstract

**AIM:** To assess spectrum and etiology of gallstones and biliary sludge in the pediatric population of a North American tertiary care centre.

**METHODS:** Retrospective review of abdominal ultrasounds recorded at Saint Justine Hospital over a period of 24 mo (8/2003 to 8/2005) in patients < 19 years of age. Patients < 2 years of age were analyzed separately.

**RESULTS:** The presence of gallstones was noted in 127 patients. In 107 it was a new diagnosis, in 48/105 (45.7%) patients > 2 years of age idiopathic gallstone disease was found. These 48 patients represent 2.1% of the population who required ultrasound for abdominal pain. Complicated gallstone disease occurred in 28/48 with idiopathic disease, mainly adolescent girls. Patients with hemolytic disorders, cystic fibrosis, oncologic diseases or kidney transplantation and gallstones were asymptomatic and stones were detected during routine abdominal ultrasound. Twenty two patients < 2 years of age not consulting for abdominal pain had gallstone disease of diverse etiology. Biliary sludge was seen in 84 patients, 78.5% on total parenteral nutrition. In 4 patients, sludge progressed to gallstones.

**CONCLUSION:** Idiopathic gallstone disease and its rate of complication are more frequent in our cohort than expected from previous studies. Adolescent girls with abdominal pain and idiopathic gallstones require special attention for complicated disease course.

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**Key words:** Cholecystectomy; Hemolytic disease; Cystic fibrosis; Pancreatitis; Choledocholithiasis

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### INTRODUCTION

The rising prevalence of gallstone disease in the adult populations of industrialized countries is a cause of concern. Over 10% of European and American population carry gallstones<sup>[1]</sup>. European studies in pediatric patients estimate an overall prevalence of 0.13% to 1.9% for gallstone disease in children up to 19 years of age<sup>[2,3]</sup>. However, no details on the etiology or the occurrence of symptoms and complications, as have been published for adult patients with gallstone disease<sup>[4]</sup>, are known from the pediatric cohorts. Furthermore, only scarce prevalence data for the North American pediatric population is available. In the light of this situation we decided to assess the types, predisposing diseases, modes of presentation and therapies of gallstone disease and biliary sludge in a North American pediatric tertiary care centre.

### MATERIALS AND METHODS

We reviewed the records of all complete abdominal ultrasounds, where the result of the inspection of the upper abdominal site was mentioned in the written report, and which were carried out for abdominal pain, for clinically indicated follow-up of diverse abdominal pathologies, malformation screening or urinary tract infection, in patients < 19 years of age, at Saint Justine Hospital over a period of 24 mo (8/2003 to 8/2005). Repeated ultrasounds in the same patient and for the same pathology were classified as follow-up exams. Charts of patients found to carry gallstones, or biliary sludge were reviewed, and the patients divided in 2 groups: 2 years and > 2 to < 19 years of age. This division appeared to

be logical because patients < 2 years of age were followed for diseases present from the perinatal period onwards. We also reviewed the charts of all patients undergoing cholecystectomy during the study period. Complicated biliary pain was considered an indication for laparoscopic cholecystectomy, which was usually carried out after normalization of liver and pancreatic serum parameters. A first episode of uncomplicated biliary pain was an indication for elective cholecystectomy only after exclusion of other etiologies for right upper quadrant pain with similar duration and nausea. Underlying diseases, weight and height, family history of cholelithiasis, serum lipids repeatedly recorded as elevated and done in the fasting state, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, total and direct bilirubin, amylase, lipase as well as the pathology results of cholecystectomy specimens and outcome as far as available were analyzed.

### Definitions

Patients with gallstones and no associated disease were defined as having idiopathic gallstone disease. Cholelithiasis was defined as an echogenic focus producing acoustic shadowing in the gallbladder or in the region of the gallbladder. Biliary sludge was defined as a non-shadowing, echogenic, intraluminal sediment. Biliary pain was defined as paroxysmal abdominal pain with right upper quadrant tenderness increasing over 15 min and lasting maximal 6 h<sup>[5]</sup>. Pancreatitis was defined as elevation of serum amylase > 3 times the normal value and abdominal pain. Cholangitis included cholestasis, fever, and upper abdominal tenderness<sup>[6]</sup>. Elevation of direct and total bilirubin beyond the upper limit of normal for age was considered a sign of biliary obstruction, with or without additional elevation of gamma glutamyl transpeptidase, alanine aminotransferase and aspartate aminotransferase. Overweight was defined as body mass index (BMI) > 95th, tendency for overweight as BMI > 85th percentile<sup>[7]</sup>.

### Statistical analysis

All testing was based on determining statistical significance at a 2-sided  $\alpha$  level of 0.05. The *Kolmogorov-Smirnov* test was used to flag normal distribution. The 2-sample *t*-test served to compare frequency distributions between subgroups, with the *Mann-Whitney U* test for comparison of groups without normal distribution. The study was approved by the Research Ethics Committee of Saint Justine Hospital.

## RESULTS

A total of 13259 complete abdominal ultrasounds in 9203 patients were included and reviewed. Of these, 2218 were done for abdominal pain with or without further clinical specification. Routine follow-up ultrasounds were carried out in patients with hemolytic disorders, cystic fibrosis, chronic liver and intestinal diseases, oncologic diseases or transplanted patients. Age distribution of patients with gallstones detected and the indication of the ultrasound are shown in Table 1. While reviewing all these ultrasounds we also found biliary sludge in 84 patients (0.91%). Table 2

**Table 1** Indications for abdominal ultrasounds in < 2 or 2-19 years old patients with gallstone disease

Ultrasound	For abdominal pain (n = 55)		For follow-up (n = 72)		Total (n = 127)	
New diagnosis	No	Yes	No	Yes	No	Yes
> 2 yr	4	51	16	34	20	85
< 2 yr	0	0	0	22	0	22

shows the associated diseases and age distribution of patients with gallstone disease and sludge. A minority of patients with gallstones or sludge required radiological examination for indications other than biliary tract disorders and data on radiopacity of the gallstones are not available.

### Associated disorders in patients older than 2 years of age

**Idiopathic gallstones:** Idiopathic gallstone disease was found in 48/105 (45.7%) patients > 2 years of age (33 girls with a median age of 15 years, and 15 boys with a median age of 12 years, 35.4% of non French or English origins: immigrants from the South American continent (8), Eastern and Southern Europe, Russia, Arabic or Far East countries), 2.1% of all patients requiring ultrasound for abdominal pain. Biliary pain was the reason for an abdominal ultrasound in 19/48 patients, and unspecified abdominal pain in 29/48. The male to female ratio was 1:2. Body mass index > 85th percentile was noted in 14/48 (29.2%, all girls); family history of gallstone disease and cholecystectomy was positive in 25, negative in 3, and not recorded in 20/48 patients. Gallstones evolved with complications such as elevated serum bilirubin and serum amino-transferases without visible choledocholithiasis (13), with pancreatitis (13) and/or choledocholithiasis (8) in 28/48 patients. All had cholecystectomy, 27 within 4 wk after the end of the acute episode, and one pregnant patient after delivery (Table 3). Endoscopic retrograde cholangio-pancreatography and papillotomy for symptomatic and obstructive common bile duct stones were carried out before cholecystectomy in 4/28 patients and intra-operative cholangiography in one. The pathological analysis of cholecystectomy specimens was limited to the description of stone colour and gallbladder wall histology. Stones were described as yellow, pale or yellowish green in 24/28 patients, and as black or predominantly black in 4/28 (4 boys). Gallbladder histology was normal in 3, with signs of chronic cholecystitis in 25/28, and of cholesterosis in 8 of these 25. In patients with cholesterosis (2 boys, 6 girls, 12-18 years old at cholecystectomy), serum cholesterol was normal in 3 and not tested in 5. BMI was > 85th percentile in 2/28 patients.

Of the 20/48 patients with abdominal pain and no complications or cholecystectomy (Table 3), 9/20 were lost for follow-up, 11 had regular follow-up for other conditions (asthma in 6, epilepsy in 2, orthopedic problems in 3), and no recurrence of abdominal pain was recorded. Only 2/11 patients were on ursodeoxycholic acid. Positive family history of gallstone disease and cholecystectomy was found in 3, negative in 2, not recorded in 15. BMI was > the 90th and > 95th percentile in 2 patients each.

Table 2 Numbers of patients with gallstones or sludge and associated diseases

Age (median, range)	Hemolytic	CF	Oncologic/transplantation	Infectious	Surgery + TPN	Idiopathic	Total	Male patients (% total patient number)
Gallstones								
< 2 yr (2 mo, 0.5-17)				12	10		22	11 (50)
> 2 - < 19 yr (13 yr, 3-18)	19	10	10	8	10	48	105	37 (35)
Sludge								
< 2 yr (2 mo, 0.2-16)	2	2	31	9	12		28	18 (64.3)
> 2 - < 19 yr (13 yr, 2.3-17)	12	4	121	10 + 1 <sup>1</sup>	14	3	56	23 (41.1)
Total	33	16	25	40	46	51	211	89 (42.2)

CF: Cystic fibrosis; TPN: Total parenteral nutrition; <sup>1</sup>Plus TPN.

Table 3 Age, gender and associated diseases in 2-19 years old patients with and without cholecystectomy

	Cholecystectomy, <i>n</i> = 37 (median age, yr)			No cholecystectomy, <i>n</i> = 68 (median age, yr)		
Associated disorders and gender (female/male)	Female	Male	%	Female	Male	%
Idiopathic	23 (14.5 <sup>1</sup> )	5 (13 <sup>1</sup> )	58	10 (16 <sup>1</sup> )	10 (10.5 <sup>1</sup> )	42
Hemolytic	4 (13 <sup>1</sup> )	5 (9.5 <sup>1</sup> )	47	4 (16 <sup>1</sup> )	6 (11 <sup>1</sup> )	53
Cystic fibrosis	0	0	0	7 (15.5 <sup>1</sup> )	3 (15 <sup>1</sup> )	100
Oncologic	0	0	0	8 (9 <sup>1</sup> )	2 (9 <sup>1</sup> )	100
Infectious/TPN/surgery	0	0	0	13 (12 <sup>1</sup> )	5 (11 <sup>1</sup> )	100

<sup>1</sup>Age differences between male and female patients not significant.

**Hemolytic disorders:** Hemolytic disorder was present in 19 (18%) patients > 2 years of age with gallstones (sickle cell disease in 11, hereditary spherocytosis in 6, hemolytic uremic syndrome and autoimmune hemolytic anemia in 1 each), and 3/19 had abdominal pain requiring ultrasound (Table 1 and Table 3). No genetic testing for Gilbert disease had been performed in these patients<sup>[8]</sup>. Preventive cholecystectomy was performed in 9/19 and for gallstone disease with choledocholithiasis in 1 patient only.

**Cystic fibrosis (CF):** None of the 10 patients with CF and gallstone disease had complicated disease, and there was no cholecystectomy (Table 3).

**Oncologic diseases or post-transplantation status:** Ten patients with oncologic diseases or post-transplantation status (Table 3) were found to carry gallstones and no complication occurred and no cholecystectomy was required.

**Diverse diseases:** Multifactorial and chronic disorders were present in 18 patients > 2 years of age and the gallstones were associated with total parenteral nutrition (TPN) or intestinal disorders (Crohn's disease, lymphangiectasia) in 7, hepatic disease in 4, and recurrent, severe infections in 7 patients.

#### Associated disorders in patients younger than 2 years of age

In total, 22 (17.3%) patients < 2 years of age had gallstones. The underlying diseases were infections (12), diseases requiring TPN (7), or congenital hepatic disease [progressive familial intrahepatic cholestasis (1), malformation of the common bile duct (2)] (Table 1). All patients had clinical

follow-up visits, but only 2 required follow-up ultrasound for pain. Eventual stone disappearance was not documented.

**Biliary sludge:** Biliary sludge was found in 84 patients, and 66/84 (78.5%) had TPN at the time of, or until 2 wk before the diagnosis of biliary sludge. 28/84 patients were < 2 years of age (21 TPN, 5 cardiopathies, 2 CF). 56/84 patients were > 2 years of age (8 hemolytic disorders, 31 TPN, 13 severe infections, 4 CF). Biliary sludge evolved with complications, such as bile duct dilatation (2), pancreatitis (12) or thickened gallbladder wall (7) in 21/84 patients (25%, 6 < 2 and 15 > 2 years of age). Cholecystectomy was carried out in 2 patients, in 1 with recurrent pancreatitis, and 1 with sickle cell disease and suspicion of acalculous cholecystitis. Progression from biliary sludge to gallstone disease was documented in 4/84 patients (4.7%), 1 each with sickle cell disease, CF, hemolytic uremic syndrome and sepsis.

## DISCUSSION

Our study revealed 127 patients with gallstone disease: 105 were older than 2 years of age, and about 50% of these had idiopathic gallstone disease. Idiopathic gallstone disease was therefore found in 2.1% of all patients having an abdominal ultrasound for abdominal pain. Half of the patients with idiopathic gallstone disease presented with complications such as cholestasis, choledocholithiasis and/or pancreatitis. Most patients with idiopathic gallstone disease, and most of those with complications were adolescent girls. Furthermore, over 50% of patients > 2 years of age were symptomatic at the time of stone detection, and the majority had idiopathic gallstone disease. In contrast, patients with gallstones of defined etiologies often were not symptomatic.

Comparability of our results with those of recently published studies was limited by discrepancies in the study duration and patient selection. The work with the most comparable design, an European study recently published by Wesdorp *et al*<sup>[2]</sup>, had to go through 11 years' data (1988-1999) to review a similar number of abdominal ultrasounds as we had the opportunity to accumulate in a 2 years interval (2003-2005). They found idiopathic disease in 23% of their gallstone carriers. No comparison was possible with the Italian survey carried out by Palasciano *et al*<sup>[3]</sup>, because this study included only healthy children. We therefore reverted to older data<sup>[9-11]</sup>, where temporary conditions such as sepsis, TPN, trauma, antibiotics or immobilization were found in 22% of children with gallstone disease, and other specific conditions, such as short bowel disease, inflammatory bowel disease, and cystic fibrosis in 38%. In those cases, up to another third of children suffered from hemolytic diseases<sup>[1]</sup>. The gallstone rate in our patients with hemolytic disorders was similar to that of the North American surveys<sup>[9,10]</sup>, whereas a much lower rate was found in Europe<sup>[2]</sup>. Differing prevalence of Gilbert syndrome may explain this discrepancy<sup>[8,9]</sup>. The gallstone rate in patients with cystic fibrosis or Crohn's disease was lower in our cohort than in previous pediatric studies<sup>[9]</sup>, but similar to that of the adult North American patient population<sup>[12,13]</sup>, and the European studies. The lower prevalence of these presumed pigment stones and the lack of complications may reflect generally improved treatments for both diseases.

The most noticeable finding, however, was the larger proportion of idiopathic gallstone disease in patients > 2 years of age when compared to the results of the Wesdorp's study (45.7% *vs* 23%), and also in comparison to older North American pediatric surveys<sup>[9-11]</sup>. Furthermore, more than half of the patients with idiopathic disease presented with complications, such as pancreatitis or elevated liver enzymes and/or elevated serum bilirubin, and they all required cholecystectomy. The majority were adolescent girls, and nearly all had yellowish, presumably mixed cholesterol stones. In contrast, the majority of the few male patients in the idiopathic gallstone group with cholecystectomy had black or dark colour stones, and the patients without cholecystectomy classed as idiopathic gallstone disease had an equal gender distribution. We therefore conclude that adolescent female patients with complicated gallstone disease and yellowish gallstones are a patient group with adult type of idiopathic gallstone disease<sup>[13,14]</sup>, as opposed to the remaining patients who may have diverse etiologies, as previously described<sup>[15,16]</sup>.

Patients < 2 years of age (17.3%) were examined as a separate group, because in most cases their conditions had been requiring medical care since birth. Their lithiasis evolved asymptotically, with no cholecystectomy or long-term sonographic follow-up required, and their stones were assumed to be of infectious origin. No gender difference was found in this age group and the rates found were comparable with those published by others<sup>[1,17]</sup>.

Biliary sludge occurred without gender difference, was equally distributed in all age groups and was associated with a lack of enteral feeding due to surgery, intestinal

disease requiring parenteral nutrition, hemolysis or systemic infections. The rate found in our study was similar to that of adult patients<sup>[18-20]</sup>. Complications such as pancreatitis and dilatation of the common bile duct occurred in 25%, which is more than expected<sup>[21,22]</sup>. The high prevalence of complications can be attributed to the high proportion of chronically- and severely-ill patients hospitalized at Saint Justine Hospital. However, cholecystectomy was only exceptionally indicated. The rate of progression of sludge to gallstone disease was comparable with that of other studies<sup>[20]</sup>.

In summary, a higher than expected rate of idiopathic gallstone disease was detected in our patient cohort. Complications such as pancreatitis, elevated liver enzymes and/or elevated serum bilirubin or choledocholithiasis requiring cholecystectomy occurred more frequently than expected. The patients afflicted were mainly adolescent girls, a third of them of non-French Canadian origin. Pediatricians should be aware of the increasingly frequent adult type gallstone disease occurring in adolescent girls presenting with abdominal pain. Further research is necessary to predict children at risk for complicated idiopathic gallstone disease and prevent complications before cholecystectomy.

## COMMENTS

### Background

The prevalence of gallstones in adults of industrialized countries approximates 10% and shows a tendency to rise. Prevalence data in pediatric patients are scarce.

### Research frontiers

Current doctrine teaches that adult gallstone disease is predominantly idiopathic and most stones are composed of cholesterol, whereas the same disease in pediatric patients is due to specific causes like infectious diseases, and intestinal, hepatic or haemolytic disorders, and stones are predominantly composed of bilirubin polymers and calcium salts.

### Innovations and breakthroughs

We found 2.1% patients ( $n = 48$ ) with idiopathic gallstone disease as new diagnosis, mainly adolescent girls, 35% of other than French Canadian origin among patients requiring abdominal ultrasound for abdominal pain. Of these 48 patients, 58% presented with complications such as pancreatitis, cholestasis or choledocholithiasis. Idiopathic gallstone disease and complicated disease presentation were much more frequent than expected from previous studies.

### Applications

Pediatricians should become more aware of a disease until now attributed to adult patients only. In the light of the recent detection of a human lith gene ABCG5/G8 and its association with the risk for cholesterol gallstone formation, the value of genetic evaluations of such families in order to prevent complicated disease presentation should be discussed.

### Terminology

Gallstones of unknown etiology are referred to as idiopathic gallstone disease, in contrast to gallstones of known etiology, such as for instance hemolytic disorders.

### Peer review

This is a well written and informative paper. The study estimated the prevalence of gallstones in the pediatric population (9203 patients < 19 years of age) of Canadian tertiary care centre by reviewing abdominal ultrasounds recorded over two years. Gallstones were found in 127 patients, 50% of these were considered idiopathic which was more than expected from previous studies.

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