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Research Paper

Gallstone in Children: A Retrospective Study of 37 Cases in Southeast of Turkey

Medical Science

KEYWORDS : children, gallstone, obesity, ultrasonography.

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ABSTRACT

Aims: To evaluate the children diagnosed with cholelithiasis in clinical retrospective study.

Materials and Methods: The children who were treated and diagnosed with gallstones in our clinic were analyzed retrospectively between May 2013-April 2014.

Results: A total of 37 cases, 20 males and 17 females (54%, 46% respectively). The mean age was 116.4 ± 61.5 months. Predisposing factors in patients were ceftriaxone usage history, obesity, hemolytic diseases, insulin resistance, hypertriglyceridemia, cystic fibrosis and a history of premature birth and parenteral nutrition. Eleven patients (29.7%) had no risk factors.

Gallstone resolution was detected in 11 patients (29.7%) treated with ursodeoxycholic acid. Resolution was observed in 33.3% of children with ceftriaxone-associated gallstone.

Conclusion: Due to the frequent use of ultrasonography and increased incidence of obesity, gallstones have been increased in children recently. An underlying risk factors were not detected in the majority of our cases (29.7%). Especially patients who had risk factors should be monitored closely for signs and complications.

INTRODUCTION

Cholelithiasis in children has been reported by Gibson in 1737 for the first time (1). Pathogenesis of gallstones and sludge in children is still unclear (2).

Because of asymptomatic patients, it is difficult to determine the actual incidence of the disease. The prevalence of gallstones has been reported rarely in children, rates vary between countries. Although the prevalence of gallstone in infant and children was estimated at 0.13-0.2% in Italy, 0.79% has been reported in India (3,4). Prevalence of gallstone was found 1.9% with USG screening in the Netherlands (2). Gallstones prevalence was found 0.13% in another study (5).

The higher incidence of obesity in children and the widespread use of USG has a significant effect in the diagnosis of gallstones, therefore prevalence has been increased recently (2,4,6-8). Obesity in children and adolescents has been reported to increase from 3% to 17% between the years 2000-2004 in the United States (9).

In the present study, we aimed to analyze the patients diagnosed with gallstones in our clinic at the last 1 year follow-up retrospectively. This study is also important as the first comprehensive report from Southeast of Turkey.

MATERIALS and METHODS

The patients diagnosed with gallstones in Department of Pediatric Gastroenterology-Hepatology and Nutrition, Gaziantep University, between May 2013-April 2014 were analyzed retrospectively. The cases which gallstones were echogenic but did not show acoustic shadow with ultrasound in the lumen of the gallbladder, were excluded from the study. Patients' age, gender, presenting symptoms, physical examination findings, history of drug use, family history, laboratory tests, triglyceride, cholesterol, fasting blood glucose, insulin, ceruloplasmin, sweat test, hemoglobin electrophoresis, osmotic fragility test and the glucose-6-phosphate dehydrogenase levels were evaluated. After diagnosis, patients were followed with physical examination and ultrasound in outpatient clinics by one to three month intervals. Cases according to age were divided into 5 groups; <1year, 1-5 years, 6-10 years, 11-15 years and > 15 years old.

Cholecystitis was detected by right upper quadrant pain with fever and leukocytosis. Additionally if jaundice presents, it was evaluated as cholangitis. Acute pancreatitis was diagnosed with abdominal pain, vomiting, three times higher serum amylase and lipase levels.

Data were analyzed with SPSS v.22.0. for Windows. Kolmogorov-Smirnov test was used for checking normal distribution of continuous variables. Descriptive statistics were used to describe the sample. Numerical variables are expressed as mean±SD (range). Categorical variables were shown as number and percentage. Variables were compared using Mann Whitney U-test, chi-square (χ^2) test. P values <0.05 were considered statistically significant.

The study was retrospective and based on file records, therefore the ethics committee approval was not received. Informed consent was obtained from patients who participated in this study.

RESULTS

A total of 37 cases, 20 male and 17 females (54%, 46% respectively). The mean age was 116.4 ± 61.5 months (range 12-203 months) (Table 1). Six of our cases (16.2%) had ceftriaxone use history, 4 of them (10.8%) had obesity, 3 of them (8.1%) had Glucose-6-phosphate dehydrogenase (G-6PD) deficiency, 3 of them (8.1%) had insulin resistance. Two patients had hereditary spherocytosis plus ceftriaxone use history. Other predisposing factors were seen in table 2. Eleven patients (29.7%) had no risk factors.

When we compared the cases according to sex, in terms of number of cases, age, height, weight, weight for age, weight for height, age at diagnosis and drug use, there was no difference between them (p> 0.05).

The distribution of patients according to age groups was seen in figure 1.

Family history was present in 12 of our cases (32.4%).

Accompanying diseases were seen in Table 3. Complications were seen in eight of our cases (Table 3). Cholecystectomy was performed in one patient and one patient had also been operated due

to choledochal cyst. Endoscopic retrograde cholangiopancreatography was applied in 5 patients.

Stones disapeared in 11 patients (29.7%) treated with ursodeoxycholic acid. Stone size was <5mm in eight of these patients, and 7 of them had stones more than one. Size of the other stones were 6 mm and 9mm in other 2 patients. The last one had two stones, the largest size of them was 14mm.

DISCUSSION

Gallstones in children have rarely been reported in the past. The higher incidence of obesity in children and the increased use of USG have a significant effect in the diagnosis of gallstones, therefore prevalence of gallstones has been increased recently (2,4,6).

It has been reported that cholelithiasis associated with systemic infection was seen mostly in children under age 5 years old (2). In contrast to this study, 2 of our patients had APSGN and 1 of our cases had rapidly progressive glomerulonephritis and age of all these cases was over five years (121 months, 74 months and 193 months respectively). Obesity, ileal disease and family history have been identified in older children (2). In accordance with this study, family history was seen in 12 of our cases, 6 of them was over five years old (ages; 110,128,145,160,165 and 181 months old); obesity was present in 7 of our cases, five of them was over 7 years old (84, 110, 148, 173, 191 months old).

While cholesterol stones were seen mostly in adults, the pigment stones developed from the hemolytic disease were seen mostly in children (6). Contrary to this study, hemolytic disease was detected in eight of our patients (21.6%). In additional, 15 of our patients (40.5%) had concomitant diseases. Because of this, they were diagnosed earlier. Also, it may result from the different etiological factors in the different regions. Another possible interpretation is that may be the limited number of our patients.

More cases have been observed in the groups of 6-10 years (19.6%) and 11-16 years (69.6%) in a study (4). In another study, most cases were detected in groups of 6-11 years (41.7%) and 12-18 years group (26.7%). Similar to these studies, the majority of patients was detected in 5-10 years (24.3%) and 10-15 years group (29.7%) in present study.

While gallstones are seen equally in boys and girls in early childhood, it is more common in girls from the beginning of adolescence (4,6,10). In contrast to these studies, Pokorny et al. (11) have reported gallstones were higher in boys than girls. Our study was compatible with that study, the majority of our cases (54%) were male. But this can only be said for these studies, can not be generalized to the general cholelithiasis population. It may result from the limited number of the cases.

It has been reported that forty-five patients (75%) had symptoms and nonspecific findings were present in 24 of them in a study (6). When the patients were evaluated according to risk factors in that study, 15 patients (25%) had ceftriaxone use, six patients (10%) had hemolytic disease, 5 patients had Down syndrome, 4 patients (6.7%) were obese, two patients had sepsis. Also, in that study the risk factor was not determined in twenty-six patients (43.3%) and these cases were considered as idiopathic. The present study was congruent with this study; symptoms were present in 24 patients (64.9%) and 3 of them (8.1%) were nonspecific. According to risk factors, 9 patients (24.3%) had ceftriaxone use history, 8 cases (21.6%) had the hemolytic disease and 7 patients (18.9%) had obesity and no risk factor has been identified in 11 cases (29.7%).

Stones less than 3 mm are defined as microlithiasis. These stones may occur in intrahepatic and extrahepatic way, and these can cause biliary colic, cholecystitis and pancreatitis and the symptoms may recur after cholecystectomy and may continue (12). Microlithiasis which is difficult to diagnose especially in children, may be overlooked by the standard USG. Reliability of USG in the diagnosis of cholelithiasis is 95% confidence. Other methods of diagnosis are endoscopic ultrasound, endoscopic retrograde cholangiopancreatography (ERCP) and nasobiliary aspiration (13,14). Due to the low sensitivity of magnetic resonance cholangiopancreatography (MRCP), it has been especially less role to diagnose gallstone in children (8). All of our patients were diagnosed with ultrasound. MRCP was applied to 3 patients, the stone could not be detected in one of them. In our hospital, there were no doctors experienced in endoscopic ultrasonography and nasobiliary aspiration, therefore these processes could not be performed for any patients. ERCP was performed for 5 patients in both diagnosis and treatment and millimetric multiple stones were removed by this process.

The most common predisposing factors in children were hemolytic disease, prematurity, cystic fibrosis, obesity, insulin resistance, crohn's disease, ceftriaxone and furosemide use, cardiac surgery, ileal disease, parenteral nutrition, systemic infections, prolonged fasting, rapid weight loss, biliary stasis and weak gallbladder contractility (2,15). Our study is consistent with literature; six of our cases (16.2%) had ceftriaxone use history, 4 of them (10.8%) had obesity, 3 of them (8.1%) had G-6PD deficiency, 3 of them (8.1%) had insulin resistance. Also other predisposing factors in other cases seen in table 2.

There has not been a serious work about a relationship between obesity and cholelithiasis in children until Koebnick et al. (16) large-scale study on children in 2012. In that study, the definition of obesity was made according to World Health Organisation (WHO) and Centers for Disease Control and Prevention (CDC) (17,18). In that study, 19.6% overweight, 13.7% obesity and 7.7% extreme obesity was determined. Koebnick et al (16) determined that overweight in children was associated with gallstones, also relationship between excess weight and gallstones has been found to be stronger especially in females. Also, the use of oral contraceptives was found to contribute to gallstone disease in females. Risk of gallstone disease in obese and overweight is 4-6 times more than the others. Although the risk of cholelithiasis was detected three times more in obese boys, this risk was determined eight times more in obese girls. In accordance with literature, four cases (10.8%) were moderately obese, and three patients (8.1%) were overweight in our study. No patients were using oral contraceptives.

Fradin K et al.'s (19) study is the first epidemiological analysis showing an increase in hospitalization rates of cholelithiasis cases in children from 1997 to 2009 in the United States. This study has showed that this increase in child cholelithiasis rate was proportional to the increase in obesity rates and also highly correlated. Understanding this relationship can help clinicians to diagnose earlier and to determine proper treatment for cholelithiasis cases in children. Seven patients (18.9%) were found to have obesity in our study. And this is compatible with literature.

Prevalence of asymptomatic cholelithiasis has been reported 17-50.5% in children (2,4,7,20,21). Our results were consistent with literature; 13 of 37 patients (35.1%) were asymptomatic. Gallstones were diagnosed incidentally by USG due to another reason (for example; chronic renal failure, glomerulonepritis, cystic fibrosis...) in our study (Table 3).

Nonspecific symptoms are seen mostly in children under five years of age, because there is no jaundice in this group and these children are inadequate to express what the biliary symptoms are (2). In accordance with this study, symptoms of restlessness have been identified in 2 of our patients (ages; 12 and 18 months).

The majority of children with biliary symptoms, acute abdominal pain and tenderness has been treated with ERCP and cholecystectomy. However, this treatment does not provide guarantees for res-

olution of symptoms because approximately 45% of the cases has been reported to be in clinical recurrence (2). At the same study, high-rate initial symptoms were seen again in patients treated with ERCP and cholecystectomy. ERCP was applied to 5 of 21 patients with acute abdominal pain and tenderness in our study. Cholecystectomy was performed for one patient. Then symptoms were seen again in half of these patients. The stone were formed again in all patients applied to ERCP (after the ERCP procedure 7,9,11,13 and 22 months respectively), but irregular use of ursodeoxycholic acid treatment had been identified in last two patients.

No information is available about positive family history in the etiology of gallstones (4). Positive family history were present in 12 patients (32.4%) in our study.

Hemolytic disease has been reported in 8.9-50% of cases in some studies (2,4,10,11,21,22). Hemolytic disease was detected in 8 patients (21.6%) in present study. The differences in these rates may result from the different etiological factors in the different regions.

The rapid increase of obesity and its associated lipid dysregulation plays an important role in the etiology of gallstones in the developed world countries (8). Similar to this, hypertriglyceridemia was detected in three of our patients.

Etiology of gallstones has not been identified in 23-52% of patients with gallstones in studies and then these cases were considered as idiopathic (2,6,10,20,21,23,24). In accordance with literature, etiology was not found in 11 patients of our cases (29.7%). The risk factors in children are diverse and may vary according to age, geographic localization, ethnicity, referral status and facilities of centers (21).

It has been reported that the ages of idiopathic group patients were older (2,6,25). Similar to the literature, 6 of 11 (54.5%) patients in idiopathic group were older (3 of them in 11-15 years and 3 of them in > 16 years group) in our study.

The rate of disappearing stones spontaneously has been detected higher especially in children under 1 year of age than the other age groups. In the patients aged under and over 1 year the rates were identified as 34% and 13% respectively (7). As far as we know, according to previous literature there is no data on the mechanism of disappearance of gallstones (7). There was no patient who had disappeared stones spontaneously in present study. Probably the reason is that we had just one patient who was under 1 year old.

If gallstone is larger than 2 cm, the possibility of causing gallbladder carcinoma is more than the smaller one, because there is also no chance to disappear spontaneously Cholecystectomy is recommended in this cases even if they are asymptomatic (26). There was no case with gallstone larger than 2 cm in our study.

Gallstones are diagnosed mostly in the second decade, but there are also many patients diagnosed in infancy (27,28). In contrast, many of our patients (56.7%) were diagnosed in the first decade, the reason for this may be that USG was applied to our 15 patients due to concomitant diseases (table 3).

The most common symptom is the pain associated with biliary colic and cholecystitis and is often seen in right upper quadrant (85-94%), less frequently seen in the epigastric region (34%). Nausea and vomiting may be accompanied with 60% of the pain. Cholangitis, choledocholithiasis and pancreatitis may be seen in 7-20% of cases. Fever, pain and jaundice may also accompany. Nonspecific abdominal pain and restlessness may be seen in 24-46% of children under five years of age and with hemolytic disease (2,7). There were 4 patients with cholangitis, 2 patients with pancreatitis, 1 patient with pancreatitis and cholangitis, 2 patients with restlessness (ages; 18 months and 1 year) in our study. Symptoms were detected in 24 of 37 patients (64.8%) in our study. Sixteen of them (66.6%) had abdominal pain, vomiting was also accompanied to three of them. Hemolytic disease was detected in 8 of our patients, 4 of them had G-6PD deficiency diagnosis, and also all of them had abdominal pain. Abdominal pain was also present in 1 of 3 patients with hereditary spherocytosis. The other 2 patients had no symptoms, the diagnosis was made by incidentally. Abdominal pain was also present in 1 patient with thalassemia minor.

Leukocytosis are nonspecific, can be seen in cholangitis and pancreatitis. The higher levels of amylase is important in the diagnosis of pancreatitis and it is also useful marker to follow the resolution of disease (8). Pancreatitis was observed in 3 of our patients, amylase levels were higher at the time of diagnosis.

Ceftriaxone which is a third-generation cephalosporin can reach 20-150 times more concentration in the gallbladder than normal serum. Gallstone is made of calcium-ceftriaxone and also a small amount of a combination of cholesterol crystals and bilirubin granules in patients who had gallstones and treated with ceftriaxone. Possibility of gallstones may be increased especially in long-term and high dose use of ceftriaxone. The stones disappear spontaneously with discontinuation of treatment. That's why they are called "pseudolithiasis" (6,29,30). It has been reported that gallstones were formed 25-40% in children treated with ceftriaxone and gallstones disappeared in a short time after cessation of treatment (2,30,31). Contrary to this, Gökçe S, et al. (21) have reported that gallstone resolution was seen only in 7 of 16 (43.8%) children with ceftriaxone use. As compatible with that study, we detected that gallstones disappeared in 3 of 9 (33.3%) patients using ceftriaxone, but we have less number of cases than Gökçe S, et al (21) study. But this is incompatible with other literature. The reason for this may be that these patients had multiple stones and there were less number of cases in our study.

The most commonly used agent in the treatment of gallstones is ursodeoxycholic acid. This is a secondary bile acid present in low concentration in human bile (32). Ursodeoxycholic acid causes to decrease cholesterol saturation of bile by reducing secretion of cholesterol to bile. However, it has been detected that it was ineffective to dissolve gallstones in the majority of patients having treatment and 50% of soluble gallstones was repeated. But the positive effects of treatment are the disappearance of symptoms in the majority of patients who presented the symptoms and findings were not seen again follow-up (33). Published studies are rare in children. Fifteen children who had symptomatic radiolucent gallstones were treated with ursodeoxycholic acid for 1 year in a study. Then all children became asymptomatic, but the resolution was seen in 2 patients (34). The stone was formed again in both of these patients within 6 months after the treatment. In another study, 180 pediatric patients was treated with ursodeoxycholic acid. One hundred seventeen (65%) children have become asymptomatic, but the stone has disappeared only in 8 patients and stone formation was observed again in 3 patients after treatment (25). Gallstones that are formed by a large portion of cholesterol can be affected with ursodeoxycholic acid treatment; so it is necessary to exclude potential pigment stones, and these stones are distinguished by the fact that radiolucence (8). Gallstones disapeared in 11 patients (29.7%), treated with ursodeoxycholic acid in our study. Three of them had hemolytic diseases; two of them was hereditary spherocytosis and 1 of them was thalassemia minor. Stone size was <5mm in eight of these patients, and 7 of them had stones more than one. Size of the other stones were 6 mm and 9mm in other 2 patients. The last one had two stones, the largest size of them was 14mm. According to literature, ursodeoxycholic acid therapy seems to be ineffective in gallstone resolution (25,33,34). Further studies are needed to evaluate its efficiency.

The only remedy is cholecystectomy in patients with recurrent biliary findings and complications. Because of lower costs and shorter length of hospital stay, laparoscopic cholecystectomy is preferred

nowadays (35).

The limitations of the present study are several. Firstly, the retrospective and cross-sectional nature of the study allows only association rather than causation when we mention about the relation of gallstones with risk factors, demographic and laboratory features, and the relation of gallstone resolution with demographic factors, etiology. Secondly, the sample size of the present study is lower. Given the diverse and multiple risk factors for gallstone formation, low sample size may decrease the strength of the conclusion regarding the distribution of risk factors and their relation with gallstone formation.

As a result; due to the widespread use of ultrasonography and increased incidence of obesity, gallstones have been increased in children recently. Possibility of gallstones may be increased especially in long-term and high dose use of ceftriaxone. Ceftriaxone associated gallstones are most likely to resolve, but do not always disappear spontaneously with discontinuation of treatment. Thus, these patients should be followed by USG if clinical signs are. An underlying risk factor was not detected in the majority of our cases (29.7%). Especially patients who had risk factors should be monitored closely for signs and complications of gallstones.

Ethics Committee Approval:
The study was retrospective and based on file records, therefore the ethics committee approval was not received. Informed consent was obtained from patients who participated in this study.

Conflicts of interest:
The authors declared no conflicts of interest.

Authors' contributions:
Concept - Y.Ş.; Design - Y.Ş., D.A.Ş.; Supervision - Y.Ş., D.A.Ş.; Resource - Y.Ş., D.A.Ş., F.B.,A.I.T., A.R.G.; Materials - Y.Ş., D.A.Ş., F.B., A.I.T., A.R.G. ; Data Collection&/or Processing - Y.Ş., D.A.Ş., F.B.; Analysis&/or Interpretation – Y.Ş.; Literature Search - Y.Ş., D.A.Ş., F.B., A.I.T., A.R.G.; Writing - Y.Ş.; Critical Reviews – YŞ. All authors read and approved the final manuscript.

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Table 1. The demographic characteristics of patients

	Girl (mean±SD)	Boy (mean±SD)	Total	(Min-Max)
Number (n)	17	20	37	
Age (months)	133.3±67.9	102.0±53.0	116.4±61.5	(12-203)
Height (cm)	132.8±31.7	121.0±40.0	126.5±36.4	(64-184.8)
Weight (kg)	35.9±17.8	30.4±17.2	32.9±17.4	(7.8-68.9)
Height for age (%)	95.7±25.0	99.4±26.5	97.7±25.5	(43.5-166.3)
Weight for height(%)	103.5±18.5	103.7±15.4	103.6±16.6	(75.8-143.5)
Age of diagnosis (months)	114.0±68.2	91.7±53.8	101.9±61.0	(2-193)
Medication time (months)	11.6±10.5	7.8±7.5	9.6±9.6	(1-36)

Table 2. Predisposing factors in our cases

	Number (n)	(%)
Predisposing factors	**26**	**70.3**
Ceftriaxone use	6	16.2
Ceftriaxone use and insulin resistancy	1	2.7
Hemolytic diseases	8	21.6
G-6PD deficiency	3	8.1
Hereditary spherocytosis and ve ceftriaxone use	2	5.4
G-6PD, obesity and insulin resistancy	1	2.7
Hereditary spherocytosis and hypertriglicerydemia	1	2.7
Thalassemia minor	1	2.7
Obesity	4	10.8
Obesity, hypertriglicerydemia and insulin resistancy	1	2.7
Obesity and insulin resistancy	1	2.7
Insulin resistancy	3	8.1
Insulin resistancy and cystic fibrosis	1	2.7
Hypertriglyceridemia	1	2.7
Prematurity and parenteral nutrition history	1	2.7
No risk factors	**11**	**29.7**
Total	**37**	**100**

***G-6PD: Glucose-6-phosphate dehydrogenase**

Table 3. The clinical characteristics of patients, comorbidities, complications and stone size

	Patients (n=37)	(%)
Age (months)	116.4±61.5	-
Family history	12	32.4
Stone size		
<5mm	21	56.8
5-10mm	11	29.7
10-15mm	4	10.8
>15mm	1	2.7
Number of stone		
Single	11	29.7
Multiple	26	70.3
Symptoms		
Absent	13	35.1
Typical symptoms	21	56.8
Atypical symptoms	3	8.1
Complications	8	21.6
Cholangitis	4	10.8
Pancreatitis	2	5.4
Cholangitis and pancreatitis	1	2.7
Cholecystectomy	1	2.7
Stone disappeared	11	29.7
<5mm	8	21.6
5-10mm	2	5.4
>10mm	1	2.7
Accompanying diseases	14	37.8

CRF	2	5.4
GER	2	5.4
Renal atrophy	2	5.4
APSGN	1	2.7
GH deficiency	1	2.7
VUR	1	2.7
Klinefelter Synd. and PFO	1	2.7
RPGN	1	2.7
Nephrolithiasis	1	2.7
HIE	1	2.7
APSGN and FMF	1	2.7

CRF: chronic renal failure
GH: growth hormone
GER: gastroesophageal reflux
VUR: vesicoureteral reflux
APSGN: acute poststreptococcal glomerulonephritis
PFO: patent foramen ovale
HIE: hypoxic ischemic encephalopathy
Synd.: syndrome
RPGN: rapidly progressive glomerulonephritis
FMF: familial mediterranean fever

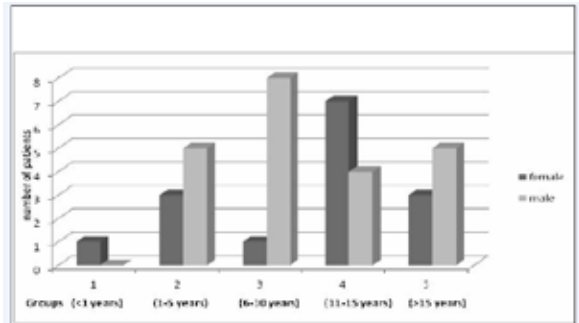

Figure 1. The distribution of patients according to age groups.

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