Original Article

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Ceftriaxone Induced Biliary Pseudolithiasis in Children: Report of 14 Cases

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Abstract

Objective: Biliary pseudolithiasis has been reported in patients who received ceftriaxone therapy. In this study we evaluated children with ceftriaxone associated pseudolithiasis that was discovered incidentally in US examination.

Material & Methods: The study includes 14 children with gallstones in Ultrasound without biliary symptoms with recent ceftriaxone administration. All of them were treated for suspected or definite bacterial infection with ceftriaxone 50-100mg/kg/day divided into 2 equal intravenous doses under conditions of adequate hydration. There were no other known underlying diseases for gallstone.

Findings: Fourteen patients (11 boys and 3 girls) with mean age of 4.5 years (range: 2 months to 14 years) were studied. Following cessation of treatment with ceftriaxone, a complete resolution of the lithiasis was seen in most of followed cases. All patients were free from biliary symptoms (Right upper quadrant pain, Cholestasis) during observation. Consultations with surgeon or subspecialist due to reported "gallstone in the Ultrasound" were performed in about two-thirds of patients.

Conclusion: Development of pseudolithiasis after ceftriaxone administration is not uncommon and should be known by pediatricians and radiologists in order to avoid unnecessary surgery or additional consultations.

Key Words: Pseudolithiasis, Ceftriaxone, Gallstone, Ultrasound

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Introduction

Cholelithiasis is uncommon in otherwise healthy children and usually occurs in patients who have predisposing conditions like: total parenteral nutrition, malabsorption, cystic fibrosis, sepsis, Crohn's disease, hemolytic anemia, metachromatic leukodystrophy, hepatobiliary disease and bowel resection. Cholelithiasis may also develop due to use of some medications. Ceftriaxone is one of the most common drugs for drug-associated biliary sludge[1].

Ceftriaxone, a third generation cephalosporin, was first introduced in 1984 and since that time it has gained considerable popularity among pediatricians with its wide spectrum of activity, long half life, ease of administration and few adverse effects. Ceftriaxone is indicated for prevention and treatment of a variety of infections and also used for surgical prophylaxis. It is often well tolerated by most patients. However, in addition to its general side effects; biliary sludging and pseudolithiasis were also reported[2]. Schaad et al first reported sonographic evidence of ceftriaxone associated participants in gallbladder in 1986[3]. Thereafter terms such as “biliary pseudolithiasis”, “reversible cholelithiasis”, or “apparent pseudolithiasis” have been used to describe ultrasonographic (US) abnormalities in the gallbladder of patients treated with ceftriaxone in an attempt to differentiate the reversible abnormalities which have been observed in ceftriaxone-treated patients from those of true operative stones.[3-5] Some studies have suggested that between 17 and 50 % of ceftriaxone-treated children develop sonographic abnormalities on imaging of gallbladder, with no more than a tenth of these developing symptoms of biliary colic including right upper quadrant pain[5-8].

In our clinical experience we incidentally observed pseudolithiasis in a child whose previous (3 weeks before) US was normal and the only risk factor was treatment with ceftriaxone. Therefore, we conducted a prospective study to evaluate children with ceftriaxone associated pseudolithiasis that was discovered incidentally in US examination.

Material & Methods

In this prospective descriptive study, data of patients were collected over a two-year period from 2005 to 2007 in Bahrami Children's Hospital, a tertiary care children's hospital in Tehran, Iran.

The inclusion criteria were admitted patients that treated with intravenous ceftriaxone referred for US study and without any clinical or laboratory presentations of cholelithiasis which in their US study pseudolithiasis or sludge were found. Patients with secondary cholelithiasis due to known conditions like hemolytic anemia, liver disease, malabsorption, total parenteral nutrition and whom used drugs such as octerotide, cyclosporine, furosemide or had any conditions known to be associated with gallbladder lithiasis were excluded. Consent was obtained from the parents by informing about study.

All patients received intravenous ceftriaxone infusion (50, 75 or 100 mg/kg/day) in divided equal doses (every 12 hours) with particular attention to maintaining a state of good hydration for suspected or definite bacterial infections. All patients had at least one abdominal US for evaluation of underlying disease after admission but the requests were not for evaluation of gallstone. When US showed gall stones, follow up US were obtained 1-4 times in patients from 1 week to one year until the resolution of the pseudolithiasis was seen. Follow up US studies scheduled by invitation call and were free of charge.

Criteria for positive gallstones in US were the presence of mobile, gravity dependent, echogenic material accompanied by clear acoustic shadowing and sludge was diagnosed when hyperechogenic bile showed no acoustic shadowing. Ultrasound exams and interpretation were performed by a radiologist with using convex or linear

transducers 3.5 -10 MHz (Siemens G50, Germany). Other possible complications such as choledocholithiasis or nephrolithiasis also noted in US exams. Routine physical examination and laboratory tests like cell blood count, liver function tests (SGOT, SGPT, Alkaline Phosphatase, Bilirubin), kidney function tests (Urea, Creatinine), serum electrolytes (Calcium, Sodium, Potassium) and urine analysis were performed for all patients and repeated as needed.

Besides demographics, season of admission, rate of consultations with surgeon or sub specialists were assessed.

Findings

Fourteen patients (11 boys and 3 girls) with mean (SD) age of 4.5 (4.1) and range 2 months to 14 years were studied. Characteristics of patients were depicted in table1. Following cessation of ceftriaxone, in 10 cases complete resolution of the lithiasis were seen. In 3 cases with three US before, during and at follow up of treatment showed normal gallbladder, lithiasis formation and complete resolution respectively. Two cases had a few stones in long term follow up without any complication. The duration of

Table 1- Characteristics of patients in regard to their demographics and clinical data

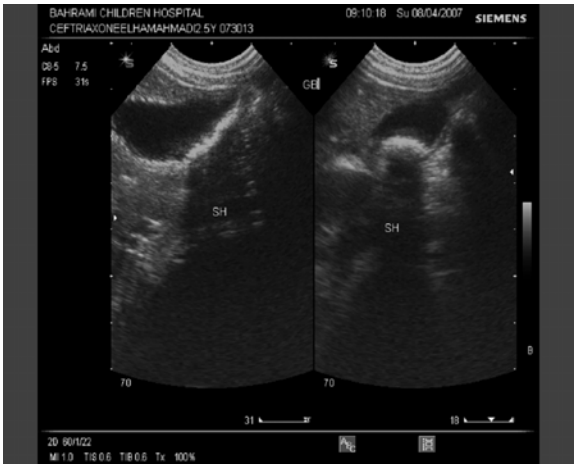
	Sex/Age (year)	Weight (kg)	Season of admission	Consultation for gallstone	Main disease
1	M/7	16	winter	Surgeon, Hematologist	Appendicitis
2	M/9	23	spring	No(explained in US report)	Appendicitis
3	F/1	10	summer	Hematologist, Gastroenterologist	Wilm's tumor
4	M/0.16	4	fall	-	Lower Respiratory Infection
5	F/3	13	summer	Gastroenterologist	Urinary Tract Infection
6	M/1.16	8	summer	-	Gastroenteritis
7	M/10	37	summer	- (bad condition, expired)	Acute Lymphocytic Leukemia
8	M/4	12.75	Summer	Surgeon, Gastroenterologist	Appendicitis
9	M/14	45	summer	Radiologist	Acute Lymphocytic Leukemia, Appendicitis
10	M/0.5	7	fall	Surgeon	Gastroenteritis, Colostomy
11	M/3.5	14	fall	Hematologist	Respiratory distress
12	M/2	10.5	fall	No(explained in US report)	Urinary Tract Infection
13	M/6	18	spring	Gastroenterologist	Chronic Renal Failure
14	F/2.5	12	summer	No(explained in US report)	Gastroentritis

Table 2- Characteristics of patients in regard to dose and duration of treatment with ceftriaxone and US studies

	Dose mg/kg/ day	Duration of treatments (days)	US baseline	US after ceftriaxone administration	US Follow up	Time of stone developmen*
1	100	7	Normal	Multiple round stone 5-15 mm	Normalized 8 weeks later	5 days
2	100	3	-	Multiple tiny stones	Normalized two weeks later	5 days
3	100	1.5	-	Many stones 5-6 mm	Persistent after 1 year	8 days
4	50	10	-	Few small stones	Normalized One week later-	7 days
5	75	2	-	Few tiny stones 2-3mm + sludge	Normalized 11 months later	2 days
6	100	3	-	Few tiny stones + sludge	Not followed-	3 days
7	75	14	Normal	Few round stones 5-10mm	expired	14 days
8	100	7	-	Multiple flat stones 5-10mm	Nearly normalized 3 weeks later (sludge)	6 days
9	50	25	-	Multiple stones up to 15mm	Normalized 5 weeks later	25 days
10	50	1.5	Normal	Few round stones 6-8 mm	3 small stones after 4 months	1.5 day
11	50	-	-	A few stones as large as 9.6 mm	Normalized 2 weeks later	6 days
12	75	8	Normal	Multiple small round stones 5-6mm	Normalized 12 weeks later	5 days
13	100	6	Normal	Multiple round stones largest 10mm	Normalized 8 weeks later	6 days
14	50	4	-	Multiple tiny stones	Normalized 3 weeks later	4 days

*Interval between ceftriaxone administration and stone development

treatment was 1.5 to 25 days. Treatment data and character of pseudolithiasis were summarized in Table 2. Sonographic changes of pseudolithiasis were identical to the changes seen in true cholelithiasis with bright mobile echoes and prominent posterior shadowing (Figure 1- a, b).



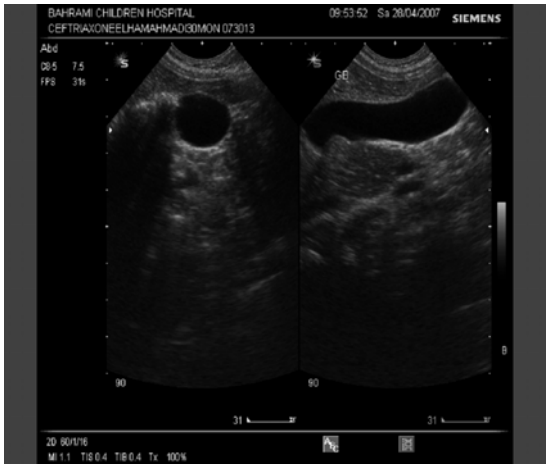


Fig 1.a (left)- Sonogram of case 14 showed echogenic materials with acoustic shadowing
Fig 1.b (right)- Sonogram of the same case; three weeks after discontinuation of drug, sonogram was normalized

All patients were free from biliary symptoms (abdominal pain, cholestasis) during the observation except one with borderline periumblical pain in the post appendectomy state. He improved spontaneously at time of the discharge. Laboratory data (especially serum calcium and alkaline phosphatase) in regard to cholelithiasis were in normal range except three cases: one with impaired liver enzymes and neutropenia (case3). Another with hypocalcemia, tumor lysis syndrome and renal failure (case7). The third case had impaired renal function tests (case 13). Consultations with surgeon or sub specialist were performed in about two-thirds of cases due to reported "gallstone in the Ultrasound". Two cases had additional evaluation for rule out of spherocytosis. The results of all surgical and other consultations were negative.

In US examinations of all patients gallbladder wall's thickening, dilated biliary tree or pancreatitis were not detected. Gallstones were found in all 14 cases and 3 cases had sludge. Concomitant nephrolithiasis was not detected in any patient. Seven patients received ceftriaxone alone and others also received other antibiotics such as Metronidazol, Ampicillin or Amikacin. Two patients received chemotherapy agents.

Discussion

Inappropriate prescribing of third generation cephalosporin has been noted in as much as one third of all hospital prescriptions[6]. In patients with normal renal function, 60% of ceftriaxone is excreted unchanged into the urine, and 40% is excreted into the bile[9]. Ceftriaxone is an anion, can concentrate in bile 20 to 150 times more than in serum, and readily forms an insoluble salt with calcium that precipitates when the solubility product constant of the salt in the bile exceeded by a factor of 10.4[9,10].

Passive entry of ionized calcium in response to the concentrative biliary secretion of drug leads to precipitation of a calcium-ceftriaxone salt in the biliary tract and these results in formation of sludge and pseudolithiasis. In an *in vitro* study, it was calculated that precipitation of calcium– ceftriaxone may occur at doses of 2 g or more daily. It is believed to occur in a dose dependent manner, and may be more common in children who, by weight, receive proportionately higher doses than adults.[11] In our study, the least dose for causing pseudolithiasis was 50 mg/kg. Some additional risk factors for biliary sludge formation include conditions that increase

calcium secretion into the bile (e.g. hypercalcemia), decrease bile flow (e.g. fasting or total parenteral nutrition), increase ceftriaxone excretion in bile (e.g. renal failure or high-dose or long-term treatment with ceftriaxone) and patients recovering from surgical operation because of gallbladder stasis[12]. Fasting, recent operation and long–term treatment as much as 25 days in some of our patients are seen. Other predisposing contributing factors to"stone" formation in ceftriaxone associated biliary pseudolithiasis have been proposed. Gram negative sepsis has been shown to increase susceptibility to stone formation[6]. Our three gastroenteritis cases were suspicious for shigellosis.

Age greater than 24 months confers a higher risk for development of pseudolithiasis. In our study mean age of the patients was 4.5 years. There is no sex predominance in most studies[4]; however, there is male predo-minance in one recent case study[13] and also in our series. Biliary precipitation forms after approximately 9 days of treatment and usually resolves completely within 2-63 days after discontinuation of ceftriaxone therapy[3]. In our study, two cases had persistent gall stones in their follow up US after 4 months and 1 year, respectively. The first was a case of neonatal intestinal obstruction with three consecutive operations and the second was an undertreatment case of Wilm's tumor. Both of them had several hospitalizations with frequent uses of ceftriaxone. In Papadopoulou study, the formation of pseudolithiasis was reported within 2 days in 3 of 11 children in lithiasis group[5]. In our study, pseudolithiasis was seen in a case as early as 1.5 days of ceftriaxone therapy with a dose of 50 mg/kg/day.

In the present study we could not definitely determine the time of appearance or resolving of the pseudolithiasis because the times of US examination were limited and some patients did not appear on time for examination.

Ceftriaxone therapy has been reported to be related more with biliary sludge than gall stones[6,13]. However, only 2 of 14 patients of our study group had biliary sludge accompanying stone. The highest reported incidence of pseudolithiasis was related to restriction of oral fluid intake and high weather temperature in summer[13]. In our study there were more cases in summer in spite of well hydration and without fasting or significant fever. However, one prospective study showed no significant relation between the fasting period and incidence of pseudolithiasis[14].

Rate of ceftriaxone intravenous infusion was also an important factor of pseudolithiasis formation[3]. Schaad et al reported that incidence of biliary pseudolithiasis decreased from 55% to 29% when ceftriaxone was given in a 30-minute infusion; however, in a subsequent study they concluded that the duration of drug administration did not influence the frequency of biliary pseudolithiasis[7]. However, these clinical data have not been supported by any randomized, prospective trial.

Rate of consultation in our series was high. Cases without consultation received at least a phrase of" highly probable association of ceftriaxone therapy and gallstones" in the US report. In spite of some reports of symptomatic course possibly leading to surgical intervention[4,11], ceftriaxone–associated biliary pseudolithiasis however, is usually asymptomatic and resolves spontaneously. Cessation of drug therapy is unnecessary, and cases can be managed conservatively by observation[13]. In our study no patient needed surgery or discontinuation of the drug.

Conclusion

As ceftriaxone becomes more commonly prescribed, practitioners should be more aware of potential side effects especially if the adverse event can lead to medically inappropriate interventions. On the other hand, during routine abdominal US examination of a hospitalized child, if gallstones are detected incidentally (less likely with vague abdominal symptoms), recent ceftriaxone therapy must be questioned in the US report.

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