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Concomitant Ceftriaxone-induced Nephrolithiasis and Biliary Pseudolithiasis in a Small Toddler

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Abstract Ceftriaxone is commonly used in pediatric practice and has been associated to biliary pseudolithiasis, nephrolithiasis and bladder sludge. We report a case of a 5-month old male toddler previously treated with high ceftriaxone doses for interstitial pneumonia; after one week an improvement of respiratory symptoms was noticed but extreme agitation and excessive crying occurred. He eliminated small white crystals that were found in the diaper and were proven to be constituted from calcium carbonate; abdominal ultrasound showed also a hyperechoic image of 4 mm in the gallbladder. Laboratory data were within normal rangers except a slight increase of the urinary calcium and calcium/creatinine ratio. The patient didn't have any risk factor for ceftriaxone- induced lithiasis except high dosage of the antibiotic together with idiopathic hypercalciuria. Antibiotic interruption together with hydrochlorothiazide, adequate hydration and antispasmodics led to the remission of the symptoms and disappearance of the gallbladder image within 5 weeks. Ceftriaxone treatments should be routinely monitored by ultrasounds for the urinary and biliary system; appropriate dosage and administration with an adequate hydration are required.

Keywords: *ceftriaxone, children, nephrolithiasis, biliary pseudolithiasis*

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1. Introduction

Ceftriaxone, a third generation cephalosporin is largely used in pediatric hospitals due to its broad spectrum of activity. The general administration rate of ceftriaxone was reported as being 82% in US hospitals, 65% in Spain and 62% in Koreea and Africa. [1] In Romania the usage of ceftriaxone in hospitals reaches up to 57%. [2] Adverse effects have been described, comprising local reactions (phlebitis), gastrointestinal reactions (diarrhea), hematologic modifications (trombocitosis, leukopenia, haemolitic anemia) and rare events (allergic pneumonitis, bronchospasm, billiary sludge or pseudolithiasis and nephrolitiasis). [3] The frequncy of lithiasis and biliary sludge has been reported in population-based studies from USA as 1.9% and respectively 1.46%; these studies indicate an increase of the incidence and prevalence of this pathology, probably due to a possible underestimation in the previous years and to an extensive use of ultrasonography nowadays. [4] The predisposing factors for biliary lithiasis are age, gender, body weight, hormonal and metabolic factors together with drugs i.e. oral contraceptives and cefalosporines like ceftriaxone in high doses and prolonged administration. [3] The exact prevalence of gallstones associated with ceftriaxone in children is not very well known, some studies from Europe reporting 0.13% to 0.2% while in Japan lower percentages were found. [4,5] We report a case of a five-months-old toddler with nephrolitiasis and billiary sludge due to cefriaxone administration.

2. Material and Methods

Data was collected from clinical records and ultrasonography charts of the patient. Parents signed an informed consent that allows the usage of patient's data for research and teaching purposes. The references were selected after performing a literature review conducted in Medline using the keywords ceftriaxone combined with children, biliary pseudolithiasis, gallbladder lithiasis and nephrolithiasis.

3. Results

A five-months-old male toddler was admitted into our pediatric tertiary center with extreme agitation, excessive crying and mild respiratory symptoms. Before admission into our unit the child received intravenously ceftriaxone 100mg/kg/day for 7 days bid in a county hospital for interstitial pneumonia. Physical examination at admission: the patient was a well-developed, well-nourished male, W=6.8 kg, vital signs: temperature 98.4 F, pulse 141 bpm, respiratory rate 26/m, productive cough, blood pressure 86/57 mmHg; head was normocephalic and atraumatic, extraocular muscles were intact, pupils were equal, round,

and reactive to light and accommodation, narines appeared normal, mouth was well hydrated and without lesions, mucous membranes were moist, normal skin color, lungs crackles to auscultation; cardiac: regular rate and rhythm, mild systolic murmur; abdomen: soft, nontender, and nondistended, positive bowel sounds, no hepatosplenomegaly was noted; extremities: warm without edema or cyanosis; neurologic: no focal deficits. A few hours after admission his mother found small white crystals in the diaper that were sent to the laboratory and were proven to be constituted mainly of calcium carbonate (Figure 1).

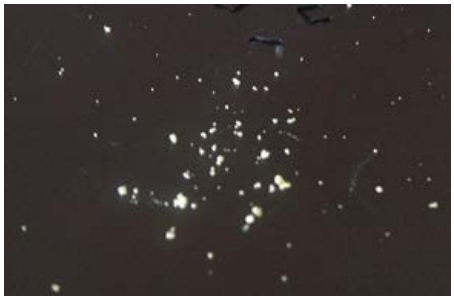

Figure 1. Small CaCo3 crystals

Other laboratory data included complete blood count, urea, creatinine, creatinine clearance, calcium (total and ionized), serum phosphorus, bilirubinemia, alkaline phosphatase, serum glucose that were within normal limits, slightly increased urinary calcium and increased calcium/creatinine ratio. (Table 1)

Table 1. Patient's laboratory data

Parameter	Patient's values	References range
HBG	120 g/L	112-165 g/L
WBC	$6x10^9$/L	3.5-12.0 x 10^9/L
PLT	$300x10^9$/L	150-400 x 10^9/L
Urea	4.1 mmol/L	2.9-8.2 mmol/L
Creatinine	67 µmol/L	50-110 µmol/L
ALT	49 U/L	5-35 U/L
AST	56 U/L	7-40 U/L
Creatinine clearance	89 mL/min	75-125mL/min
Calcium total ionized	 2.25mmol/L 1.11mmol/L	 2.18-2.58mmol/L 1.05-1.3mml/L
Phosphorus	0.97mmol/L	0.80-1.50mmol/L
Serum bilirubin Total Direct Indirect	 14 µmol/L 3 µmol/L 0.3µmol/L	 < 26µmol/L < 7 µmol/L <2 µmol/L
Alkaline phosphatase	86U/L	35-100U/L
Glucose	4.1mmol/L	3.3-5.8mmol/L
Urinary calcium	2.9 mg/kg 24 h	<2.7mg/kg 24h
calcium/creatinine ratio	4.3	<2.1mg/g

Ultrasound examination revealed the presence of sediment in the bladder and a hyperechoic image of 4 mm in the gallbladder. (Figure 2)

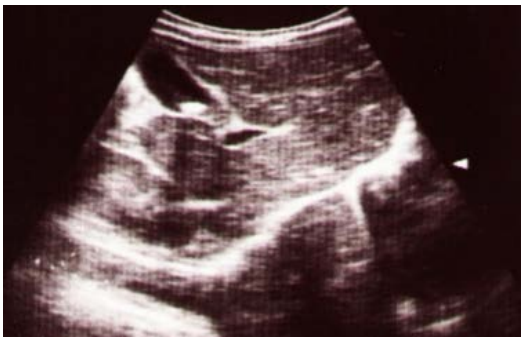

Figure 2. Hyperechoic image in the gallbladder

EKG, EEG were normal; chest X-Ray revealed discrete bilateral interstitial infiltrate. The echocardiography found permeable foramen ovale and left ventricular diastolic dysfunction. Treatment consists in suspending ceftriaxone administration, age appropriate diet without supplemental calcium intake, hydrochlorothiazide 6.25 mg/daily, adequate hydration and antispasmodics. The child was dismissed after 5 days of hospitalization in good general condition, disappearance of bladder sediment but persistence of the gallbladder image. Subsequent ultrasound evaluations showed disappearance of gallbladder image within 5 weeks from ceftriaxone interruption.

4. Discussion

Ceftriaxone, an antibiotic commonly used in pediatric practice has been associated to biliary pseudolithiasis, nephrolithiasis and bladder sludge. The kidneys eliminate approximately 33-67% of this agent, and the remainder is removed throught the biliary system. Formation of urine crystals that cling to renal tubular cells has been observed during ceftriaxone treatment, with the potential for causing acute renal failure, however, only a few studies have reported this condition. [6] Ceftriaxone is an anion; if the blood concentration is high these anions bind to calcium ions and form insoluble complexes that precipitate in the biliary system. This complication has been described as biliary pseudolithiasis or reversible cholelithiasis and appears in 25–45% of patients treated with ceftriaxone. [7] The same mechanism has been postulated for stones formation in the renal collecting system. [8,9] Risk factors that may contribute to ceftriaxone-induced nephrolithiasis are: a positive family history, urinary tract infection and obstruction, high doses of ceftriaxone (over 2g/day), rapid administration of the drug, dehydration together with the administration of nephrotoxic drugs and metabolic disorders such as hypercalciuria. Urinary calcium excretion is conditioned by complex interrelationships between intestinal calcium absorption, renal calcium reabsorption and bone metabolism. [10] Hypercalciuria occurs in about 5-10% of the population and is the most common identifiable cause of calcium kidney stone disease. Ceftriaxone at therapeutic urinary excretion levels could directly interact with free calcium at physiologic urinary concentration to generate ceftriaxone/Ca crystals. Ceftriaxone crystallisation is a dose and time-dependent reaction being influenced by drug concentration and incubation time. Therefore, a high-dose of ceftriaxone (which leads to an increased urinary drug level) and urinary stasis of any cause (which leads to retention of ceftriaxone crystals in the urinary tract, allowing crystal growth and aggregation) may aggravate ceftriaxone calculi formation. [11] In our case a negative familial history of kidney stones, a normal intake of vitamin D3, the absence of biochemical abnormalities (normal levels of serum calcium, phosphate and alkaline phosphatase) and the absence of other suggestive clinical features excluded the previously mentioned etiologies, except for drug toxicity and idiopathic hypercalciuria. Our patient received a dose of 100mg/kg/day bid of ceftriaxone for 7 days. Other authors found that ceftriaxone-induced nephrolithiasis occurred after a mean period of 8 to10 days at doses ranging from 50 to 100mg/kg/day. [12]

Pediatric reports include cases of neonates with biliary pseudolithiasis. [13] In our case young age (five months), idiopathic hypercalciuria contributed together with the administration of high-dose ceftriaxone to the mentioned complication (drug induced nephrolithiasis and biliary pseudolithiasis). The evolution of the child was favorable, with disappearance of the gallbladder image after 5 weeks of therapy interruption and without other complication. To our knowledge this is one of the youngest patients in literature with this pathology and the first report from Romania.

5. Conclusion

Ceftriaxone is a frequent choice in Romanian hospitals for empiric antimicrobial therapy because of its broad spectrum, long half-life, safety and tolerability; however, some relatively rare side effects as renal lithiasis and biliary pseudolithiasis may occur. In our opinion ceftriaxone treatements should be routinely monitored by ultrasounds for the urinary and biliary sistem; appropriate dosage and administration as well as an adequate hydration are required.

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