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Ceftriaxone-Induced Gallbladder Stones in Children

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Abstract

Gallbladder stones in children are one complication, most seen in such diseases as hemolytic disease, liver disease, and obesity. They can be a secondary complication of long duration used of antibiotics like ceftriaxone. However, Gallbladder stone and together with sludge themselves is unusual within the children population. We were observed in some instances by a particular sort of antibiotic that is being referred by Ceftriaxone. It is the third-generation cephalosporin with a wide broad-spectrum utilized in treating multiple complicated infected organisms. Here, in this study, we report three cases of children with age degrees from eleven months to seven years who have been treated with high doses and long duration of ceftriaxone for complicated systemic bacterial infection. The purpose of this study was to determine the dose and duration of ceftriaxone in children who developed gallbladder stones after treating complex bacteria with ceftriaxone and to evaluate the outcome of the treatment in these patients.

Index terms— ceftriaxone, gallbladder stone, child, complication.

1 I. Introduction

allbladder stone has been reported in both adults and children due to different complications of illness, mainly hemolytic disorder, procedure, and even with the long-term duration use of antibiotics which is being seen by ceftriaxone. It is also seen as less common in children compared to adults. Ceftriaxone is a third-generation of the cephalosporins class with a broad-spectrum antibacterial coverage and is used for the treatment of severe bacterial infections like osteomyelitis, gastrointestinal, and meningitis in the children's population [4,10]. It is far more extensively distributed in most body tissues and fluids and can penetrate bloodbrain barriers into the meninges [3,4,14]. Because of the prolonged plasma half-life, it can also be excreted by the urine, and 40% is secreted by the bile duct [3], and it can be administered once daily and every 12 hours in the case of complex infection in some children.Most medications have adverse drug reactions, including ceftriaxone that has been reported as a causative agent for pseudolithiasis either in the gall bladder or renal tract [4,5,14]. It is also known as biliary pseudolithiasis or reversible Choleolithiasis based on Ultrasound findings [10]. This name is given by radiological image because it is a transient condition, which resolves after discontinuation of the causative agent. In this study, we evaluated children with ceftriaxone-associated gall bladder stone discovered in an abdominal ultrasound examination. It includes three children with gallstones on Ultrasound of the abdomen after presentation with short duration severe abdomen pain and with recent concurrent long-duration use of intravenous ceftriaxone.

2 II. Case Description a) Case one

An eleven-month-old boy who had previously been well was brought to the Emergency Department with a diagnosis of meningoencephalitis and a history of fever, seizures, and skin rash. He later developed septic shock with a diagnosis of Disseminated intravascular coagulation (DIC) and acute kidney injury. Investigations showed high White blood cell (WBC of 23,10^9\l), high C-Reactive Protein (CRP of 153 mg\l), and initial Liver Function Test (LFT) within the normal range. Lumbar Puncture revealed: no organism in cerebrospinal fluid (CSF) in gram stain and microscopy, 4 cell/mm2 White Blood Cell, 3320 cell/mm2 Red Blood Cell, 2.73gL protein, and 2.9 mmol/l glucose.CSF culture was negative, but blood culture revealed sensitive streptococcus pneumonia. A

radiological study with an initial head-CT scan showed ischemic change then repeated after a few days showed acute right intraparenchymal bleeding in the right parietal region measuring 15 * 15 * 8 mm surrounded by a thin rim of edema. Magnetic resonance imaging (MRI) of the head later showed a dilated ventricular system. The diagnosis of streptococcus pneumonia Meningitis was made based on clinical, CSF results and radiological findings. Later in his course, a ventriculoperitoneal (VP) shunt was inserted by a neurosurgery team. Ceftriaxone therapy started and was planned initially to be for four weeks. The patient developed acute abdominal pain with irritability. A pediatric radiologist performed an abdominal ultrasound, which revealed a distended gall bladder with a clump of soft calculi, indicating that ceftriaxone should be discontinued and replaced with levofloxacin. A liver function test was done by the team after ten days of ceftriaxone which revealed ALT 20 IU\L and ALP 226 IU/L.

After two weeks of stopping ceftriaxone, the abdomen ultrasound repeated and showed a single mobile echogenic focus.. After switching to intravenous levofloxacin, the child's abdominal pain improved.

3 b) Case Two

A two-year-old boy is on prophylaxis for asthma. He was presented to the pediatric Emergency Department with a history of fever for two days. It was documented to be high-grade fever 39Co, which did not respond to antipyretics. He also had a history of vomiting and productive cough associated with lethargy and reduced activity for two days. He was sluggish, irritable, dehydrated, and had a large head, more than 97th centile for his age. He also had neck stiffness. The investigations revealed leucocytosis of 28 109l, primarily neutrophils with 24 109l in the complete blood count (CBC), and a high C reactive protein of 171 mgL. Lumbar puncture revealed turbid cerebellar spinal fluid CSF with high white blood cell WBC 453UL and low glucose. Cerebrospinal fluid (CSF) culture revealed streptococcus pneumonia. The respiratory viral panel was positive for parainfluenza 3. The first radiology image was a Non-contrast CT Scan of the head which showed mild brain edema. An MRI of the head reveals right frontal-parietal meningitis with bilateral subdural effusion but no abscess. The diagnosis of complicated streptococcus pneumonia meningitis with bilateral subdural effusion was given to this infant. He was treated with a long course of intravenous Ceftriaxone. After week four of treatment, it noted that the child was complaining of abdominal pain. The initial ultrasound abdomen was normal, but as the child continued to complain of abdominal pain, it was repeated, and it revealed gallbladder stones, so it was decided to switch from ceftriaxone to levofloxacin for another 3-6 weeks. As noted, it was associated with a deranged liver function test (LFT) with high alkaline phosphate (ALP) of 265 IU\L, GGT=42IU/L and alanine transaminase (ALT) of 91 IU\L which is initially normal LFT. Follow up; Abdomen Ultrasound showed improvement after changing ceftriaxone to intravenous Levofloxcillion. Liver Enzyme also improved.

4 c) Case Three

A seven-year-old girl who had previously been healthy and had no previous medical illnesses. She presented to an orthopedic clinic with a brief history of left knee pain and swelling and was diagnosed with an impression of left distal femur and proximal tibia osteomyelitis. She was treated for three weeks with intravenous ceftriaxone based on blood laboratory findings and radiological findings of MRI of femurs and tibias that revealed bone marrow edema in the lateral femoral condyle and bordies abscess in the metaphysis of the left distal femur and proximal tibia, an impression of acute on subacute changes of osteomyelitis in the lateral femoral condyle. She was doing well until three weeks after beginning ceftriaxone, when she presented to the ER complaining of a day of severe abdominal pain and vomiting. Her gallbladder was found to have multiple tiny calculi on abdominal ultrasound. Laboratory investigations done at the time of presentation showed normal total blood count with White blood cell 11 * 109/l, Haemoglobin (HB) 11.7 g/dl, Normal Liver function test, and Normal amylase level. She referred to pediatric gastroenterology and pediatric infectious diseases for further management and her antibiotic was changed to oral clindamycin. She continued on clindamycin, and her symptoms improved.

5 III. Discussion and Literature Review

There are limited studies that have looked into ceftriaxone-induced gallstones in the children's population. Within most literature reviews, gallbladder stone occurs because of organic cause or illness, but few numbers reported predisposing factors with the specific type of antibiotics use that presented as symptomatic illness. Ceftriaxone is a broad-spectrum antimicrobial agent. It is one of the third-generation cephalosporin. It has a broad-spectrum effect against most bacterial infections, mainly causing meningitis, gastrointestinal, and osteomyelitis. As we all know that supported different literature reviews, the exact pathology of it was unclear [14,15]. Some studies explained this as a result of genetic/genome variation on the UGT1A1 gene, which encodes the enzyme UDPglucuronosyltransferase (UDP).This enzyme acts on glucuronidation and formation of bile salts that transform small lipophilic molecules, (i.e., steroids, bilirubin, and drugs) into water-soluble (Fretzayas et al., 2011) [14,15].

In our study, we reported three cases of children with an age ranging from eleven months to seven years treated in tertiary hospital for severe bacterial infection. One of the children, a seven-year-old female, was referred from an orthopedic clinic to pediatric infectious diseases services for further evaluation and management of her acute osteomyelitis of the left distal femur and proximal tibia.children,The remaining two cases were treated with a high

dose of ceftriaxone 80-100mg/kg/twice daily dose for complicated meningitis. The three cases presented with nausea, vomiting, abdominal pain, and irritability during the third to fourth week of ceftriaxone administration. They were admitted and evaluated by different teams (General pediatric, pediatric infectious disease, pediatric surgeon, and gastroenterology team). All basic blood investigations were done, including full blood count and liver enzymes at time of admission; abdomen US was also done. We found one case which was treated with ceftriaxone for meningitis had a deranged liver function (high aminotransferase ALT= 91/IU/L and high GGT=42IU/L). The other two children had a normal range of laboratory findings with blood count and liver enzymes). Abdomen Ultrasound, for two children, showed a distended gallbladder with multiple tiny calculi/clumps or soft calculi, which was done at three weeks of intravenous ceftriaxone. The abdomen US of the third child showed that the GB is filled with multiple small calculi, average=5mm, nobiliary dilation. The pediatric surgery team was also involved, but none of the patients required any surgical intervention.

After the abdomen US findings, ceftriaxone was discontinued for all cases. In the two patients with meningitis, ceftriaxone changed to Levofloxacin, and therefore the other case of osteomyelitis was changed to clindamycin. All children didn't require other medications. All investigations normalized after discontinuing ceftriaxone. Abdomen ultrasound repeated and showed improvement in gall stones together with normalized liver enzymes. Our review found that almost all of the biliary pseudolithiasis were self-resolving after cessation of ceftriaxone. Most Literature (Pacifici, 2019) reported the common adverse reaction of ceftriaxone is gastrointestinal symptoms (nausea, vomiting with most predominant abdomen pain). We discovered that all three patients had the same incidental finding of pseudolithiasis in the abdomen Ultrasound **??**4.15].The same findings were reported in an Iranian study; different predisposing factors cause Choleolithiasis in children, which may be an organic illness such as Haemolytic disease, Hepatobiliary disease, obesity, metabolic syndrome, and secondary to ceftriaxone use that is reported in the majority of cases in the children group as represented with a high 27.3% during a study compared to hematological disorder.Gokce et al. [5] reported that gallstones were resolved by using Ursodeoxycholic acid (UDCA) treatment in 29.4% of symptomatic children. Hypercalcemia, kidney failure, a high dose of ceftriaxone (> 200mg/kg/day), and gallbladder stasis are all risk factors that determine whether or not ceftriaxone causes pseudolithiasis [10]. In our three cases, only one risk factor, which was noticed in our case, is a high dose of ceftriaxone along with a prolonged duration of more than three weeks to four months. Palanduz, et al. [11] reported in their study that 118 children were admitted to hospital for severe infection and received intravenous ceftriaxone at a dose of 100 mg/kg /day for three weeks. On days one, seven, and fourteen, an ultrasound abdomen was performed at regular intervals to monitor the adverse effects of ceftriaxone. After 14 days of intravenous ceftriaxone, twenty children (17%), all asymptomatic, had abnormal ultrasound findings: 8 had gallbladder sludge, and 12 had pseudolithiasis. By discontinuing ceftriaxone, the abnormalities spontaneously resolved within two weeks after stopping ceftriaxone. However, Choleolithiasis may have very different causative reasons in childhood. It is frequently detected by using abdominal ultrasound in symptomatic children. Most symptomatic cases are resolved after cessation of ceftriaxone use. Ursodeoxycholic acid is now commonly used as an alternative to surgery to treat cholelithiasis, particularly in children with biliary sludge. They concluded that Ceftriaxone-associated biliary pseudolithiasis is usually asymptomatic and was rapidly reversible after cessation of therapy. It has to be monitored in children who receive high dose and long term treatment by blood investigations that include fullblood count, liver function test, renal function test, and an ultrasound of the abdomen with different intervals.

6 IV. Conclusion

Prolonged use (more than two weeks) of intravenous Ceftriaxone, a third-generation cephalosporin with broad antibacterial activity against a variety of bacterial infections, is a known risk factor for gallbladder stone in both adults and children.

The correct diagnosis of ceftriaxone-induced gallstone was usually delayed as most of the patients are asymptomatic and most cases were detected only by incidental radiological findings. These findings promote proper clinical assessment with radiological findings in such cases where risk factors are present to prevent complications. The complication resolved spontaneously after discontinuation of the causative antibiotics.

Figure 1:

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Figure 2: Figure (2)

Figure 3:

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Case No.	Age	sex	Ceftriaxone therapy Dose (mg/kg)	Duration(days)	Symptom	Biliary complication Type
1	11months	M	100 mg/kg/days	21 days	Abdomen pain	After 3 weeks from started ceftriaxone
2	2years	M	100 mg/kg/days	120 days	Abdomen pain & irritable	After 4months from started ceftriaxone
3	7years	F	100 mg/kg/days	26 days	Abdomen pain vomiting	After 4 weeks from started ceftriaxone

Figure 4: Table 1 :

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