Ceftriaxone-induced immune hemolytic anemia in a case with large vestibular aqueduct syndrome after cochlear implant

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To the Editor: Drug-induced immune hemolytic anemia (DIIHA) is a rare but severe condition. Ceftriaxone, a third-generation cephalosporin with a wide antibacterial spectrum and effective antibacterial action, is one of the most common drugs causing DIIHA.¹ Ceftriaxone-induced immune hemolytic anemia (CIIHA) is a potentially fatal complication.¹² Most of the patients were children. The reported fatality rate of CIIHA was as high as 40%.¹³ Acute renal failure and cardiovascular decompensation are the most lethal complications in pediatric patients with CIIHA.¹² Early diagnosis is difficult but extremely important to the outcome. Clinical treatment consists of immediate drug discontinuation and supportive care, including blood transfusion wherever appropriate.

Ceftriaxone has been widely used in cochlear implant surgery because of the broad spectrum and the ability to overcome the blood–brain barrier (BBB). In many centers, ceftriaxone is the first choice for cochlear implant patients as antibiotic prophylaxis. Up to date, no cochlear implant patients with CIIHA have been reported. We experienced a CIIHA of a child with congenital hearing loss. The patient successfully recovered with immediate cessation of ceftriaxone therapy and supportive treatment. We report this case to share a clinical experience in this serious but rare adverse reaction.

A 7-year-old boy diagnosed with profound bilateral sensorineural hearing loss (SNHL) and large vestibular aqueduct syndrome (LVAS) was admitted to Peking University Third Hospital. His parents found that he had poor hearing and undeveloped speech when he was 3 years old. He was sent to a local hospital. Audiological tests revealed severe bilateral SNHL. CT scan and MRI of the ear indicated bilateral enlarged vestibular aqueducts. While wearing hearing aids, he could react to loud sounds, but was not able to perform intelligible speech. Finally, he was admitted to our hospital for cochlear implant surgery. He was previously healthy according to his father and grandmother who were with him in the hospital. They also confirmed no history of drug allergy, including local reactions, systemic reactions, and positive history of skin test. In the family history, elder sister of the patient’s grandmother also suffered from congenital hearing loss. The preoperative diagnosis was profound bilateral SNHL caused by LVAS.

The child underwent cochlear implantation of the left ear under general anesthesia, and ceftriaxone was given as routine prophylactic antibacterial therapy. He received 1 g of intravenous ceftriaxone intra-operatively and subsequently daily post-operation. The operation was performed smoothly without local complications. Two days after surgery, the patient felt itching of urethral orifice. However, he did not complain until 1 day later when pain and swelling appeared after scratching. He was diagnosed with balanitis upon urology consultation and given local disinfection treatment whereas ceftriaxone therapy was continued. Five days after surgery, the patient had a sudden abdominal and back pain, with high fever up to 38.2°C and chills. Physical examination found that the patient’s abdomen was soft, but the bladder was full and the penis was more red and swollen than before. Routine blood test showed that the leukocyte was 17.55 × 10⁹/L, the percentage of neutrophils was 87.7%, and the hemoglobin was 103 g/L. After taking Merrill, the patient urinated 400 mL without hematuria while the fever and abdominal pain was relieved. During intravenous drip of ceftriaxone on the next day which was the seventh day of his antibiotic therapy, the child once again suffered from sudden abdominal pain, with high fever up to 38.2°C and chills. Physical examination revealed apparent pale and tortured face, and a soft abdomen with epigastric tenderness without rebound tenderness. The heart rate was 155 per
minute and BP was 150/90 mm Hg. Routine blood test indicated that the leukocyte was $19.00 \times 10^9/L$, the percentage of neutrophils was 78.4%, and the hemoglobin was 79 g/L, which used to be 126 g/L before operation. There was no clinical source of acute bleeding either around the surgery area or of any other organs according to the evaluations including ultrasound and CT scan. The laboratory tests revealed a reticulocyte of 2.08%, a total bilirubin level of 60.0 µmol/L, and a lactate dehydrogenase level of 723 mmol/L. The direct antibody test was strongly positive (4+), indicating immune hemolytic anemia. Ceftriaxone therapy was immediately discontinued whereas intravenous immunoglobulin was used after the episode of hemolysis and the hemoglobinuria ceased then. We further asked about the patient’s history when his mother first arrived to the hospital the next day. According to the history provided, the child had a short period of tea-colored urine after using cephalosporin antibiotics. Finally, the diagnosis was confirmed as CIIHA. The antibiotic therapy was then changed to ertapenem and was discontinued 4 days later since the blood and secretion cultures were negative and the urethral orifice recovered. The nadir hemoglobin was 71 g/L on day 2 of ceftriaxone cessation (day 9 of initiate antibiotic therapy) and gradually increased since then (Figure 1). The patient was discharged on day 7 of ceftriaxone cessation. The post-aucular surgical incision and the area of cochlear implant recovered well after operation. However, the effusion of external auditory canal (EAC) was detected on the 10th day after surgery without local pain, redness, or swelling. Ear examination revealed an intact but cloudy tympanic membrane with exudation on the posterior wall of the EAC. This symptom disappeared and tympanic membrane returned to normal on the 17th day after surgery.

DIIHA is a rare condition. The incidence was estimated as 1 to 2 per million individuals per year. Ceftriaxone was found to be one of the most common drugs causing DIIHA. Ceftriaxone has been widely used in cochlear implant surgery because of the broad antibacterial spectrum and the ability to overcome the BBB. In many centers, it is a standard protocol for cochlear implant patients to receive ceftriaxone as antibiotic prophylaxis. CIIHA is a rare but potentially fatal complication. Most of the patients suffering from it were children and 36% of all patients had a fatal hemolysis. A review of reported cases from 1995 to 2016 found that children under 10 years account for 64.7% of all 68 cases and the mortality rate was 15.9%. Most of the pediatric patients had previous exposure to ceftriaxone. Reported time window from initiation of ceftriaxone administration to the development of symptoms ranges from less than 1 hour to 1 or 2 weeks. Treatment of CIIHA consists of prompt discontinuation of ceftriaxone therapy and supportive care, including blood transfusion wherever appropriate.

DIIHA was difficult to identify in our case since the symptoms occurred several days after the first dose of medication. In the beginning, there was some confusion on the etiology of immune hemolytic anemia in this patient. The initial symptom was an unexplained urogenital infection during ceftriaxone therapy. Infectious hemolysis was to be considered first because the clinical manifestations and laboratory tests indicated prominent infection. In that way, intravenous ceftriaxone should be continued and even increased in quantity. However, on the other hand, all intervention factors should be taken into account, including surgical stress, anesthesia, and drug use. The onset of hemolytic reaction was 5 days after surgery, ruling out the first 2 factors. Although CIIHA is rare, it should be highly suspected since both hemolytic reaction episodes occurred during intravenous drip of ceftriaxone. Therefore, we stopped ceftriaxone therapy on time, which is an extremely important treatment transition landmark. Adding history of previous adverse reaction to cephalosporin and the subsequent treatment outcome further supported the diagnosis of CIIHA. The definitive diagnosis was based on the clinical presentation and laboratory results.
on medical history, clinical presentation, laboratory evaluation, and treatment outcomes. Correct conclusion on the cause of hemolysis is crucial in this case. Misdiagnosis might probably lead to rapid progression of the severe reaction. Acute renal failure is the most common and fatal complication of CIIHA and has been reported in at least 40% of pediatric patients.[5] In this case, we paid close attention to the renal function and urine volume both of which presented no problem all along. There had been transient effusion of the EAC from the 10th day after cochlear implant surgery. We considered it as a reactive middle ear effusion caused by hemolytic anemia and hypoproteinemia since it disappeared quickly with the recovery of hemolysis. Fortunately, CIIHA caused neither renal failure nor severe complications involving the cochlear implant in this patient.

In summary, CIIHA is a rare but potentially fatal condition. Timely diagnosis and immediate drug discontinuation were the crucial factors in avoiding fatal complications and improving the outcome.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form, patient/patient’s guardians have given their consent for their images and other clinical information to be reported in the journal. The patient/patient’s guardians understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

**Acknowledgements**

None.

**Funding**

None.

**Conflicts of interest**

None.

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How to cite this article: Wang Y, Pan T, Ma FR, Wang JJ, Zhang K, Pan WW, Zhang JH, Yi ZM, Ying YQ. Ceftriaxone-induced immune hemolytic anemia in a case with large vestibular aqueduct syndrome after cochlear implant. Chin Med J 2019;132:100–102. doi: 10.1097/CM9.0000000000000017