Research Article

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ARCHIVES OF MEDICINE
ISSN 1989-5216

2016
Vol.8 No.6:12

DOI: 10.21767/1989-5216.1000181

Cephalosporin-induced Neurological Toxicity in Elderly Patients with Preserved Renal Function

Gideon Charach*, Ori Argov, Hilla Nochomovich, Karyn Geiger, Lior Charach, Ronen Steinvil, Ori Rogowski and Itamar Grosskopf

Department of Internal Medicine "C", Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel

***Corresponding author:** Gideon Charach, Department of Internal Medicine "C", Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel, Tel: +97236973766; Fax: +972 3 6973929; E-mail: drcharach@012.net.il

Received date: December 06, 2016; **Accepted date:** December 12, 2016; **Published date:** December 19, 2016

Citation: Charach G, Argov O, Nochomovich H, Geiger K, Charach L, et al. Cephalosporin-induced Neurological Toxicity in Elderly Patients with Preserved Renal Function. Arch Med. 2016, 8:6

Abstract

Cephalosporins are widely used in patients for the treatment of serious gram positive and gram-negative infections. Cephalosporins can induce some serious side effects, including neurotoxicity, mood disorder, hallucinations; however, non-convulsive status epilepticus has rarely been reported. We report three cases of acute reversible neurotoxicity associated with cephalosporins. Three patients without chronic kidney disease developed altered consciousness, hallucinations during ceftriaxone treatment for urinary tract infection and pneumonia and non-convulsive status epilepticus (NCSE) during cefazoline treatment for cellulitis-three days after initiation of the treatment. The electroencephalogram demonstrated continuous bursts of generalized, high-voltage, 1 Hz to 2 Hz sharp wave activity. Neurologic symptoms disappeared two days following withdrawal of ceftriaxone or cefazolin. The possibility of cephalosporin-induced neurotoxicity should be considered in patients developing neurological signs especially cognitive and seizures appearance during cephalosporin use and the discontinuation of the drug could lead to rapid complete neurological improvement.

Keywords: Ceftriaxone; Cephalosporins; Chronic Kidney Disease; Seizures; Neurotoxicity

Introduction

Neurologic side effects of cephalosporin are infrequent; however, there have been reports of associated encephalopathy, cognitive disorders hallucinations, myoclonus, and seizures [1-5]. Encephalopathy is a rare side effect of third and fourth-generation cephalosporins, however it is especially rare with ceftriaxone [2-7]. Neurotoxicity occurs when exposure to natural or artificial neurotoxins alters the normal activity of the nervous system. It has been documented in chemotherapy, radiotherapy, drug therapies, certain drug abuse, and organ transplants, as well as exposure to heavy metals, certain foods and food additive [1], pesticides [2,3] industrial and/or cleaning solvents, cosmetics, and some naturally occurring substance [2-5]. Symptoms may include limb weakness or numbness, loss of memory, vision, and/or intellect, uncontrollable obsessive and/or compulsive behaviors, delusions, headache, cognitive and behavioral problems and sexual dysfunction. Individuals with certain disorders, such as neurological disease, dementia, renal failure, may be especially vulnerable to such side effects of neurotoxins [3-11].

Neurotoxicity has been reported with first-generation (e.g. cefazolin), second generation (e.g. cefuroxime), third generation (e.g. ceftazidime) and fourth generation (e.g. cefepime) cephalosporins, and it can range from encephalopathy to non-convulsive status epilepticus [5,7]. Those sequelae are, however, rare with the use of ceftriaxone. Renal impairment imposes an increased risk of neurotoxicity in association with the use of cephalosporins, but it has also been reported in patients with normal creatinine clearance [5-14]. In addition, a history of neurological disease has been suggested as a source of decreased threshold of nervous system toxicity with the use of third- and fourth-generation cephalosporins [5-9]. Reduced creatinine clearance, impaired renal function and excess dosage of medication have been described as independent risk factors for neurotoxic effects, [5-8] and symptoms may appear immediately after exposure or they can be delayed. The typical latency period for the appearance of encephalopathy induced by cephalosporin use is 1 to 10 days after the initiation of medication, and resolution in 2 to 7 days following its discontinuation [7].

Ceftriaxone is a third-generation cephalosporin commonly used in the treatment of serious gram-negative infections due to its broad antimicrobial spectrum, long half-life, and easy penetration into the cerebrospinal fluid [9,10]. Unlike other cephalosporins, dose adjustment is not required even in the presence of renal insufficiency, making its use convenient for patients with chronic renal failure (CRF) [11]. We present three cases of cephalosporin-induced neurotoxicity in patients with normal renal function, and review the literature on this rare potentially transient adverse event. The patients gave consent anonymously publish their cases.

Case Reports

Case 1

A 96-year-old cognitively intact male patient was admitted to a large community teaching hospital because of fever (38°C), urgency, frequency and burning during urination. Urinalysis showed abundant leukocytes in the field under the microscope, and blood tests revealed a total leukocyte count of 14000 per ml with a neutrophilia left shift of 83%, BUN 28, and creatinine 0.9. Treatment by ceftriaxone (1 g intravenously once daily) was started. On the fourth day of treatment, the fever resolved, however, signs of confusion, agitation and tremor appeared. There were no significant changes in the repeat blood test results, blood and urine cultures were negative. The leucocyte count decreased to 11000/ml, BUN 21 and creatinine 0.8. The sodium, glucose, calcium, and liver enzymes levels were within normal ranges. The ceftriaxone treatment was discontinued and intravenous diazepam 10 mg once daily was administered for two days, after which all neurological signs including confusion disappeared. The antibiotic treatment was not resumed.

Case 2

A 78-year-old male was admitted to a large community teaching hospital because of fever (39°C), rigor and pain in the lower part of the left tibia. His past history consisted of coronary artery disease, heart failure and lower limb edema. Examination of the left leg revealed signs of erythema, edema and tenderness in the distal anterior part of the tibia. Blood tests showed a leukocyte count of 17000 per ml with a shift to the left, BUN 30, and creatinine 1.0. Treatment consisting of cefazolin 1 g three times daily was started. The patient developed signs of confusion on the second day of the treatment, and experienced an epileptic attack of general tonic clonic seizures after five days of treatment. Electroencephalographic (EEG) findings showed diffuse slow-wave delta activity. The cefazolin was discontinued and the patient was administered intravenously phenytoin 300 mg daily. His brain computerized tomographic (CT) scan was normal. An EEG was performed five days later and showed no epileptic pattern. He was released symptom-free from hospital and no recurrent neurological signs were apparent three months later.

Case 3

An 83-year-old female patient was admitted to a large community teaching hospital due to productive cough and fever (38.8°C). Her past history included a smoking habit of ~15 cigarettes per day for 55 years. The laboratory analysis showed a leukocyte count of 13000/ml and C-reactive protein 110 (normal ≤ 5). A chest X-ray revealed right basal pneumonia without pleural effusion. Blood, sputum and urine cultures were taken, and treatment with IV ceftriaxone 1 g/day was initiated. Three days later, the patient developed a confusional state with delirium and both auditory and visual hallucinations. The results of the liver and kidney function tests (including glucose, sodium, and calcium levels) were all within normal range. The brain CT was normal. Ceftriaxone was replaced by oral haloperidol 5 mg for two days. All signs of neurotoxicity disappeared two days later.

Discussion

Neurotoxicity has been reported with both third- and fourth-generation cephalosporins [7-9,11]. Epileptogenic activity of β-lactam antibiotics was first reported in 1945, when seizures were observed in experimental animals following intraventricular injection of penicillin,12 particularly in the settings of renal failure and excessive dosage [13,14]. The exact mechanism is not fully understood, but it has been proposed to be mediated by competitive antagonism of brain γ-aminobutyric acid (GABA), which is the principal inhibitory neurotransmitter in the brain [12]. Inhibition of the GABA action could lead to a low neuronal threshold and subsequent excitation. Other authors [13], have proposed that cephalosporin might induce the release of cytokines, including tumor necrosis factor-α, which could cause direct cerebral toxicity.

Cephalosporin-induced neurotoxicity may manifest itself in a variety of clinical presentations, such as encephalopathy or mental status changes, myoclonus, asterixis, and seizures [5,6,11]. The period of latency of neurotoxicity, i.e., the period between the start of cephalosporin treatment and the appearance of neurologic manifestations, varies between one and ten days, and the neurologic symptoms typically resolve within two to seven days after discontinuation of the drug [5-15]. In our three reported patients, the neurological signs and symptoms first appeared on the third and fourth day into treatment, and they were similar to those described in earlier reports [5,6,11]. An increased cerebral penetration of the drug has also been reported [5,6,11-15].

Different EEG patterns have been described in association with cephalosporin neurotoxicity. Those EEG findings included diffuse slow-wave delta activity and semi-periodic triphasic sharp wave activity [5], similar to our second reported patient in whom the temporal relationship between the start of cephalosporin therapy and the manifestation of NCSE as well as the withdrawal of ceftriaxone and the disappearance of the symptoms strongly indicated that cefazolin and ceftriaxone were the causative agents of the neurotoxicity in a patient with normal renal function. These EEG abnormalities may serve as evidence in support of the impact of cephalosporin on the CNS. Given that the majority of patients receiving cephalosporin are elderly and have co-morbidities associated with mental alteration, an EEG can support the diagnosis of antibiotics-associated.

Careful monitoring for the prevention of cephalosporin-induced neurotoxicity in high-risk patients is very important. It is generally not common practice to measure the cephalosporin levels in the blood. Keeping in mind that cephalosporin-including ceftriaxone-may cause neurological toxicity, such careful monitoring of medication dosages and serum levels may be especially relevant for elderly patients, even those without kidney disease [7]. All the neurotoxic symptoms resolved completely after discontinuation of the drug in all three of our patients. They received anticonvulsants, e.g. phenytoin,

neuroleptics, e.g. haloperidol, and oxazepam and their symptoms improved two days after cephalosporins treatment was withdrawn [11]. Moreover, we stopped using the anticonvulsants because of the rapid (<2 days) clinical improvement after discontinuation of cephalosporins. Data are still lacking as to whether patients with cephalosporin-induced NCSE require antiepileptic drug therapy or if the cessation of drugs alone results in improvement [16]. Since neurotoxicity related to cephalosporin is reversible, it is unlikely that patients would need long-term anticonvulsant therapy.

In ceftriaxone which is not affected by renal failure, its pharmacokinetic characteristics might be related to its neurotoxicity [5]. Only seven cases of ceftriaxone-induced neurotoxicity have been reported to date [5]. Unlike our three reported patients, all of those patients had renal impairment and four of them were on hemodialysis. Finally, overdose (i.e., no dose adjustment is needed) did not seem to play a role in ceftriaxone-associated neurotoxicity.

Conclusions

Neurotoxicity is a potentially fatal but reversible complication of cephalosporin therapy, even among patients who are free of kidney disease. Awareness and recognition of the neurotoxic manifestations of cephalosporins, especially in elderly patients, are essential for the diagnosis and timely treatment of neurologic squeal. Further studies are needed to determine the most appropriate algorithms for diagnosis and treatment paradigms for patients who develop status epilepticus as a result of cephalosporins.

Acknowledgment

Esther Eshkol is thanked for editorial assistance.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' contributions

All authors contributed to the treatment of the patient and in writing and final approval of the manuscript. All the authors work in a municipal university-affiliated hospital.

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