Cephalosporins - A Friend or Foe? An Uncommon Cause for Encephalopathy: A Case Report

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Abstract

Background: Metabolic Encephalopathy can occur due to various causes. These causes include endocrine, toxin induced, nutritional disorders, infectious diseases and many more. One extremely under reported cause is Neurotoxicity due to antibiotics.

Case Presentation: Here we present a case of a 48-year-old woman, with known Systemic Hypertension and Chronic Kidney Disease. She developed fever which was treated with a fourth-generation cephalosporin following which she showed signs of altered sensorium. Various investigations were done which lead towards the diagnosis of Cephalosporin Induced Encephalopathy (CIE).

Conclusion: Our Case Report highlights the risk factors for developing CIE and the correct investigations to be done for any case of Encephalopathy. Even though this is not a common diagnosis, proper surveillance should be undertaken for any patient with risk factors who are treated with Cephalosporins.

Keywords: Cefepime; Cephalosporin induced Encephalopathy; Chronic Kidney Disease; Reversible Encephalopathy.

Introduction

Encephalopathy is a known adverse effect of several drugs. However, antibiotics, in particular cephalosporins being a cause is extremely under reported. Here, we discuss a case of an adult woman with altered sensorium which developed following the administration of cefepime, a commonly used cephalosporin.

Case report

A 48-year-old woman, with history of systemic hypertension for 21 years and Chronic Kidney Disease stage 5 for three years on regular dialysis presented to a local hospital due to decreased responsiveness and left upper limb focal seizures. She has had one previous episode of hypertensive encephalopathy. On arrival at the hospital, she underwent a session of hemodialysis along with blood pressure control due to suspicion of hypertensive encephalopathy, following which she showed an improvement. However, she developed fever following the dialysis. Under the suspicion of meningitis, she was started on Cefepime-Tazobactam and received 4 doses. The dose could not be confirmed as it was at a different hospital. She continued to show a further deterioration in her mental state and was referred for further management to our tertiary care referral centre.

On arrival, the patient was unresponsive and her Glasgow Coma Scale (GCS) was 3/15 (E1V1M1), gasping for breath and pupils reacting to light. Her blood pressure was 210/100mmHg with a Heart Rate of 100 bpm. Her airway was immediately secured. She was administered antihypertensives, antiepileptics and was admitted to the ICU. Cefepime was discontinued and she was empirically treated with Piperacillin and Tazobactam.

Blood investigations showed leucopenia with an elevated creatinine of 4.7 mg/dl with not so high urea of 66mg/dl. Hepatic encephalopathy was excluded as liver function tests and ammonia were normal. A CT Brain plain was done which showed a chronic infarct in the right thalamus with no evidence of acute infarct or hemorrhage. MRI Brain plain shows confluent T2/FLAIR hyperintensities in bilateral periventricular, deep white matter with suspicion of toxic/metabolic encephalopathy, but no features of PRES (Posterior Reversible Encephalopathy Syndrome seen in hypertensive encephalopathy). A Lumbar Puncture was done and found to be normal (Cell count: 1 cell/cumm, CSF glucose and protein within normal limits, culture had no growth), both blood and urine cultures had no growth as well which ruled out infective cause. Her blood pressure was under control. Having excluded the common causes of encephalopathy, EEG was taken to see for non-convulsive status epilepticus, but EEG showed the classic triphasic waves with diffuse slowing suggestive of metabolic encephalopathy and no epileptiform activity (Fig 1). As both uremic (Urea: 66mg/dl) and hepatic encephalopathy (Ammonia: 34 microgram/dl) was already excluded, this pointed towards antibiotic induced encephalopathy, cefepime in our case.

On arrival to the probable diagnosis of Cephalosporin Induced Encephalopathy (CIE), it was decided to dialyze her

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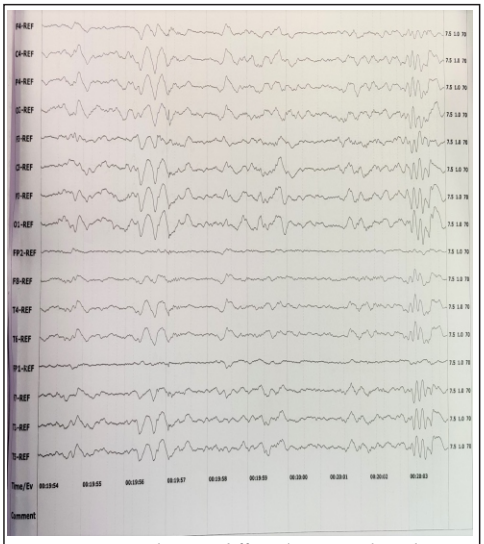

Figure 1: EEG showing diffuse slowing with triphasic waves.

aggressively to remove the drug and wait for improvement in consciousness. She underwent 4 cycles of hemodialysis during her first week of admission during which she had developed spontaneous eye opening. She slowly started obeying simple commands but with persisting muscle weakness. Tracheostomy was done by the second week. She was eventually weaned off the ventilator and shifted out of ICU. Her renal functions were continuously monitored and she underwent intermittent maintenance hemodialysis. She showed a gradual improvement in the next few weeks and was decannulated almost 20 days later. Her blood pressure was brought under control. Repeat EEG done 2 weeks later was normal, devoid of triphasic waves. She attained near normal mental status and was mobile, following which, she was discharged.

Discussion

Metabolic encephalopathy is a term coined by Kinnier Wilson as a clinical state of global cerebral dysfunction induced by systemic stress. It can present in several forms anywhere from mild dysfunction to coma [1]. There are numerous causes of metabolic encephalopathy like organ failure, electrolyte abnormalities, Endocrine disorders, nutritional disorders, infectious diseases, toxins, systemic illness and withdrawal states [2]. Drugs are also a common cause of reversible encephalopathy. However, antibiotic induced encephalopathy is under diagnosed [3] particularly due to third and fourth generation cephalosporins [4]. Other antibiotics known to cause similar encephalopathy include Penicillin G procaine, Penicillin, Isoniazid, Ciprofloxacin, Ofloxacin, Clarithromycin, Metronidazole and Trimethoprim-Sulfamethoxazole [3]. As of 2016, there were only 69 reported cases of cephalosporin induced encephalopathy out of which 33 were cefepime induced [3].

Generally, if a patient develops features of encephalopathy, first a complete history must be checked to rule out any toxin contact. Serum electrolytes, renal function tests, liver function tests and appropriate cultures should be done secondly. Following this, the patient should undergo imaging with either CT or MRI and finally an EEG. If required, a lumbar puncture may be done [3]. In our patient, all these investigations were done and they pointed towards a metabolic encephalopathy. As the patient had taken four doses of cephalosporins, it was ruled in as the cause.

CIE has been noted to occur more in patients with a preexisting CNS abnormalities[5]. Renal impairment, as seen in our patient also, predisposes to encephalopathy [5]. Cephalosporins are excreted renally, and thus they get accumulated in patients with renal impairment. The usual dose of Cefepime is 2gm IV q8h. Patients with renal dysfunction require a corrected dose: CrCl >60 : 2gm q8-12h, CrCl 30-60 : 2gm q12h, CrCl 11-29 : 2gm q24h, CrCl <11 : 1gm q24h and in Hemodialysis : 1gm q24 hrs (with extra 1gm AD). Despite dose adjustment, there have been cases of patients developing encephalopathy. It has also been seen in patients with normal renal functioning [6].

Antibiotic associated encephalopathy is usually classified into three and the one caused by cephalosporins belongs to type 1 [3]. The mechanism of CIE is the same regardless of the generation of the drug. Cephalosporins reduce the release of Gamma Amino Butyric Acid (GABA) and also act as a competitive antagonist to the same. However, the exact mechanism is not known [4,6]. The patient may present with myoclonus, seizure, epilepsy or altered consciousness usually within 10 days of starting treatment with the causative drug [7]. Although this pathology may have various presentations, it is not very common to present with severe neurological suppression as seen in our patient.

Diagnosis is usually one of exclusion. A characteristic finding is the presence of Triphasic waves with High Negative Component (Tri-HNC) in EEG [7]. Other common causes of triphasic waves in EEG include hepatic and uremic encephalopathy. Hence these must be excluded by laboratory investigations. This EEG finding is both used for diagnosis (along with history of recent cephalosporin drug use) and for management as they resolve after discontinuation of the drug [8]. Our patient showed similar findings which resolved following clinical improvement. There have been reports of increased cephalosporin levels in the CSF of affected patients [8], however this not was checked in our patient.

The encephalopathy is reversible [7] and the patient will show improvement once the offending drug is stopped. Our patient was treated with anticonvulsants and hemodialysis while ensuring the offending drug was stopped.

Conclusion

A patient who has developed features of neurotoxicity following cephalosporin administration must be suspected for Cephalosporin Induced Encephalopathy(CIE). Other causes of encephalopathy must be excluded first. While the main treatment is exclusion of the causative drug, supportive management is required until the patient improves.

Clinical significance

Cephalosporin Induced Encephalopathy is a rare pathology. It is even more rare for a patient to develop severe neurological suppression. Our patients' clinical status heavily influenced the family's decision on whether to continue life supports or not. It was a challenge to convince them of a possible optimistic outcome based on a tentative diagnosis of exclusion. CIE should always be considered as a diagnosis wherever possible as it can drastically change the prognosis.

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