A Challenging Case of Beta-Lactam Induced Encephalopathy. A Case Report

Shaikha Asheer[1], Salihah Al Mani[2], Ali Alshehri[2], and Mohammad Alasmri[2]

[1]King Hamad University Hospital
[2]Affiliation not available

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Abstract

Beta-lactams are widely utilized as a first-line therapy with a broad-spectrum coverage, bactericidal properties and few side effects as they are commonly considered as safe drugs. Although these antibiotics are essential in the treatment of infections, their misuse and unnecessary prolonged duration may cause harm. Drug-induced neurotoxicity is a rare adverse reaction associated with beta-lactams. Encephalopathy is a type of neurotoxicity that is defined as a diffuse disease of the brain that alters brain function or structure. We report a case of a patient with normal renal function that developed beta-lactam induced encephalopathy with full resolution of her symptoms following discontinuation of the offending antibiotics. This case highlights the importance of early recognizing this rare adverse effect and its impact on clinical outcomes.

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Shaikha Asheer, MD[1], Salihah Al Mani, MD[2], Ali Al Shehri, MD[3], Mohammad Alasmri, MD[4]

[1] Department of Internal Medicine, King Hamad University Hospital, Busaiteen, Kingdom of Bahrain.

[2] Department of Internal Medicine, Armed Forces Hospital - Southern Region, Khamis Mushait, Kingdom of Saudi Arabia

[3] Department of Internal Medicine, Division of Infectious Diseases, Armed Forces Hospital - Southern Region, Khamis Mushait, Kingdom of Saudi Arabia

[4] Department of Internal Medicine, Division of Pulmonology, Khamis Mushait General Hospital, Khamis Mushait, Kingdom of Saudi Arabia

Address correspondence to:

Shaikha Asheer, MD

Department of Internal Medicine

King Hamad University Hospital

Building 2435, Road 2835, Block 228

P.O Box 24343

Busaiteen

Kingdom of Bahrain

E-mail: ssa080107@gmail.com

Abstract

Beta-lactams are widely utilized as a first-line therapy with a broad-spectrum coverage, bactericidal properties and few side effects as they are commonly considered as safe drugs.[1] Although these antibiotics are essential in the treatment of infections, their misuse and unnecessary prolonged duration may cause harm. Drug-induced neurotoxicity is a rare adverse reaction associated with beta-lactams.[2, 3, 4] Encephalopathy is a type of neurotoxicity that is defined as a diffuse disease of the brain that alters brain function or structure.[2] We report a case of a patient with normal renal function that developed beta-lactam induced encephalopathy with full resolution of her symptoms following discontinuation of the offending antibiotics. This case highlights the importance of early recognizing this rare adverse effect and its impact on clinical outcomes.

Keywords

Beta-lactams, drug-induced encephalopathy, drug-induced neurotoxicity

Background

Neurotoxicity refers to the ability to induce adverse effects in the central nervous system (CNS), peripheral nerves, or sensory organs.[1] Neurological adverse events induced by beta-lactams were first described in 1945 after the intraventricular administration of penicillin G.[5] Drug induced neurotoxicity carries a wide spectrum of clinical manifestations ranging from confusion, encephalopathy and hallucinations to myoclonus, convulsions and non-convulsive status epilepticus which can be life threatening.[1] Encephalopathy is a type of neurotoxicity that is defined as "a diffuse disease of the brain that alters brain function or structure and is characterized by an altered mental state with additional symptoms including progressive loss of memory and cognitive ability, personality changes, myoclonus, nystagmus, tremor, and seizures".[2]

In recent years, beta-lactams adverse effects on the CNS have become more widely recognized. Overexposure and high plasma concentrations of these antibiotics due to unadjusted dosing in renally impaired patients have been frequently implicated in neurological side effects.[6,7] We report a patient with normal renal function who developed beta-lactam induced encephalopathy requiring ICU admission with complete recovery of her symptoms after discontinuing the causative drug.

Case presentation

Our patient is a 66-year-old Saudi female with a past medical history of hypertension, chronic obstructive pulmonary disease with secondary polycythemia. She had a surgical history of laparoscopic cholecystectomy, and an iatrogenic large bowel perforation following a colonoscopy with subsequent right hemicolectomy in 2017.

The patient was admitted to our hospital with 1 month history of recurrent dysuria and urinary incontinence. She also complained of progressive lower limb weakness for the last 2 weeks.

On clinical examination she was alert and oriented with normal vitals. She had suprapubic tenderness on palpation, but no renal angle tenderness. Her neurological examination was significant for reduced power in both lower limbs 3/5 without loss of sensations, planter reflexes were preserved. The rest of her examination was unremarkable. Labs on admission are summarized in (table 1), and (figure 1) lists the patient's medications at hospital admission.

Parameters
White blood cells (wbc)
Red blood cells (rbc)
Hemoglobin (Hb)
Platelets
C-reactive protein (CRP)
Serum sodium
Serum potassium

Parameters
Creatinine
Corrected calcium
Urine culture: Klebsiella pneumoniae $> 10^5$ c.f.u/ml (sensitive to nitrofurantoin, Trimethoprime/sulfamethaxazole, ci
Blood culture negative

Table 1. **Summary of Our Patient's Blood Test Results on Admission.**

Abbreviations: L: litre, g/dL: gram per deciliter, mg/dL: milligram per deciliter, mmol/L: millimols per litre, umol/L: micromoles per litre, c.f.u/ml: colony forming unit per milliliter

Amlodipine 10 mg oral daily Aspirin 81 mg oral daily Enoxaparin 50 mg subcutaneous injection daily Ceftriaxone 1 gram i

Figure 1. **List of patient's medications at admission.**

Upon admission the patient was started on empirical ceftriaxone 1 g IV every 12 hours. On day 3 of admission she developed high grade fever reaching 39°c, and was switched to pipercillin/tazobactam 4.5 g IV every 6 hours by respiratory team due to suspicion of hospital acquired pneumonia, further septic workup including sputum culture, respiratory panel and Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) screening were all negative.

Magnetic resonance imaging (MRI) lumbar spine revealed spondylo-degenerative changes noted at L1-L2, L2-L3, L4-L5, with no significant disc bulge or nerve roots compression.

On day 8 of admission the fever persisted and the patient developed confusion and disorientation to place and person. Metabolic workup was non-contributory. Brucella, malaria and Mycobacterium tuberculosis work up all came negative. Lumbar puncture was performed with following results:

Cerebral spinal fluid (CSF) results:

CSF wbc: 1 (0-5)

CSF rbc: 425 (0-20)

CSF protein: 226 mg/L (150-450)

CSF glucose: 4.4 mmol/L (serum glucose 6.5 mmol/L)

CSF Mycobacterium tuberculosis Polymerase Chain Reaction (MTB PCR) GeneXpert and Ziehl–Neelsen stain were negative

Computed tomography (CT) of chest with contrast was remarkable for an enlarged heart and pulmonary trunk, minimal right sided pleural effusion/thickening. CT brain, abdomen and pelvis were unremarkable

The patient was started by neurology team on intravenous immunoglobulin (IVIG) at a dose of 0.4 mg/killogram/day for the suspicion of Guillain-Barre syndrome, however it was stopped after 3 days due to persistent fever. After IVIG discontinuation the patient became afebrile.

On day 13 of admission patient was afebrile with normal vitals however her level of consciousness continued to deteriorate and became obtunded and was shifted to intensive care unit, and her antibiotic was escalated to meropenem 1 g IV every 8 hours and vancomycin 1 g IV every 12 hours. She was reviewed by infectious disease team with suspicion of beta lactam induced encephalopathy; therefore meropenem and vancomycin were stopped and she was kept on Trimethoprime/sulfamethaxazole (Bactrim) 960 mg orally twice daily based on previous urine culture and sensitivity. Repeated septic work up remained negative.

Within 24 hours patient became alert and oriented to place and person, with normal vitals and was shifted to general ward. The remaining of hospital stay was uncomplicated. Patient received regular physiotherapy and her lower limb weakness improved and was able to mobilize with assistance as her baseline. The patient was discharged home after completing 7 days of Bactrim and to continue home physiotherapy.

Discussion and Conclusion

Our report describes a case of beta-lactam induced encephalopathy leading to an altered mental status and somnolence. She received several courses of beta lactam antibiotics including ceftriaxone, pipercillin-tazobactam (Tazocin) and meropenem. The patient symptoms dramatically improved and resolved within 24 hours after beta-lactam discontinuation, consistent with previous case reports describing the neurotoxicity of these antibiotics.[1-8] There was no other medical cause identified or other medication regimen changes done to explain her alteration in cognitive status & its resolution. The diagnosis of drug induced neurotoxicity can be challenging, and so far, the discontinuation of the offending agent is the best approach to retrospectively diagnose beta-lactam induced neurotoxicity after ruling out other causes.[1]

Antibiotic-associated encephalopathy (AAE) can be classified into three unique clinical phenotypes: encephalopathy which usually associated with seizures or myoclonus occurring within days after antibiotic initiation (caused by penicillins and cephalosporins); encephalopathy characterized by psychosis (caused by procaine penicillin, macrolides and quinolones); and encephalopathy with cerebellar signs and MRI abnormalities seen within weeks after initiation of antibiotics (caused by metronidazole).[9]

The main risk factor associated with beta-lactam neurotoxicity is renal failure, especially if doses were not appropriately adjusted which may lead to significant and rapid accumulation of drug level.[4,10,11] Other risk factors include advanced age, low body weight, previous CNS disease, concurrent use of other neurotoxic medications, and critical illness with ICU admission.[2] Beta-lactam neurotoxicity have been reported in 10-15% of ICU patients with clinical manifestation ranging from confusion, hallucinations to myoclonus, convulsions and non-convulsive status epilepticus.[1] Our patient is unique as she had a normal renal function and body weight, no previous known CNS disease, not critically ill with the only known risk factor was her advanced age.

Not all beta-lactams carry equal risk for neurotoxicity. With regards to pro-convulsing activity of beta-lactams, the highest risk was seen with cefazolin, followed by cefepime, penicillin G, and imipenem, while lower seizure risk was observed with ceftriaxone, piperacillin, cefotaxime, and cefoxitine respectively.[1]

There are studies reporting neurotoxicity and pro-convulsive effects of imipenem especially in patients suffering from a brain injury.[12, 13] In addition, there have been increasingly more studies and reports of neurotoxicity associated with cefepime which can manifest with or without seizures.[14-17] In one report, it was found that 7-15% of critically ill patients on cefepime developed neurotoxicity.[8] Our patient did not receive the previous commonly reported beta-lactams to be associated with neurotoxicity, as she received ceftriaxone and tazocin before developing the encephalopathy.

Since the clinical picture was highly suggestive of beta-lactam induced neurotoxicity, we used the Naranjo Adverse Drug Reaction Probability Scale and our patient received a score of 6, suggesting a probable adverse drug reaction (Table 2).

Question	**Yes**
1. Are there previous conclusive reports on this reaction?	+1
2. Did adverse event appear after the suspected drug was given?	+2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1
4. Did the adverse reaction appear when the drug was re-administered?	+2
5. Are there alternative causes that could have caused the reaction?	-1
6. Did the reaction reappear when a placebo was given?	-1
7. Was the drug detected in any body fluid in toxic concentrations?	+1

Question	Yes
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1
10. Was the adverse event confirmed by any objective evidence?	+1
Total score = 6*	**Total score =**

Table 2. **Naranjo Adverse Drug Reaction Probability Scale* (Total score 5-8 : A probable drug reaction, with a reasonable temporal sequence to support the reaction)**

The pathophysiology of beta-lactam induced neurotoxicity is not yet fully known. However, several mechanisms have been linked to beta-lactam induced CNS toxicity as following:

- By decreasing gamma-aminobutyric acid (GABA) neuroinhibitory tone through a concentration dependent inhibition GABAA receptor complex subunits either in a competitive (cephalosporins) or non-competitive (penicillins) way.[1] Therefore, benzodiazepines and barbiturates which act as positive modulators of GABAA receptors, are more effective than phenytoin and other anti-convulsive agents to treat seizures induced by beta-lactams.[1,18]

- The direct GABAA receptor complex antagonistic action as beta-lactam antibiotics can bind directly to it due to the GABAA receptor similarity with the beta-lactam ring.[1]

- In addition, cephalosporins can induce endotoxin and cytokine release leading to neurotoxic effects.[1]

Our case highlights the importance of keeping in mind the pros and cons when using antibiotics including beta-lactams in "at risk patients" such as those with renal impairment, advanced age, or underlying CNS abnormalities, and to appropriately choose the dose and duration of therapy. When a patients is receiving a beta-lactam and develops an altered mental status, hallucinations with or without seizures, it is essential to think about adverse drug reactions after ruling other causes. Having a low threshold of suspicion, therapeutic drug monitoring, and a continuous electroencephalogram (EEG) monitoring could improve the early detection of beta-lactam induced neurotoxicity and therefore, improve patients' outcome by discontinuation of the offending agent.

Declarations

Ethical Approval

This case report was approved by the Institutional Review Board (IRB) at Armed Force Hospital – Sothern Region, Khamis Mushait, Kingdom of Saudi Arabia (Code: AFHSRMREC/2022/Infectious Diseases/626)

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Authors' contributions

S.A.: writing original draft, gathering data, review and editing. S.M.: writing original draft, gathering data, A.A.: conceptualization, supervision, and reviewing. M.A.:investigation.

All authors read and approved the final manuscript.

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