CASE REPORT

Colistin neurotoxicity mimicking Guillain-Barré syndrome in a patient with cystic fibrosis: case report and review

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Abstract

Guillain-Barré syndrome (GBS) is an immune-mediated polyneuropathy, which is characterized by areflexia and ascending paresthesia which can progress to a respiratory failure. Certain conditions, such as vasculitis and heavy metal and drug toxicity, may have misleadingly similar clinical presentation to GBS. We describe a case of a patient with cystic fibrosis and intravenous colistin-induced neurotoxicity mimicking GBS. The patient had used inhaled colistin on five occasions with no adverse effects, however, developed symptoms on the second day of intravenous treatment. Overlapping findings between immune-mediated polyneuropathy and drug-induced neurotoxicity include limb paresthesia and decreased reflexes. Perioral tingling, however, is a common presentation of colistin-induced neurotoxicity, and therefore, is an important differentiating factor. Early diagnosis prevents further neurologic decline, extensive unnecessary workup and potentially harmful incorrect management.

INTRODUCTION

Polyneuropathy and paresthesia in a critically ill patient prompts investigation for Guillain-Barré Syndrome (GBS) [1]. Other medical conditions can mimic the presentation of GBS, such as vasculitis, heavy metal and drug toxicities, including colistin. This polymyxin antibiotic is largely used to treat resistant gram-negative bacteria [2]. We present a case of intravenous colistin-induced neurotoxicity mimicking GBS in a patient with cystic fibrosis.

CASE REPORT

A 38-year-old woman (Patient A) with cystic fibrosis (CF), who underwent double-lung transplant, Stage 3B chronic kidney disease, CF-related diabetes and pancreatic insufficiency, was transferred to the intensive care unit (ICU). She was admitted for an acute-on-chronic hypoxemic respiratory and renal failure. Three weeks prior, she was treated for acute-on-chronic sinusitis caused by methicillin-resistant Staphylococcus aureus and Aspergillus fumigatus infections. A bronchoscopy...
with bronchoalveolar lavage cultures revealed Stenotrophomonas maltophilia infection, so she was started on intravenous colistin. On Day 2 of treatment, she developed numbness and tingling in her fingers, toes and perioral region. Neurologic consultation was requested and revealed intact cranial nerves, sensation and proprioception. Motor strength was preserved, reflexes were reduced bilaterally in the patellae and Achilles but were normal in the upper extremities. In the setting of a recent upper respiratory infection, subjective muscle weakness, paresthesia and decreased lower extremity reflexes, GBS was suspected. A lumbar puncture and electromyography were ordered. Cerebrospinal fluid was unremarkable with no cytoalbuminologic dissociation (1 erythrocyte, no neutrophils, 71 lymphocytes, 29 monocytes, glucose 81 mg/dl and protein 23 mg/dl). This decreased the likelihood of GBS, and the presence of perioral paresthesia prompted investigation of alternate diagnoses. After review of the patient’s medication list (Table 1) for potential drug-induced toxicity, intravenous colistin was identified as a possible culprit. Colistin was suspended and replaced with trimethoprim and sulfamethoxazole. Symptoms subsided within 24 h, and further neurologic testing, including electromyography, was canceled. This patient had made use of inhaled colistin on five occasions and had not had adverse effects.

**Illustrative case**

Within days of this patient’s admission, we had a second case of colistin-induced neurotoxicity. A 59-year-old woman (Patient B) with a double-lung transplant, end-stage renal disease and chronic colonization of pulmonary *Burkholderia cepacia* and history of *Clostridium difficile* (*C. difficile*) infection was admitted to the ICU. She had been receiving inhaled colistin for *B. cepacia* for 3 months and was started on the intravenous form. On Day 2 of treatment, she presented with tongue, hand and perioral paresthesia. Her symptoms were tolerable and neurologic examination was unremarkable. Given the mild quality of her symptoms and considering the risk–benefit ratio, she continued to receive intravenous and inhaled colistimethate. The ICU team promptly diagnosed colistin-induced neurotoxicity since this was the second case in a short time interval.

**DISCUSSION**

**Mimicking GBS**

Patient A’s clinical presentation raised suspicion for GBS, an acute immune-mediated polyneuropathy that can rapidly progress to severe neurologic weakness and respiratory failure. The National Institute of Neurological Disorders and Stroke and Brighton Criteria [1] has established that the diagnosis of GBS is based on clinical history and examination findings as well as ancillary testing (i.e. lumbar puncture and electrodiagnostic studies). Required diagnostic criteria are progressive bilateral weakness of arms and legs and absent or decreased tendon reflexes in affected limbs [1]. Although normal protein levels do not rule out GBS, cytoalbuminologic dissociation is a classic finding. There is a spectrum of conditions that present very similarly to GBS, such as heavy metal or chemical intoxication, vasculitis and drug-induced toxicity (e.g. colistin) [2]. Although most presenting symptoms of GBS and colistin-induced neurotoxicity coincide, there are important distinguishing findings (Table 2) [3, 4].

Early identification of the culprit drug, followed by its discontinuation, may prevent unnecessary electromyography testing and possible GBS treatment with intravenous immunoglobulin. In addition to medically guided decisions, there are financial aspects to be considered: the average cost of intravenous immunoglobulin treatment ranges from $5000 to $25 000 [5].

**Colistin uses and neurotoxicity**

**Pharmacology** Colistin, also known as polymyxin E, is a bactericidal drug used against gram-negative bacteria, especially *Pseudomonas aeruginosa*. Colistin was widely used until the 1970s, when it was replaced by other antibiotics due to its toxicity profile. In the 1990s, however, it was reintroduced because of increasing antibiotic resistance and lack of options against gram-negative bacteria [6]. Multidrug-resistant *P. aeruginosa* are frequent in adult CF patients, so colistin is commonly used.

**Toxicity** Colistin can be administered intravenously, parentally, intrathecally, intraventricularly or inhaled. Current data support that the frequency of neurotoxicity and nephrotoxicity is significantly lower than previously believed [1, 7] and that intravenous administration minimizes toxicity while maximizing efficacy [7]. Nonetheless, both patients we presented used inhaled colistin without adverse effects but developed toxicity on the second day of intravenous treatment. We suspect this may attributed to the systemic effect of the intravenous form [8]. Both patients had renal failure, possibly contributing to the pharmacokinetics of the drug and increased odds of adverse effects. To further investigate toxicities, we performed an IBM Micromedex (IBM Corporation) search for all the medications Patient A was on (Table 1). No cross-reactivity was found.

Colistin-induced neurotoxicity and neuromuscular blockage is explained by two main mechanisms. The first involves the presynaptic action of colistin, which prevents release of acetylcholine into the synaptic gap. The second is biphasic, a short phase of competitive blockade between acetylcholine and colistin, followed by a prolonged phase of depolarization, resulting in calcium loss from the neurons [9]. This change in electrolytes alters mitochondrial permeability, leading to mitochondrial dysfunction in neuronal cells and consequent accumulation of reactive oxygen species. This, in turn, leads to oxidative stress and further nerve damage [10].

**Literature review**

We performed a literature review on colistin-induced neurotoxicity in patients with CF (Table 3). The keywords searched on PubMed were: ‘colistin’ OR ‘colistimethate’ AND ‘neuropathy’ OR ‘neurologic’ AND ‘cystic fibrosis’. Perioral tingling was frequently reported.

**CONCLUSION**

Colistin-induced neurotoxicity may have misleadingly similar clinical presentation to GBS. GBS is a potentially fatal condition, so it should be considered as a differential diagnosis in the setting of paresthesia and decreased reflexes. Additionally,
Table 1: IBM Micromedex search for all drugs on the patient’s medication list

| Drug                        | Dose                                 | Drug–drug interaction with colistin | Alcohol or food interaction |
|-----------------------------|--------------------------------------|------------------------------------|-----------------------------|
| Amlodipine                  | 5 mg/d, oral                         | -                                  | -                           |
| Atovaquone                  | 1500 mg/d, oral                      | -                                  | -                           |
| Azithromycin                | 500 mg/d                              | -                                  | -                           |
| Colistimethate              | 2.5 mg/kg/d                           | N/A                                | -                           |
| Colistimethate              | 150 mg every morning                  | N/A                                | -                           |
| Fluticasone furoate/vilanterol | 1 puff/d, inhalation              | -                                  | Grapefruit juice may cause increased fluticasone exposure |
| Ganciclovir                 | 1.25 mg/kg/d (adjusted)              | -                                  | Avocado reduces anticoagulant effectiveness and celery increases the risk of bleeding |
| Heparin                     | 5000 units BID, subcutaneous         | -                                  | Concurrent use of hydralazine and enteral nutrition may result in decreased hydralazine concentrations. Concurrent use of hydralazine and food may cause decreased hydralazine exposure and efficacy |
| Hydralazine                 | 50 mg, every 8 h SCH, oral           | -                                  | Concurrent use of insulin and ethanol may cause decreased hydralazine exposure and efficacy |
| Insulin aspart              | U-100 (carbohydrate count), 0–10 units TID | -                                  | Concurrent use of insulin and ethanol may result in impaired glucose regulation |
| Insulin glargine            | 5 units every morning, subcutaneous  | -                                  | Concurrent use of insulin and tobacco may result in decreased insulin absorption and increased insulin resistance. Concurrent use of insulin and ethanol may cause impaired glucose regulation |
| Levalbuterol                | 0.63 mg BID, nebulization            | -                                  | Concurrent use of levothyroxine and soy may cause decreased effectiveness of levothyroxine. Concurrent use of levothyroxine and enteral nutrition may result in hypothyroidism |
| Levothyroxine               | 100 mcg/d, oral                      | -                                  | -                           |
| Lipase–protease–amylase     | 40 000 units TID                      | -                                  | Concurrent use of pancreatin and alkaline foods and may result in reduced pancreatin effectiveness |
| Meropenem                   | -                                    | -                                  | -                           |
| Metoprolol succinate        | 100 mg BID, oral                     | -                                  | Concurrent use of montelukast and grapefruit juice may result in increased montelukast exposure |
| Montelukast                 | 10 mg/d, oral                        | -                                  | -                           |
| Mycophenolate               | 360 mg BID, oral                     | -                                  | Concurrent use of proton pump inhibitors and cranberry may cause reduced effectiveness of proton pump inhibitors |
| Pantoprazole                | 40 mg BID, oral                      | -                                  | Concurrent use of posaconazole and food may cause increased posaconazole exposure and plasma concentrations |
| Posaconazole                | 300 mg/d                              | -                                  | -                           |
| Prednisone                  | 10 mg/d, oral                        | -                                  | -                           |
| Sennosides–docusate sodium  | 1 tablet BID, oral                   | -                                  | -                           |
| Sodium chloride             | 3 ml BID, intravenous                | -                                  | -                           |
| Vancomycin                  | 250 mg BID                            | -                                  | -                           |

Abbreviations: -, no interaction; BID, twice a day; N/A, not applicable; TID, three times a day.
Table 2: Clinical clues in the diagnosis of GBS and colistin-induced neurotoxicity

| GBS findings                       | Clinical features shared between GBS and colistin-induced neurotoxicity | Colistin-induced neurotoxicity findings |
|------------------------------------|------------------------------------------------------------------------|----------------------------------------|
| Cytoalbuminologic dissociation     | Perioral paresthesia                                                   | Predominantly sensory deficits [4]     |
| Psychiatric adverse effects (e.g. hallucination) [3] | Abnormal electrodiagnostic findings: slowing nerve conduction | Predominantly sensory deficits [4]     |
| Abnormal electrodiagnostic findings: slowing nerve conduction | Bilateral limb weakness                                                 | Predominantly sensory deficits [4]     |
| Decreased reflexes                 | Sensory deficit                                                        | Predominantly sensory deficits [4]     |
| Perioral paresthesia               |                                                                       | Bad taste in mouth                    |
| Abnormal electrodiagnostic findings: slowing nerve conduction | Bilateral limb weakness                                                 | Predominantly sensory deficits [4]     |
| Decreased reflexes                 | Sensory deficit                                                        | Predominantly sensory deficits [4]     |

Table 3: Studies investigating neurotoxicity in patients with CF

| Reference | Mode of administration | Colistin dose | Days on colistin | Neurotoxicity cases in patients with CF | Type of neurotoxicity |
|-----------|------------------------|---------------|------------------|----------------------------------------|-----------------------|
| [11]      | IV and nebulized       | 150 mg, nebulized q8h 1.25 mg/kg | N/R, the reaction occurred with the first dose | 4 | Perioral paresthesia; tingling in hands, face, fingertips, knee and jaw |
| [12]      | IV and nebulized       | 5 mg/kg       | 7–30             | 0/6 | None |
| [13]      | IV                     | N/R           | 9                | 2 | Paresthesia, bad taste |
| [14]      | IV                     | 5–7 mg/kg/d   | 6–35             | 26/31 | Oral and perioral paresthesia, headache and lower extremity weakness |
| [15]      | Parenteral             | N/R           | N/R              | 0 | None |
| [16]      | IV                     | 1.63–3.11 mg/kg | 2               | 0/12 | None |
| [17]      | IV                     | 2 MU t.d.s.   | 1–14             | 0/52 | None |
| [18]      | IV                     | 5.3–12.9 mg/kg | 12              | 37/53 | Dizziness, numbness, tingling, incoordination, unsteadiness and muscle weakness |
| [19]      | IV                     | N/R           | N/R              | 6/19 | Perioral paresthesia, ataxia |

Abbreviations: IV, intravenous; MU, million units; N/R, not registered; t.d.s., three times a day.

it is essential to promptly recognize perioral paresthesia as a classic sign of colistin-induced neurotoxicity in patients with CF, especially for patients taking the intravenous form. Efficiently ruling out GBS when confronted with GBS mimicking conditions avoids unnecessary testing and treatments and reduces hospital and patient costs.

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CONFLICT OF INTEREST

None declared.

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ETHICAL APPROVAL

No ethical approval was required for this project.

CONSENT

Both patients consented to the use of their medical information for educational and research purposes.

GUARANTOR

Dr Freeman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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