Case Report

Ciprofloxacin-Induced Peripheral Neuropathy: A Case Report

Alexander Refaeian, BS1; Eric L Vest, MD2; Michael Schmidt, MD3; Jorge D Guerra, BS2; Mohd N Refaei, MD4; Michael Refaeian, BS4; Ryan A Floresca, BS2; Manouchehr Refaeian, MD2,3,4

Abstract

Introduction
Fluoroquinolones, a class of antibiotics, are commonly employed in the treatment of a wide array of bacterial infections. Recognized for their effectiveness against a broad spectrum of pathogens, fluoroquinolones have played a pivotal role in managing conditions like urinary tract infections and respiratory diseases. Nevertheless, their usage is not without contention due to their association with a variety of adverse effects, including tendon rupture and the less frequently reported issue of peripheral neuropathy.

Case Presentation
We present the case of a 42-year-old male who developed peripheral neuropathy several days after completing a 10-day course of ciprofloxacin for gastroenteritis. The patient’s presenting complaint was bilateral upper and lower extremity weakness for which inpatient treatment was initiated and workup for other causes was negative. Nerve conduction studies (NCS) and electromyography (EMG) demonstrated peripheral neuropathy. The patient was treated with intravenous immunoglobulin (IVIG), steroids, and physical therapy. Follow-up NCS and EMG showed continued neuropathy but with significant improvement.

Conclusion
The case aligns with existing research, demonstrating that fluoroquinolone use is linked to peripheral neuropathy, particularly axonal polyneuropathy, and emphasizes the importance of investigating the underlying mechanism for improved therapeutic strategies. The potential combination of intravenous immunoglobulin and physical therapy has exhibited promising results.

Keywords
ciprofloxacin; fluoroquinolones; peripheral nervous system diseases; polyneuropathies; electromyography; drug-related side effects and adverse reactions
to the many confounding etiologies in a patient’s history, thus making it difficult to link fluoroquinolones with peripheral neuropathy.\textsuperscript{10} The exact mechanism of fluoroquinolones that cause peripheral neuropathy is uncertain. Fluoroquinolones have undergone regular safety reviews to investigate the risk of chronic effects on muscles and the nervous system.\textsuperscript{11-12} Morales et al conducted a nested case-control study in which fluoroquinolone use was associated with an increased relative incidence of neuropathy of 1.47 compared with those not exposed to fluoroquinolone, with the highest risk occurring in men over 60. The major strength of this study was that the control group was exposed to different antibiotics that did not increase the risk of neuropathy.\textsuperscript{13} However, the tendinopathies that mimic neuropathic symptoms make it challenging to diagnose fluoroquinolone-induced neuropathy.\textsuperscript{14}

**Case Presentation**

A 42-year-old male with a past medical history of hypertension and diverticulitis presented to an urgent care facility after a 2-week episode of gastroenteritis associated with watery diarrhea, nausea, and vomiting. The patient was evaluated and treated with a 10-day course of ciprofloxacin 500 mg twice daily.

Ten days after completing his course of ciprofloxacin, he presented to the emergency department with bilateral upper and lower extremity weakness. The patient was admitted due to a high suspicion of Guillain-Barré syndrome. Subsequent cerebrospinal fluid (CSF) analysis was negative for Guillain-Barré syndrome, but the spinal tap did reveal a high level of protein. The patient was seen by neurology, undergoing an extensive physical examination to rule out other causes. There were no viable explanations for the patient’s symptoms at this time. He was discharged on duloxetine and pregabalin to treat his symptoms of weakness and was referred to undergo nerve conduction studies (NCS) and electromyography (EMG) before following up with neurology.

The patient was seen at the Physical Medicine and Rehabilitation clinic, where extensive NCS/EMG studies were conducted. At presentation, the patient had intact sensation and proprioception in all extremities. There was no numbness or tingling present at that time. No coordination deficits were noted and no abnormal movements were observed. The patient had difficulty rising from a seated position due to weakness. The patient also demonstrated weakness in the anterior and posterior bilateral leg compartments. The neurological examination was notable for 3/5 in all the muscles of the lower limbs bilaterally. Muscle strength was 3/5 for the biceps brachii and brachioradialis on the upper limbs bilaterally. The remaining muscles of the upper limb demonstrated muscle strength of 5/5. There was no pain on examination, and the patient’s upper and lower limb reflexes were 2+.

**NCS and EMG studies**

NCS evaluation of the bilateral fibular and tibial motor nerves showed prolonged distal onset latency. The right fibular motor nerve and the left and right tibial motor nerves also demonstrated reduced amplitude respectively. All other remaining nerves were within normal limits (Supplemental Tables 1 and 2).

On EMG, there were diffuse abnormalities in the lower extremities with increased insertional activity, increased spontaneous activity, increased motor unit duration, diminished recruitment, and a decreased interference pattern with positive short waves and fibrillation potentials present. These same findings were also observed in the bilateral upper brachioradialis and bicep muscles. The lumbar paraspinals and cervical paraspinals showed no abnormalities (Supplemental Table 3). Based on the interpretation of the NCS and EMG studies, the patient had a mixed polyneuropathy—axonal dominant.

**Management and Treatment**

The patient followed up with neurology after the initial NCS/EMG studies. Due to the patient’s persistent upper and lower extremity weakness, high protein content in cerebrospinal fluid, as well as positive NCS and EMG findings, neurology suggested hospital admission with intravenous immunoglobulin (IVIg) therapy. The patient had an uneventful 5-day hospital stay with subsequent clinical improvement. He was discharged with a referral to physical therapy and was also instructed to repeat
NCS/EMG studies in 2 months. He returned to the Physical Medicine and Rehabilitation clinic 2 months after IVIg treatment. Repeated NCS/EMG studies showed persistent abnormalities in both upper and lower extremities but with significant improvement (Supplemental Tables 4, 5, and 6).

Discussion
Particular medications have been associated with the development of drug-induced peripheral neuropathy (DIPN), including antimicrobials, chemotherapeutic agents, among others.\(^\text{15}\) Most of these drugs cause damage at the dorsal root ganglia through various mechanisms including metabolic dysregulation and intracellular inflammatory signaling.\(^\text{16}\) Morales et al\(^\text{13}\) conducted a nested case-control study and showed a statistically significant association between fluoroquinolone use and an increased relative incidence of neuropathy of 1.47 compared with those not exposed to fluoroquinolone. Over the past 2 decades, an expanding body of evidence has supported the use of high-dose intravenous immunoglobulins. These immunoglobulins are used as an immunomodulatory for the treatment of polyneuropathy secondary to inflammatory conditions such as DIPN, as seen in our patient.\(^\text{17-19}\)

In 2004, the Food and Drug Administration (FDA) added peripheral neuropathy to product labels as an identified risk of systemic treatment with fluoroquinolones. In 2013, the FDA followed up by both strengthening the original warning and adding recommendations to discontinue use if peripheral neuropathy occurred. It is also important to consider the fact that the number of peripheral neuropathy reports increased notably since 2004, which may be a result of clinicians’ increased index of suspicion due to the FDA’s decision to include peripheral neuropathy on product labels.\(^\text{3}\)

Since peripheral neuropathy is a relatively lesser-known adverse reaction attributed to fluoroquinolone use, many characteristics, including time of onset and initial presenting symptoms, are relatively unknown. Ali et al\(^\text{3}\), however, found the median onset of peripheral neuropathy was 4 days after fluoroquinolone administration, with the most commonly reported neurologic complaint being a burning sensation. Furthermore, many related case reports also describe painful neuropathy as the chief complaint.\(^\text{6,8}\)

Etminan et al\(^\text{20}\) found that current users of fluoroquinolones were at a higher risk of developing peripheral neuropathy when compared to control groups. New current users of fluoroquinolones had an even higher risk of developing peripheral neuropathy when compared to controls. These authors excluded cases that had other risk factors for peripheral neuropathy, including a history of diabetes, history of hereditary peripheral neuropathy, or suspected drug-induced peripheral neuropathy. Thus, the cases chosen for their study only included men between the ages of 40 and 85, making it less generalizable to other groups of patients.

Ali et al\(^\text{3}\) used the FDA Adverse Event Reporting System to identify cases of reported peripheral neuropathy and Guillian-Barré syndrome (GBS) from 1997 to 2012. Peripheral neuropathy represented 1% of all submitted adverse events, with females being affected more often than males, and a median age of 48 years in affected patients. The study also found that the vast majority of peripheral neuropathy events resulted in a serious outcome, with the most common serious outcome being significant physical disability.

Treatment
There is no agreed-upon treatment for fluoroquinolone-induced peripheral neuropathy other than discontinuing the antibiotic immediately upon presentation of symptoms. The exact mechanism active in peripheral neuropathy induced by fluoroquinolones is unknown, which can make identifying appropriate treatment more difficult.\(^\text{4}\) A thorough workup is therefore necessary to rule out other causes of peripheral neuropathy.

Estofan et al\(^\text{8}\) reported on a patient treated with several pain medications to manage painful neuropathy. Treatment included intravenous lidocaine, methadone, ketamine infusions, and intravenous acetaminophen, all of which provided only minor, temporary relief. These treatments were followed by IVIG infusion as inpatient for 3 days with significant improvement in pain. The patient was continued on outpatient IVIg for 6 months with gradual improvement of symptoms.
Dukewich et al. reported on a patient who was treated with various pain medications, including intravenous lidocaine, gabapentin, fentanyl patches, and methadone that were ultimately discontinued due to inefficacy. The patient was then given a 5-day course of ketamine infusion, which provided moderate management of the pain. No further treatments were administered.

In our patient’s case, diagnosis and treatment followed a similar course of action. The patient was primarily placed under medications for symptomatic relief with little-to-no improvement. After a complete diagnostic work-up, a diagnosis of ciprofloxacin-induced peripheral neuropathy was considered. The patient underwent a 5-day inpatient course of IVIG, accompanied by regular physical therapy, with marked clinical improvement. The patient’s progress was also tracked via NCS/EMG studies with a significant improvement in nerve conductivity and musculoskeletal function.

A differential diagnosis of GBS could be postulated due to the presentation of peripheral neuropathy; however, we believe that this patient’s presentation was more likely due to ciprofloxacin-induced peripheral neuropathy (CIPN) for the following reasons. Our patient presented with bilateral upper and lower extremity weakness where the paresthesia/weakness did not move proximally as is commonly seen in GBS. In addition, the symmetrical muscle weakness is typically accompanied by the absence or depression of deep tendon reflexes in GBS, which was not seen in our patient. Furthermore, patients with GBS may present with diaphragmatic and oropharyngeal weakness, which was not seen in our patient. Another test we used was the CSF results on lumbar puncture. Analysis of CSF results can help differentiate etiologies for similar clinical presentations, such as the weakness seen in our patient. Normally, CSF has a clear appearance with 0–5 white blood cells (WBCs)/µL, greater than 60% of serum glucose, and protein levels less than 45 mg/dL. CSF results showing increased WBCs, elevated protein levels, and varying glucose levels can suggest an infectious etiology. On the other hand, an elevated protein level with a normal WBC count points toward GBS. For our patient, despite the lack of clinical features mentioned above, the CSF analysis indicated high protein levels (albuminocytologic dissociation) and a normal WBC count, which made a diagnosis of GBS unlikely. Electrophysiologic studies in GBS will show conduction block or decreased conduction velocities with the addition of F-waves and dispersion. Needle electromyography will show reduced recruitment of motor unit potentials. NCS results for our patient showed increased latency on both upper and lower peripheral nerves (Supplemental Tables 2, 3, and 5) with no F waves noted. The patient’s EMG showed increased insertional activity, increased spontaneous activity, increased motor unit duration, diminished recruitment and a decreased interference pattern with positive short waves, and fibrillation potentials present in both bilateral upper and lower extremities (Supplemental Table 3). Given these findings on clinical presentation of non-ascending weakness, central nervous system analysis negative for GBS, and NCS/EMG results we suspected the etiology of the peripheral neuropathy was more likely due to CIPN.

**Conclusion**

The case presented supports previous case reports and studies indicating that fluoroquinolone use is associated with the development of peripheral neuropathy—specifically axonal polyneuropathy. This report highlights the need to further understand the mechanism of fluoroquinolone-induced peripheral neuropathy to better guide treatment. A potential combination treatment of IVIg and physical therapy has shown promising results, as supported by past and present clinical findings.

**Conflicts of Interest**

The authors declare they have no conflicts of interest.

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Author Affiliations
1. Texas Christian University Burnett School of Medicine, Fort Worth, TX
2. Texas Tech University Health Sciences Center El Paso, TX
3. Las Palmas Medical Center, El Paso, TX
4. Eastside Rehabilitation Medicine and Pain Clinic, El Paso, TX

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