

Case Report

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# Severe Acute Axonal Neuropathy Induced by Ciprofloxacin: A Case Report

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## Keywords

Fluoroquinolones · Therapy-induced peripheral neuropathy · Side effects · Acute motor and sensory axonal neuropathy · Folate deficiency

## Abstract

Fluoroquinolones increase the risk of peripheral neuropathy. The present work aims to report a case of fluoroquinolone-related severe axonal neuropathy. The subject of this study was a 62-year-old man who exhibited generalized sensory disturbances 4 days after treatment by ciprofloxacin prescribed for urinary infection. Electrodiagnostic studies revealed severe motor-sensory axonal neuropathy with widespread fibrillation potentials in support of generalized motor polyradiculopathy. There was no evidence of conduction blocks or albuminocytologic dissociation in favor of an autoimmune inflammatory reaction. The only pathological biomarker was the reduction of serum folate. According to this case, we suggest that folate level could be routinely measured and supplementation should be performed in patients with fluoroquinolone-induced neuropathy.

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## Introduction

Fluoroquinolones (FQs) are antibiotics that are widely used against urinary infections. Overall, the frequency and severity of adverse events are rather low [1]. Among the most serious adverse events are peripheral neurologic events [2–5]; these are less common than central nervous system or gastrointestinal involvement, which occurs with an estimated frequency of 1 in 17,000 ciprofloxacin-treated patients [6]. We report an extremely rare case of axonal neuropathy induced by ciprofloxacin with peripheral nerve symptoms that lasted more than 6 months, while electrodiagnostic features have almost been normalized after 5 years of observation.

## Case Report

A 62-year-old man was admitted to hospital with urinary infection 1 week after a surgical intervention for nephrolithiasis. He received ciprofloxacin 500 mg twice a day. Four days after the first intake of the antibiotic therapy, the patient started to present severe numbness in the feet gradually ascending towards the calves and sensory disturbances in the hands, but not flaccid paresis. During the examination of the patient, he had full strength in his extremities and only vibratory sensory distal deficit. Patellar and Achilles reflexes were absent. Cranial nerves were not involved, and no ataxic or autonomic features were reported. An electrodiagnostic test performed in the fourth week revealed that the peroneal and tibial nerves, as well as the sensory nerves in the lower limbs, were not excitable. In the upper limbs, the amplitudes of the compound motor action potentials (CMAPs) of the median and ulnar nerves were extremely low, less than 80% of the lower normal limit of motor amplitude, indicating axonal degeneration [7]. The sensory and motor nerve conduction velocity was severely diminished with temporal dispersion, especially at common entrapment sites, but no conduction blocks were registered (Table 1). Distal CMAP latencies in the median and ulnar nerves were prolonged as electrophysiological evidence of demyelination features [8]. The H reflex recorded from the soleus muscle after the stimulation of the tibial nerve was bilaterally abolished. The electromyography revealed active denervation with increased temporal recruitment in the distal part of the lower limbs with no neurogenic pattern in the proximal muscles. One month later, it was discovered that the same clinical phenotype with lack of tendon reflexes was present in the lower limbs. The electrodiagnostic test reported more than 50% reduction of normal values of the sensory amplitudes in the median and ulnar nerves and inexcitability of the sural nerve (Table 1). In our case, the involvement of the upper limbs was also prominent, even if the length-dependent pattern was respected. The fibular and tibial nerves became electrically excitable late in the disorder, but the compound motor action amplitudes were severely reduced with a comparatively lower reduction of motor conduction velocities. The subsequent reduction of nerve velocities of more than 30% and the increase in distal motor latencies of more than 50% fulfilled demyelination criteria [7]. Therefore, we concluded that the demyelination features were secondary to axonal degeneration.

Cerebrospinal fluid analysis did not detect albuminocytologic dissociation. The routine laboratory testing, including comprehensive metabolic profile, erythrocyte sedimentation

rate, thyroid-stimulating hormone levels, and also vitamin B<sub>1</sub>, B<sub>12</sub>, and E, was normal. Furthermore, we found that the antibodies anti-GM1b and anti-GD1a were absent. The vitamin profile showed low amounts of serum folic acid at 2.7 ng/mL. The patient denied excessive alcohol consumption, which was confirmed by biological features. Additionally, there was no evidence that the neuropathy occurred secondary to other known causes. Despite the discontinuation of the antibiotics treatment, there was no relief of symptoms, and the patient was treated with pregabalin [9] and, at the same time, with oral folate supplementation for 3 months. The electrophysiological studies 6 months after the first ciprofloxacin intake showed an important improvement, particularly in the excitability of the sural nerve, which regained a normal amplitude, and also in the distal compound motor action latencies of the amplitudes of the peroneal, tibial, median, and ulnar nerves, respectively. The H reflex of the tibial nerve remained abolished. The serum folate level became normal again at 33.8 ng/mL. Acute inflammatory demyelinating polyradiculoneuropathy (AIDP) as a differential diagnosis was ruled out due to the lack of albuminocytologic dissociation. The clinical recovery lasted more than 6 months after drug intake.

## Discussion

The occurrence of peripheral neuropathy has already been reported with FQs [2–5]. Small-fiber neuropathy has been described as an adverse effect of ciprofloxacin [10] as well as Guillain-Barré syndrome (GBS) during treatment with ofloxacin [11]. In this study, we reported a case of severe FQ-induced peripheral neuropathy with long-term recovery. In our case, the time between the ciprofloxacin intake and the first symptoms was 4 days, knowing that in one-third of patients, the neuropathic symptoms occurred within 24 h of treatment initiation [5], and in more than two-thirds of patients within 1 week after the start of treatment [3]. The patient did not know whether this was his first FQ treatment, but probably that was the case, because new users have the highest risk of developing FQ-associated neuropathy [12]. There was no evidence of diabetes or other metabolic, hematological, or neoplastic conditions. The symptoms were solely sensitive; paresthesia with little objective sensory loss is regarded as the most common initial symptom of GBS [13]. However, this case is different from those reported concerning IDP, given its exclusive sensory clinical presentation, moderately reduced nerve conduction velocities, a marked reduction in the amplitude of motor and sensory nerve action potentials, and evidence of denervation on needle examination of the affected muscles [14]. The axonal degeneration is, therefore, the cause of secondary demyelination features, which explains the increase in distal motor latencies of more than 50% in relation to the normal values previously established [7]. Moreover, compared to our case, marked slowing of motor conduction is the essential feature of chronic IDP [15]. The electrophysiological features are, therefore, compatible with acute motor and sensory axonal neuropathy (AMSAN), defined as severe involvement of the motor and sensory nerves with more than 50% reduction of the amplitudes in at least 2 sensory nerves [16]. In AMSAN patients, the reduction of the sural nerve amplitude is more prominent than in AIDP patients, and sural sparing is considered a marker of demyelinating neuropathy [17]. Indeed, our electrophysiological features showed the inexcitability of the sensory nerves in the legs. Length-dependent conduction was also reported as an essential marker of the axonal type of GBS [8]; a drop of

sensory nerve action potentials and CMAPs with only slightly diminished conduction velocities is required for the diagnosis of axonal neuropathies. Nine percent of patients with FQ neuropathy have the GBS phenotype [18]. Moreover, the laboratory findings did not show any evidence of albuminocytologic dissociation in favor of AIDP.

After 5 years of observation without relapsing and remitting course, we noted that the monophasic course of this axonal neuropathy is in favor of axonal GBS. Although the antibiotic treatment was stopped, there was no prompt relief of symptoms, and sensory disturbances have continued for more than 6 months; this required treatment with pregabalin as the analgesic of choice [9]. Overall, reports showed variable recovery delays with neuropathic features lasting more than 3 months in 71% of cases and more than 1 year in 58% of cases [5]. Elderly patients with pre-existing risk factors are more frequently affected; age over 60 years and chronic renal diseases, as in our case, are considered as risk factors for FQ-induced side effects [19]. Possible FQ toxicity occurs more frequently in patients with diabetes, impaired renal function, hematological diseases, and neurotoxic-associated drugs [3].

It is worth to note that, in our case, folate deficiency without macrocytic anemia was probably due to a long-standing nutritional folate deficiency, which could be a possible enabling factor for FQ-induced neuropathy. Folate deficiency has been recognized as a risk factor for polyneuropathy [20, 21]. The phenotype of folate-deficiency neuropathy is predominantly deep sensory, slowly progressive, essentially axonal, and responding to folate supplementation [22]. Folate therapy significantly reversed abnormalities in motor and sensory nerve distal latencies in patients on long-term anticonvulsant therapy [23]. One-tenth of the neurological patients presented low serum folate levels [24]. FQs block the bacterial complex of DNA and DNA gyrase, but they are not involved in folate synthesis as a reductase inhibitor like other antibiotics [25]. We can speculate on the involvement of methylenetetrahydrofolate reductase (MTHFR) gene variants, which have already been associated with diabetic neuropathy [26, 27]. In this pathology, folic acid seems to have neuroprotective effects on experimental diabetic peripheral neuropathy [28]. Supplementation with folic acid may be a solution to facilitate the recovery of FQ-induced neuropathies, especially in those who experienced folate deficiency. The best choice of antibiotics, while respecting guidelines and contraindications, is necessary.

We reported a severe axonal GBS phenotype induced by ciprofloxacin. Considering the fact that the initial biological investigations revealed folate deficiency, we propose the supplementation of serum folate as an additive factor in order to hasten recovery. Clearly, it is difficult to conclusively demonstrate that FQ was the cause of neuropathy, but the chronological aspect and the peculiar features of electrodiagnostic tests are in favor of an axonal GBS-like phenotype with unobtainable sensory nerve action potentials, low CMAPs, and acute denervation.

### Statement of Ethics

The author has no ethical conflicts to disclose.

### Disclosure Statement

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### Author Contributions

The author conceived and designed the study, examined and frequently monitored the patient, performed the electrophysiological studies, analyzed the data, and wrote the manuscript.

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**Table 1.** Electrophysiological findings

	MNCV, m/s (normal values)			Distal latency, ms (normal values)			CMAPs, mV (normal values)			Sensory amplitude, $\mu$ V (SNAPs) (normal values)	
	median	ulnar	peroneal	median	ulnar	peroneal	median	ulnar	peroneal	median	sural
<i>Time after drug intake</i>											
28 days	R: 32.2 L: 36.2 (51.1 $\pm$ 3.7)	R: 36.2 L: 37.2 (52.4 $\pm$ 3.5)	R: 0 L: 0 (48.3 $\pm$ 3.9)	R: 5.21 L: 7.23 (1.82 $\pm$ 0.19)	R: 4.51 L: 4.53 (3.7 $\pm$ 0.2)	R: 6.40 L: 6.11 (3.9 $\pm$ 0.8)	R: 0.7 L: 0.5 (6 $\pm$ 2.2)	R: 0.2 L: 0.2 (52.5 $\pm$ 3.8)	R: 0 L: 0 (4.5 $\pm$ 2.7)	R: 9.92 L: 7.73 (24.4 $\pm$ 3.3)	R: 0 L: 0 (23.6 $\pm$ 3.5)
2 months	R: 32.2 L: 36.2 (51.1 $\pm$ 3.7)	R: 32.2 L: 36.2 (52.4 $\pm$ 3.5)	R: 32.2 L: 36.2 (48.3 $\pm$ 3.9)	R: 5.21 L: 7.23 (1.82 $\pm$ 0.19)	R: 4.23 L: 4.14 (3.7 $\pm$ 0.2)	R: 4.63 L: 5.21 (3.9 $\pm$ 0.8)	R: 0.7 L: 0.5 (6 $\pm$ 2.2)	R: 0.2 L: 0.2 (52.5 $\pm$ 3.8)	R: 0.64 L: 0.48 (4.5 $\pm$ 2.7)	R: 14.94 L: 12.65 (24.4 $\pm$ 3.3)	R: 0 L: 0 (23.6 $\pm$ 3.5)
6 months	R: 50.17 L: 36.2 (51.1 $\pm$ 3.7)	R: 32.2 L: 36.2 (52.4 $\pm$ 3.5)	R: 32.2 L: 36.2 (48.3 $\pm$ 3.9)	R: 5.21 L: 7.23 (1.82 $\pm$ 0.19)	R: 3.56 L: 3.52 (3.7 $\pm$ 0.2)	R: 3.56 L: 3.71 (3.9 $\pm$ 0.8)	R: 0.7 L: 0.5 (6 $\pm$ 2.2)	R: 0.2 L: 0.2 (52.5 $\pm$ 3.8)	R: 0.64 L: 0.48 (4.5 $\pm$ 2.7)	R: 35.9 L: 34.3 (24.4 $\pm$ 3.3)	R: 0 L: 0 (23.6 $\pm$ 3.5)

MNCV, motor nerve conduction velocity; SNAPs, sensory nerve action potentials; R, right; L, left.