ISSN: 2754-4974

Journal of Clinical Epidemiology & Toxicology

SCIENTIFIC Research and Community

Review Article

Open Access

Secondary Intracranial Hypertension After Ciprofloxacin Treatment: A Case Report

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ABSTRACT

A 30-year-old man developed secondary osteomyelitis after a traumatic amputation of his right index finger. The infection was treated with ciprofloxacin. Approximately 4 weeks after starting treatment, he complained of a progressive decrease in visual acuity, retro-ocular pain and bitemporal headache. A diagnosis of intracranial hypertension was established. Blood sample analysis, infectious profile, cerebrospinal fluid analysis, and neuroimaging were normal. Visual acuity and other symptoms progressively improved after stopping drug treatment. There were no complications or sequelae. Intracranial hypertension due to fluoroquinolones is described in the medical literature, its appearance during such treatments, despite being a rare adverse event, should be monitored.

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Received: December 15, 2021; **Accepted:** December 24, 2021; **Published:** December 31, 2021

Keywords: ciprofloxacin, idiopathic intracranial hypertension, pseudo tumor cerebri, adverse drug reaction.

Introduction

Idiopathic intracranial hypertension (IIH) is considered an infrequent entity. The overall age-adjusted and gender-adjusted annual incidence is increasing and was reported to be 2.02 per 100,000 within the last decade (2002–2014), has a striking association with obesity and women of childbearing age; the most frequent sign is papilledema and the symptom is headache [1]. Previously this entity was referred to as Pseudo Tumor Cerebri (PTC) and it is considered a diagnosis of exclusion. It is defined as the increase in intracranial pressure in the absence of intracranial structural cause or lesions in the neuroimaging and with normal cerebrospinal fluid microscopy and biochemistry, with no other findings that may explain its appearance. Its pathophysiology has not been clearly described yet. Primary intracranial hypertension involves cases where no cause can be found and secondary is where a causative factor can be identified [2,3]. Many conditions have been described for explain that secondary intracranial hypertension (SIH) ranging from metabolic, nutritional, infectious, autoimmune, vascular and specifically with medications are multiple associations [3,4].

Ciprofloxacin is a second-generation fluoroquinolone (FQ), is a synthetic fluorinated analogue of nalidixic acid and has depicted a considerable and myriad spectrum of activity for several infectious conditions and against a broad range of bacteria. Since its approval, its safety profile has been well-documented in a commendable number of scientific publications. However safety review has shown that when fluoroquinolones used systemically (ie tablets, capsules, and injectable) there is a possibility of developing disabling and potentially permanent serious side effects like QTc prolongation, arrhythmia, anxiety, hallucination, paranoia, delirium, tremors, insomnia, peripheral neuropathy, tendon rupture, hepatotoxicity, alteration of blood glucose levels and kidney injury [5]. Here we describe the development of secondary intracranial hypertension (SIH), related to the use of ciprofloxacin.

Case Report

A 30-year-old man of afro-descent, weight 78 Kg and height 1.78 m2. With a pathological history of hypertension, in management with metoprolol tartrate 50 mg, twice a day. Who had suffered a traumatic amputation of the distal phalanx of the 3rd right hand, after which he had osteomyelitis due to P. aeruginosa. Orally antibiotic therapy with ciprofloxacin 500 mg, twice a day for 6 weeks was prescribed. On the fourth week of treatment, progressive reduction of visual acuity, bifrontal headache, and retro-ocular pain began; the patient has unilateral sixth nerve palsy, visual acuity 20/50 RE, 20/40 LE and fundus oculi examination showed papilledema. There is no reference of basal visual acuity.

The blood count, TSH, folic acid, vitamin B12, serum complement C3, serum complement C4 and complete metabolic profile was normal. HIV negative, non-reactive VDRL, low rheumatoid factor, antinuclear antibodies and anticardiolipin negative. A lumbar puncture had an opening pressure of 49-cm water and closing pressure of 16-cm water. The cerebrospinal

fluid (CSF) studies showed no white blood cells, no red blood cells, no xanthochromia and normal protein and glucose. The bacterial, fungal, mycobacterial cultures and cryptococcal antigen were negative. Cerebral magnetic resonance imaging (MRI) reported mild tortuosity of the left optic nerve sheath with slight prominence of the subarachnoid space, without evidence of structural injury. With the suspicion of an adverse drug reaction (ADR), the antibiotic was suspended, and acetazolamide prescribed for one month. Clinical symptoms improved after 5 days. After 2 months, follow-up ophthalmologic evaluation showed visual acuity 20/30 RE, 20/25 LE, no papilledema, normal extraocular movements, and no symptoms.

Discussion

The relationship of IH with ciprofloxacin can be traced back to nalidixic acid, quinolone prototype antibiotic, the first case of nalidixic acid-associated PTC was reported in 1967 [6]. Considered compatible with an idiosyncratic ADR and there are reports with other fluoroquinolone family drugs. Sodhi et al retrospective cohort of more than 3 million people, reported 339 cases of PTC in patients with current use of FQs, in the sensitivity analysis, the RRs for current users of FQs for the 30-day and 60-day definitions were 4.68 (95% CI 2.79–7.86) and 3.98 (95% CI 2.59–6.10) [7]. In medical literature, several cases of IIH and quinolones have been published, Alfieri et al, in a case report of IIH and levofloxacin, report having found several associations in the literature, twenty-seven with nalidixic acid, four with ciprofloxacin, one with ofloxacin, one with pefloxacin, one as moxifloxacin and 2 with levofloxacin [8]. We found only three IIH cases associated with the use of ciprofloxacin have been published; in 1990 Winrow reported the case of a 14-year-old girl with cystic fibrosis who was receiving treatment with ciprofloxacin and 10 days later developed headache, nausea, vomiting, diplopia, paralysis of the 6th left cranial nerve, and decreased visual acuity. Other causes was ruled out and improvement after discontinuation of the drug and drainage of cerebrospinal fluid [9]. In 2011, Fernando et al, reported a case of a 22-year-old African American woman with no pathological history, who after 2 days of treatment with ciprofloxacin 500 mg 2 times a day for pyelonephritis, presented with headache, bilateral blurred vision, and diplopia. Papilledema, with normal brain MRI, very high lumbar puncture pressure, other causes was ruled out and she improved after stopping treatment and with serial drains [10]. In 2011, Milanlioglu. et al, reported the case of a 36-year-old man receiving ciprofloxacin for a urinary infection and at 3 days consultation for severe headache, diplopia, vomiting and tinnitus, with bilateral papilledema and bilateral abducens paralysis, resonance and additional normal studies, suspend ciprofloxacin, fluid was drained and treatment was given with carbonic anhydrase inhibitor and the patient improved [11]. Close to 102,000 ADR to ciprofloxacin has been reported to Vigiaccess, and only 53 (0,05%) of this, are classified like ´intracranial pressure increased` or `idiopathic intracranial hypertension [12]. In Canada Vigilance Adverse Drug Reaction online database, we found three reports of IIH associated with the use of ciprofloxacin [13]. We think little is known about this ADR and therefore it is rarely reported, which gives this case more relevance, because there is a growing interest in the adverse effects in this family of drugs that are widely used and otherwise considered very safe. The mechanisms that explain it are not clear, some postulated mechanisms might be inferred through the specific capacity of ciprofloxacin to antagonize GABA A and B receptors and interact with glutamate receptors, thus being able to generate excitability of the CNS and partially explaining the presence of seizures [14,15]. Furthermore, positive regulation of the glutamate receptor and increased excitatory neurotransmission can cause intracranial hypertension and decrease the water content of brain tissue [7,16,17].

In conclusion, in this case there is a reasonable temporality between the administration of ciprofloxacin and the onset of IH symptoms. No other risk factors appear to exist (female sex, obesity, other medicines or medical conditions). Further improvement was evident after stopping the product and the diagnostic criteria for this type of case were met [2]. In addition, when performing the algorithms of causality of Naranjo, a possible relationship was found (See Table 1) and all authors agreed with this classification [18]. This case provides further evidence of the risk of developing SIH during ciprofloxacin treatment. Early diagnosis of SIH is important to prevent long-term complications.

Table 1: Naranjo-ADR probability scale

	Yes	No	Do not know	Score
Are there previous conclusive reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	-1
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total score	5			

ADR: adverse drug reaction

Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authors' contributions

PAL, DVL and RPS were involved in the management of the patient, performed the literature search, and were a contributors in writing the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

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