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Sensory-motor polyneuropathy due to the use of antiparasitic drugs: A case report

Marco Antônio Orsini Neves, Ilana Cwajgenberg, Daniel Antunes Pereira, Wladimir Bocca, Acary Bulle de Oliveira, Antonio Marcos da Silva Catharino

ABSTRACT

Introduction: The term polyneuropathy refers to a generalized involvement of peripheral nerves, usually involving mainly the distal nerves and, more often, presenting with sensory, motor, and autonomic symptoms and clinical findings. Drug-induced peripheral neuropathy (DIPN) is a persistent condition, most often associated with anticonvulsants, chemotherapy, cardiovascular, psychotropic, and antimicrobial drugs, such as Metronidazole. In this article, we report the case of a patient who developed polyneuropathy secondary to the use of Metronidazole.

Case Report: D.D.S.L., a 45-year-old female, previously healthy, presented with abdominal discomfort. *Entamoeba histolytica* was detected after investigation, and she started a 7-day cycle of 500 mg of Metronidazole three times a day for seven days, without clinical response. A new therapeutic approach was attempted, with three cycles of 2 grams of Secnidazole single dose and Tinidazole for four weeks. However, the patient presented dysesthesia in the distal third of the thighs, followed by allodynia in the four limbs and trunk. After new abdominal discomfort, three months after the first medication cycle, another pharmacological cycle was started. Neurological examination and electroneuromyography (ENM) examination suggested axonal sensorimotor polyneuropathy in all four limbs.

Conclusion: Polyneuropathy can be caused by many factors, including some frequently prescribed drugs such as Metronidazole and other medications in the 5-nitroimidazole group. Therefore, although the relationship between these drugs and polyneuropathy is not fully elucidated, their neurotoxicity is indisputable, even in rare cases, but with significant variability in terms of the dose-dependent potential for this disease.

Keywords: Antiparasitic agents, Metronidazole, Neuropathology, Tinidazole, Toxicity

Marco Antônio Orsini Neves[1], Ilana Cwajgenberg[2], Daniel Antunes Pereira[3], Wladimir Bocca[4], Acary Bulle de Oliveira[5], Antonio Marcos da Silva Catharino[6]

Affiliations: [1]Physician, Neurologist, Adjunct Professor of Medicine at Universidade Iguaçu, Iguaçu University - UNIG/Nova Iguaçu, RJ, Brazil; [2]Medical student at Universidade Federal Fluminense - UFF/Niterói - RJ, Brazil; [3]Medical student at Iguaçu University - UNIG/RJ, Nova Iguaçu - RJ, Brazil; [4]Division of Neuromuscular Diseases, Federal University of São Paulo (UNIFESP), São Paulo, SP, Brazil; [5]Physician at the Paulista School of Medicine of the Federal University of São Paulo - UNIFESP SP, São Paulo - SP, Brazil; [6]Department of Neurology of Hospital Geral de Nova Iguaçu, PhD student in Neurology at the Federal University of the State of Rio de Janeiro - UNIRIO, Adjunct Professor of Medicine at Iguaçu University - UNIG/Nova Iguaçu, RJ, Brazil.

Corresponding Author: Antônio Marcos da Silva Catharino, Rua Gavião Peixoto 70, Sala 811, CEP 24.2230-100, Icaraí, Niterói - RJ, Brazil; Email: catharino.antonio@gmail.com

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INTRODUCTION

The term polyneuropathy refers to a generalized involvement of peripheral nerves, usually involving mainly the distal nerves and, more often, presenting with

symptoms and clinical sensory, motor, and autonomic findings. With an estimated prevalence of 5–8%, they are the most prevalent type of peripheral nervous system disorder in adults, particularly in the elderly [1].

Among the main symptoms and clinical findings, it is possible to enumerate tingling, burning, paresthesia, dysesthesia, allodynia, sensory ataxia, weakness, muscle loss, fasciculations, diarrhea, and dry skin [1].

A wide variety of factors can lead to neuropathy, including toxic, inflammatory, infectious, and metabolic disorders such as diabetes, alcohol abuse, and medication, as reported in the case. Drug-induced peripheral neuropathy (DIPN) is a persistent condition, most often associated with anticonvulsants, chemotherapy, cardiovascular, psychotropic, and antimicrobial drugs. It usually affects patients with previous risk factors such as diabetes, genetic diseases, and pre-existing neuropathy [1], but it can affect previously healthy patients.

This condition is related to the neurotoxicity of the drug and depends on the exposure time and dose. Furthermore, some drugs are reported in the literature as possible causes of polyneuropathy, namely, Chloroquine, Lithium, Phenytoin, Hydralazine, Metronidazole, Quinolones, and amiodarone [1, 2].

Drug-induced peripheral neuropathy is an exclusion diagnosis based on the clinical history and administration of a triggering drug associated with neuropathy, leading to paresthesia in the half-glove distribution, usually weeks to months after the drug regimen. Most frequently, the distal segments of the most vulnerable nerves are most affected [2].

Metronidazole, a 5-nitroimidazole, is a commonly prescribed antibiotic used to treat conditions such as trichomoniasis, amoebiasis, and giardiasis. Among the 5-nitroimidazole group, only Metronidazole and Tinidazole [3] have been related to neurotoxicity, which may affect both the central and peripheral nervous system, although their mechanism is still not well understood. However, some theories have been proposed, such as that nerve damage is the result of free radicals produced during metronidazole metabolism or that metronidazole and its metabolites are capable of causing inhibition of protein synthesis, generating degeneration of nerve fibers [4] and, in rats, it was observed that the drug bound to RNA, leading to inhibition of protein synthesis and axonal damage [5, 6].

With short-term use of Metronidazole, approximately three weeks, peripheral neuropathy is uncommon. However, when used in high doses and for a prolonged period, the risk of peripheral neuropathy increases; however, this effect is usually reversible when drug therapy is interrupted. There have also been reports of cerebellar dysfunction, vestibulotoxicity, cochlear toxicity, ataxic gait, and seizures [3–5].

In this article, we report the case of a patient who developed polyneuropathy secondary to the use of Metronidazole.

CASE REPORT

D.D.S.L., a 45-year-old female, previously healthy, without comorbidity and chronic diseases, presented abdominal discomfort in September of 2021. The patient sought help from a Gastroenterologist, who requested some complementary exams for investigation: a parasitological stool sample, which detected *Entamoeba histolytica*; complete blood test screening, with no abnormalities; an upper digestive endoscopy, which showed a mild inflammatory process with minimal erosion, suggesting gastritis; an ultrasound and a computerized abdominal tomography (CT), both within normality.

After 30 days, she initiated a seven-day cycle of 500 mg of Metronidazole three times a day for seven days, with no clinical response. In December of the same year, a new therapeutic approach was attempted, with three cycles of 2 grams of Secnidazole single dose and Tinidazole (dose not informed) for four weeks. Meanwhile, the patient presented mild tingling and dysesthesias in the distal third of the thighs, followed by allodynia in the four limbs and upper body. In January 2022, the patient was discharged after the resolution of symptoms and a new negative parasitological stool sample.

In March of 2022, abdominal discomfort recurred. A new parasitological stool sample identified *Giardia lambda*, which was unsuccessfully treated with one more cycle of 2 grams of Secnidazole single dose and 400 mg of Albendazole once a day. The paresthesias in the arms and legs became more exacerbated, evolving into allodynia. In June, ten more days of 500 mg of Metronidazole three times a day were attempted. An infectious disease specialist ordered three parasitological stool samples, one every other day, and complete intestinal analysis, namely molecular screening of gastrointestinal pathogens, which detected enteropathogenic *Escherichia coli*. At this moment, the paresthesia presented a stocking-glove distribution. In August, the patient underwent a new treatment, with five days of Ciprofloxacin, leading to the resolution of the abdominal symptoms.

In the neurological exam, she presented an ataxic gait, a static and dynamic balance compromised due to sensory impairment, and a positive Romberg Test. A superficial tactile, thermal, and painful hypoesthesia was observed, in addition to proprioceptive hypoesthesia and impaired vibratory sensation in the brachial and distal third of the thighs. The Achilles reflexes were abolished bilaterally, and muscle strength was normal. Motor coordination was unreliable due to impaired sensitivity—normal higher functions and sphincter control. Thoracic and lumbar magnetic resonance imaging demonstrated the presence of mild disc protrusion in L5-S1. The electroneuromyography (ENM) exam suggested an axonal sensory-motor polyneuropathy in the four limbs.

DISCUSSION

This patient used several medications, but before the onset of neurological symptoms, only Metronidazole, Secnidazole, and Tinidazole were used. Secnidazole has not yet been related to neuropathy, and Tinidazole has been reported in only a few cases but not as monotherapy [3, 7]. On the other hand, much has been discussed about the potential neurotoxicity of Metronidazole, and although it is not a frequent condition, various cases have been published. Therefore, after excluding other possible etiologies for the patient's symptoms, the polyneuropathy was associated with Metronidazole.

Metronidazole, an antibiotic and antiprotozoal drug that passes freely through the blood-brain barrier [5], is neurotoxic and can affect the central nervous system (CNS)—presenting as ataxia, altered mental status, dysarthria, as well as, with lower frequency, seizures, encephalopathy, cerebellar dysfunction [5, 8] and slurred speech [9]. It can also affect the peripheral nervous system, causing peripheral neuropathy, although it is considered a rare condition, four times less frequent than CNS impairment [10, 11]. Central nervous system symptoms are potentially reversible, usually improving within a few days, and symptoms may disappear within weeks [12], in contrast to what has been observed with symptoms of polyneuropathy [5, 10]. When the CNS is affected, typical image findings include symmetrical T2/FLAIR hyperintensities of the dentate nuclei, dorsal aspect of the pons, medulla, genu, and splenium of the corpus callosum [9], and one study suggests an electroencephalogram (EEG) pattern—a marked theta activity with progressive anteroposterior diffusion [13].

Metronidazole-induced neurotoxicity has an estimated incidence of less than 1% [14], although the prevalence of this condition may be underestimated due to its frequent use for different diseases and the lack of knowledge that Metronidazole can be neurotoxic. It is still unclear whether metronidazole neurotoxicity is dose-dependent or an idiosyncratic reaction; some authors suggest that prolonged treatment and higher doses are risk factors for the onset of the disease [14]. In addition, patients with concomitant liver and kidney disease, alcohol use, and neurotropic medications are at increased risk of complications [5, 15].

A systematic review concluded that peripheral neuropathy is uncommon in therapies lasting less than four weeks [14]. However, the patient used a total of seven days of Metronidazole (first cycle) without clinical improvement, and symptoms appeared after three cycles of Secnidazole and Tinidazole for four weeks, followed by worsening of the neurological symptoms after a new 10-day cycle of metronidazole (second cycle). Clinical manifestations usually appear after at least 6–7 weeks of drug use. However, it may occur with shorter treatments. In a review including 110 cases, the mean cumulative dose was 65.4 g, despite a wide variability of doses (5–2000 g), not supporting a dose-dependent analysis of the drug's relationship with polyneuropathy [5]. A recent study published in 2022 suggests that patients using less than 42 grams of Metronidazole have a lower risk of developing peripheral neuropathy, which appears reversible on discontinuation of therapy [14].

Taking into consideration both cycles of Metronidazole, the patient used a total of 25.5 grams of Metronidazole, which is below the average dose of 42 grams mentioned in the above mentioned article. However, Tinidazole was also used by the patient before the onset of symptoms, and the possibility of mutual cumulative toxicity of the drugs must be considered in this case. Nonetheless, the chance that Secnidazole is also potentially neurotoxic must also be considered.

CONCLUSION

Polyneuropathy can be caused by many factors, including some frequently prescribed drugs such as Metronidazole and Tinidazole, although its mechanism is still not fully elucidated. The prevalence of this condition is very low, although it may be underestimated due to the frequent use of these drugs and the lack of knowledge that they may be neurotoxic. Therefore, more research is needed to define better the pathophysiology and epidemiology related to the case and identify further classes of drugs related to neurotoxicity.

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Author Contributions

Marco Antônio Orsini Neves – Conception of the work, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Ilana Cwajgenberg – Conception of the work, Design of the work, Acquisition of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Daniel Antunes Pereira – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Wladimir Bocca – Conception of the work, Analysis of data, Drafting the work, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Acary Bulle de Oliveira – Design of the work, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Antonio Marcos da Silva Catharino – Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.