Arch Argent Pediatr. 2025;e202410599

Voriconazole-associated peripheral polyneuropathy: A case report

Bárbara J. González[1], Paula Ivarola[1], Miguel Miranda[1], Roberto Caraballo[1], M. Soledad Monges[1]

ABSTRACT

Invasive fungal infections, especially aspergillosis, severely affect immunocompromised patients. The use of azoles, particularly voriconazole, has been considered an effective antifungal therapy for the treatment of these infections and prevention. However, cases of peripheral neuropathy have been reported in patients treated with this drug.

We present two clinical cases of patients with immunocompromise (acute myeloblastic leukemia and primary immunodeficiency) who, during treatment with voriconazole, developed peripheral sensory motor axonal polyneuropathy, which completely resolved after discontinuation of the medication. Given the rapid resolution of the clinical manifestations after discontinuation of the drug, we consider it essential to keep this neurotoxicity in mind as a differential diagnosis in children exposed to multiple medications.

Keywords: *drug-related side effects and adverse reactions; toxicity; voriconazole; polyneuropathy.*

doi: http://dx.doi.org/10.5546/aap.2024-10599.eng

To cite: González BJ, Ivarola P, Miranda M, Caraballo R, Monges MS. Voriconazole-associated peripheral polyneuropathy: A case report. *Arch Argent Pediatr.* 2025;e202410599. Online ahead of print 31-JUL-2025

[1] Neurology Department, Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan, Autonomous City of Buenos Aires, Argentina.

Correspondence to *Bárbara J. González: barbi.jg@gmail.com*

Funding*: None.*

Conflict of interest: *None.*

Received*: 11-21-2024*
Accepted*: 6-17-2025*

INTRODUCTION

Invasive fungal infections affect immunocompromised patients severely and require prolonged antifungal therapy. *Aspergillus* spp. is one of the most frequent invasive mycoses. Azoles are considered the safest alternative for treatment. They are divided into two groups: the imidazoles, limited to superficial mycoses (ketoconazole, miconazole, clotrimazole), and the triazoles for invasive mycoses (fluconazole, itraconazole, voriconazole, posaconazole, and isavuconazole).[1] Voriconazole is considered the drug of choice for both treatment and prevention of invasive aspergillosis (IA) in these patients. It is the first therapeutic option, and there is evidence of better responses as initial treatment for IA in survival and safety of administration compared to amphotericin B.[2] The Food and Drug Administration approved it for treatment of IA in May 2002.[3] The literature describes severe central and peripheral neurological adverse effects, which have not been associated with toxic therapeutic levels of the medication in the blood.[4]

This article aims to report two pediatric patients diagnosed with acute myeloblastic leukemia and primary immunodeficiency who presented with peripheral polyneuropathy during treatment with voriconazole. An analysis of the patients' medical records was performed with a literature review of articles on voriconazole-associated neurotoxicity published in the international literature.

CLINICAL CASES

Clinical case 1

A 5-year-old boy with no relevant perinatal or family history, diagnosed with acute myeloblastic leukemia, who received chemotherapy with cytarabine and etoposide. After the third block of chemotherapy, he started treatment with voriconazole for invasive aspergillosis. Twelve days later, he developed pain in the posterior aspect of both lower limbs and weakness, predominantly distal, and hyporeflexia. As he was an immunosuppressed patient, complementary studies were performed, including normal neuroimaging, cerebrospinal fluid (CSF) cytochemistry without albumin-cytological dissociation or presence of neoplastic cells in flow cytometry, and determination of heavy metals (lead, mercury, chromium, and arsenic) normal, determination of voriconazole in blood with subtherapeutic levels, thyroid profile and vitamin B12 within normal limits. The evaluation was completed with electromyogram that showed moderate sensory-motor polyneuropathic compromise of primary axonal character, without signs of denervatory activity, with slowing of conduction velocities and prolonged latencies (*Figure 1*).

Clinical case 2

A 10-year-old girl with no relevant perinatal or family history had a diagnosis of primary immunodeficiency in 2014 and a history of hematopoietic precursor cell transplantation (HPTCT) in 2018. She started treatment with voriconazole in 2017 for pulmonary aspergillosis and developed an acute symptoms of functional impotence and pain in the lower limbs five years after the start of medication. The following studies were performed: normal neuroimaging, normal CSF cytochemistry, blood laboratory with thyroid profile, and vitamin B12 within normal limits. The evaluation was completed with electromyogram that showed mild/moderate polyneuropathy, mild/moderate primary axonal involvement, without signs of denervation activity with slowed conduction velocities and slightly prolonged latencies (*Figure 2*).

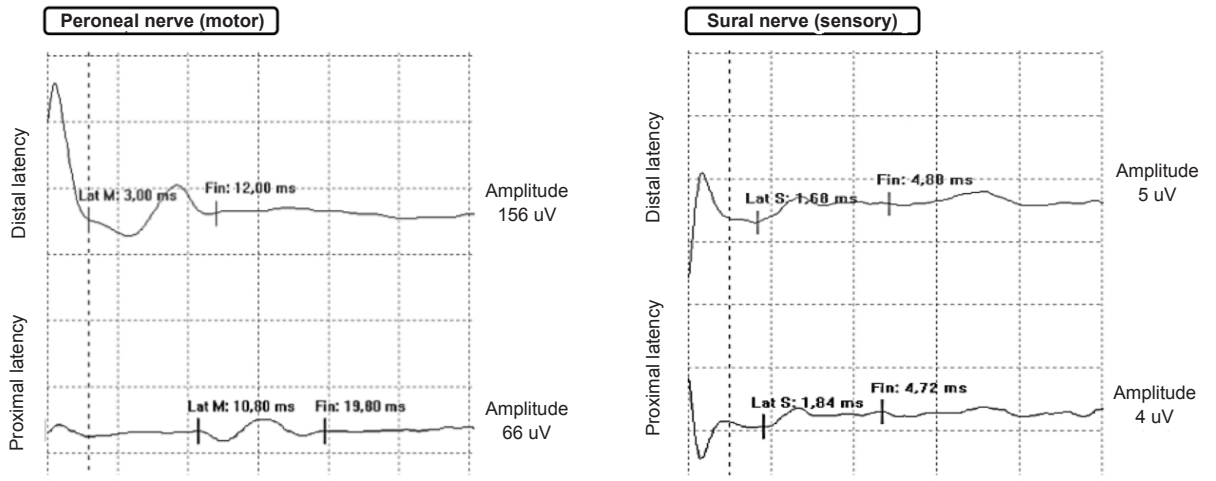
In both clinical cases, complementary studies were performed to rule out causes of peripheral polyneuropathy secondary to their underlying disease. With normal complementary studies in both clinical cases, the first presumptive diagnosis was toxicological-drug cause; both were receiving voriconazole as treatment for *Aspergillus* infection, so it was decided to suspend the treatment, and the clinical manifestations were completely resolved after 7 days. A diagnosis of neurotoxicity secondary to voriconazole was finally assumed (*Figure 3*).

DISCUSSION

Invasive mycoses have a high mortality, which reaches more than 50% in the case of IA. The risk factors described for these infections include immunosuppression, chemotherapy for neoplastic diseases, and individuals receiving HPTCT or solid organs, among others.[1]

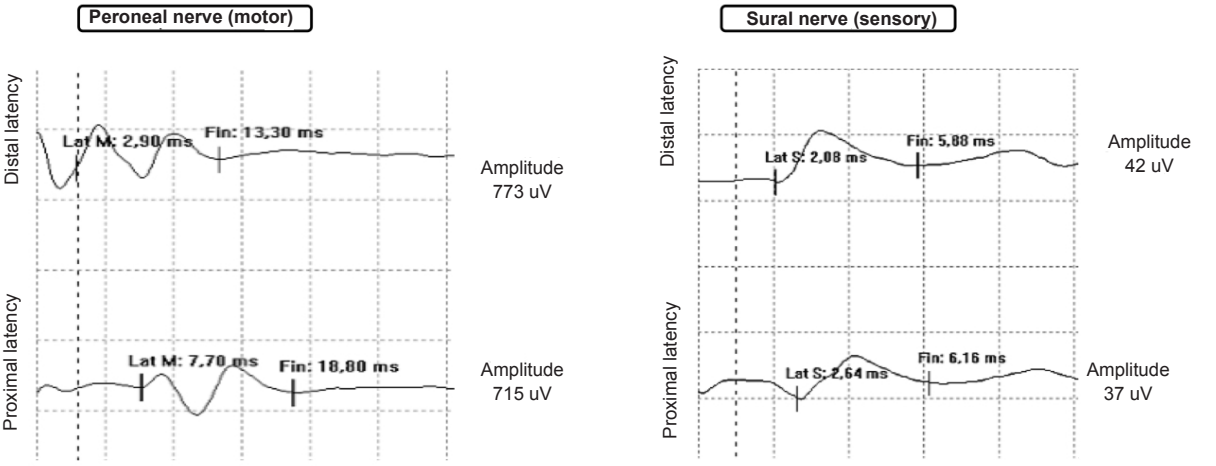
Azole antifungal agents are nowadays the safest alternative for the treatment of invasive mycoses. They form a heterogeneous group characterized by a free imidazole ring, joined by carbon-nitrogen bonding to other aromatic rings. The physicochemical properties, therapeutic effects, and toxicity of each compound depend on the number of nitrogens present in its bonds. The target of action of the azoles is in the fungal

Figure 1. Clinical case 1: electromyogram with tracing of the motor peroneal nerve and sensory sural nerve showing a pattern consistent with sensory-motor axonal polyneuropathy



Marked reduction in the amplitudes of motor and sensory evoked potentials in the peroneus motor (0.15 mV, normal reference value 3.5 mV) and sural sensory (0.05 mV, normal reference value 1.5 mV) nerves. Conduction velocities remained within normal or slightly decreased limits in the peroneal motor (24.3 m/s, normal reference value 51.0 m/s) and sensitive sural (38 m/s, normal reference value 56 m/s) nerves, indicating relative myelin integrity.

Figure 2. Clinical case 2: electromyogram with tracing of the peroneal motor and sensory sural nerve showing a pattern compatible with sensory-motor axonal polyneuropathy



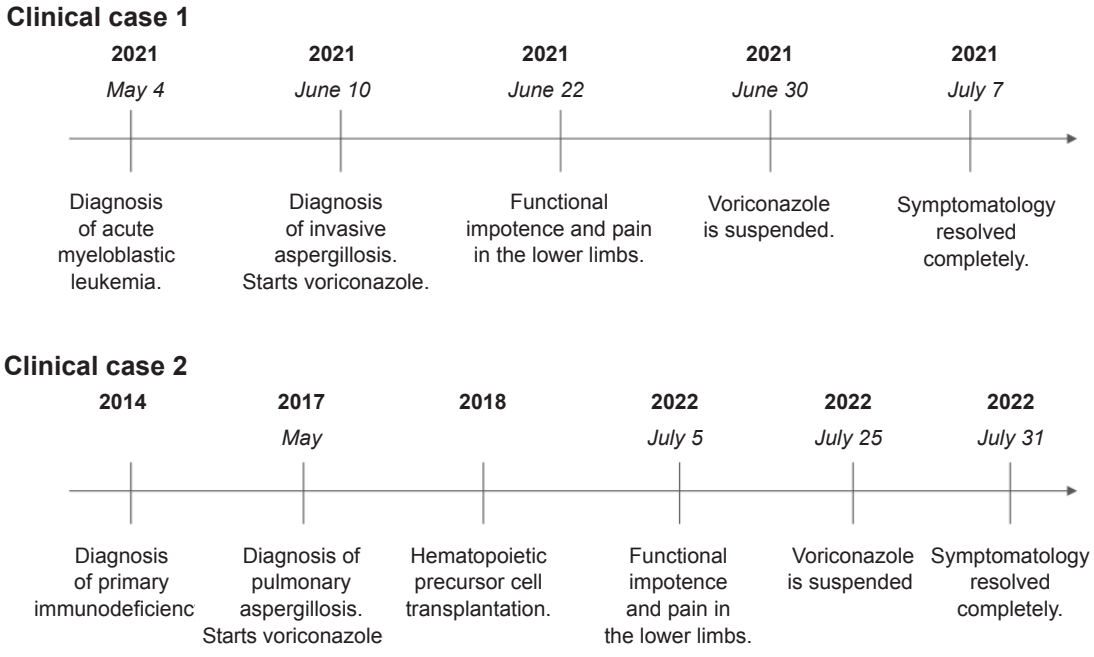
Marked reduction in amplitudes of motor and sensory evoked potentials in the peroneus motor (0.71 mV, normal reference value 3.5 mV) and sural sensory (0.04 mV, normal reference value 1.5 mV) nerves. Conduction velocities remained within normal or slightly decreased limits in the peroneal motor (45.8 m/s, normal reference value 51.0 m/s) and sensitive sural (48 m/s, normal reference value 56 m/s) nerves, indicating relative myelin integrity.

cell wall. The integrity of the cell wall is given by the sterols that form it (ergosterol, the main lipid component). The azoles inhibit cytochrome P450-dependent 14 alpha-sterol-demethylase, whose function is to bind ergosterol precursors. This leads to the formation of a membrane fungal plasma with structural and functional alterations.[1]

The reported incidence of peripheral neuropathy in patients treated with azoles is very varied in the literature. It should be emphasized that the studies performed are based on small cohorts. For example, Boussaud et al. report an incidence of 30% in transplant recipients receiving voriconazole[5] and Baxter et al. report incidence rates of 9% and 17% in patients treated with voriconazole and itraconazole, respectively.[6]

Symptoms include paresthesias, neuropathic pain, severe weakness, and functional

Figure 3. Timeline of clinical cases 1 and 2



impotence that develop within 2 to 3 weeks of treatment initiation and resolve 1 month after discontinuation. The acute presentation reported in this article coincides with the cases published in the international literature.[3-5]

In such patients with hematologic malignancies or solid organ or hematopoietic stem cell transplantation, treatment with voriconazole is usually for prolonged periods (weeks to months). It is often associated with other chemotherapeutic or immunosuppressive medications in their background treatment that can also produce neurotoxicity.[7,8] For example, in patients with hematologic malignancies, the exposure to vinca alkaloids is the most common risk factor for the development of peripheral neuropathies. Due to the dose-dependent nature of vinca toxicity, concomitant use of vinca alkaloids and azole antifungals increases the patient's risk of developing peripheral neuropathies.[8] This interaction with triazoles is well documented and is attributed to a potent inhibition of CYP3A4-mediated metabolism of chemotherapeutic agents by azoles and inhibition of P-glycoprotein-mediated efflux of vinca alkaloids by itraconazole or posaconazole;[9] therefore, avoidance of this combination is recommended.[9-11]

Although the pathophysiology of azole-induced peripheral neuropathy is still not entirely clear, it has been theorized that the azole group plays a vital role in the development of peripheral neuropathy; however, other drugs that include the azole group in their molecular structure were not shown to induce peripheral neuropathy.[6]

A possible predisposition may be the wide variety of genetic polymorphisms in the voriconazole metabolism system via CYP2C19.[12]

The risk of peripheral neuropathy associated with azole therapy appears to be higher in patients with elevated predisposition to neuropathies, e.g., diabetes mellitus.[13,14]

Another parameter to highlight in the first clinical case is that serum voriconazole levels were found in subtherapeutic concentrations, which speaks of an idiosyncratic reaction to the drug, which also coincides with what has been reported in the literature analyzed.[4-6,8]

To prevent potentially irreversible voriconazole-associated neuropathy, some experts suggest using a scale to detect early peripheral neuropathy during the first 6 months of treatment;[8] and, if suspected, nerve conduction studies (NCS) should be performed. If normal, it is worth considering small nerve fiber studies, as small nerves tend to be affected earlier.[4,7]

From this electromyographic point of view, the neuropathy detected is typically axonal and symmetrical, motor and sensory.[3,6]

As reported, symptoms improve with drug discontinuation; this was also observed in our

patients. It is essential to rule out all probable etiologies, as many of them may be irreversible, so we consider voriconazole polyneuropathy to be a diagnosis of exclusion.

Given the rapid resolution of the clinical picture upon discontinuation of voriconazole, we believe it is crucial to keep in mind this peripheral neurotoxicity in children exposed to multiple drugs and highlight the idiosyncratic characteristic of this condition, since no toxic blood concentrations of voriconazole were found in the literature or our patients. ■

REFERENCES

1. Nocua-Báez LC, Uribe-Jerez P, Tarazona-Guaranga L, Robles R, Cortés JA. Azoles de antes y ahora: una revisión. *Rev Chilena Infectol*. 2020;37(3):219-30.
2. Herbrecht R, Denning D W, Patterson T F, Bennett J E, Greene R E, Oestmann J W, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347(6):408-15.
3. Aksoy F, Akdogan E, Aydin K, Yilmaz M, Altunayoglu V, Sozen EE, et al. Voriconazole-Induced Neuropathy. *Chemotherapy*. 2008;54(3):224-7.
4. Levine MT, Chandrasekar PH. Adverse effects of voriconazole: Over a decade of use. *Clin Transplant.* 2016;30(11):1377-86.
5. Boussaud V, Daudet N, Billaud EM, Lillo-Le Louet A, Amrein C, Maud Bergé M, et al. Neuromuscular Painful Disorders: A rare side effect of voriconazole in lung transplant patients under tacrolimus. *J Heart Lung Transplant*. 2008;27(2):229-32.
6. Baxter CG, Marshall A, Roberts M, Felton TW, Denning DW. Peripheral neuropathy in patients on long-term triazole antifungal therapy. *J Antimicrob Chemother*. 2011;66(9):2136-9.
7. Benitez LL, Carver PL. Adverse Effects Associated with Long-Term Administration of Azole Antifungal Agents. *Drugs*. 2019;79(8):833-53.
8. Azanza JR, Mensa J, Barberán J, Vázquez L, Pérez de Oteyza J, Kwon M, et al. Recommendations on the use of azole antifungals in hematology-oncology patients. *Rev Esp Quimioter*. 2023;36(3):236-58.
9. Moriyama B, Henning SA, Leung J, Fadale-Nwulia O, Jarosinski P, Penzak SR, et al. Adverse Interactions between Antifungal Azoles and Vincristine: Review and Analysis of Cases. *Mycoses*. 2012;55(4):290-7.
10. Sathiapalan RK, El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. *Pediatr Hematol Oncol*. 2001;18(8):543-6.
11. Gubbins PO, Heldenbrand S. Clinically relevant drug interactions of current antifungal agents. *Mycoses*. 2010;53(2):95-113.
12. Theuretzbacher U, Ihle F, Derendorf H. Pharmacokinetic/ pharmacodynamic profile of voriconazole. *Clin Pharmacokinet.* 2006;45(7):649-63.
13. Neundörfer B. Polyneuropathies – symptoms, causes and diagnostic procedure. *Ther Umsch.* 1993;50(11):761-5.
14. Tsiodras S, Zafiropoulou R, Kanta E, Demponeras C, Karandreas N, Manesis EK. Painful peripheral neuropathy associated with voriconazole use. *Arch Neurol*. 2005;62(1):144-6.