

Vincristine-Induced Neuropathy Presenting as Ptosis and Ophthalmoplegia in a 2-Year-Old Boy

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ABSTRACT

Vincristine is used in the treatment of leukemias, solid tumors, and lymphomas. A case of a 2-year-old boy undergoing treatment for leukemia who developed sudden onset bilateral ptosis and ophthalmoplegia along with generalized neuropathy due to vincristine's neurotoxic effects is presented. He was successfully treated with pyridoxine and pyridostigmine. The possible mechanisms of action and the treatment for vincristine-induced neuropathy are discussed. Prompt treatment and close follow-up is needed, especially in children because prolonged ptosis and motility restriction may have a profound effect on a child's visual function. [*J Pediatr Ophthalmol Strabismus*. 2015;52:e34-e37.]

INTRODUCTION

Vincristine is a vinca alkaloid used in the treatment of leukemias, solid tumors, and lymphomas in children and adults. It is a marrow-sparing cytotoxic agent but has known side effects such as neurotoxicity, which was first reported in 1967.¹ The mechanism of action of vincristine's neurotoxicity is that it interferes with the functioning of the axonal microtubule,² which results in axonal degeneration and delayed axon transportation.^{3,4} Vincristine has poor penetration into the central nervous system⁵; therefore its neurotoxic effects are seen largely in the peripheral nervous system. As a result, autonomic and

cranial neuropathy are relatively uncommon and may present individually or along with severe peripheral neuropathy. In this case report, we describe a patient with precursor B-cell leukemia undergoing treatment who presented with bilateral ophthalmoplegia as a rare manifestation of vincristine-induced neurotoxicity.

CASE REPORT

A 2-year-old boy with precursor B-cell acute lymphoblastic leukemia was undergoing treatment as per MCP 841 protocol consisting of vincristine, prednisolone, L-asparaginase, methotrexate, and daunorubicin. He developed febrile neutropenia on day 13 of induction, which responded to parenteral antibiotics. Five weeks after induction, his mother noticed bilateral drooping of the eyelids, abnormal head position, and jerky movements of the eyes. The cumulative dose of vincristine that he had received before development of ptosis was 2.8 mg. There were no previous clinical symptoms of neuropathy and no positive history for inherited neuropathies. There was no use of any other drugs known to cause neurotoxicity.

On examination, vital signs were normal and the child was afebrile. Ophthalmologic examination showed severe, bilateral ptosis with chin elevation and eyelid edema (**Figure 1A**). Sleep test and ice test were negative. He was not fixing or following light

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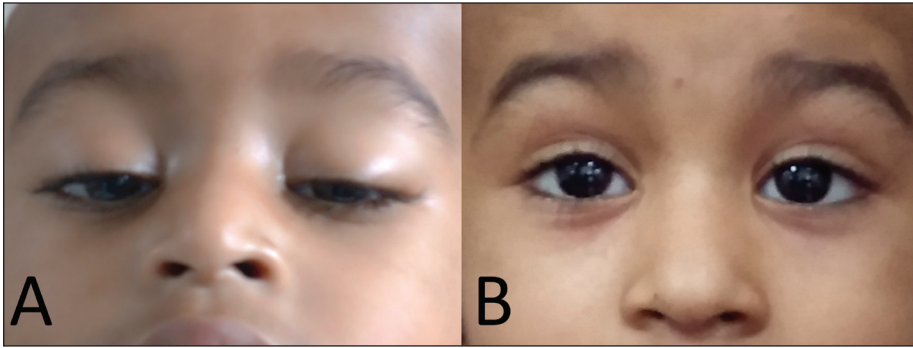


Figure 1. (A) Photograph depicting the acquired ptosis. Note the chin-up position adopted by the child due to ophthalmoplegia. (B) Post-treatment photograph demonstrating complete recovery of the ptosis.

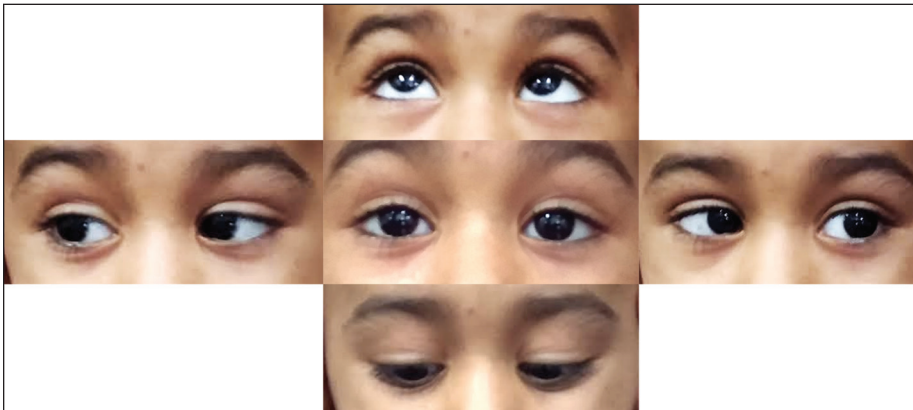


Figure 2. A montage of motility photographs showing complete recovery of extraocular muscle function following treatment.

with small amplitude disjugate nystagmoid movements. There was difficulty in initiating voluntary saccades, but doll's eye reflex was present. Corneal and pupillary reflexes were normal and fundus examination was unremarkable.

A neurological examination revealed difficulty in walking with lower limb weakness. The tone in the lower limbs was normal, power was graded as 3/5, and deep tendon reflexes were depressed. To rule out central nervous system involvement of the leukemia, a cerebrospinal fluid sample was examined and found to be clear with normal opening pressure, protein, and glucose levels, and no atypical cells. Serum electrolytes and calcium levels and liver enzyme were normal. Magnetic resonance imaging of the brain and orbit showed no abnormalities. Electromyography was normal with full recruitment of the motor unit potential. Motor nerve conduction velocity study was normal with no decremental response on repetitive nerve stimulation. Anti-acetylcholine receptor antibodies were also negative on serological testing. The clinical evaluation, electrophysiological tests, and serological investigations conclusively ruled out myasthenia gravis, which could have been drug induced. Therefore, a working diagnosis of vincristine-induced neurotoxicity as the

cause for external ophthalmoplegia was made and treatment was instituted.

A neuroprotective and neuroregenerative regimen with pyridoxine (40 mg orally twice daily) and pyridostigmine (3 mg/kg/day) was initiated and vincristine was withheld subsequently. The two drugs were well tolerated and bilateral ptosis markedly improved and completely resolved after 4 weeks (**Figure 1B**). The ocular movements on last follow-up were full, free, and painless (**Figure 2**). Vincristine was withheld for the remainder of chemotherapy.

DISCUSSION

Neurotoxicity is considered to be one of the major dose-limiting side effects of vincristine. Symptoms of toxicity usually appear 2 to 19 weeks after the commencement of vincristine.⁴ As described previously, the pathogenesis of neuropathy is explained by vincristine causing structural changes in the microtubules of the nerves and interfering with axoplasmic transport.⁶ In addition, secondary to axonal damage, reduction of myelin thickness,⁷ shortening of inter-nodal length, and segmental demyelination can occur due to vinca alkaloids.⁸

In our patient, the cumulative dose was well below the toxic high dose of vincristine and there was

TABLE 1

**Risk Factors for
Vincristine-Induced Neuropathy**

1. Cumulative dosage exceeding maximum cumulative dose of 30 to 50 mg⁵
2. Hypersensitivity to vincristine
3. Preexisting liver dysfunction
4. Poor nutritional status
5. Hereditary neuropathy
6. Concomitant use of neurotoxic agents (allopurinol, erythromycin, mitomycin C, phenytoin, itraconazole)¹⁵

no concomitant administration of any other neurotoxic drug (Table 1). However, the eyelid edema increased suspicion toward orbital metastasis, which was ruled out on imaging, as was myasthenia gravis. However, an increased latency period suggested motor axonal neuropathy. The presence of concurrent peripheral neuropathy also favored a diagnosis of a drug-induced neuropathy. However, the definitive diagnosis of vincristine-induced neurotoxicity is attained by exclusion of various other etiologies presenting with similar clinical picture.⁵ Ptosis with ocular movement disorder is a rare combination of cranial neuropathy in vincristine toxicity. Furthermore, the timing of the ophthalmic symptoms with relation to the onset of chemotherapy, the normal cerebrospinal fluid study, and normal brain magnetic resonance imaging tilted the diagnosis in favor of vincristine-induced neurotoxicity.

Vincristine-induced neurotoxicity is usually reversible when therapy is discontinued. The median duration of paresthesias and motor weakness after treatment discontinuation is 3 months.⁸ There are a few case reports of full recovery of bilateral ptosis associated with vincristine (cranial polyneuropathy) after treatment with pyridoxine and pyridostigmine.⁹⁻¹³ Although neuropathic manifestations are largely reversible, residual weakness can be detrimental, especially in children younger than 6 years. Prolonged untreated or neglected ptosis or strabismus can lead to stimulus deprivation amblyopia or suppression, respectively. Reduction in dose level and frequency of administration or, if required, treatment discontinuation, are the only certain methods to ameliorate and limit the progression of vincristine-induced neurotoxicity.⁸ The suggested

guidelines for dose adjustment of vincristine depend on the severity of the neuropathy. In mild cases, where only areflexia is noted, vincristine may be continued at 100% dosage, whereas in cases where abnormal buttoning is observed or writing is affected, the recommended dose up to 67% is advised. Withholding vincristine until recovery followed by dose reduction up to 50% is recommended in cases where moderate motor neuropathy (including cranial neuropathy) is seen, and avoiding vincristine altogether is advised in cases where severe motor neuropathy is noted.^{4,8}

Studies in animals have indicated that pyridoxine can afford some amount of neuroprotection during intrathecal administration of lethal doses of vincristine.¹² Pyridostigmine has also shown improvement in patients with autonomic neuropathy.¹⁴ Although there is no class I evidence suggesting a regimen for the treatment of vincristine-induced neurotoxicity, the presence of anecdotal reports that have reported considerable success in the treatment of vincristine-induced neuropathy prompted a trial of the same agents.

We highlight through our case report that a detailed history and careful ophthalmologic and neurologic examination with a high degree of suspicion can identify vincristine-induced neurotoxicity. Prompt treatment and close follow-up is needed, especially in children because prolonged ptosis and motility restriction may have a profound effect on a child's visual function.

Vincristine is used to treat many pediatric malignancies, such as retinoblastoma, rhabdomyosarcoma, and leukemia. Therefore, ophthalmologists and oncologists alike must be sensitive to the possibility of children undergoing chemotherapy developing vincristine-induced neurotoxicity, which may present in unusual ways and require their immediate intervention.

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