CASE REPORT

Vincristine-induced polyneuropathy in a child with stage I Wilms' tumour presenting with unilateral abducens nerve palsy

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SUMMARY

A 4-year-old boy presented with right esotropia while receiving vincristine and dactinomycin for stage I Wilms' tumour according to the National Wilms Tumour Study-5 protocol. On examination, he had isolated limitation of his right lateral gaze. CT of the brain and cerebrospinal fluid examination were normal. A nerve conduction velocity study which was performed on the peripheral nerves revealed predominant motor polyneuropathy compatible with axonal loss involving the upper limbs. The patient had received a cumulative vincristine dose of 17 mg/m² before developing esotropia. Vincristine-induced abducens nerve mononeuropathy and subclinical motor polyneuropathy was suspected. Unilateral esotropia markedly improved after the discontinuation of vincristine and a short course of oral pyridoxine treatment.

BACKGROUND

Vincristine is one of the vinca alkaloid chemotherapies that is widely used in haematological malignancies and solid tumours. Vincristine interrupts the mitotic phase of cell proliferation by inhibition of mitotic spindle function, disrupting the spindle microtubule organisation and at high concentrations causing microtubule depolymerisation.¹ Vincristine causes a proteasome-mediated degradation of tubulin in neural cells, leading to axonopathy.² The dose-limiting side effect of vincristine is neuropathy. Most common manifestations are constipation and peripheral neuropathy. Cranial neuropathy is uncommon.³ The presentation includes ptosis, ophthalmoplegia, diplopia, facial palsy, jaw pain and vocal cord paralysis.^{3–8}

CASE PRESENTATION

A 4-year-old boy presented with right esotropia. He had been diagnosed with stage I Wilms' tumour of the right kidney. After a right nephrectomy, he was given adjuvant chemotherapy, which consisted of vincristine (1.5–2 mg/m²/dose) and dactinomycin (1.35 mg/m²/dose) according to the National Wilms Tumour Study-5 treatment protocol. He was doing well until the 16th week of chemotherapy, after the 11th dose of vincristine (cumulative dose 9 mg, 17 mg/m²) and the 5th dose of dactinomycin when his parents noticed the right esotropia. He did not have any fever or illnesses prior to developing the symptoms. Apart from being glucose-6-phosphate dehydrogenase deficient, he did not have other

underlying diseases. There was no history of neuropathy in the family. Physical examination revealed an isolated right lateral rectus palsy. The motor power, sensory and other cranial nerves were normal. Grading of deep tendon reflexes was unreliable as the patient did not cooperate well.

INVESTIGATIONS

Laboratory results revealed a haemoglobin level of 11 g/dL, a white cell count of 5100/mm³ with normal differential count and a platelet count of 242 000/mm³. Blood chemistry and liver function tests were normal. CT of the brain showed normal findings. Cytological examination of the cerebrospinal fluid showed an acellular specimen. Nerve conduction velocity (NCV) study was performed on the peripheral nerves (bilateral median nerves, left ulnar nerve, bilateral tibial and sural nerves). The result revealed predominant motor polyneuropathy compatible with axonal loss involving the upper limbs. The sensory studies were normal.

DIFFERENTIAL DIAGNOSIS

Vincristine-induced neuropathy of the abducens nerve was suspected. Differential diagnoses were other toxic neuropathies and intracranial metastasis.

TREATMENT

Vincristine was discontinued. The patient was given 100 mg/day (7.5 mg/kg/day) of oral pyridoxine for 10 days.

OUTCOME AND FOLLOW-UP

The esotropia gradually improved. The patient was well with only mild residual esotropia at 8 months after the onset. He did not have any clinical symptoms of motor weakness or peripheral neuropathy. Follow-up CT of the abdomen showed no evidence of recurrent tumour.

DISCUSSION

Although neurotoxicity is a major side effect of vincristine, the toxicity is mostly peripheral neuropathy.³ Apart from jaw pain associated with the trigeminal nerve involvement, other cranial neuropathies are uncommon. The manifestations vary from facial weakness, jaw pain, ptosis, ophthalmoplegia, diplopia to vocal cord paralysis.^{3–8}

With the history of exposure to vincristine and the abnormal NCV, the cause of the abducens palsy

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in our patient was most likely to be vincristine-induced cranial neuropathy. The abnormal NCV study also depicted subclinical peripheral neuropathy. The findings of axonal neuropathy were also seen in several patients.^{5–7} The abnormal NCV study helps to support the diagnosis of vincristine-induced neurotoxicity.

Vincristine neurotoxicity is related to the dosage and frequency of administration.³ In children from 3 to 11 years old who receive chemotherapy for Wilms' tumour, the predicted neurotoxicity risk at the cumulative dose of 25 mg/m² is 30%.⁹ Our patient had received only a cumulative dose of 17 mg/m² of vincristine when the right esotropia developed. The cumulative dose of vincristine was lower than most cases from earlier reports.

Other factors that may heighten the neurotoxicity of vincristine are pre-existing hereditary neuropathy, such as Charcot-Marie-Tooth disease and ataxia telangiectasia,^{10–11} concomitant use of certain medications that inhibit CYP450 3A and liver dysfunction.^{12–14} Vincristine is metabolised in the liver through the CYP450 3A enzyme system. Medications that inhibit the enzyme include antifungal azoles, cyclosporine, isoniazid and nifedipine, which will increase the plasma concentration of the vincristine when given concurrently.^{12–13}

Our patient had no known risk factors as mentioned for vincristine-induced neurotoxicity. There was no history of neuropathy in the family. The patient was not taking any other medications apart from chemotherapy, and his liver function was normal during the course of chemotherapy. The cause of vincristine-induced neurotoxicity at the lower dose remained unexplained.

There is no definite treatment of vincristine-induced neuropathy. There are several clinical reports of using pyridoxine, pyridostigmine and glutamic acid as a prevention or treatment of the neurotoxicity. Pyridoxine alone or in combination with pyridostigmine is more widely used.^{4–7} Pyridoxine, levocarnitine and N-acetylcysteine have been used together in a neonate with good results.¹⁵ A complete recovery of vincristine-induced cranial polyneuropathy using pyridoxine alone has been reported.⁴ The neuropathy was reversible by months or years, however some were irreversible. Oral glutamic acid was also reported to minimise the side effects of vincristine-induced neuropathy.¹⁶

Our patient received a short course of oral pyridoxine. Vincristine was discontinued. The symptom improved, although mild residual deficit persisted at 8 months. The choice of further chemotherapy between omission of vincristine and alternative chemotherapy was discussed with the family. Although the risk of recurrence was low in stage I Wilms' tumour,¹⁷ alternative chemotherapy was preferred. A combination of cyclophosphamide and etoposide was used.¹⁸

Contributors PP and PC conceived the study and were responsible for the collection of clinical and laboratory data and the drafting of the paper. KK and WC reviewed the clinical data and gave critical comments. All authors were involved in the final revision of the article and approved the final manuscript.

Competing interests None.

Patient consent Obtained.

Learning points

- ▶ Cranial neuropathy, although an infrequent side effect, should be watched for in patients receiving vincristine.
- ▶ Nerve conduction velocity studies can be helpful for the detection of combined cranial and peripheral neuropathy even in a case that presents with isolated cranial nerve involvement, and can be used to support the diagnosis of vincristine-induced neurotoxicity.
- ▶ The neurotoxicity is reversible on the discontinuation of vincristine.
- ▶ Pyridoxine may help with the neurological recovery in cases of vincristine-induced neurotoxicity.

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