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Case Report

Successful Treatment of Vincristine Induced Unilateral Ptosis with Pyridoxine and Pyridostigmine in a Child with Langerhans Cell Histiocytosis (LCH)

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ABSTRACT

We report the case of a 2-year-old boy with langerhans cell histiocytosis who developed vincristine (VCR)-induced unilateral ptosis and recovered on treatment with pyridoxine and pyridostigmine. He was treated with LCH TRAIL (Initial treatment) chemotherapy regimen. Two days after the fifth dose of VCR, he presented with unilateral ptosis. VCR as an antineoplastic drug causes neurotoxicity frequently. Neurological examination revealed unilateral ptosis, without pupillary or other oculomotor dysfunction. The other cranial nerves and peripheral nerves examinations were normal. Cranial magnetic resonance imaging and cerebrospinal fluid examination were normal. The unilateral ptosis markedly improved after two weeks of pyridoxine and pyridostigmine treatment and completely resolved after 3 weeks and there was no further recurrence of ptosis on follow up.

Key words: *Ptosis, vincristine, langerhans cell histiocytosis*

Langerhans Hücreli Histiositozisli Bir Çocukta Vinkristin Nöropatisine Bağlı Unilateral Pitozun Piridoksin ve Piridostigmin ile Tedavisi

ÖZET

Vinkristin bir vinka alkaloidi olup lenfoma, lösemi ve bazı solid tümörlerin kemoterapi protokolünde sıklıkla kullanılır. Periferal nöropati, otonomik nöropati, kranial sinir paralizileri ve ensefalopati olmak üzere dört farklı şekilde vinkristin nörotoksisitesi görülebilmektedir. Bu nörotoksik etkiler vinkristin kullanımında sınırlayıcı faktörler olarak rol oynar (1). Burada, vinkristin içeren kemoterapi protokolünü alırken unilateral pitoz gelişen 2 yaşındaki bir erkek Langerhans hücreli histoisitoz (LCH) olgusu takdim edilmiştir. Hastamızdaki pitozis vinkristin tedavisine bağlı kraniyal nöropati olarak değerlendirilerek, piridostigmin ve piridoksin tedavileri başlanmış ve daha sonra hastamızın pitozisi düzelmiştir.

Anahtar kelimeler: *Ptozis, Vinkristin, Langerhans hücreli histiyositoz*

INTRODUCTION

VCR is a vinca alkaloid used in combination with other agents in the treatment of pediatric malignancies. VCR reversibly binds to spindle proteins in the S phase and inhibits RNA synthesis. This drug is associated with dose-limiting neurotoxicity (1). The mechanism of neurotoxicity is explaned by VCR causes structural changes in the microtubules of peripheral nerves and interference with axoplasmic transport (2). We describe a 2- year-old boy with langerhans cell histiocytosis who were successfully treated with pyridoxine, pyridostigmine.

CASE

A 2-year-old boy was diagnosed langerhans cell histiocytosis with systemic involvement. The patient was treated with tree cycles of methotrexate (500 mg/m^2), six cycles of VCR (1.5 mg/m^2), 42 cycles prednisone(40 mg/m^2). Two days after the fifth VCR treatment, he developed unilateral ptosis without pupillary or other oculomotor dysfunction (Figure 1). He received 3.75 mg (7.5 mg/m^2) cumulative dose of vincristin before development of ptosis. The neurologic examination revealed a unilateral ptosis without ophthalmoplegia. Pupillary and corneal re-

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Figure 1. Unilateral ptosis

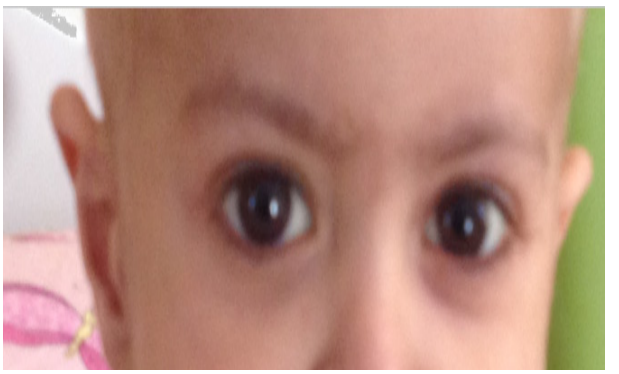

Figure 2. Complete resolution of unilateral ptosis

flexes were normal, as were as the remaining neurologic findings, including deep tendon reflexes and sensibility. Ophthalmologic/ophthalmic examination confirmed that visual acuity and fundus region were normal. He received chemotherapy including following values: hemoglobin, 9.5 g/dL; platelet count, 35 000/mm^3; white blood cell count, 4500/mm^3; aspartate aminotransferase, 33 U/L;

alanine aminotransferase, 15 U/L; lactate dehydrogenase, 950 U/L; triglyceride 195 mg/dl and total bilurubin 9.4 mg/dl. Cerebrospinal fluid examination and cranial MRI was normal. VCR toxicity was suspected. Pyridoxine (150 mg/m^2/day per oral bid) and pyridostigmine (3 mg/kg/day per oral bid) were used in the treatment of VCR-neuropathy. The unilateral ptosis markedly improved after two weeks of pyridoxine and pyridostigmine treatment and completely resolved after 3 weeks . During the follow up of 4 months we did not observe residue or recurrence of the ptosis (Figure 2).

DISCUSSION

When diagnosing the drug related neurophaty, the other causes that may lead similar clinical scenarios should be excluded. The diagnosis is confirmed by the occurence of ocular changes during vincristin treatment, the resolution of symptoms with using of pyrodoxin and pyrodistigmine, the normal examination of cerebrospinal fluid examination and not determining any pathology of brain parenchymal lesion on central imaging. In our case, the ocular examination was normal before chemoteraphy and there is no family history of neuropathy. Unilateral ptosis was occured 2 days after treatment of fifth cycles of VCR. The central imaging was normal and examination of cerebrospinal fluid revealed no pathology in our case. The unilateral ptosis was recovered completely with treatment of pyridoxine (150 mg/m^2) and pyridostigmine (3 mg/kg p.o. bid) which is known as having evidence of neuroprotective and neuroregenerative effect.

VCR exert their antitumor activities by binding to tubulin followed by disruption of mitotic spindle in actively dividing cells. Furthermore, axonal microtubules are also composed of tubulin and neurotoxicity caused by VCR is mainly attributed to disruption of microtubule structure leading to impairment of axoplasmic transport and dying back neuropathy (3). Though some studies have suggested the small increase in an average diameter of C fibers and other subtle changes in axons in A and C fibers with low dose of VCR and paclitaxel (4,5). Neuroprotective and/or neuroregenerative agents have been sought after as an effective therapy for treating such complications.

Puneet Jain et al. reported that , neuropathy electrophysiologically was occured 33.75%.of patients. Symmetric motor axonal polyneuropathy was the most common pattern of involvement seen in 19 (23.8%) children (6). VCR-induced neuropathy is usually mild and severe complications including partial or total paralysis are reported in rare cases (2). The neurotoxicity is dose related and cumulative with repeated dosage such that the drug therapy has to be stopped after a cumulative dose of 30 to 50 mg. Symptoms usually appear 2 to 19 weeks after the commencement of VCR (7). As consistent with literature, in our case, the ptosis was diagnosed after the fifth weeks of treatment with VCR . VCR neurotoxicity may be aggravated by higher dosage (>30 mg), hypersensitivity to the drug, pre-existing liver dysfunction or a hereditary neuropathy, and concomitantly use of other drugs

such as allopurinol, erythromycin, isoniazid, mitomycin C, phenytoin and itraconazole (8). In our patient we did not use high dose vincristin and the other concominant accelerating drugs.

Akbayram et al (9) reported a case of 3-year-old girl who developed unilateral palpebral ptosis during chemotherapy for stage 2a Wilms tumor. They reported that unilateral ptosis was improved after two weeks of pyridoxine and pyridostigmine treatment. A report by Duman et al. described a patient with VCR neurotoxicity with ptosis and facial nerve palsy and treated with pyridoxine alone, which showed complete recovery (10). Recently, several authors reported full recovery of VCR-induced bilateral ptosis after treatment with usual dose of pyridoxine (150 mg/m2 orally twice daily) and pyridostigmine treatment (3 mg/kg orally twice daily) (7,11). In all of these reported patients, treatment was well tolerated and no side effect was documented. The authors also used the same treatment regimen in the present cases.

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