CASE REPORT

SEVERE PERIPHERAL NEUROPATHY SECONDARY TO VINCRISTINE THERAPY

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ABSTRACT

Patients with hereditary neuropathy at high risk of severe vincristine neurotoxicity are well known. Here, along with a review of the literature, we described two patients with unrecognized hereditary neuropathy who developed foot drop following low dose vincristine therapy. With this report, we wanted to emphasize the importance of detailed neurologic examination and history taking before initiating therapy.

Keywords: Hereditary neuropathy, Vincristin, Neurotoxicity

VİNKRİSTİN TEDAVİSİNE BAĞLI GELİŞEN AĞIR PERİFERİK NÖROPATİ

ÖZET

Herediter nöropatisi olan hastaların vinkristin nörotoksisitesi için yüksek risk taşıdığı bilinmektedir. Burada, daha önceden bilinen nöropatisi olmayan ve düşük doz vinkristin tedavisi sonrası düşük ayak gelişen iki olgu literatür eşliğinde sunulmuştur. Olguların rapor edilmesinin amacı tedavi öncesi ayrıntılı nörolojik muayenenin ve öyküde herediter nöropati varlığının araştırılmasının önemini vurgulamaktır.

Anahtar Kelimeler: Herediter nöropati, Vinkristin, Nörotoksisite

INTRODUCTION

The vinca alkoloid vincristine is a commonly used chemotherapeutic agent in the treatment of different types of malignancies. Its usage can be limited because of the peripheral neurotoxicity which is related to dosage, frequency of administration and patient age [1]. Patients with hereditary neuropathies are at risk for severe neurotoxic reactions [2,3]. Several patients with hereditary neuropathy in whom severe vincristine toxicity developed during their treatment have been reported in the literature [3-8]. Here, along with the review of the literature, we described two patients with unrecognized hereditary neuropathy who developed severe sensorimotor neuropathy following vincristine treatment.

CASE REPORT

Case 1

A 12-year-old boy diagnosed as hepatic tumor, developed rapid foot drop on the left side following 1.5 mg/m^2/wk intravenous (iv) vincristine treatment. The patient was admitted to our neurophysiology department on the seventh day of his weakness. On neurologic examination the muscle strength of the tibialis anterior and peroneus longus muscles were 0/5 on the left and the muscle strength of the other lower extremity muscles were 4/5 bilaterally. Deep tendon reflexes were decreased at the upper and absent at the lower limbs. He had atrophy in the tibialis anterior muscles bilaterally. Figure 1 shows atrophy in the tibialis anterior muscles and foot drop on the left side (Figure 1).

Electrophysiological examination included nerve conduction studies (NCs) and needle electromyography. Ulnar, peroneal and posterior tibial motor NCs including F-waves were performed. Sensory NCs included ulnar nerve on the left side and sural nerve bilaterally. The amplitudes of ulnar and posterior tibial compound muscle action potentials (CMAP) were moderately reduced.

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Marmara Medical Journal 2007;20(2);122-126

The distal latencies and conduction velocities of the ulnar nerve were normal. The distal latency of the posterior tibial CMAP was normal on the left while moderately prolonged on the right side. The CMAPs of peroneal nerves could not be obtained and peroneal F-waves were absent bilaterally. The amplitude and conduction velocity of the ulnar sensory nerve action potentials (SNAPs) were moderately reduced while sural nerve SNAPs could not be obtained. Nerve conduction studies revealed severe axonal degeneration in the lower extremities, more pronounced on the left, while there was a moderate degree of axonal degeneration in the upper limbs. Needle electromyography showed severe chronic denervation with reduced recruitment of polyphasic, large amplitude, and long duration motor unit potentials. The tibialis anterior muscle showed fibrillation potentials and positive sharp waves at rest and no voluntary activation on the left side. Table I summarizes the results of the electrophysiological studies of the patient (Table I).

Case 2

A 15-year-old boy was diagnosed as having acute myeloid leukemia and received induction chemotherapy consisting of vincristine, cytosine arabinoside and mitoxantron. He developed bilateral foot drop following three 1.5 mg/m^2/wk iv doses of vincristin treatment. He was admitted to our neurophysiology department on the sixth day of his complaints. On neurologic examination, the muscle strength of the tibialis anterior and peroneus longus muscles were 1/5, the tibialis posterior muscle was 2/5 bilaterally. The strength of the other muscles was normal. Deep tendon reflexes were absent. Besides glove-stocking type hypoesthesia, he had hammer toe and pes cavus deformities bilaterally (Figure 2).

Electrophysiological examination included only NCs. Needle electromyography could not be performed because of low platelet levels. Ulnar, peroneal and posterior tibial motor NCs including F-waves were performed. Sensory NCs included ulnar nerve on the left side and sural nerve bilaterally. The amplitudes of ulnar CMAPs were moderately reduced and the distal latencies were moderately prolonged. The amplitudes of posterior tibial CMAPs were severely reduced and the distal latencies were prolonged. The CMAPs of the peroneal nerves could not be obtained bilaterally. F-waves of the peroneal and posterior tibial nerves were absent. The latencies of the ulnar and sural SNAPs were moderately prolonged. These electrophysiological findings revealed severe axonal sensory-motor polyneuropathy. Table II summarizes the results of the electrophysiological studies of the patient (Table II).

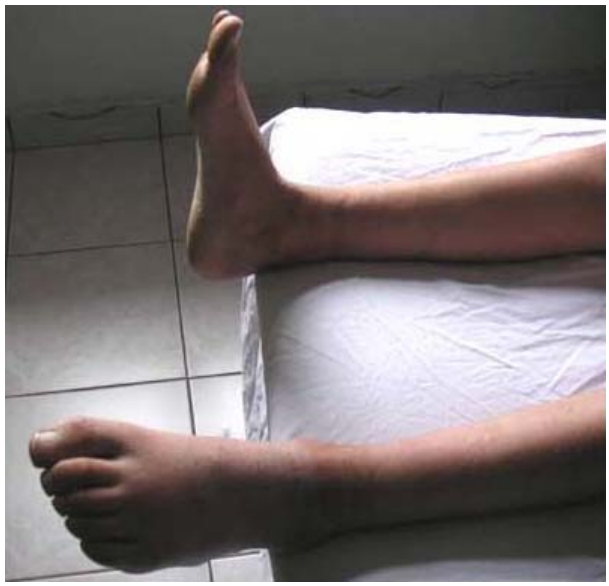

Figure I: Figure 1shows atrophy in the tibialis anterior muscles and foot drop on the left side.

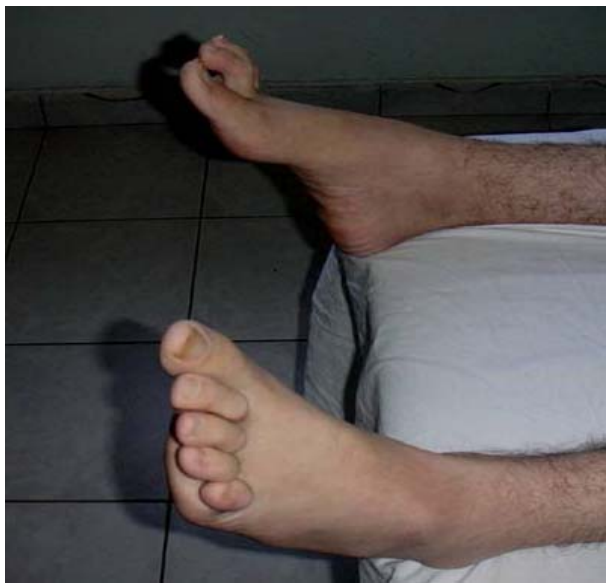

Figure II: Figure 2 shows the hammer toe and pes cavus deformity of the patient.

The severe neurologic involvement following low doses of vincristine and the findings after neurologic examination of both cases indicated an underlying chronic process like a hereditary neuropathy.

Table I: Results of the nerve conduction study of the first patient

Side	Nerve	Recording	Latency	N	Amplitude (mv-µV)	N (Mv-µV)	Distance (cm)	NCV (m/s)	N	F min. latency	N
Left	**Ulnar**	ADM wrist	3.0	<3.3	**6**	>6.0	180	60	>36	22.9	<29.6
		elbow	6.0	<7.2	**6**		70	90			
		above elbow	6.7	<9.1	**6**						
Left	**Peroneal**	**EDB ankle**	**Not obtained**							-	
Right	**Peroneal**	**EDB ankle**	**Not obtained**							-	
Left	**Post.tibial**	AHL ankle	5.0	<5.0	**2**	>6	300	40	>40	43	<53.5
		popliteа	12.7		**2**						
Right	**Post.tibial**	AHL ankle	**5.4**	<5.0	**2**	>6	300	44	>40	43	<53.5
		popliteа	**12.2**		**1.5**						
Left	**Ulnar 5th finger**	Sensory	3.3	<3.6	**15**	>21	120	**36**	>39		
Left	**Sural**	**Sensory**	**Not obtained**								
Right	**Sural**	**Sensory**	**Not obtained**								

Footnotes: Abbreviations for both tables
NCV: Nerve conduction velocity EDB: Extensor digitorum brevis
ADM: Abductor digiti minimi Min. latency: Minimal latency AHL: Adductor hallucis longus
N: Normal value (According to our lab. normals in the same age group) cap.fib: Capitulum fibulae
mv: milivolt

***Pathologic values are written in bold**

TableII: Results of the nerve conduction study of the second patient

Side	Nerve	Recording	Latency	N	Amplitude (mv-µV)	N (Mv-µV)	Distance (cm)	NCV (m/s)	N	F min. latency	N
Left	**Ulnar**	**ADM wrist**	**3.9**	<3.3	**3**	>6.0	230	47	>36	**31.8**	<29.6
		elbow	8.9	<7.2	**3**		90	94			
		above elbow	9.8	<9.1	**3**						
Left	**Peroneal**	**EDB ankle**	**Not obtained**								
Right	**Peroneal**	**EDB ankle**	**Not obtained**								
Left	**Post.tibial**	**AHL ankle**	**8.5**	<5.0	**0.3**	>6	380	**33**	>40	**-**	<53.5
		poplitea	**20.3**		**0.3**						
Right	**Post.tibial**	**AHL ankle**	**9.0**	<5.0	**0.2**	>6	380	**32**	>40	-	<53.5
		poplitea	**21.0**		**0.2**						
Left	Ulnar 5th finger	Sensory	3.6	<3.6	27	>21	120	33	>36		
Left	**Sural**	**Sensory**	**5.4**	<4.0	11	>9	140	**25**	>32		
Right	**Sural**	**Sensory**	**5.3**	<4.0	*9*	*>9*	*140*	***26***	*>32*		

DISCUSSION

Vincristine neurotoxicity is well known and characterized with a mixed distal sensory-motor polyneuropathy. Toxicity is related to the dosage, frequency of administration and patient age[1]. Significant neurotoxicity is not generally seen with cumulative dosage, although severe neurotoxicity has been reported after small dosages of vincristine in patients with subclinical neurological diseases[3-8].

McGuire et al. reported a patient with unrecognized hereditary neuropathy who developed a severe sensorimotor polyneuropathy following 3.5 mg of vincristine treatment. They noted global weakness, decreased tendon reflexes and atrophy of the anterior compartment muscles and prominent foot arches. The patient had a family history of hereditary neuropathy. They also reviewed six similiar cases from the literature and these cases suggested that there may be an increased sensitivity to low doses of vincristine in patients who have a pre-existing inherited polyneuropathy[4]. Two similar cases with hereditary polyneuropathy have been described where a severe neuropathy developed after receiving 6 mg vincristine. The diagnosis of hereditary neuropathy in one of the cases was prompted by the observation of an abnormal foot shape and so the authors recommended a careful examination including inspection of hands and feet to exclude hereditary neuropathy before initiating vincristine treatment[5]. Graf et al reported three patients with hereditary neuropathy who had at least one family member with 17p11.1-12 duplication and developed severe neuropathy after receiving initial doses of vincristine. They recommended taking a detailed family history before vincristine treatment in such cases[6]. Similar experiences have been described in a

patient with Ewing's sarcoma who developed severe weakness of upper and lower extremities[7] and in a patient who developed areflexia, lower extremity weakness and an increase in cavus deformity[8]. Schiavetti et al described a patient with Wilms tumor who was previously asymptomatic and had no family history for hereditary neuropathies. Neurologic examination revealed global weakness, decreased tendon reflexes and distal wasting of the legs and high arches. The patient developed severe but reversible neuropathy after vincristine treatment and genetic studies suggested a diagnosis of hereditary neuropathy[3]. Most of these cases reported in the literature concerned pediatric or teenage patients. The common clinical findings were muscular weakness, atrophy, decreased or absent tendon reflexes and foot deformities, as in our cases.

Patients with hereditary neuropathy are at high risk of severe vincristine neurotoxicity and this makes the exclusion of diagnosis of hereditary neuropathy a necessity before initiating therapy. The studies including nerve biopsies and electrophysiological examinations demonstrate that vincristine causes primary axonal degeneration by binding and inactivating tubulin[9]. This effect was found consistent with disruption of the fast component of axonal transport[10]. On the other hand, slow axonal transport was abnormal in most of the hereditary neuropathies, therefore severe vincristin toxicity in patients with hereditary neuropathies was thought to be related with the impairment of both slow and fast axonal transport[4].

Our cases had no family history or known neurological diseases. One of our cases had atrophy in the tibialis anterior muscles bilaterally while the other had hammer toe and pes cavus deformities bilaterally. The severe neurologic involvement following low doses of vincristine and the findings of neurologic examinations of both of the cases suggested an underlying chronic process like a hereditary neuropathy, although genetic examination could not be performed. We recommend a careful neurologic examination to exclude an underlying hereditary neuropathy and taking a detailed family history before initiating vincristine in order to protect the patients from the severe neurotoxic effects of vincristine therapy.

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