Vincristine Induced Cranial Neuropathy

Gaurav Dixit*, Atul Dhingra**, Diksha Kaushal***

Abstract

Neuropathy is a well known side effect of vincristine, however cranial nerve toxicities are reported less frequently which can involve any cranial nerve in mostly bilateral pattern. As many patients have primary tumors or metastatic lesions in sites that could cause the clinician to overlook this reversible cause of neurologic dysfunction, the potential for misdiagnosis is high. Here, along with review of literature we describe three cases on vincristine who developed cranial neuropathy while on treatment.

Introduction

Vincristine is a vinca alkaloid used in combination with other agents in the treatment of solid tumors, lymphoma, and leukemia1. Its usage can be limited because of the peripheral neurotoxicity, which is related to dosage, frequency of administration and patient’s age. However, neurological injury can also occur in the central or autonomic nervous system. Motor dysfunction and gait disorders are initially manifested as lower extremity weakness. Less frequently, cranial nerve palsies, transient cortical blindness, ocular motor nerve dysfunction, jaw pain, facial palsy, sensorineural hearing loss, and laryngeal nerve paresis have been attributed to vincristine. Depending on severity of neuropathy recovery may take weeks or months and residual minor abnormalities sometimes persist2. We report few cases of ALL who developed cranial nerve palsies while on treatment with vincristine.

Case No.1

A 23 year old male, a diagnosed case of ALL, on third month of maintenance phase of chemotherapy presented with numbness in bilateral feet and palms, ptosis and jaw pain for 3 days. He had received a total of 7 doses of 2 mg of vincristine during induction and maintenance phase. There was no history of any other drug intake, snake bite, diabetes, any history of contact with sex workers or any such complaints in the family and no history of any such complaints in the past prior to this episode.

On examination his vital signs and body temperature were normal. On neurological examination there was bilateral ptosis (Figure 1), however corneal and pupillary reflexes were normal, rest of cranial nerves were also normal, his tendon reflexes were decreased in upper limb while ankle reflex was absent, patient had a sensory loss of about 30% in feet and palms when compared to normal areas. His investigations revealed Hb 9gm% TLC 6200 D.L 172, L24, M2, E2 CSF examination and MRI scan was normal. His nerve conduction study was done which showed mainly axonal involvement with decreased amplitude (Table 1).

Diagnosis of vincristine induced neuropathy was entertained and patient was put on pyridostigmine (60 mg BD) and recovered after 4 weeks and there was no further recurrence of ptosis on follow up.

Case No. 2

A 28 year old male on fourth month of maintenance chemotherapy for ALL came with numbness in bilateral feet and palms, ptosis and jaw pain for 7 days. There was no history of fever, drug intake, diabetes, contact with sex worker, any such complaints in the family or any such similar complaints in the past. He received a total of 16 mg of vincristine before developing present symptoms.

Examination revealed his vital signs and other systems were normal. Neurological examination showed complete external ophthalmoplegia with preserved corneal and pupillary reflexes. Visual acuity testing revealed – PL(perception of light) +ve in left eye and FC(finger counting) +ve in right eye along with bilateral ptosis. Indirect laryngoscopy revealed right vocal cord palsy. Power was 3/5 in bilateral lower limb muscles and 4/5 in upper limb, tone was decreased in all the four limbs and tendon reflexes were absent in lower limbs while they were decreased in upper limbs. There was globe and stocking type of sensory loss for all modalities in upper and lower limbs. His investigations revealed Hb 9.5gm% TLC 7200 D.LC 76, 22,1,1 CSF and MRI scan was normal. His nerve conduction study was done which showed mainly axonal involvement with decreased amplitude (Table 2).

After evaluating clinical features and investigations patient was considered to be a case of vincristine induced cranial neuropathy and was put on pyridostigmine (60 mg BD) and

Fig. 1: Patient 1 showing bilateral ptosis

---

*Senior Resident, Department of Medicine, **Junior Resident, Department of Medicine, ***Senior Resident, Department of Surgery, Pt. B.D. Sharma PGIMS, Rohtak 124001
Received: 30.01.2009; Revised: 28.04.2009; Accepted: 17.09.2011
markedly decreased amplitude. Bilateral upper and lower limb is very less with increased latency and markedly decreased amplitude.

Nerve conduction study of patient 1 shows that conduction velocity of 
Lt Peroneal 19.3 m/s 17.6 ms 0.1 mv 
rt Peroneal 20 m/s 16.9 ms 0.2 mv
Lt Tibial 29.6 m/s 12.5 ms 0.3 mv 
rt Tibial 28.2 m/s 13.1 ms 0.4 mv
Lt Ulnar 37 m/s 6.7 ms 1.1 mv 
rt Ulnar 43 m/s 5.8 ms 1.6 mv
Lt median 34 m/s 7.0 ms 0.1 mv 
rt median 40 m/s 7.4 ms 0.2 mv

Nerve conduction study of patient 2 shows that conduction velocity of 
Lt Facial 30 m/s 11.1 ms 0.1 mv 
rt Facial 22 m/s 10.5 ms 0.4 mv
Lt Peroneal 29 m/s 12.4 ms 0.6 mv 
rt Peroneal 26 m/s 13.5 ms 0.2 mv
Lt Tibial 34.6 m/s 11.4 ms 0.6 mv 
rt Tibial 37 m/s 10.3 ms 0.3 mv
Lt Ulnar 36.4 m/s 6.3 ms 1.0 mv 
rt Ulnar 34 m/s 5.8 ms 1.4 mv
Lt median 58 m/s 3.96 ms 17.1 mv 
rt median 55 m/s 4.2 ms 6.4 mv

Nerve conduction study of patient 3 shows that conduction velocity of 
Lt Peroneal 29 m/s 12.4 ms 0.6 mv 
rt Peroneal 26 m/s 13.5 ms 0.2 mv
Lt Tibial 28 m/s 12.3 ms 0.3 mv 
rt Tibial 22 m/s 10.5 ms 0.4 mv
Lt Ulnar 36.4 m/s 6.3 ms 1.0 mv 
rt Ulnar 34 m/s 5.8 ms 1.4 mv
Lt median 34 m/s 7.0 ms 0.1 mv 
rt median 43 m/s 5.4 ms 0.3 mv

Table 1: NCV study of case no.1

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Conduction velocity</th>
<th>Latency</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lt Median</td>
<td>44 m/s</td>
<td>5.4 ms</td>
<td>0.3 mv</td>
</tr>
<tr>
<td>Rt Median</td>
<td>34 m/s</td>
<td>7.0 ms</td>
<td>0.1 mv</td>
</tr>
<tr>
<td>Rt Ulnar</td>
<td>43 m/s</td>
<td>5.8 ms</td>
<td>1.6 mv</td>
</tr>
<tr>
<td>Lt Ulnar</td>
<td>37 m/s</td>
<td>6.7 ms</td>
<td>1.1 mv</td>
</tr>
<tr>
<td>Rt Tibial</td>
<td>28.2 m/s</td>
<td>13.1 ms</td>
<td>0.4 mv</td>
</tr>
<tr>
<td>Lt Tibial</td>
<td>29.6 m/s</td>
<td>12.5 ms</td>
<td>0.3 mv</td>
</tr>
<tr>
<td>Rt Peroneal</td>
<td>20 m/s</td>
<td>16.9 ms</td>
<td>0.2 mv</td>
</tr>
<tr>
<td>Lt Peroneal</td>
<td>19.3 m/s</td>
<td>17.6 ms</td>
<td>0.1 mv</td>
</tr>
</tbody>
</table>

Nerve conduction study of patient 1 shows that conduction velocity of bilateral upper and lower limb is very less with increased latency and markedly decreased amplitude.

Table 2: NCV study of case no.2

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Conduction Velocity</th>
<th>Latency</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rt Median</td>
<td>40 m/s</td>
<td>7.4 ms</td>
<td>0.2 mv</td>
</tr>
<tr>
<td>Lt Median</td>
<td>23 m/s</td>
<td>6.8 ms</td>
<td>0.3 mv</td>
</tr>
<tr>
<td>Rt Ulnar</td>
<td>34 m/s</td>
<td>5.8 ms</td>
<td>1.4 mv</td>
</tr>
<tr>
<td>Lt Ulnar</td>
<td>36.4 m/s</td>
<td>6.3 ms</td>
<td>1.0 mv</td>
</tr>
<tr>
<td>Rt Tibial</td>
<td>28 m/s</td>
<td>12.3 ms</td>
<td>0.3 mv</td>
</tr>
<tr>
<td>Lt Tibial</td>
<td>34.6 m/s</td>
<td>11.4 ms</td>
<td>0.6 mv</td>
</tr>
<tr>
<td>Rt Peroneal</td>
<td>22 m/s</td>
<td>10.5 ms</td>
<td>0.4 mv</td>
</tr>
<tr>
<td>Lt Peroneal</td>
<td>19 m/s</td>
<td>11.1 ms</td>
<td>0.1 mv</td>
</tr>
</tbody>
</table>

Nerve conduction study of patient 2 shows that conduction velocity of bilateral upper and lower limb is very less with increased latency and markedly decreased amplitude.

Table 3: NCV study of case no.3

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Conduction Velocity</th>
<th>Latency</th>
<th>Amplitude</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rt Median</td>
<td>55 m/s</td>
<td>4.2 ms</td>
<td>6.4 mv</td>
</tr>
<tr>
<td>Lt Median</td>
<td>58 m/s</td>
<td>3.96 ms</td>
<td>17.1 mv</td>
</tr>
<tr>
<td>Rt Ulnar</td>
<td>43 m/s</td>
<td>5.8 ms</td>
<td>1.6 mv</td>
</tr>
<tr>
<td>Lt Ulnar</td>
<td>51 m/s</td>
<td>4.6 ms</td>
<td>5.6 mv</td>
</tr>
<tr>
<td>Rt Tibial</td>
<td>36.7 m/s</td>
<td>10.7 ms</td>
<td>4.7 mv</td>
</tr>
<tr>
<td>Lt Tibial</td>
<td>37 m/s</td>
<td>10.3 ms</td>
<td>2.6 mv</td>
</tr>
<tr>
<td>Rt Peroneal</td>
<td>26 m/s</td>
<td>13.5 ms</td>
<td>0.2 mv</td>
</tr>
<tr>
<td>Lt Peroneal</td>
<td>29 m/s</td>
<td>12.4 ms</td>
<td>0.6 mv</td>
</tr>
<tr>
<td>Rt Facial</td>
<td>22 m/s</td>
<td>4.0 ms</td>
<td>0.2 mv</td>
</tr>
<tr>
<td>Lt Facial</td>
<td>30 m/s</td>
<td>3.0 ms</td>
<td>2.0 mv</td>
</tr>
</tbody>
</table>

Nerve conduction study of patient 3 shows that conduction velocity of right facial and bilateral peroneal is less with increased latency and markedly decreased amplitude.

Case No. 3

A 17 year old male on treatment for ALL presented to us with 7 days history of deviation of angle of mouth and inability to close his one eyelid properly (Figure 2). There was no history of any vesicles in the ear, or any other cranial nerve involvement.

Examination revealed his vital signs and other systems were normal. On neurological examination there was lower motor neuron type of facial palsy of right side, rest of the cranial nerves were normal. On motor examination power and tone in all the four limbs were normal but deep tendon reflexes in lower limb were absent and decreased in upper limbs. Sensory examination was normal and there was no bladder and bowel trouble. Investigations showed Hb 10 gm% TLC 8400 DLC 78, 20, 1,1 his nerve conduction studies were done and we found that conduction velocity of right facial and bilateral peroneal was less with increased latency decreased amplitude (Table 3). MRI and CSF was normal.

Patient was put on pyridoxine and pyridostigmine, patient recovered in 4 weeks time and was symptom free thereafter.

Discussion

Vincristine-induced neuropathy is usually mild, severe complications including partial or total paralysis are reported in rare cases. Symptoms usually appear 2 to 19 weeks after the commencement of vincristine. Vincristine neurotoxicity is more severe under the following circumstances: if more than cumulative dose of 12 mg is given, if the patient is hypersensitive to this drug, if there is pre-existing liver dysfunction or a hereditary neuropathy, and if other drugs such as allopurinol, erythromycin, isoniazid, mitomycin C, phenytoin, and itraconazole are concomitantly used. Neurotoxicity with the vinca alkaloids is qualitatively similar but quantitatively different (vincristine > vindesine > vinblastine > vinorelbine). Previous neurotoxicity or neurological disorders may result in decreased tolerance and increased sensitivity. Neurotoxicity is generally reversible, but recovery may be slow.

The most frequent manifestation of nervous system toxicity is peripheral neuropathy, the earliest indication of which is depression of the Achilles reflex. After 3 or more weekly doses, loss of other deep tendon reflexes occurs and is accompanied by peripheral paresthesias, pain and tingling. If therapy is prolonged or high doses are administered, wrist and foot drop, ataxia, a slapping gait and difficulty in walking may occur. Young children may refuse to walk due to extremity pain.

Cranial neuropathy may lead to vocal cord paresis or paralysis (hoarseness, weak voice), ocular motor nerve dysfunction (ptosis, strabismus), bilateral facial nerve palsies, or jaw pain. Severe jaw pain can occur within a few hours of the first dose of vincristine. Cranial nerve toxicities tend to be bilateral and reversible when treatment with vincristine is discontinued.

Autonomic neuropathy is manifested as constipation (which can be severe), abdominal pain, urinary retention and paralytic ileus. Constipation may be associated with impaction of stool in the upper colon; therefore the rectum may be empty on digital examination. This condition is responsive to high enemas and stimulant laxatives. Laxatives or stool softeners should be given routinely to prevent constipation. These symptoms resolve with time and may not occur with subsequent treatment.
Urinary retention may occur in older patients with obstructive uropathy. If bladder atony occurs, vincristine should be held until symptoms resolve. Other neurotoxicities include seizures, hallucinations, insomnia, ataxia, agitation, depression etc.

Dose recommendation in neuropathy cases is as follows. Areflexia only continue vincristine at 100% dose. Abnormal buttoning, writing reduce dose to 67%. Moderate motor neuropathy hold until recovery and reduce by 50%. Severe motor neuropathy omit vincristine.

The definitive diagnosis of a drug-induced neuropathy depends on the exclusion of other etiologies that may produce a similar clinical picture. The neurotoxicity of the vinca alkaloids is well known; however the potential for cranial nerve involvement is not widely recognized. Patients with hereditary neuropathy are at high risk of severe vincristine neurotoxicity and this makes the exclusion of diagnosis of heredity neuropathy a necessity before initiating therapy. Studies including nerve biopsies and electrophysiological examinations demonstrate that vincristine causes primary axonal degeneration by binding and inactivating tubulin.

We recommend through our case reports a careful neurological examination and detailed family history before initiating vincristine and to keep vincristine neuropathy as a differential diagnosis in patients of ALL developing neurological symptoms.

References