Case Series

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Effectiveness of Pyridostigmine and Pyridoxine in Vinca Alkaloid-Induced Cranial Neuropathy – A Case Series

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Abstract

The neurotoxicity of the vinca alkaloids in the form of peripheral neuropathy is well known, however, cranial neuropathy is not widely recognized especially in children. We describe here in three children with malignancies who developed vinca alkaloid induced cranial nerve palsies during treatment which resolved on institution of pyridoxine and pyridostigmine. Vinca-alkaloid-induced cranial nerve palsies represent a potentially dangerous but reversible condition.

Introduction

Vinca alkaloids include anti microtubule agents like Vincristine, Vinblastine and Vinorelbine which act against the tubulin subunit of the microtubules, causing interference in its assembly and secretory function ultimately leading to primary axonal degeneration.[1] Vinca alkaloids based chemotherapeutic regimen is used for the treatment of various paediatric haematological and solid organ malignancies. However, the use of Vinca alkaloids is restrained by the development of dose related slowly progressive peripheral sensorimotor neuropathy which mandates delay or change in the treatment protocols as well as dose reductions. Cranial neuropathy in the form of oculomotor, facial, trochlear, and recurrent laryngeal nerve paresis is reported rarely in patients on Vinca based protocols, however the onset of this condition is life threatening and requires prompt identification and urgent management.[2] We herein describe the development of cranial neuropathy in three children with malignancies which was successfully managed.

Case 1

Our first case was a $3^{1/2}$ years old female toddler with bony lesions in the jaw and diabetes insipidus of six months duration with a diagnosis of primary Langerhans Cell Histiocytosis. She was started on induction chemotherapy consisting of weekly Vinblastine (3 mg / m^2) along with daily prednisolone (40 mg / m^2). After six weeks of induction chemotherapy, she was planned to be maintained on Vinblastine (3 mg / m^2) every three weeks, prednisolone (40 mg / m^2) for the first five days of a 21- day cycle and 6 - mercaptopurine (50 mg / m^2) daily. After two cycles of maintenance chemotherapy, she developed a lower motor neuron facial palsy of the right side with deviation of the angle of the mouth, mild ptosis and drooling of saliva. There were no other focal neurological deficits or any otological symptoms. There was no history of a previous neuropathy or family history of inherited neuropathies. Further doses of Vinblastine were withheld, and she was started on pyridoxine at 150 mg / m^2 and pyridostigmine at 3 mg / kg. Four weeks later the facial palsy had resolved and there was no recurrence of the symptoms (Figure1).

Figure 1. Facial palsy after instituting Vinblastine therapy and recovery of facial palsy after 4 weeks

Case 2

The second case was a one year old female infant who presented with bleeding per vaginum with a solid mass in the uterus which was subsequently diagnosed as Embryonal Rhabdomyosarcoma. She was started on induction chemotherapy with Vincristine (VCR), Adriamycin, and Cyclophosphamide. VCR was given at the dose of 1 mg / m^2 weekly for four cycles. Immediately after the fourth dose she was noticed to have bilateral ptosis (Left > right). Extra ocular eye movements and pupillary reactions were normal. There were no other focal neurological deficits. MRI brain was done to rule out any metastatic lesion which was normal. VCR was withheld and she was started on combination therapy of pyridoxine (150 mg / m^2) and pyridostigmine (3 mg / kg). Ten weeks later her ptosis had resolved and there was no recurrence of symptoms on further follow up (Figure 2).

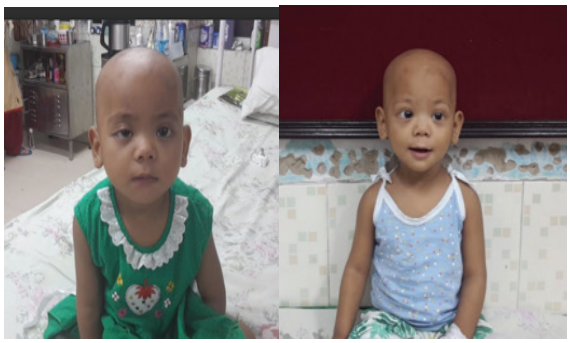

Figure 2. Right sided III CN palsy after instituting Vincristine and recovery of ptosis after 10 weeks

Case 3

Our third case was a four year old male child with generalised lymphadenopathy of six months duration and was subsequently diagnosed as Hodgkin's lymphoma. He was started on the Adriamycin, Bleomycin, Vinblastine and Dacarzibine (ABVD) regimen. Vinblastine was given at 6 mg / m^2 on D_1 and D_{15} every 28 days. After the first cycle the child initially complained about diplopia, and on examination was found to have developed complete ophthalmoplegia. Pupillary and corneal reflexes were normal. There was no other focal neurological deficits. His complete blood count, electrolytes, CSF examination and MRI were normal. One week later he developed bilateral ptosis (Left > right) with normal pupillary reaction. Further doses of Vinblastine were withheld, and the child was started on a neuroprotective regimen consisting of pyridostigmine and pyridoxine at appropriate doses. Two weeks later his ptosis had completely resolved and there was no recurrence of symptoms on further follow up.

Discussion

The neurotoxicity caused by Vinca alkaloids manifests in the form of a peripheral neuropathy, autonomic neuropathy and rarely as cranial neuropathy and encephalopathy.[1] Although peripheral neuropathy is commoner, the onset of cranial neuropathy though rare, causes severe life-threatening illness. Neurological deficits in the form of external ophthalmoplegia, ptosis, jaw pain, facial paralysis, and hoarseness of voice with dysphagia are the reported manifestations of cranial neurotoxicity. Recurrent laryngeal nerve paralysis manifesting as hoarseness of voice and autonomic neuropathy manifesting as cardiac rhythm abnormalities with hypotension are the most life-threatening manifestations of a toxic neuropathy due to vinca alkaloids.[3,4] Children with these symptoms should be subjected to an urgent laryngoscopy to directly visualise the vocal cords and not be just labelled as due to an upper respiratory infection, laryngitis or due to leukemic infiltrates. None of our patients had features of recurrent laryngeal nerve paralysis.

Although there is no defined timeline for the onset of the neurotoxicity, symptoms usually occur two to 19 weeks after the initiation of Vinca alkaloids-based regimen.[5] All three patients developed signs of neuropathy between one to nine weeks. The various factors presumed to accelerate the development of neuropathy are, exceeding the maximum recommended cumulative doses, predisposition to hereditary neuropathy or family history of peripheral neuropathy, parallel administration of drugs like allopurinol, isoniazid, phenytoin, and poor nutritional status.[2,6] None of our patients had poor nutritional status, concomitant administration of other drugs other than chemotherapeutic agents nor did they have any family history of inherited neuropathies. The cumulative doses of vincristine and vinblastine did not exceed the recommended doses of 2 mg / m^2 / week and 6 mg / m^2 / week respectively in any of the patients.

Diagnosis of Vinca alkaloid induced neuropathy in children with malignancies requires exclusion of other aetiologies most importantly CNS disease. The time course of onset of the cranial neuropathies in relation to the initiation of Vinca alkaloid therapy, normal CSF and MRI brain, complete resolution of the symptoms with pyridoxine and pyridostigmine and absence of recurrence of symptoms on withholding further Vinca alkaloid-based therapy lends credence to the diagnosis of a pure drug induced toxic neuropathy in all our cases. Why some children develop toxic neuropathy while others do not is not understood. Further there is a wide range of duration of timeline for the recovery of the symptoms as was seen in our patients (Minimum two weeks and maximum 10 weeks) which is also unexplainable. Currently there are no objective predictive methods to determine the neurotoxic effects of Vinca alkaloid-based therapy and therefore the key to minimise the toxicity is to keep a close watch on development of the symptoms, some of which may begin in the form of generalised weakness, paraesthesia, abdominal pain, constipation, and urinary retention. In the absence of a pathophysiological model

for the drug induced toxicity, management especially in children is either by omitting further doses of the vinca alkaloids, reducing the dose and at the same time instituting drugs like pyridoxine and pyridostigmine which are reportedly used effectively to reverse the toxicity.[7] Although there are isolated reports on the use of folinic acid, glutamate, and lithium for reversing the neurotoxicity associated with Vinca alkaloids, no recommended regimen for these drugs is available as of now.[8-10] At our centre, children developing neurotoxicity due to Vinca alkaloids are promptly started on pyridoxine (150 mg / m^2 BD) and pyridostigmine (3 mg / kg BD) along with withdrawal of Vinca alkaloids. All children in our series were symptom free with this regimen. It is unclear whether Vinca alkaloids can be re-started once neuropathy has been demonstrated.

Conclusions

To conclude children receiving Vinca alkaloid-based therapy need to be monitored closely for development of neurotoxicity especially cranial neuropathy, some of which may be innocuous and life threatening. At the same time the symptomatology may easily be ascribed to the secondary effects of the malignancies on the CNS. Early initiation of therapy with pyridoxine and pyridostigmine hastens recovery.

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