

Short report

Cisplatin neuropathy with Lhermitte's sign

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SUMMARY Following chemotherapy with cis-diamminedichloroplatinum II (cisplatin) three patients developed Lhermitte's sign and peripheral neuropathy. The toxic side effects did not become apparent until after treatment had ceased. Because of increasing use of cisplatin to achieve lasting remission in patients with malignant disease proprioceptive and myelopathic side effects may become increasingly common.

Cis-diamminedichloroplatinum II (cisplatin) is a cytotoxic cancer chemotherapeutic agent which is very effective in the treatment of various neoplasms.¹ Significant numbers of young patients with tumours of germ cell origin may go on to long-term survival and perhaps cure.² With increasing use of the drug treatment related morbidity has become more common. Peripheral neuropathy is one example of treatment-related toxicity,¹ but our observations on three patients in a small centre in one year suggest that a less well recognised neurotoxic effect of cisplatin may contribute significantly to morbidity.

Case reports

Patient 1

A 61-year-old housewife underwent surgical excision of an ovarian carcinoma in February 1984. Between April and July 1984 she received a total dose of 500 mg/m² of cisplatin and 250 mg/m² of doxorubicin (adriamycin). Three weeks after the completion of chemotherapy pins and needles developed in the hands and feet, which spread over several weeks to the elbows and knees. Associated with this was clumsiness of the hands and feet and unsteadiness of gait. Hearing became worse around the middle of the course of chemotherapy. One month after stopping chemotherapy on nodding her head forward small electric shock sensations were felt down both shins.

In October 1984 there was no evidence of recurrent malignancy. The abnormal features on neurological exam-

ination were minimal weakness distally in the arms and legs, limb areflexia, depressed sensation to light touch and pin prick at the fingertips and distal half of the feet. Vibration sense was present above the neck but not below. Position sense was markedly decreased in the fingers and toes and moderately decreased at the ankles. Pseudoathetosis was present at the fingers. Gait was ataxic and a frame was required for walking.

Cervical radiculogram and cerebrospinal fluid examination were normal. Nerve conduction studies showed absent right median, ulnar, radial and sural sensory potentials.³⁻⁵ Lateral popliteal nerve action potential was also absent.⁶ Motor conduction was normal in the right medial, ulnar, lateral popliteal and tibial nerves. Electromyographic fibrillations were present in right tibialis anterior and abductor pollicis brevis. The motor units in the tibialis anterior were of increased duration ranging from 15-25 ms and 30-40% of these were polyphasic. Review two months later showed slight improvement of proprioception, but major disability remained.

Patient 2

A 36-year-old male presented in February 1984 with a malignant teratoma. He received chemotherapy between April and June 1984, with a cumulative dose of 640 mg/m² of cisplatin, 1200 mg/m² of etoposide (VP16), vinblastine 40 mg and bleomycin 180 units. Two months after the last dose of chemotherapy tingling of the hands and feet was present. This became more intense over the next month. Numbness of the hands became such that buttons were difficult to do up and when walking he tripped on uneven surfaces. With head nodding momentary pins and needles were felt in the ankles and feet.

Examination in December 1984 revealed no evidence of tumour. There were no clinical abnormalities in the cranial nerves. Limb strength was normal. Biceps jerks were depressed and other limb reflexes absent. Sensation to light touch was absent over the fingers and toes, but to prick these areas were hyperaesthetic. Vibration sense was absent in the fingers and lower legs. Position sense was

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reduced in the fingers, absent in the toes but normal at ankles and wrists and more proximally. Minor finger pseudoathetoid movements were present. Unstressed gait was normal but heel-toe walking was markedly unsteady. Rhomberg's test was positive. Neither cervical radiculography nor CSF examination were performed. Conduction studies showed absent right sural sensory action potential, tibial nerve motor conduction velocity at the lower limit of normal (41 m/s), peroneal nerve motor conduction velocity from fibula head to ankle was slightly slowed (38 m/s), but a significant decrement in the amplitude of the surface recorded proximal evoked muscle action potential was present (4 mV at the ankle, 2.0 mV at the fibula head). Electromyography was not performed owing to patient intolerance.

Patient 3

A 37-year-old male had an atypical iliac fossa teratoma removed in February 1984. Between March and June he received 560 mg/m² of cisplatin, 60 mg/m² of vinblastine, 910 units of bleomycin and 700 mg/m² of etoposide (VP16). During chemotherapy there was exacerbation of pre-existing tinnitus and hearing loss which subsequently improved. Ten days after the last course of chemotherapy, hypersensitivity of the soles was first noticed. Numbness of feet and hands associated with difficulty doing up buttons and walking on uneven surfaces followed. After onset of the sensory symptoms grip felt poor, but this returned to normal over several months. During August 1984 while receiving radiotherapy to his right iliac fossa neck flexion produced "electric shocks" radiating down the front of both legs. This persisted for three months.

When examined in December 1984 he had metastatic tumour in lung and liver. Hearing was slightly impaired for whispering but there were no other cranial nerve abnormalities. Strength was normal except for minimal weakness of finger abduction only. Reflexes were absent in limbs and abdomen. Light touch sensation was decreased at the fingers and absent in the feet. Pin prick produced hyperaesthesia in these areas. Vibration sense was absent in the lower arms and in both legs. Position testing impaired at the fingers and absent at toes and ankles and normal at wrists, knees and hips. Heel-toe testing was unsteady. Unstressed gait was normal but on turning and heel-toe walking marked unsteadiness occurred. Rhomberg's testing was positive. Pseudoathetoid movements were present in extended fingers. Nerve conduction studies showed an absence of right sural, ulnar, median and radial sensory potentials. Right median forearm conduction was normal (52 m/s) as was distal median motor latency (3.2 ms). Ulnar motor forearm conduction velocity was slightly slowed (47 m/s) but from above to below the elbow it was normal (45 m/s). Distal ulnar motor latency was also normal (2.7 ms). In the legs lateral popliteal motor conduction was slowed (36 m/s from fibula head to ankle, 21 m/s popliteal fossa to fibula head). Distal motor latency to extensor digitorum brevis was normal (5.4 ms). Significant decrement in the amplitude of the surface recorded proximal evoked muscle action potential was present (1.5 mV at ankle and fibula head, 0.5 mV at popliteal fossa). Medial popliteal distal motor latency and motor conduction velocity from popliteal fossa to ankle were both normal (5.0

m/s and 43 m/s respectively), but significant decrement in amplitude of the surface recorded evoked muscle potential from abductor hallucis was present (2.5 mV at ankle, 1 mV at popliteal fossa). Electromyographic examination of right abductor pollicis brevis, extensor communis digitorum and vastus medialis was normal. The tibialis anterior motor units on weak effort were excessively polyphasic and prolonged and at full effort their amplitude was greatly increased (up to 12 mV). Enlargement of these motor units was confirmed by computerised analysis of the interference pattern.⁷ CSF was not examined and cervical radiculography was not performed.

All patients had light or no alcohol consumption; B12, random glucose, urea and electrolytes and serum VDRLs were normal.

Discussion

Transient parthesiae or "electric shocks" in the limbs brought about by flexing the neck, known as Lhermitte's or "Barber's Chair" sign indicates a lesion in the spinal cord, probably in the dorsal columns.⁸ Thus all three patients had clinical evidence of myelopathy.

At presentation these patients had extensive malignant disease, but no evidence of myelopathy. This did not develop until chemotherapy had been completed, at a time when one patient had active disease but the other two had no detectable disease. There was no evidence of recurrent tumour nor any other demonstrable lesion near the spinal cord nor intercurrent conditions known to cause myelopathy. One patient was being treated with radiotherapy when he first noted Lhermitte's sign, but the spinal cord was not in the radiation field and neither of the other two patients had been treated with radiotherapy.⁹ When Lhermitte's sign develops following a clearly defined episode of trauma to the spinal cord a variable latent period of one to two and a half months has been observed.¹⁰ In our patients the sign developed 4 to 8 weeks after completion of their chemotherapy. The timing and lack of other obvious causes suggested that these myelopathies had been caused by cytotoxic chemotherapy.

In animal experiments doxorubicin (adriamycin) can cause necrosis of dorsal root ganglion cells.¹¹ In clinical use both vinblastine and cisplatin cause autonomic and peripheral neuropathy.^{12,13} Etoposide (VP16) may cause peripheral neuropathy.¹³ Bleomycin does not seem to be neurotoxic. In seeking a single drug for these myelopathies, cisplatin appears the only likely candidate since it was the only drug with which all three patients were treated. The case of a child who died having been treated with eleven courses of cisplatin has been reported.¹⁴ Post mortem histology showed marked degeneration and gliosis of the dorsal col-

umns, substantial axonal loss in dorsal roots with normal appearances in the ventral roots. Administration of cisplatin in massive doses caused axonal degeneration in the spinal cords of rats.¹⁵ Morphologic findings in peripheral nerves have shown both axonal degeneration with secondary myelin break-down¹⁶ and destruction of myelinated sheaths with intact axons.¹⁷

Single agent studies have established cisplatin as a cause of predominantly sensory neuropathy.¹⁸ Apart from Lhermitte's sign the neurological findings in all three patients were consistent with this. The neurophysiologic studies in Patient 1 suggested axonal degeneration. In Patients 2 and 3 a partial conduction block suggestive of acquired demyelination was demonstrated.¹⁹ These neurophysiological findings have not been reported with cisplatin peripheral neuropathy. All three patients showed unequivocal evidence of peripheral nerve damage. The dorsal column and peripheral nerve lesions may be an example of central distal axonopathy.²⁰

There are many clinical features of these patients reminiscent of subacute sensory neuropathy associated with carcinoma.^{21,22} In this disorder dorsal column degeneration also occurs, though Lhermitte's sign has not been described. Even though cisplatin has been in use for more than twelve years, there have been only two previous reports of cisplatin-induced myelopathy. One report¹⁶ described in passing "a brief accentuation of paresthesias in the anterior legs and dorsa of the feet in response to flexion of the neck" and another¹⁴ reported histological changes in the dorsal columns following cisplatin. Only the first of our three patients volunteered the information that "electric shocks" occurred with head nodding. The relevant history was elicited from the other two by direct (but not leading) questioning. None of the patients appeared to be distressed by their symptom which they regarded as a minor curiosity. Cisplatin neuropathy is probably dose related.^{1,16,23} Since its introduction the doses of the drug given in various treatment regimes have been progressively increased, so possibly the risk of myelopathy has been increasing with this.

The latent period between cessation of treatment and development of further clinical signs indicates that by the time a patient on treatment with cisplatin has clinical signs of neurotoxicity, stopping the drug may not prevent further deterioration and disability. Cisplatin is highly effective in the treatment of some tumours which are invariably fatal if inadequately treated. Under these circumstances the decision to discontinue treatment is not taken lightly and it is probable that patients suffering from cisplatin neurotoxicity will be seen in increasing numbers.

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