n-HEXANE NEUROPATHY DUE TO SHOEMAKING: REPORT OF FIVE CASES

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Abstract- n-hexane neuropathy has been described after glue sniffing and industrial exposure. Onset may be subacute and reminiscent of Guillain-Barre' syndrome. Five patients (15-18 years old) presented with paresthesia, severe weakness of the extremities particularly lower extremities, as well as muscular atrophy, total areflexia and gait disturbances were admitted in hospital in March 2003. All of these boys were workers of a small footwear production unit. They worked as gluers of leather pieces. Nerve conduction velocity studies showed latency prolongation and cerebrospinal fluid (CSF) analysis showed normal protein. In the workplace assessment, it was found that hexacarbone-containing adhesives were used in an inappropriate ventilated place and without any personal protective devices. These patients were re-examined 8 months later. Sensory and autonomic symptoms were alleviated but two of them still had gait disturbance and decreased reflexes.

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Key words: n-hexane; peripheral neuropathy; Guillain-Barre' syndrome

INTRODUCTION

n-hexane, an aliphatic hexacarbon with many industrial uses, is a well-known cause of peripheral neuropathy, both in industrial settings (1-3) and in recreation glue sniffers (4). The typical clinical course is one of early sensory symptoms, followed by progressive weakness predominantly in lower extremities. Weakness develops in the legs, then the arms, and tends to affect distal muscles mostly. In severe cases, marked distal atrophy and proximal weakness occur. Muscle cramping and weight loss are common. Progression continues for some time after discontinuation of exposure (coasting) and is followed by variable recovery (2). Based on pathologic evidence, the primary lesion in n-hexane neuropathy is axonal, beginning distally with proximal spread, with secondary myelin changes.

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The exact mechanism of neuropathy is uncertain, although it is speculated that neurofilaments are the primary site of injury (5). The active metabolite is thought to be 2,5 hexanedione.

We report 5 patients with n-hexane neuropathy secondary to occupational exposure.

CASE REPORT

First case

A 17 year old boy presented with progressive weakness of the lower extremities, numbness, and tingling was admitted in the neurology ward of a Tehran University affiliated hospital in April 2003, with initial diagnosis of Guillain-Barre syndrome.

The symptoms had been started 3 weeks before admission after a common cold. Initially the patient had numbness in the hands and then he developed weakness and cramps of the lower extremities. The weakness aggravated progressively and in 10 days the patient was unable to stand up or walk. There was no past history of admission, head trauma, drug consumption, smoking, alcoholism, addiction or

positive family history of neuropathy.

The patient had been working as a gluer in a small footwear production unit in the south west of Tehran for one year. Previously he had also worked in another production unit with the same task for one and half year.

General physical and cranial nerve examinations were normal. Positive neurological signs were weakness, more in the distal parts of the lower extremities, mild muscle atrophy more in the lower extremities, total areflexia of the lower extremities, decreased deep tendon reflexes (DTR) of the upper extremities and bilateral foot drop. No fasciculation was noted and muscle tone and superficial and deep sensory evaluation were normal.

Laboratory evaluation included normal electrolytes, blood urea nitrogen, creatinine, calcium, magnesium, phosphate, liver function tests, and complete blood count. A sedimentation rate, serum protein electrophoresis, antinuclear antibody, urine porphyrin screen and brain CT scan were normal. Spinal fluid protein was 15 mg/dL, with glucose of 57 mg/dl and three lymphocytes. A sural nerve biopsy was performed, revealing decreased density of large myelinated fibers with several focally swollen axons. Nerve conduction studies revealed borderline low sensory nerve action potential (SNAP) amplitudes with minimally prolonged sensory distal latencies. Compound muscle action potential (CMAP) amplitudes were diminished, motor distal latencies were prolonged and motor conduction velocities were reduced, findings compatible with demyelinating polyneuropathy.

Other cases

Case 2, case 3, case 4 and case 5 had been admitted in another Tehran university affiliated hospital. Their symptoms initiated in March 2003. Due to lack of improvement, the case 5 was dismissed with his personal consent. Although the chief complaint of all patients was lower extremities weakness, at the beginning of the disease they all had numbness and tingling. The symptoms were significantly more severe in the lower extremities. In contrast to other cases, cases 2 and 3 didn't have history of viral infection. The symptoms were more severe in cases 2 and 5, and they couldn't walk at all. All of them had total areflexia of the lower extremities and didn't have any improvement during hospitalization; and in fact the symptoms of case 2 had been aggravated. These patients had several courses of plasmapheresis and IVIG without any response (Table 1).

Paraclinical findings were similar to case 1. Blood and urine examination, brain CT scan, and pulmonary function tests (PFT) were normal. EMG and NCV showed demyelinating polyneuropathy with lower extremity predominance in the first 3 cases. Only case 3, which was the last admitted case, had axonal neuropathy (Table 2).

Table 1. Clinical data of the five patients

Cases	Age (year)	Duration of employment (year)	Chief complaint	Clinical course	Clinical course 8 months after admission
Case 1	17	2	Lower extremities weakness and numbness	Progressive	---
Case 2	17	2	Lower extremities muscle cramps and numbness	Progressive	Lower extremities weakness and areflexia-gait disturbance
Case 3	15	1	Lower extremities weakness and gait disturbance	Partial improvement	Right lower extremities weakness-bilateral areflexia
Case 4	15	1	Lower extremities weakness and numbness	Partial improvement	Left lower extremities weakness bilateral areflexia
Case 5	16	1.5	Lower extremities weakness and numbness	Progressive	Lower extremities weakness and areflexia-gait disturbance

Table 2. Paraclinical data of the five patients

Cases	CSF analysis	PFT	EMG/ NCV
Case 1	Normal	Normal	Demyelinating motor-sensory neuropathy predominantly in lower extremities
Case 2	Normal	Normal	Demyelinating motor-sensory neuropathy predominantly in lower extremities
Case 3	Normal	Normal	Axonal neuropathy predominantly in lower extremities
Case 4	Normal	Normal	Demyelinating motor-sensory neuropathy predominantly in lower extremities
Case 5	Normal	Normal	Demyelinating motor-sensory neuropathy predominantly in lower extremities

Abbreviations: CSF, cerebrospinal fluid; PFT, pulmonary function tests.

DISCUSSION

According to the clinical presentation of our patients which is compatible with a subacute sensory-motor polyneuropathy with motor predominance, and NCV findings of demyelinizing pattern, the most likely diagnosis is neuropathy due to exposure to the hexacarbone-containing adhesives. The time course of the symptoms, their progression despite more than one month cessation of exposure and normal CSF support this diagnosis.

Peripheral neuropathy is well described after exposure to n-hexane in industrial exposure particularly in shoemakers (6-8).ln many industrial cases the onset is gradual, with predominant sensory findings (9). In one large series of 93 patients, 57% had a sensory neuropathy, and only 8.6% also had amyotrophy. Distal lower extremity numbness was the first symptom in 88% of patients (8). In glue sniffers and severely affected industrial workers the onset may be subacute and reminiscent of Guillain-Barre' syndrome (4). After termination of exposure, patients may continue to worsen for many weeks, as in our patients. The “coasting” phenomenon is well described, both clinically and electrophysiologically and is observed in other toxic neuropathies including acrylamide, thalidomide, and the multiple cranial neuropathies of trichloroethylene. The pathologic hallmark of n-hexane neuropathy is loss of large myelinated fibers with focally enlarged “giant” axons filled with neurofilaments and associated thinning of the overlying myelin (5). Such findings are not unique to n-hexane neuropathy, having been described in methyl n-butyl ketone (10), acrylamide, triorthocresyl phosphate, and inherited giant axonal neuropathy. Electrophysiologic findings depend on the neuropathy's severity. Of 56 workers exposed to n-hexane in an offset printing shop, 46% had subclinical peripheral neuropathy evident on nerve conduction studies, with markedly diminished SNAP amplitudes, diminished motor conduction velocity, mildly prolonged motor distal latencies, and reduced CMAP amplitudes. Among those with symptomatic neuropathy, motor nerve conduction velocities were markedly slowed. There was no relationship between duration of employment and development of neuropathy, suggesting that host factors such as individual variability in the hepatic p-450 system play a role (9). Many others have emphasized the reduction in motor conduction velocities in severely affected patients (4, 9). Motor conduction velocities are slowest distally, with only mildly slowed proximal conduction velocity.

After considering the occupational etiology of the disease, the work site evaluation was performed by occupational medicine specialists. The production unit was in a basement in the south west suburb of Tehran. The basement had no proper ventilation and none of the workers used personal protection devises. There were 20 workers between 14-18 year old working with adhesives for 12 hours per day. Seven workers were absent due to same symptoms and we didn't have access to them for examination. Air samples were not tested because management had removed n-hexane containing glues from the unit at the onset of evaluation.

Except for case 1, 8 months later we re-examined the patients. Muscle weakness and decreased DTR persisted with different severity in the patients. Cases 2 and 5 still had severe weakness, gait disturbance, and total areflexia and had difficulty in rising and walking.

Prognosis for recovery from n-hexane neuropathy depends on the severity, with excellent clinical outcome in most patients with sensory neuropathy. Among 93 industrial workers, 57% of whom had sensory neuropathy, 34% sensorimotor neuropathy, and 9% amyotrophy, 92% achieved a full recovery after 4 years, with the remaining patients left with only sensory abnormalities (8). Despite existence of sensory symptoms in 4 of our patients, the chief complaint was weakness and paralysis.

Sources of toxic exposure should be sought in any patient with a subacute neuropathy with demyelinating features on nerve conduction studies and distal denervation on needle electromyography. While there are minimal prognostic data in the literature, our experience demonstrates partial clinical recovery after 8 months, despite severe weakness and denervation.

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