Toxic neuropathies

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Abstract

Toxic neuropathies generally result in length dependent axonal neuropathy with the exception of diphtheria and a few toxic neuropathies. In spite of occurrence of diphtheria in India there is paucity of published reports on diphtheritic neuropathy. Arsenic neuropathy commonly occurs in Bengal and Bangladesh because of ground water contamination whereas in Punjab it is due to contamination of opium. Lead neuropathy is rare and has been reported in battery workers and silver refining workers. It produces motor neuropathy resulting in foot drop and wrist drop. Organophosphates are used as pesticides, industrial chemicals and food adulterant. Certain organophosphates such as triorthocresyl phosphate used for or oil adulteration inhibit neurotoxic esterase and result in a delayed type of axonal neuropathy. Alcohol related neuropathy is a controversial issue whether it is due to alcohol related toxicity or due to nutritional deficiencies. Indian studies have revealed that neuropathy occurs both in alcoholic and nonalcoholic cirrhosis. Hexane neuropathy is reported in screen printers and these cases highlight the need for better preventive and occupational measures. Iatrogenic toxic neuropathies have been reported with cisplatin and vincristine. Because of geographical, occupational and health related conditions toxic neuropathies are likely to be more common than reported and greater awareness is needed.

Key words: *Arsenic, thallium, hexane, India, toxic neuropathy, organophosphate*

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Introduction

Toxic neuropathies are often misdiagnosed as there are no easily available specific or biological tests for the diagnosis. Toxic neuropathies are suspected on the basis of clinical examination and electrodiagnostic features. In ancient India, the toxins were categorized into movable (animal) and static (plant) toxins. Later chemical toxins were added. In the modern era, however, the toxins can be categorized into environmental, occupational, recreational and iatrogenic toxins. Although occupational and environmental toxins provide the greatest risk of toxic neuropathy, its incidence has substantially reduced because of greater awareness and improvement in work practices. Improvement in the economy and healthcare facilities has resulted in greater use of various anticancer, immunomodulator and other drugs which result in iatrogenic toxic neuropathies which are likely to become increasingly important. Because of socioeconomic and behavioral factors, toxic neuropathies as a result of recreational drugs are difficult to document and study. In India Ayurveda, Homeopathy and Arabic medicine are practiced and serve as a source of poisoning and drug toxicity.

In a survey, 14 of the 70 herbal medical products available commercially were found to contain lead in 13 (median concentration, 40 μg/g; range, 5-37000), mercury in 6 (median concentration, 20225 μg/g; range, 28-104000), and/or arsenic in 6(median concentration, 430 μg/g; range, 37-8130). If taken as recommended by the manufacturers, each of these 14 drugs could result in heavy metal intakes above published regulatory standards. Users of herbal medical products may be at risk for heavy metal toxicity; therefore, testing of Ayurvedic drugs for toxic heavy metals should be mandatory.[1]

When to Suspect?

Often there is a question if prior or ongoing exposure has caused peripheral neuropathy. In many instances the agent in question may not have been systematically studied and it may be impossible to conclusively

exclude a relationship. The Bradford Hill criteria define a systematic approach for assessing the issue of causation. Before an agent is implicated to cause neuropathy, there must be strong association between the toxin and neuropathy, temporal relationship, dose response relationship, improvement following removal from exposure, animal model, a consistent clinical spectrum across studies, and biological possibility. More the criteria are met; stronger is the association between the toxin and neuropathy. The diagnosis of toxic neuropathy may be complicated by progression of neuropathy for weeks or months even after cessation of exposure which is known as coasting effect. Toxic neuropathies are frequently associated with systemic manifestations (liver, kidney, mucus membrane, skin and nail) and other components of nervous system (cerebellar encephalopathy or spinal cord) involvement, which serve as a useful indicator of toxic etiology. Some of the examples of systemic involvement with different toxic substances producing neuropathy are summarized in Table 1. The possible sites of toxins are shown in Figure 1.

Electro diagnostic (EDx) studies are an important part of diagnostic evaluation of toxic neuropathy. Most neurotoxins result in axonal sensory motor neuropathy. Sensory nerve action potentials are reduced or absent in a length dependent manner. Compound muscle action potential may also be reduced if there is significant motor axon loss. On needle EMG there are fibrillations and reduced recruitment of large motor units may be observed in the distal muscles. Very rarely, toxic neuropathies result in demyelination such as diphtheria, n-hexane, arsenic, tacrolimus, gold, procainamide, cytosine arabinoside. The cliniconeurophysiological types of toxic neuropathies are summarized in Table 2. The patients with preexisting neuropathy are at a risk of developing significant worsening of their neuropathy following exposure to neurotoxic medication e.g. Charcot

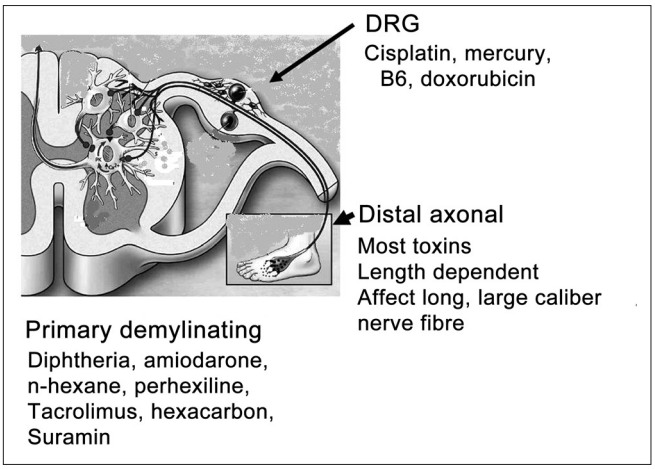

Figure 1: Schematic diagram shows site and types of toxic neuropathy (DRG = dorsal root ganglion)

Table 1: Cutaneous and systemic manifestations of various toxic agents producing neuropathy

Acrylamide	Irritant dermatitis, palmar erythema, desquamation, hyperhydrosis
Arsenic	Gastrointestinal symptoms, hyperpigmentation, hyperkeratosis, Mee's lines, cardiomyopathy, hepatomegaly, renal failure, anemia
Colchicine	Neuromyopathy
Dapsone	After decades of use, possibly in slow acetylators
Ethyl alcohol	Nutritional factors, Wernicke- Korsakoff's syndrome, cerebellar degeneration, abnormal liver function, cirrhosis
n-hexane	Irritant dermatitis
Lead	Gastrointestinal symptoms, musculoskeletal complaints, weight loss, lead line, Mees' lines, renal failure, anemia, basophilic stippling of red blood cells
Lithium	Postural tremor
Mercury	Anorexia, gingivitis, hypersalivation, papular rash, hyperkeratosis, lens opacities, postural tremor, nephrotic syndrome, respiratory tract irritation, metal fume fever
Nitrofurantoin	Elderly with impaired renal function
Nitrous oxide	Myelopathy
Organophosphate	Irritant dermatitis, acute cholinergic effects, corticospinal tract residua, noncardiogenic pulmonary edema
Phenytoin	Gingival hyperplasia, cerebellar ataxia
Thallium	Gastrointestinal symptoms, irritant dermatitis, alopecia, noncardiogenic pulmonary edema
Trichloroethylene	Vasodilation with ethanol ingestion, irritant dermatitis, abnormal liver function, cirrhosis
Toluene	Respiratory tract irritation, irritant dermatitis
L-tryptophan	Peau d'orange, eosinophilia

Table 2: Clinical and neurophysiological types of toxic neuropathies

Motor/motor > sensory neuropathy with or without conduction slowing
Arsenic
Amiodarone
N-hexane
Tacrolimus
Carbon disulphide
Cytosine arabinoside
Methyl n-butyl ketone
Perhexilline
Suramin
Exitotoxin
Saxitoxin
Motor and Motor > sensory neuropathy without conduction slowing
Organophosphate
Vincristine and vinca alkaloids
Nitrofurantoin
Cimetidine
Dapsone
Lead
Sensory neuropathy/neuronopathy without conduction slowing
Thallium
Thalidomide
Cisplatin
Pyridoxine
Ethyl alcohol
Metronidazole
Nitrofurantoin

Marie tooth disease patients worsen following an exposure to vincristine. Toxic neuropathies are too numerous to be included in this review, therefore, only the important ones reported from India will be briefly discussed.

Ancient Perspective

According to ancient Indian texts, the poisons originated from the churning of sea and were of two types; the fixed type (plant origin) and the mobile type (animal origin); the latter included snakes, scorpion, insects, bees, hornet, fish centipede etc. The clinical picture of animal and plant poisons and their treatment has been described in detail in the ancient Ayurvedic literature. There is detailed description about alcohol, its good and bad effects, categorized according to the nature (prakriti-satwa, rajas and tamas). The clinical picture and treatment of snake poisoning using local methods has been described in detail.

Homicidal poisoning has been described in reference to the king who is at the risk of poisoning by enemies, relatives or scheming women. The royal physician is advised to diagnose suspicious person by his abnormal behavior. The poison through food can be suspected by death of flies or animals that have been fed before serving to the king.The poisoned food burns with variegated flame and sound. Poisoning occurs through food, drink, and fumes results in headache, chest pain and fainting. On touching there is pain, tingling, numbness and burning sensation with change in nail color and swelling of hands. The detailed description of toxic neuropathies is not available but there are precise descriptions of many poisons and some relevant treatment.

The important toxic neuropathies reported from India can be categorized as follows:
Animal/Bacterial: Diphtheria
Metals: Arsenic, lead, thallium
Chemicals: Carbon disulphide, organophosphate, ethanol.
Drugs: Cancer Chemotherapeutic agents (cisplatin, vincristine), thalidomide, nitrofurantoin.

Diphtheria

Developing countries contribute to 80-90% of the global burden of diphtheria. During 1990-1996, 150000 cases were reported in the states of former Soviet Union with over 5000 deaths; 60-70% of these deaths were among adults.[2-4] Waning immunity in adults, absence of booster/adult vaccination, deteriorating health infrastructure and turbulent socioeconomic structure were responsible for this outbreak. Cases of diphtheria have been reported from West Bengal[5] and Delhi.[6] In the Russian outbreak, 11% patients with diphtheria had neurological complications. The diphtheritic neuropathy can be differentiated from GB syndrome by higher frequency of bulbar onset, respiratory failure and a biphasic course so as to cause death or long term disability. Diphtheria antitoxin appear to be ineffective if started 2 days after the diphtheritic symptoms.[7] In another study on 32 patients with diphtheria peripheral neuropathy appeared three to five weeks after onset of diphtheria. The cranial nerve palsy included IX and X in 32, VII in 28 and III, IV, VI in 27 patients. One-third of the patients had quadriplegia and all had sensory signs, especially loss of proprioception; 24 needed artificial ventilation and two died.[8]

Arsenic

Arsenic is used as pesticide (copper acidoarsenate, Paris green) in the leather industry and wood preservative. Inorganic arsenic exposure has been described in smelting industry. Neuropathy may occur from inhalation of smoke from burning wood which has been preserved with arsenic or from occupational dust or soil. Exposure to contaminated water via wading or oral consumption may result in toxicity; however, intentional poisoning with a rodenticide is also a common cause of arsenic intoxication. Acute arsenic toxicity causes hemorrhagic gastritis and hepatocerebral syndrome followed by encephalopathy. Chromic arsenic intoxication in India occurs through two main sources 1) adulteration of opium or country liqueur, 2) contaminated ground water.

Arsenic adulteration of opium

In north India, arsenic is added to opium to increase its potency. Analysis of 35 samples of opium obtained from illegal street vendors revealed arsenic concentration 0.4 to 17 ppm which was six to 100 times more than government registered opium.[9] The neuropathy in the opium addicts results in distal sensory impairment of touch, pain and temperature. Painful paresthesia and muscle cramps are common. In more severely affected patients, distal weakness, wasting and foot drop occurs in 30% patients and tendon reflexes are absent. Skin pigmentation and Mee's lines are also noted in 30% and are associated with gastrointestinal symptoms.[10] Nerve conduction studies show absence of sensory nerve action potential, reduced amplitude of compound muscle action potential and normal conduction velocity indicating axonal involvement.

Arsenic contaminated ground water

West Bengal and Bangladesh have high arsenic content of ground water. It is estimated that 42.7 million people in nine districts of West Bengal and 79.9 million in Bangladesh in 42 districts, drink well water containing high arsenic level.[11] In a survey collecting 10991 water

samples from Bangladesh and 58661 from West Bengal; 59% and 34% respectively contained Arsenic level above 50 μg/L which is the WHO recommended upper limit. Hair and nail samples also contained arsenic levels in toxic range. A large number of subjects had typical arsenic dermatitis. Arsenicosis was considered as the worst toxicological calamity in the whole world.[12] Analysis of arsenic concentration in 4780 tube well water samples from Uttar Pradesh, India revealed more than 10 μg/L in 26.7%, 50 μg/L in 46.6% and 300 μg/L in 10%. Survey in 11 affected villages revealed typical arsenic skin lesions in 19.8% adults and 5.7% children.[13] In West Bengal peripheral neuropathy was reported in 29 out of 248 arsenic exposed patients. Abnormal nerve conduction was noted in 11 patients. Improvement in nerve conduction studies was reported five years after consumption of arsenic free water in two patients, and in another no neurological improvement was found.[14] Another study from three districts of West Bengal (Murshidabad, Nadia and Burdhwan) reported peripheral neuropathy in 187 out of 451 patients; peripheral neuropathy was more common in subacute (86%) compared to chronic (37.3%) exposure group. Nerve conduction studies were performed in 88 and revealed sensory abnormality more commonly than motor. Prognosis was favorable in mild and early diagnosed cases.[15]

Patients with keratosis [Figure 2] are more prone to develop arsenic induced health effects and genetic damage; arginine variant of P53 can influence repair capacity of arsenic exposed individuals leading to increased accumulation of chromosomal abnormalities![16] The individual with skin lesion show significant retention of arsenic in hair and nail compared to the group without keratosis, (OR 7.33, 95% CI 5.0-10.59) and peripheral neuropathy (OR 3.95, 95 CI 2.61-5.73).[17] There are reports of subacute arsenic neuropathy simulating GB syndrome with respiratory failure.[18] Asymmetric phrenic nerve involvement in a patient with arsenic neuropathy was reported which responded to oral penicillamine therapy.[19]

Arsenic poisoning is traditionally treated with British antilewisite (BAL). D Penicillamine, dimercaptosuccinic acid (DMSA) and untheol (DMP) are more effective in preventing deposition of arsenic in the nervous system and have the advantage over BAL that these drugs can be administered orally A study on 21 patients with arsenicosis has shown benefit of DMSA compared to placebo.[20]

Lead

Two chief manifestations of lead toxicity are lead encephalopathy in children and lead neuropathy in adults. Lead enters the body through inhalation. In India the main sources of lead exposure were automobile exhaust, silver refining and welding. In a survey on 50 petrol pump workers and garage attendants in Orissa, blood lead levels ranged between 20-80 ng/dl and complained of fatigue (50%), abdominal pain (20%), sleep disturbance (20%) and tremors (14%). Nerve conductions studies revealed subclinical motor neuropathy in 4 whose blood lead levels were higher.[21] Radial neuropathy due to occupational lead exposure was reported in five patients aged 30-37 years engaged in battery factory or battery shop for a mean duration of seven years. They had acute onset (15 days) to chronic (three months) neuropathy in the form of wrist drop in four and finger drop in one. All the patients had elevated blood lead level, which were in toxic range (37.8-107.8 μg/dL). On nerve conduction studies there were subtle charges in the form of reduced CMAP or changes in sensory conduction.[22]

Silver refining industry is a traditional small scale industry in India, in which for refining silver equal amount of lead and silver are boiled in hand operated furnace. During this process the workers are exposed to lead fumes and develop lead poisoning. In a study on 17 workers, abdominal colic was present in 15, sweet taste in mouth in 12, constipation in 12, weakness and fatigue in four, cough and dyspnoea in four.

On examination nine patients had burn marks on forearm due to sparks of charcoal fire, four had lead lines and one had motor neuropathy. Median motor and peroneal nerve conduction velocity of patients was not significantly different from controls. However, median sensory and sural nerve conductions were slowed significantly and sensory nerve action potentials were reduced. Zinc protoporphyrin, δ aminolevulenic acid dehydrogenase and lead levels in blood and urinary δ aminolevulenic acid were significantly higher in lead exposed group. Silver refining is an important cause of lead poisoning. Lead colic and anemia are common clinical pointers. Lead neuropathy occurs rarely and one third patients had subtle abnormalities on nerve conduction studies (Misra UK, unpublished observation).

Thallium

Thallium is used as insecticide, rodenticide and intentional poison. It is absorbed from dermal, oral ingestion, and through inhalation. Its clinical picture is similar to arsenic poisoning but for alopecia which manifests after two weeks of poisoning. There are isolated case reports of thallium poisoning from India. A 42-year-old man reported with acute flaccid weakness, severe paresthesia, diarrhea and renal impairment. In the second week he developed skin

lesion, tremor, nystagmus and alopecia which clinched the diagnosis [Figures 3 and 4]. His serum thallium level was very high. In the initial stage, motor and sensory conduction and nerve biopsy were consistent with axonal degeneration. He was treated with dialysis, multivitamins and oral potassium. Later he also developed visual loss.[23] Long term follow-up revealed recovery in peripheral neuropathy but mild residual deficit in the central nervous system as evidenced by extrapyramidal symptoms, nystagmus and limb ataxia persisted.[24] The importance of alopecia in the diagnosis of thallium poisoning has also been highlighted in another report.[25]

Thallium poisoning followed wheat contamination in 26 members of a family (14 females and 12 males). They had headache (92.3%), hair fall (84.6%), abdominal pain (61.5%), vertigo and lethargy (42.3%), tingling numbness (38.5%), sleep disturbance (26.9%) and tremor (15.4%). The authors highlighted erosion of proximal part of nail as a useful sign of thallium poisoning.[26] Role of hemodialysis, laxative and vitamin B complex therapy has been highlighted in the management of thallium poisoning.[23]

Organophosphates

There are over 20,000 organophosphate (OP) compounds which are used as pesticide, industrial chemicals and in chemical warfare. Organophosphates produce muscarinic, nicotinic, CNS effects and delayed peripheral neuropathy. The first medical report of organophosphate pesticide intoxication was from Pune in which 25 cases and two deaths were reported.[27] After this, a large number of reports appeared in medical literature.[28-31] Change in AchE blood level following diazinon has been reported by Rao *et al*.[32] Following this report, correlations between AChE and clinical signs as a marker of OP poisoning have been evaluated.[33]

Because of easy availability, OP pesticides are commonly used for suicide. In a report on 200 cases of OP poisoning for suicidal ingestion- the clinical manifestations included miosis in all, impaired consciousness in 10%, fasciculations in 27%, convulsions in 11%, delirium in 50% and paralysis in 26%. The paralytic signs was divided into type I (present on admission) and type II- (appeared later). Type I paralysis manifested with impaired consciousness and bipyramidal signs and responded to atropine. Type II paralysis manifested with wasting and weakness of proximal muscle, areflexia and cranial nerve palsy did not respond to atropine. Of 36 cases with type II paralysis, 15 died from respiratory failure and 21 recovered without sequelae. Type II paralysis differs from delayed neurotoxicity.[34] In 1987 Senanayake and Karallidde described a similar

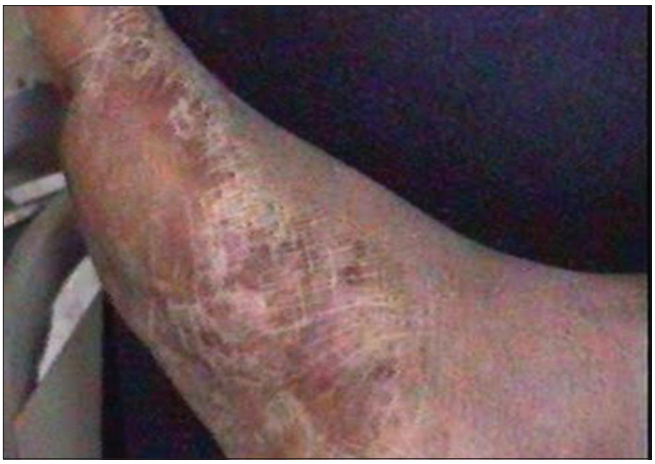

Figure 2: Keratosis in a patient with arsenic neuropathy

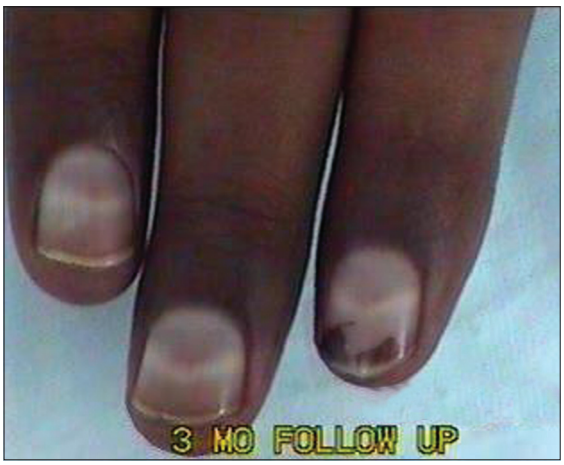

Figure 3: Mee's line in a patient with thallium poisoning

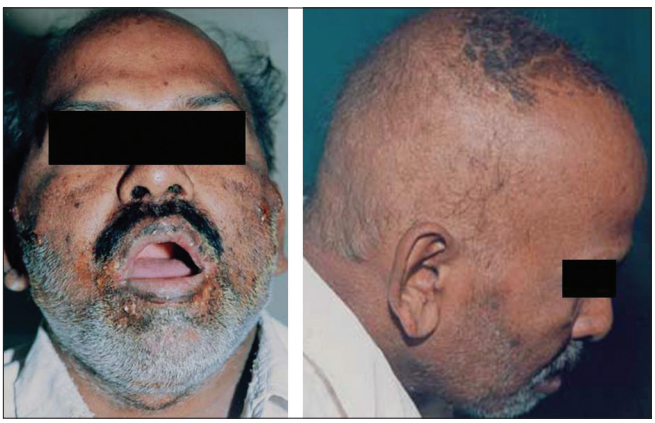

Figure 4: A patient with thallium poisoning who had furunculosis, angular stomatitis and glossitis in the second week and developed alopecia in the third week (Misra *et al* 2003,Post Grad Med J with permission)

phenomenon as intermediate syndrome because this syndrome appeared between the first phase of illness and delayed polyneuropathy which appears after several weeks. It appears that the intermediate syndrome refers to type II paralysis.[35,36]

Inhibition of plasma AchE following OP exposure is responsible for clinical manifestation; inhibition of AchE by 50% is associated with autonomic dysfunctions and 80% is associated with neuromuscular weakness. On nerve conduction studies, the compound muscle action potential is followed by repetitive after potentials. The delayed neurotoxicity of organophosphates manifests with axonal neuropathy.

At high rate RNS, there is decremented response. Decremented incremental activity is seen in severe OP poisoning and is attributed to axon blocking by collision of 1st and second stimuli introduced during prolonged refractory period. Electrophysiological studies in patients with suicidal OP poisoning were reported by Indian investigators. During such paralysis distal latency and nerve conduction velocity were normal even in severely paralyzed patients. The amplitude of CMAP was smaller than in controls and often showed a repetitive response. The CMAP amplitude tended to be lower in more severity affected cases. Low rate RNS did not reveal any decrement but significant decrement was observed at high rate (30 Hz) RNS even in the absence of paralysis,[37] similar observations were reported by others too.[38,39]

Delayed neurotoxicity of organophosphates

Some organophosphates particularly triorthocresyl phosphate (TOCP) produces delayed peripheral neuropathy. The initial signs of AChE inhibition are absent or mild. After 7-20 days, pure motor axonal neuropathy with wrist and foot drop develops. There is no sensory loss. Spasticity and exaggerated tendon reflexes develop after one to three months of initial illness.

Delayed OP neurotoxicity especially in relation to TOCP has been reported following outbreaks in Bombay in which 58 patients were affected.[40] After that four outbreaks have been reported from Bengal. The first outbreak was due to imported flour contaminated with TOCP through a broken barrel[41] and the latest by adulteration of rape seed oil.[42] In a report on 592 patients, 50% patients had diarrhea and vomiting initially. After an interval of one to three weeks the paralytic phase developed ranging from quadriplegia to foot drop and wrist drop. Proximal lower limb muscles were affected in 40% patients and upper limb involvement was rare. The ankle reflexes were absent in all but later pyramidal signs appeared in up to 65% cases. After two years, 25% patients recovered completely but 50% had mild weakness and 25% were severely disabled. About 65% patients returned to their previous occupation. Electrodiagnostic studies revealed axonal degeneration and EMG showed evidence of reinnervation.[43]

A phenomenon of dual neurotoxicity has been described in which initial manifestation of AChE inhibition is followed by delayed neurotoxicity. Only a few cases are documented and in India this phenomena has been reported with Dichlorvos.[44]

Chronic effects of organophosphate pesticides: The chronic effects on neuromuscular system have been reported in 24 workers exposed to fenthion. Their mean age was 31.7 and mean duration of exposure was 8.5 (range —one to nine) years. There was no clinical evidence of neuropathy. However subclinical neurophysiological changes have been observed. Peroneal motor conduction velocity, terminal latency of median and peroneal, F latency and H latency were significantly prolonged compared to controls. About 29% workers had repetitive compound motor unit potential. Serum AchE level was significantly inhibited.[45]

Alcoholic Neuropathy

The association between alcohol and peripheral neuropathy has been recognized for over 200 years. It is estimated that neuropathy occurs is up to 10% of chronic alcoholics. The most common type of neuropathy is progressive sensory axonal neuropathy. Pain and dysaesthesia are common. Sural nerve biopsy reveals small fiber involvement. As the neuropathy progresses motor weakness and muscle atrophy develop in a length dependent manner. In alcoholics acute neuropathy resembling GB syndrome is typically painful, often associated with malnutrition and hepatic dysfunction; it differs from GB syndrome by normal CSF, and absence of demyelinating features on nerve conduction study, and sural nerve biopsy shows loss of large and small fibers without any demyelination or inflammation. These patients improve by abstinence and vitamin supplementation.[46]

The etiology of neuropathy in chronic alcoholics is controversial and is attributed to several mechanisms including liver disease and malnutrition. No neuropathy occurred in primate model.[47] There is substantial evidence that in humans malnutrition is a major contributor of alcoholic neuropathy e.g. vitamin B12, folic acid and thiamine. Most recent clinical and pathological data indicate that patients with alcoholic neuropathy are clinically and pathologically distinct from non alcoholic patients with thiamine deficiency. Alcoholic neuropathy patients have prominent pain, small fiber loss on biopsy whereas latter deficiency results in more acute motor predominant axonopathy with large fiber loss on nerve biopsy. Alcoholic patients with thiamine deficiency have variable pathological and clinical features.[48]

In a study on 33 patients with liver cirrhosis, sensory motor axonal neuropathy was present in seven (21%) and nerve conductions were abnormal in 24 (73%) which was

present in both alcohol and non alcohol related cirrhosis. Neuropathy was subclinical in majority of patients with cirrhosis (73%) and was not related to alcohol.[49] In another study, 16 out of 20 patients with cirrhosis of liver had autonomic neuropathy and the frequency was comparable between alcoholic non alcoholics. The severity of autonomic neuropathy increased with severity of liver damage suggesting liver damage was primarily responsible for autonomic neuropathy.[50]

Organic Solvent

Solvents are used in industry as degreasing agents and include acrylamide, carbon disulfide, ethylene oxide and n-Hexane. These agents produce peripheral neuropathy with characteristic pathological features. The solvents result in cross linking of neurofilaments, focal axonal swelling, slow axonal transport, segmental demyelination and secondary axonal swelling. N-Hexane is used as industrial solvent, degreasing agent, in glue, rubber, cement and spray painting. Chronic industrial exposure results in progressive sensory neuropathy followed by distal weakness. Pain is common. The diagnosis of solvent neuropathy should be suspected in a patient with subacute or progressive neuropathy with plausible source of exposure. Nerve conduction study may show demyelinating features in the early stage and axonal in chronic exposure; 25 Hexane dione, toxic metabolite can be measured in urine and is elevated if there is continued exposure. Nerve biopsy shows characteristic axonal swelling.

From India, there are two reports of peripheral neuropathy in screen presenters. In a study on 25 screen printing workers, sensory motor neuropathy was present in all except two who had pure sensory neuropathy. Motor conduction studies revealed patchy and asymmetric involvement with conduction block in three. Sensory conductions were unrecordable in upper and lower limb nerves in 18. Sural nerve biopsy showed selective loss of myelinated fibers with demyelination in all six patients biopsied and axonal swelling with focal demyelination in two.[51] Another study on 36 screen printing workers chronic neuropathy was noted in 26, subacute in six and acute in one. After nine months, 26 patients were followed up; 16 improved and eight had stationary course. Nerve conduction study was consistent with axonopathy. On biopsy chronic axonopathy was found in 10 and giant axonal swelling in one patient (Pandey S, personal communication).

Drug Induced Toxic Neuropathies

A large number of drugs including those used in cancer chemotherapy, cardiac diseases, HIV treatment and organ transplantation have potential to produce neuropathy. Many drug induced neuropathies are dose dependent and dose limiting and most of these neuropathies improve after discontinuation of drug. Discussion of all the drugs is beyond the scope of this review. There are very few reports from India about drug related neuropathy. Some important ones from India are mentioned.

Cisplatin

Cisplatin produces sensory loss in length dependent fashion and produce ataxia in severe toxicity. Weakness does not occur and neuropathy may worsen in spite of discontinuation of therapy. Nerve conduction study is consistent with sensory axonopathy. Cisplatin and etapride related toxicity was evaluated in 40 patients. Sensory neuropathy occurred in 38% patients.[52]

Vincristine

Vincristine is the most toxic of vinca alkaloids. It interferes with axonal transport and results in length dependent sensorimotor neuropathy. Early ankle reflex loss is due to muscle spindle toxicity; therefore H reflex is retained in spite of absent ankle reflex. 18 lymphoma patients underwent prospective evaluation comprising of clinical examination and nerve conduction studies before and three months after the therapy. The earliest evidence of neuropathy was absent ankle reflex (two weeks) and the earliest symptom paresthesia (four to five weeks). At the end of study ankle reflex was absent in all the patients, sensory signs and symptoms were present in 75% (impaired vibration being the most frequent). The only autonomic symptom was constipation in 62.5% patients. In the early stage H reflex was elicitable in spite of absent ankle reflex. Vincristine though produces neuropathy in usual dose but it is rarely disabling in early months.[53]

Isoniazide

Isoniazide results in dose dependent axonal neuropathy which occurs in 50% of slow acetylators. Vitamin B6 in a dose of 50-100 mg may be prescribed to prevent isoniazide neuropathy. Two cases of suicidal isoniazide poisoning who consumed 7.5 g and 5 g respectively were admitted in comatose state with hepatic dysfunction. In both the patients, peripheral neuropathy was a noticeable complication.[54]

Metronidazole

Metronidazole is used for the treatment of anaerobic bacterial and several protozoal infections. A patient with amoebic liver abscess following two weeks' treatment with metronidazole 400 mg thrice daily developed axonal neuropathy which started improving after 7-10 days of discontinuation and improved completely after one month.[55]

Toxic neuropathy in India is mostly reported in relation to environmental and industrial toxins and following adulteration. Its prevention needs socio-cultural and political will. Recreational and iatrogenic toxic neuropathy is poorly documented and future research is needed in this direction.

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