Hexacarbon neuropathy
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Introduction

This article includes discussion of hexacarbon neuropathy and hydrocarbon neuropathy. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview

The author reviews the clinical features of an interesting toxic neuropathy. This neuropathy was fairly common in the past, related to recreational glue sniffing, but is primarily occupational currently. The axonal swellings seen in hexacarbon neuropathy are similar to those seen in carbon disulfide and acrylamide neuropathy.

Key points

• Hexacarbons are present in many solvents and glues, and exposure is most commonly occupational.
• The neuropathy associated with hexacarbon exposure results in giant axonal swellings and distal slowing of conduction velocity.
• Hexacarbon neuropathy may continue to worsen for some time after cessation of exposure (coasting).

Historical note and terminology

Hexacarbons are used as solvents and are components of lacquers and glues. Exposure to the hexacarbons occurs in petroleum production and refining industries. Glues and lacquers are widely used in the shoe and cabinet-making industries (Herskowitz et al 1971; Cianchetti et al 1976). Initial reports of occupational exposure to hexacarbons centered on the sandal- and shoe-making industries of Japan (Iida et al 1969; Yamamura 1969). Subsequent similar outbreaks of hexacarbon neuropathy were reported in Italy and in cabinet-finishing plants in the United States (Herskowitz et al 1971). Substitution of methyl n-butyl ketone for methyl ethyl ketone and methyl isobutyl ketone in the manufacturing of plastic-coated and color-coated fabrics prompted an epidemic of peripheral neuropathy in 1974 and 1975 (Mendell et al 1974). Other reports have pointed out the risk of n-hexane neuropathy among automotive technicians using degreasing and cleaner solvents (Centers for Disease Control and Prevention 2001) and screen printers in India (Puri et al 2007; Puri et al 2015; Pradhan and Tandon 2015). Intentional inhalation (glue sniffing) is also a cause of high-level exposure (Gonzalez and Downey 1972). Hexacarbon-related neuropathy is less common at present because of the removal of hexacarbons from many industrial and commercial products. However, recreational abuse, usually by means of glue sniffing, remains a substantial epidemiologic problem. Occupational exposures are still the most common cause in less developed countries (Misirli et al 2008; Sendur et al 2009).

Clinical manifestations

Presentation and course

Single episodes of high-level acute exposure cause central nervous system depression and narcosis. However, with repeated massive exposure (ie, glue sniffing), a subacute, predominately motor neuropathy with cranial nerve dysfunction develops that may be confused with Guillain-Barré syndrome (Korobkin et al 1975). This neuropathy may be associated with autonomic dysfunction including impotence, hyper- or anhidrosis, and vasomotor instability. Occupational or recreational exposure to lower doses over a longer time period results in a slowly developing central-peripheral axonopathy affecting the sensory and motor systems in a length-dependent fashion. In these cases, nerve fiber degeneration affects the distal portions of peripheral axons first, but, with continued exposure, leads to damage of distal corticospinal, dorsal column, and other central pathways. Vibratory, pinprick, and thermal sensations are impaired initially in the feet with dysfunction gradually progressing proximally with continued exposure. Although ankle reflexes are lost early in the course, the other reflexes may be surprisingly preserved relative to the degree of sensory loss. Distal leg and arm muscles may be weak and with neuropathy progression, weakness and atrophy may become the prominent complaint. In severe cases, the neuropathy is complicated by malaise, weight loss, abdominal
pain, and leg cramps. Worsening of symptoms after removal from exposure (coasting) is frequently seen, including a report of 25 cases (Wang et al 2014).

**Prognosis and complications**

Recovery depends on the severity of neuropathy. Patients with mild neuropathy usually make a complete and satisfactory recovery. A large case series found that all 102 cases that were identified recovered completely with minimal intervention except cessation of exposure (Kuang et al 2001). Residual distal atrophy, weakness, and sensory loss are not uncommon with severe neuropathies. This toxic neuropathy is well-known for the "coasting" phenomenon. Coasting is the continued worsening of the clinical manifestations even after removal from exposure. The effects of central damage (spasticity, long-tract weakness) may only become evident after resolution of the neuropathy.

**Biological basis**

**Etiology and pathogenesis**

Both n-hexane and methyl n-butyl ketone are clear, colorless, volatile liquids. They are metabolized to the toxic compound 2,5-hexanedione (O'Donoghue and Krasavage 1979). 2,5-hexanedione is a gamma diketone in which the spacing of the ketone groups (3 carbons away, or gamma position) is critical for neurotoxicity (Spencer and Schaumburg 1976). Methyl ethyl ketone is not neurotoxic by itself but is present in many solvent mixtures and may potentiate the neurotoxicity of n-hexane and methyl n-butyl ketone. Hexacarbons gain entry to the body through inhalation, dermal contact, and, rarely, ingestion. Ingestion of contaminated water is a rare cause of hexacarbon exposure.

A characteristic morphological abnormality is seen in the peripheral nerves of those with hexacarbon toxicity. This involves the formation of giant axonal swellings as a result of the accumulation of neurofilaments. Similar swellings are seen with exposure to acrylamide or carbon disulfide (Davenport et al 1976) and in the genetic giant axonal neuropathy (Asbury et al 1972). The accumulation of neurofilamentous material is most prominent at the paranodal region (Spencer and Schaumburg 1977). The accumulation of neurofilaments is likely related to cross-linking and disruption of axonal transport, which leads to a distal-central dying back neuropathy (Schaumburg and Spencer 1978). The role of neurofilaments in the neuropathy and axonal swellings has been proven in neurofilament-deficient quail. These animals do not develop neuropathy when exposed to 2,5-hexanedione and have no axonal swellings (Hirai et al 1999). The neurofilament abnormalities involve loss of neurofilament proteins, which may be due to these proteins being targeted for degradation by the ubiquitin proteosome system (Wang et al 2011). The isoform of cytochrome P450 2E1 enzyme may be related to differential susceptibility of individuals exposed to similar levels of hexane (Zhang et al 2006).

**Epidemiology**

Two groups are affected by toxicity of these compounds: those exposed due to their occupation and those who intentionally inhale the vapors. The latter group tends to be adolescents or young adults who may be abusing other substances.

**Prevention**

Workers handling solvents containing n-hexane or methyl n-butyl ketone need to be informed regarding the toxic effects. In order to minimize dermal contact, gloves and other protective clothing should be worn (Feldman 1999). The work area should be well ventilated, especially in those areas where high concentrations are present. Ambient air levels can be monitored to gauge the risk of exposure (Aiello et al 1980). Measurement of 2,5-hexanedione in the urine can help detect exposure before significant toxicity occurs (Cardona et al 1993). The urinary levels of 2,5-hexanedione are tightly correlated with exposure levels (Mayan et al 2001; Mayan et al 2002). Nerve conduction abnormalities can be seen in asymptomatic individuals in the sural and median sensory nerve action potential amplitudes that correlate with the urinary 2,5-hexanedione levels and may allow for early detection of hexane-induced neuropathy (Neghab et al 2012).

**Differential diagnosis**
The slowly developing neuropathy that occurs with prolonged occupational exposure is clinically similar to that produced by a number of other toxic and acquired conditions and, therefore, requires a low threshold of suspicion in the proper exposure setting. Because of the fairly rapid evolution and the presence of conduction slowing (Korobkin et al 1975), the neuropathy associated with repeated high-level hexacarbon exposure needs to be differentiated from Guillain-Barré syndrome.

Diagnostic workup

Nerve conduction studies reveal marked slowing of distal motor conduction velocities, which is an unusual finding in other toxic neuropathies but characteristic of subacute hexacarbon neuropathy (Korobkin et al 1975). A study of 25 cases of N-hexane related toxicity confirmed prolonged distal latency, although the findings appeared very mild (Wang et al 2014). Intentional inhalation has been associated with multifocal conduction block in addition to generalized slowing (Kuwabara et al 1999; Pastore et al 2002). Slowed conduction velocities have also been reported in asymptomatic workers employed in factories with documented cases of solvent polyneuropathy. The nerve biopsy reveals the well-described giant axonal swellings. Evoked potential studies may also be abnormal (Mutti et al 1982). Spinal fluid protein is usually normal unless the nerve roots become involved, in which case cerebrospinal fluid protein may be elevated.

Management

Cessation of exposure is the primary form of treatment.

References cited


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**References especially recommended by the author or editor for general reading.

**Former authors

Alan R Berger MD

**ICD and OMIM codes

**ICD codes

ICD-9:
Polyneuropathy due to other toxic agents: 357.7

ICD-10:
Polyneuropathy due to other toxic agents: G62.2

**Profile

**Age range of presentation

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

**Sex preponderance

male=female

**Family history

none

**Heredity

none

**Population groups selectively affected

none selectively affected

**Occupation groups selectively affected

automotive technicians
cabinet makers
leather goods manufacturers
paint thinner manufacturers
petroleum workers

**Differential diagnosis list

Guillain-Barre syndrome
Other topics to consider

Chronic autonomic neuropathies
Introduction to peripheral neuropathies
Introduction to toxic peripheral neuropathies
Mercury neuropathy