

Polyneuropathy possibly caused by 30 years of low exposure to n-hexane

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BARREGÅRD L, SÄLLSTEN G, NORDBORG C, GIETH W. Polyneuropathy possibly caused by 30 years of low exposure to n-hexane. *Scand J Work Environ Health* 1991;17:205-7. A slowly developing, mainly sensory, polyneuropathy was found in a 60-year-old man exposed to n-hexane (10-100 mg/m³) for 30 years in a mountain fuel stockpile. The nerve damage was verified by electromyography and sural nerve biopsy, and it is proposed that also a low-grade, but prolonged, exposure to n-hexane may cause polyneuropathy.

Key terms: fuels, nerve biopsy, neurotoxicity.

Neuropathy caused by exposure to the hexacarbonyl n-hexane and methyl-n-butyl ketone has been described in a number of case reports and cross-sectional studies. The problem has been extensively reviewed (1, 2). The toxicity is caused by the common metabolite 2,5-hexanedione. The distal axonopathy can be reproduced in experimental animal studies. Human disease has been caused either by inhalation abuse (eg, glue thinners) or by occupational exposure. The levels of n-hexane have been high, but the exposure times limited. In this presentation we report a case of polyneuropathy possibly caused by 30 years of exposure to relatively low levels of n-hexane.

Case report

History. The patient was a 60-year-old man. There had been no neurological diseases among his relatives. He smoked two to three cigarettes per day. His present and previous alcohol consumption was less than 10 grams per week.

Pain, paresthesia, and numbness in his feet and legs started at the age of 40 years, and paresthesia began to occur in his hands and arms when he was 50 years of age. At that time he was also involved in an automobile accident, with a zygomatic fracture and 10 min of unconsciousness. A lumbar sympathetic alcohol blockade was given at the age of 52 years, with transient disappearance of the pain. Lumbar surgery (age 57 years) was tried because of a suspected disc hernia. No hernia was found, however. The symptoms in his extremities progressed very slowly. By 60 years of age

he sometimes stumbled when it was dark and his manual dexterity seemed slightly deteriorated.

Clinical examination. Examination of the circulatory and respiratory systems and the abdomen revealed no abnormalities. The patient was alert and there were no signs of dementia. The neurological examination showed polyneuropathy with symmetrically decreased sensibility to light touch and pain in his legs (up to the knees) and hands; loss of the sense of vibration in the toes, although it was preserved in the fingers; absence of reflexes in the arms and Achilles tendons but normal reflexes in the quadriceps; no obvious muscular atrophy or weakness; and no tremor, ataxia or abnormalities in the cranial nerves. Myelography and computed tomography of the back were normal. Blood tests including glucose, electrolytes, creatinine, liver and thyroid function tests, vitamin B12, folic acid, protein electrophoresis, and blood lead were normal, as were the routine urine examinations. His nerve conduction velocities were within the reference limits. Electromyography showed moderate signs of symmetric neuropathy in the lower extremities.

Sural nerve biopsy. In the sural nerve biopsy (figures 1 and 2) there was a somewhat reduced number of myelinated fibers and also signs of sparse ongoing axonal degeneration. A majority of the remaining myelin sheaths appeared thick in relation to the axonal diameter, and the sheaths were sometimes markedly folded. Numerous small lamellar dense bodies, probably remnants of degenerated organelles, were found in several of the myelinated axons. A single membrane-bound axonal glycogen body was also found. Moreover, the density of the neurofilaments appeared markedly increased, and their orientation was sometimes irregular in the scattered myelinated fibers. No paranodal swelling was found, however, in longitudinal sections or in teased nerve fibers. There were numerous Reichert granules in some of the myelin-forming Schwann cells.

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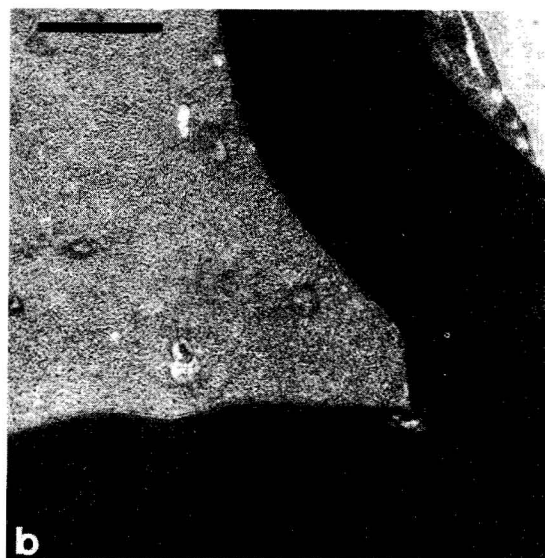


Figure 1. a. Myelinated nerve fiber (arrow) with a very dense axoplasm compared with adjacent fiber (*). Note group of atrophic unmyelinated nerve fibers (arrow heads) (bar: 4.2 μ m). b. Detail of figure a, shows closely packed neurofilaments in the electron-dense axon (bar: 0.7 μ m)

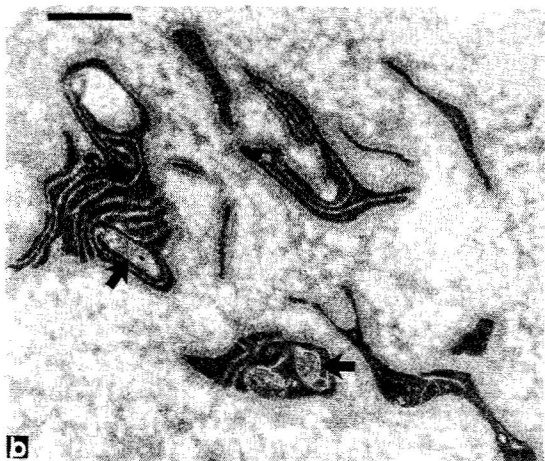


Figure 2. a. Complex folding of myelin sheath in a severely atrophic nerve fiber (bar: 2.5 μ m). b. Group of atrophic unmyelinated nerve fibers with piling of Schwann cells and few remaining axons (arrows) (bar: 0.8 μ m).

One prominent finding was a pronounced and widespread atrophy of unmyelinated fibers, many of which appeared ramified, with numerous collagen pockets and a conspicuous piling of Schwann cells. A moder-

ate number of clusters was found, and numerous unmyelinated nerve fibers were oriented along myelinated ones, indicating an element of axonal regeneration.

Occupational hygiene. The patient had worked inside a mountain storage facility for fuels since the age of 30 years, pumping, gauging the levels of fuels, and cleaning the tanks. About 60 % was jet fuel, and the rest mainly leaded gasoline or diesel oil. Jet fuels today contain 2–8 % n-hexane, while the fractions in the other fuels are lower. The concentration of n-hexane in the air at present was determined by personal sampling with 3M 3500 passive samplers. The concentration of n-hexane was 70 mg/m³ during a 28-min period of gauging, but only 6 mg/m³ as an 8-h average. The work conditions had been worse (eg, more gauging and fuel leakage and less ventilation) in the earlier periods, and thus the levels of n-hexane were higher. From an evaluation of the work tasks and the ventilation conditions, the n-hexane levels were estimated to have been about 100 mg/m³ (8-h average with higher peaks) in the first 10 years and about 25 mg/m³ in the next 15 years. In the 1980s his exposure had further diminished. Personal protective equipment had been used only during the cleaning of the tanks.

Discussion

This case involved a slowly progressing, mainly sensory, polyneuropathy verified by clinical examination, electromyography, and nerve biopsy. Careful evaluation did not reveal any alcohol abuse or systemic disorder known to induce polyneuropathy.

Age has a significant influence on sural nerve morphology. The loss of nerve fibers and the axonal de-

generative phenomena revealed in the nerve biopsy were, however, too pronounced to be explained by age alone. Rather, the light and electron microscopic findings were consistent with a slowly progressive neuropathy affecting both small and large nerve fibers. The atrophic changes in myelinated and unmyelinated fibers were nonspecific. However, the accumulation and irregular orientation of the neurofilaments in some myelinated axons indicated that n-hexane may have been one etiological factor. Moreover, a large glycogen body was found in one axon. Intraaxonal glycogen is not an aging phenomenon and has been found in sural nerve biopsies from workers with a history of chronic exposure to organic solvents (3).

N-hexane neuropathy in glue sniffers has been reported after abuse periods of six months or longer. The n-hexane concentration in inhaled air could be very high in such cases. Inhalation of pure n-hexane for 10 min at a concentration of 18 000 mg/m³ results in giddiness and narcosis (2). In most cases glue sniffers have, however, not inhaled pure n-hexane but rather mixtures of solvents containing varying fractions of n-hexane.

In occupational settings n-hexane levels of 200–9000 mg/m³ have been reported to cause serious or moderate clinical neuropathy (1, 2). In one report, four sash-cleaning workers exposed to benzene for 5–7 months developed polyneuropathy including muscular atrophy. The benzene contained 12.5 % n-hexane, and spot sampling showed n-hexane levels of 180–860 mg/m³ in the workroom (4). Low levels of n-hexane (mean 200 mg/m³) were reported in a study of Japanese workers exposed for an average of six years. In these subjects there were neurophysiological signs of peripheral neuropathy, but no impairment in a clinical neurological examination (5). Furthermore in a study of proofing workers in Taiwan, decreased nerve conduction velocities were seen in workers with an estimated exposure to n-hexane of below 40 mg/m³ (6).

Exposure to vapors from jet fuels also takes place among workers in the jet motor industry. In a cross-sectional study of such workers, an increased prevalence of signs of polyneuropathy was found in a comparison with unexposed reference groups (7). In another similar study these findings could not, however, be reproduced (8). From the levels of total hydrocarbons, it can be calculated (9) that the exposure to n-hexane in the jet motor industry was about 45 mg/m³.

In our case the estimated average n-hexane levels were about 100 mg/m³ in the first 10 years of exposure and even lower after that. The other constituents of jet fuel, gasoline, and diesel oil were mainly saturated hydrocarbons not known to cause polyneuropathy in occupational exposure. Methyl ethyl ketone is known to facilitate the development of hexacarbon neuropathy (1, 2), but this compound is normally not found in fuels. Work with leaded gasoline

implies exposure to the toxic organolead compounds tetraethyl and tetramethyl lead. These are, however, not known to cause polyneuropathy (10).

In most (but not all) cases, n-hexane neuropathy has been totally or partly reversible (1, 2, 11). In our patient, no recovery was seen in the first year after exposure ceased. The polyneuropathy of this patient slowly progressed, although the levels of n-hexane decreased over the 30-year exposure period. It is possible that exposure to neurotoxic agents interacts with normal aging, and it should be noted that most follow-up studies have been conducted on young individuals.

Our conclusion is that a prolonged exposure to rather low levels of n-hexane is the most probable cause of this case of polyneuropathy. If this conclusion is correct, the recent lowering of the Swedish occupational exposure limit for n-hexane from 180 to 90 mg/m³ seems warranted.

References

1. Spencer PS, Couri D, Schaumburg HH. N-hexane and methyl-n-butyl ketone. In: Spencer PS, Schaumburg HH, ed. *Experimental and clinical neurotoxicology*. Baltimore, MD: Williams and Wilkins, 1980:456–475.
2. Spencer PS, Schaumburg HH, Sabri MI, Veronesi B. The enlarging view of hexacarbon neurotoxicity. *CRC Crit Rev Toxicol* 1980;7:279–356.
3. Berthold CH, Nordborg C, Hildebrand C, Conradi S, Sourander P, Lugnegård H. Sural nerve biopsies from workers with a history of chronic exposure to organic solvents and from normal control cases. *Acta Neuropathol (Berl)* 1983;62:73–86.
4. Takeuchi Y, Mabuchi C, Takagi S. Polyneuropathy caused by petroleum benzene. *Int Arch Arbeitsmed* 1975;34:185–97.
5. Sanagi S, Seki Y, Sugimoto K, Hirata M. Peripheral nervous system functions of workers exposed to n-hexane at a low level. *Int Arch Occup Environ Health* 1980;47:69–79.
6. Wang JD, Chang YC, Kaok KP, Huang CC, Lin CC, Yeh WY. An outbreak of n-hexane induced polyneuropathy among press proofing workers in Taipei. *Am J Ind Med* 1986;10:111–118.
7. Knave B, Persson HE, Goldberg JM, Westerholm P. Long-term exposure to jet fuel: an investigation on occupationally exposed workers with special reference to the nervous system. *Scand J Work Environ Health* 1976;2:152–64.
8. Knave B, Anshelm Olsson B, Elofsson S, Gamberale F, Isaksson A, Mindus P, Persson HE, Struwe G, Wennberg A, Westerholm P. Long-term exposure to jet fuel: II. a cross-sectional epidemiologic investigation on occupationally exposed industrial workers with special reference to the nervous system. *Scand J Work Environ Health* 1978;4:19–45.
9. Holm S, Norbäck D, Frenning B, Göthe C-J. Hydrocarbon exposure from handling jet fuel at some Swedish aircraft units. *Scand J Work Environ Health* 1987;13:438–44.
10. Grandjean P. Organolead exposures and intoxications. In: Grandjean P, Grandjean EC, ed. *Biological effects of organolead compounds*. Boca Raton, FL: CRC Press, 1983:227–41.
11. Chang YC. Patients with n-hexane induced polyneuropathy: a clinical follow up. *Br J Ind Med* 1990;47:485–489.

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