Methyl bromide induced neuropathy: a clinical, neurophysiological, and morphological study

Methyl bromide is a colourless, odourless gas used as a fumigant to disinfect soil, grains, and warehouses. Due to its high volatility, dangerous concentrations can accumulate rapidly in working areas. Inhalation is a main route of exposure. Dependent on dose and duration of exposure, methyl bromide can cause both acute CNS symptoms1 and chronic peripheral sensorimotor neuropathy.2,4 Optic atrophy has also been described.6

A 23 year old Moroccan man working in Italy as a methyl bromide fumigator in greenhouses was admitted because of painful leg numbness. His personal history was unremarkable and he denied alcohol misuse. He had worked for the previous seven months (eight hours a day), wearing a protection mask irregularly. Neurological examination showed asymmetric lower limb weakness and areflexia, stepping gait, and sensory loss for pin prick, position, and vibration. Upper motor and cranial nerve signs were absent. Mental state was intact. Laboratory tests excluded diabetes, hepatic and collagen diseases, syphilis, tuberculosis, HIV, and Lyme related disease. Vitamin B12 and folate concentrations were normal. CSF was normal. Organophosphate and lead poisoning were excluded. One month after cessation of exposure urinary methyl bromide was 0·01 ppm. A colour vision test (Farnsworth-Munsell 100-hue test) showed defective perception of all colours, especially in the red-green axes. Eye fundi and evoked responses were normal.

Electrophysiology showed a severe motor neuropathy of axonal type confined to the legs. The right peroneal muscle action potential was undetectable from the extensor digitorum brevis muscle. The tibial and left peroneal nerves had reduced motor conduction (2·7 and 3·6 SD from mean control value) and muscle action potential amplitude (0·2 and 1·0 mV). Sensory findings in the sural nerve were normal. An EMG showed denervation and loss of motor units in distal muscles. Tibialis anterior muscle biopsy showed neurogenic changes. A sural nerve sample was examined. Light microscopy showed that the endoneurial area and total fibre density were within the normal range. Multifocal, scattered loss of myelinated fibres (4689 ± 5200–9500 in normal subjects) was detected, with a prominent loss of fibres larger than 7 μm (1321 ± 1650–3300), and relative sparing of the smaller axons.4 Degenerated fibres were seen. The frequency of clusters fell within the normal range and there was no inflammatory infiltrate. On teased, 38% of the fibres had signs of segmental remyelination; 15% had shortening of all internodes, suggesting regeneration, whereas the incidence of demyelination multifocally distributed along the fibre length was 8%. Electron microscopy showed ongoing degeneration of both myelinated and unmyelinated fibres. Numerous Schwann cell subunits were devoid of axons. Many nodes of Ranvier showed segregated axonal microtubules (figure). The patient received B1, B6, and B12 vitamins, folic acid, and amantripoline (50 mg/day). When re-examined two months later, muscle strength was normal, whereas limb numbness was still present. Peroneal muscle action potential (0·3 mV) was recordable and there were no signs of denervation. Two coworkers, similarly exposed to methyl bromide, had neither clinical nor electrophysiological signs of neuropathy, despite slightly altered colour vision.

The clinical history and laboratory data of this patient excluded known causes of peripheral neuropathy, suggesting that exposure to methyl bromide was responsible. The neurological time course corresponded with previous descriptions, where symptoms appeared after several months of exposure and the patients mostly recovered six to eight months after cessation of exposure.11

It has been proposed that methyl bromide causes a distal axonopathy.2 We report here morphological evidence for nerve abnormalities after exposure to methyl bromide. Loss of large axons and degeneration of both myelinated and unmyelinated fibres were found in the sural nerve. Spared myelinated and regenerating large fibres might account for the normal amplitude and maximal velocity of the sural action potential.

The presence of segregated microtubules in the nodes of Ranvier suggests that methyl bromide impairs axonal flow. As in most types of exogenous intoxication, myelin formation may cause degeneration of axons with a dying-back mechanism, more evident at the distal nodes. This neurotoxic agent may either alter the metabolism of the neuronal perikaryon or interfere with the dynamics of axonal transport. A metabolic mechanism for methyl bromide intoxication has recently been proposed. Based on neuropathological similarities with Wernicke’s disease, methyl bromide intoxication has been correlated with an altered glycolysis and pyruvate oxidation.

Our patient and two healthy coworkers showed an acquired type dyschromatopsia. This may be a first sign of optic neuropathy,1 which precedes electrophysiological abnormalities. We therefore propose to use the Farnsworth-Munsell 100-hue test to screen workers exposed to methyl bromide.

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Figure (A) Electron micrograph showing a node of Ranvier with segregated microtubules. Calibration bar = 0·05 μm. (B) Segregated microtubules, altered mitochondria, dense bodies, and amorphous filamentous material are packed among masses of neurofilaments. Calibration bar = 0·1 μm.

Correspondence to: Dr F Cavalleri, Dipartimento di Neurologia, Università di Modena, Via del Pozzo 71, 41100 Modena, Italy.


Anti-D immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy

Patients with immune thrombocytopenic purpura may have increases in platelet count after treatment. The mechanism of action of intravenous
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F Cavalleri, G Galassi, S Ferrari, E Merelli, G Volpi, F Gobba, G Del Carlo, A De Iaco, A R Botticelli and N Rizzuto

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