Acta Neuropathol (1996) 92:525–527

CASE REPORT

Roger Pamphlett · Patricia Waley

Uptake of inorganic mercury by the human brain

Received: 14 February 1996 / Revised: 23 May 1996 / Accepted: 28 May 1996

Abstract A 24-year-old man injected himself intravenously with metallic mercury in a suicide attempt, and died 5 months later after cutting his wrists. The brain was removed at postmortem and 7-µm paraffin sections were cut from representative blocks. Dense deposits of mercury were found on autometallography in large cortical motor neurons, but in no other cerebral neurons. Smaller mercury deposits were found in the brain stem (in the mesencephalic trigeminal nucleus, noradrenergic neurons, and in neurons for extraocular muscles), the cerebellum (in the dentate nucleus) and in lateral motor neurons in the C2/3 spinal cord. Mercury deposits were found in glial cells in all regions. The finding that elemental mercury enters human cortical motor neurons in preference to other cerebral neurons raises the possibility that this neurotoxin may play a part in the pathogenesis of some human motor neuron diseases.

Key words Mercury · Human · Neurotoxicity · Cortical motor neuron · Amyotrophic lateral sclerosis

Introduction

In experimental animals, inorganic mercury ions and elemental mercury vapour are taken up predominantly by motor neurons in the spinal cord and brain stem [19, 20]. Mercury can be demonstrated by autometallography, a technique which allows the microscopic detection of nanogram amounts of mercuric sulphide or mercuric selenide within cells [6]. We have examined the brain of a man who injected himself with metallic mercury and who committed suicide 5 months later. We found large amounts of mercury in cortical motor neurons and smaller amounts in some brain stem and cerebellar neurons.

R. Pamphlett (✉) · P. Waley
Department of Pathology, University of Sydney, Sydney, NSW 2006, Australia
Tel.: (61-2) 351-3318; Fax: (61-2) 351-3429

Case report

A 24-year-old man had a history of heroin abuse and repeated suicide attempts. He presented to the emergency ward after attempting suicide by breaking the ends off two industrial thermometers and injecting the metallic mercury via a syringe with a large-bore needle into an antecubital vein. He described no systemic symptoms related to this injection, and examination revealed no neurological abnormalities. His blood mercury level was 0.27 µmol/l (normal range 0.00–0.10 µmol/l). Radiographs showed small globules of mercury in his right ventricle, throughout both lung fields and in his pelvic venous plexuses. After a period of observation he was allowed to leave hospital without treatment, and he was lost to follow-up. Five months later he died after injecting himself with a large dose of heroin and lacerating both his wrists.

Postmortem findings

At postmortem examination 8 h after death metallic mercury globules were seen on the cut surfaces of his right ventricular myocardium, the lungs and in the pelvic veins, but no macroscopic mercury was seen in the brain. Tissue mercury concentrations (with mean normal values from autopsies of 113 persons in brackets [21]) were: liver 7.5 µg/g (0.25 µg/g), heart 106,000 µg/g (0.10 µg/g), kidney 180 µg/g (0.76 µg/g), lung 543 µg/g (0.25 µg/g) and cerebrum 0.1 µg/g (0.08 µg/g). Microscopy showed foreign-body granulomas in the myocardium and lungs. The brain was suspended in 10% buffered formalin for 3 weeks. The spinal cord was not removed. After fixation, the cerebrum was sectioned in 10-mm slices in the horizontal plane, the cerebellum in the parasagittal plane and the brain stem in 5 mm slices in the transverse plane. Representative blocks were processed routinely and 7-µm paraffin sections stained with haematoxylin-eosin and cresyl violet-Luxol fast blue. Blocks were taken from the kidney and liver and processed similarly. The brain and spinal cord from a 26-year-old man who died from respiratory complications of cystic fibrosis was treated in the same way as a control.

Autometallography

Paraffin sections were stained for mercury by autometallography [6]. Briefly, sections were pretreated with 1% potassium cyanide for 2 h to eliminate non-specific staining from silver sulphides or selenides, and in 10% potassium cyanide for 10 min to eliminate non-specific staining from gold [25]. Sections were placed in physical developer containing 50% gum arabic, citrate buffer, hydroquinone, and silver nitrate at 26°C for 70–90 min in the dark.

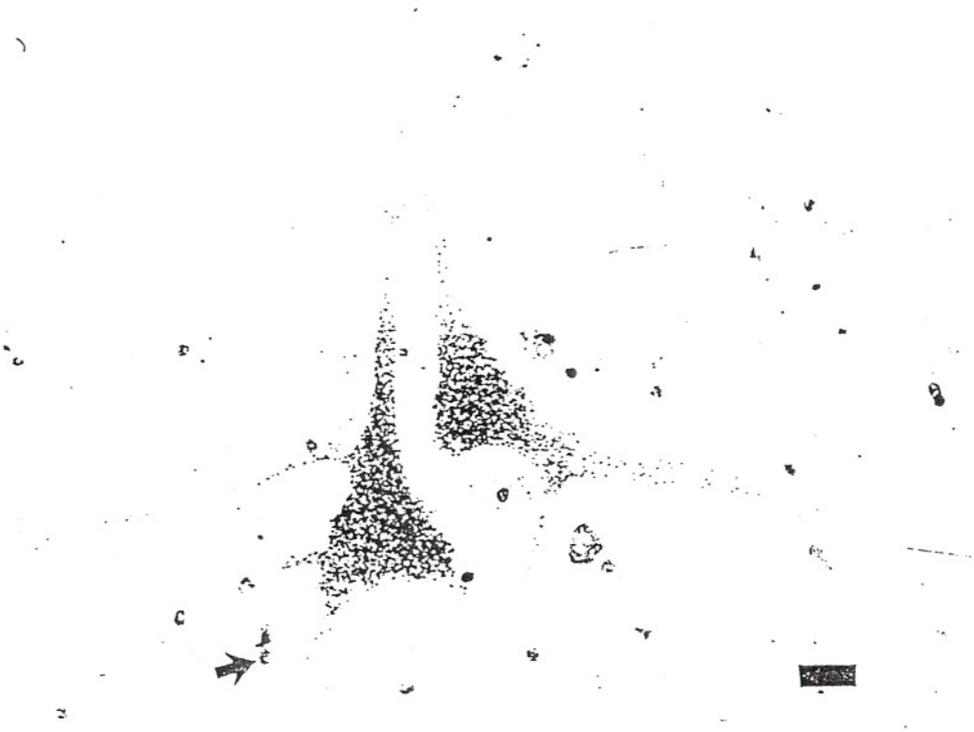

Fig. 1 Silver-labelled mercury deposits in the cell bodies and neurites of two large cortical motor neurons. Scattered glial cells (arrow) contain small amounts of cytoplasmic mercury. *Bar* 20 μm

Excess silver was removed by 5% sodium thiosulphate. Sections were counterstained with 0.5% cresyl violet and viewed under bright- and dark-field illumination. Silver granules surrounding mercury deposits are referred to as "mercury granules".

Microscopic findings

No histopathological abnormalities were seen on sections from the cerebrum, cerebellum or brain stem. Autometallography showed no mercury granules in any neurons of the control case. In the mercury-injected case, mercury granules were seen in capillary walls and in the cytoplasm of scattered glial cells throughout the brain, with no particular predilection for motor areas.

In the cerebrum, mercury granules were restricted to large motor neurons in the primary motor cortex (Fig. 1). Granules were seen throughout the perikarya of these neurons, and extended into neuronal processes for considerable distances. No granules were seen in any other cerebral neurons (in the cerebral neocortex, hippocampus, basal ganglia or diencephalon) or in the ependyma. Scattered cells in the choroid plexus contained small amounts of mercury.

In the brain stem, neurons in the mesencephalic trigeminal nucleus contained a moderate number of mercury granules. Noradrenergic neurons, both in the locus ceruleus and those scattered throughout the lateral tegmentum [7], contained a moderate number of mercury granules. Small numbers of mercury granules were seen in the perikarya of neurons in the oculomotor, trochlear and abducens nuclei. No granules were found in neurons of the facial, trigeminal motor or hypoglossal nuclei, or in the substantia nigra. In the cerebellum, small numbers of mercury granules were seen in scattered dentate neurons. No mercury was seen in Purkinje or granule cells. In the C1-3 spinal cord, small numbers of mercury granules were seen in a few neurons in the laterally placed accessory nuclei. No granules were seen in neurons of the dorsal horn. Tubules, but not glomeruli, within the kidney stained strongly for mercury. Periportal hepatocytes contained numerous mercury granules.

Discussion

Elemental mercury (Hg^0) can cross the blood-brain barrier to enter the central nervous system. Most elemental mercury is oxidised to ionic mercury (Hg^{2+}) by catalase in red blood cells, and very little Hg^{2+} crosses the blood-brain barrier [5]. Before it is oxidised, however, Hg^0 can cross the blood-brain barrier readily and enter neurons. The concentration of mercury that remains within these neurons may depend on their content of catalase which traps Hg^{2+} within the cell [9]. Ionic mercury can bypass the blood-brain barrier by entering terminal motor axons at the neuromuscular junction [2] and then reach motor neuron cell bodies by retrograde axonal transport [1]. With low doses of Hg^{2+}, entry across the neuromuscular junction seems to predominate, since low doses are taken up selectively by spinal motor neurons [23].

Transport of mercury across the neuromuscular junction cannot explain why, in this case, large cortical motor neurons contained mercury. Unfortunately, the spinal cord was not available for examination in our patient, so we do not know if mercury could have been transferred transynaptically from spinal to cortical motor neurons. Primates (but not rodents) have many direct connections between cortical and spinal motor neurons [24], so transfer of mercury from lower to upper motor neurons in humans is theoretically possible, given that tetanus toxin [8] and some viruses [14] can be transferred transynaptically.

Autometallography has been used previously to study the tissue distribution of mercury in a human exposed to elemental mercury [11]. This man developed mercurialism after filling mercury thermometers for 18 months. He died 16 years later, and mercury granules were found in

large pyramidal neurons in the cerebral cortex, large neurons in the brain stem, and large motor neurons in the anterior horn of the spinal cord. Non-motor neurons affected were those in the substantia nigra (with the largest mercury load), Purkinje cells and spinal ganglia. Non-neuronal uptake was seen in astrocytes and in blood vessel walls. The wider distribution of mercury uptake in this case compared to ours could be due to the longer exposure to mercury (18 versus 5 months), or the fact that exposure would have been primarily to mercury vapour, not to injected metallic mercury as in our case.

In our case, cortical motor neurons, rather than brain stem motor neurons, contained mercury. This would argue against a hypothesis of mercury-induced Sporadic motor neuron disease (SMND) of the amyotrophic lateral sclerosis type, where both upper and lower motor neurons are affected. However, it has been postulated that SMND is a primary disorder of the cortical motor neuron, with lower motor neurons being affected secondarily [10]. Furthermore, no large spinal motor neurons were available for examination in this case.

A small amount of mercury was present in the oculomotor, trochlear, and abducens nuclei of our case. Motor neurons for extraocular muscles are generally intact in SMND [13] but sparing is only partial since oculomotor neurons are lost in long-surviving patients [18]. Extraocular motor neurons contain calcium-binding proteins that protect against calcium-mediated cell damage [12], and these may limit mercury neurotoxicity since a number of the damaging effects of mercury appear to be mediated via calcium [16].

In conclusion, we have demonstrated that, after exposure to elemental mercury, the metal is deposited in human cortical motor neurons and in scattered groups of neurons in the brain stem and cerebellum. Mercury is a well-established neurotoxin with the potential to damage neurons via a number of mechanisms: generation of oxygen radicals [17] or excitotoxins [3], release of intracellular calcium [4] or lysosomal enzymes [15], or cytoskeleton disorganisation [22]. The predominant uptake of mercury by cortical motor neurons suggests that this metal could be a pathogenetic agent in some cases of human motor neuron disease.

Acknowledgements This work was supported by the National Health and Medical Research Council of Australia.

References

1. Arvidson B (1987) Retrograde axonal transport of mercury. Exp Neurol 98: 198–203
2. Arvidson B (1992) Inorganic mercury is transported from muscular nerve terminals to spinal and brainstem motoneurons. Muscle Nerve 15: 1089–1094
3. Brookes N (1992) In vitro evidence for the role of glutamate in the CNS toxicity of mercury. Toxicology 76: 245–256
4. Chavez E, Holguin JA (1988) Mitochondrial calcium release as induced by Hg^{2+}. J Biol Chem 263: 3582–3587
5. Clarkson TW, Hursh JB, Sager PR, Syverson TLM (1988) Mercury. In: Clarkson TW, Friberg L, Nordberg GF, Sager PR (eds) Biological monitoring of toxic metals. Plenum Press, New York, pp 199–246
6. Danscher G, Moller-Madsen B (1985) Silver amplification of mercury sulfide and selenide: a histochemical method for light and electron microscopic localization of mercury in tissue. J Histochem Cytochem 33: 219–228
7. DeArmond SJ, Fusco M, Dewey MM (1989) Structure of the human brain, 3rd edn. Oxford University Press, New York
8. Dumas M, Schwab ME, Bauman R, Thoenen H (1979) Retrograde transport of tetanus toxin through a chain of two neurons. Brain Res 165: 334–339
9. Eide I, Tore L, Syversen M (1983) Relationship between catalase activity and uptake of elemental mercury by rat brain. J Pharmacol Toxicol 52: 217–223
10. Eisen A, Kim S, Pant B (1992) Amyotrophic lateral sclerosis (ALS): a phylogenetic disease of the corticomotoneuron? Muscle Nerve 15: 219–228
11. Hargreaves RJ, Evans JG, Janota I, Magos L, Cavanagh JB (1988) Persistent mercury in nerve cells 16 years after metallic mercury poisoning. Neuropathol Appl Neurobiol 14: 443–452
12. Incè P, Stout N, Shaw P, et al (1993) Parvalbumin and calbindin D-28k in the human motor system and in motor neuron disease. Neuropathol Appl Neurobiol 19: 291–299
13. Iwata M, Hirano A (1979) Current problems in the pathology of amyotrophic lateral sclerosis. Prog Neuropathol 4: 277–298
14. Kuypers HGJM, Ugolini G (1990) Viruses as transneuronal tracers. Trends Neurosci 13: 71–75
15. Lauwerys R, Buchet J (1972) Study on the mechanism of lysosome labilization by inorganic mercury in vitro. Eur J Biochem 26: 535–542
16. LeBel CP, Bondy SC (1990) Oxygen radicals: common mediators of neurotoxicity. Neurotoxicol Teratol 13: 341–346
17. LeBel CP, Ali S, McKee M, Bondy SC (1990) Organometal-induced increases in oxygen reactive species: the potential of 2',7'-dichlorofluorescin diacetate as an index of neurotoxic damage. Toxicol Appl Pharmacol 104: 341–346
18. Mizutani T, Aki M, Shiozawa R, et al (1990) Development of ophthalmoplegia in amyotrophic lateral sclerosis during long-term use of respirators. J Neurol Sci 99: 311–319
19. Moller-Madsen B (1990) Localization of mercury in CNS of the rat. II. Intraperitoneal injection of methylmercuric chloride (CH_3HgCl) and mercuric chloride ($HgCl_2$). Toxicol Appl Pharmacol 103: 303–323
20. Moller-Madsen B, Danscher G (1986) Localization of mercury in CNS of the rat. I. Mercuric chloride ($HgCl_2$) per os. Environ Res 41: 29–43
21. Mottet NK, Body RL (1974) Mercury burden of human autopsy organs and tissues. Arch Environ Health 29: 18–24
22. Palkiewicz P, Zwiers H, Lorscheider FL (1994) ADP-ribosylation of brain neuronal proteins is altered by in vitro and in vivo exposure to inorganic mercury. J Neurochem 62: 2049–2052
23. Pamphlett R, Waley P (1996) Motor neuron uptake of low dose inorganic mercury. J Neurol Sci 1996: 63–67
24. Porter R (1985) The corticomotoneuronal component of the pyramidal tract: corticomotoneuronal connections and functions in primates. Brain Res 10: 1–26
25. Schionning JD, Danscher G, Christensen MM, Ernst E, Moller-Madsen B (1993) Differentiation of silver-enhanced mercury and gold in tissue sections of rat dorsal root ganglia. Histochem J 25: 107–111