



# PathCare Manganism or manganese poisoning

**Volker Schillack**, Analytical Toxicologist, V&M ATLS Director; e-mail: volker@vm-atls.com

**Younus Essack**, Chemical Pathologist, PathCare; e-mail: younus.essack@pathcare.co.za

**John C Stanfliet**, Chemical Pathologist, PathCare; e-mail: john.stanfliet@pathcare.co.za

## ABSTRACT

Although manganese (Mn) is an essential nutrient, toxicity has been demonstrated in workers accidentally exposed to large amounts. Chronic exposure to Mn can damage the nervous system and respiratory tract and result in symptoms similar to Parkinson disease.

## INTRODUCTION

Mn is an essential trace element and is provided for, through daily intake, in amounts of 3-7 mg. It acts as a cofactor for a number of important enzymes, namely arginase, cholinesterase, phosphoglucomutase, pyruvate carboxylase, and mitochondrial superoxide dismutase and, together with vitamin K, plays a role in the formation of prothrombin.

Occupational exposure usually occurs through inhalation or ingestion of fumes/dust produced during the mining/refining of Mn ores or the treatment of Mn alloys. Certain organic derivatives of Mn are currently used as octane-improving additives in unleaded gasoline.

Exposure to high levels of Mn may lead to a condition known as manganism/metal fever. An individual involved in the manufacture or processing of steel, welding rods, batteries, ceramics, or pesticides (Mn-containing herbicides) may be at risk, depending on exposure levels.

## MANGANESE TOXICITY

Workers absorb Mn mainly through the lungs, with gastrointestinal absorption being low (1-5%).<sup>1</sup> Mn absorption is controlled by homeostatic mechanisms and is shown to be reduced through concomitant ingestion of calcium.<sup>2</sup> There may be sex-specific differences in blood levels of Mn, lead (Pb) and cadmium (Cd), related to underlying iron (Fe) deficiency, oestrogen and variability in the absorption rates of these metals.<sup>3</sup> It is therefore important that these factors be considered by the occupational practitioner during monitoring. Mn is mainly present in the red blood cells and is 25 times higher in these cells than in serum. The liver is the main storage organ, with the kidney and brain acting as secondary reservoirs following chronic exposure. Manganism presents with symptoms and signs similar to Parkinson disease. Patients present with fixed gaze, tremors, body rigidity, and slowed movements (bradykinesia).<sup>4</sup> It has been shown that welders exposed

to Mn are more likely to develop Parkinson disease than the rest of the population, especially at an early age.<sup>5</sup> Mn has been shown to interfere with the absorption of Fe,<sup>6</sup> with long-term exposure leading to Fe-deficiency anaemia. Fe-deficiency, on the other hand, can lead to brain Mn accumulation,<sup>7</sup> and research has shown that dietary increases or decreases in Fe might contribute to brain deposition of Mn in populations exposed to Mn.<sup>8</sup> Increased Mn also impairs the activity of the copper metallo-enzymes.

## Clinical stages of manganese poisoning

Historically, three stages of manganism were described in workers with very high levels of Mn exposure.<sup>9</sup>

*Stage 1* Very subtle symptoms. Individuals present with headaches, exhaustion, weakness and apathy. Symptoms can easily be confused with depression or other illnesses. Some researchers believe that this early stage is reversible.<sup>4</sup>

*Stage 2* Individuals may present with short-term memory loss, impaired judgment, slurred speech, and even hallucinations. "Manganese madness" was the term used to describe the compulsive, strange behaviour of workers over-exposed to Mn in the Mn mines.<sup>10</sup>

*Stage 3* Symptoms and signs of the last stage include involuntary muscle movements, tremors, poor coordination, a mask-like rigid face, and a staggering strutting gait. This stage is irreversible and may lead to complete disability. Removing a patient from exposure at this point does not seem to be helpful. In one report, the disease progressed over a 10-year period even after the patient was no longer exposed to Mn.<sup>11</sup> It is important to note that the symptoms of manganism may appear any time from months to several years after an individual's initial exposure to Mn.<sup>12,13</sup>

## METABOLISM AND EXCRETION

Mn metabolism is similar to that of Fe. It is absorbed in the small intestine with the absorption process being slow. More than 90% of Mn is excreted in bile.<sup>14</sup>

Whole blood Mn, of which the majority is bound to the haemoglobin, averages 9 µg/l (3.9 – 15 µg/l) in normal adults,<sup>15</sup> whilst urinary Mn concentrations in unexposed persons have been reported to range from 1–10 µg/l.<sup>16</sup>

## BIOLOGICAL AND EFFECT MONITORING

Manganism is a clinical diagnosis that requires evidence of overexposure and a clinical syndrome consistent with basal ganglia dysfunction. The role of ancillary tests to support diagnosis, such as MRIs, chest X-rays, lung function tests, full blood count and liver function tests, is unknown. Mn has a very short half-life in blood so routine blood monitoring only provides modest information on current exposures. Moreover, no studies have demonstrated a clear relationship between blood Mn and clinical health outcomes. Urine Mn is also not a useful measure of exposure.<sup>17</sup> Hair or nails are currently considered to be more practical for determining chronic exposure to Mn,<sup>18</sup> while bone Mn levels are also good indicators of long-term exposure.<sup>19</sup> Chelation therapy of Mn intoxication with para-aminosalicylic acid maybe an alternative way to determine accumulation of Mn.<sup>20</sup>

## CONCLUSION

Manganism is a clinical diagnosis supported by motor, behavioural, and cognitive dysfunction in the setting of overexposure to Mn. Unfortunately, ancillary tests provide, at best, supportive evidence of exposure.

## REFERENCES

1. Davis CD, Zech L, Greger JL. Manganese metabolism in rats: an improved methodology for assessing gut endogenous losses. *Proc Soc Exp Biol Med.* 1993;202: 103-108.
2. Freeland-Graves JH, Lin PH. Plasma uptake as affected by oral loads of manganese calcium, milk, phosphorus, copper and zinc. *J Am Coll Nutr.* 1991;10: 38-43.
3. Finley JW, Johnson PE, Johnson LK. Sex affects manganese absorption and retention by humans from a diet adequate in manganese. *Am J Clin Nutr.* 1994;60: 949-955.
4. Levy BS, Nassetta WJ. Neurologic effects of manganese in humans: a review. *Int J Occup Environ Health.* 2003;9(2): 153-163.
5. Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Veen TO, Perlmutter JS. Welding-related parkinsonism: clinical feature, treatment, and pathophysiology. *Neurology.* 2001;56(1): 8-13.
6. Moshtaghi AA, Badii AA, Hassanzadah T. Investigation of manganese and iron absorption by rat everted gut sac. *Pak J Biol Sci.* 2006;9: 1346-1349.
7. Erikson KM, Syversen T, Aschner JL, Aschner M. Interactions between excessive manganese-exposure and dietary iron-deficiency in neurodegeneration. *Environ Toxicol Pharmacol.* 2005;19: 415-421.
8. Fitsanakis VA, Zhang N, Anderson JG, Erikson KM, Avison MJ, Gore JC, Aschner M. Measuring brain manganese and iron accumulation in rats following 14 weeks of low-dose manganese treatment using atomic absorption spectroscopy and magnetic resonance imaging. *Toxicol Sci.* 2008;103(1): 116-124.
9. Rodier J. Manganese poisoning in Moroccan miners. *Brit J Industr Med.* 1955;12: 21-35.
10. Emsley J. Manganese the protector. *Nature Chemistry.* 2013;5: 978.
11. Sadek AH, Rauch R, Schulz PE. Parkinsonism due to manganism in a welder. *Int J Toxicol.* 2003;22(5): 393-401.
12. Boojar MM, Goodarzi F, Basedaghat MA. Long-term follow-up of workplace and well water manganese effects on iron status indexes in manganese miners. *Arch Environ Health.* 2002; 57(6): 519-528.
13. Coombs M, Schillack VR. Medical surveillance and biological monitoring – the ongoing saga. *Occup Health Southern Afr.* 2009;15(2): 4-7.
14. Malecki EA, Radzanowski GM, Radzanowski TJ, Gallaher DD, Greger JL. Biliary manganese excretion in conscious rats is affected by acute and chronic manganese intake but not by dietary fat. *J Nutr.* 1996;126: 489-498.
15. Heitland P, Koster HD. Biomonitoring of 37 trace elements in blood samples from inhabitants of northern Germany by ICP-MS. *J Trace Elem Med Biol.* 2006a;20: 253-262.
16. Heitland P, Koster HD. Biomonitoring of 30 trace elements in urine of children and adults by ICP-MS. *Clin Chim Acta.* 2006b;365: 310-318.
17. Myers JE, Thompson ML, Naik I, Theodorou P, Esswein E, Tassell H, Daya A, Renton K, Spies A, Paicker J, Young T, Jeebhay M, Ramushu S, London L, Rees DJ. The utility of biological monitoring for manganese in ferroalloy smelter workers in South Africa. *Neurotoxicology.* 2003;24(6): 875-883.
18. Sriram K, Lin GX, Jefferson AM, Roberts JR, Andrews RN, Kashon ML, Antonini JM. Toxicology. Manganese accumulation in nail clippings as a biomarker of welding fume exposure and neurotoxicity. 2012;291: 73-82.
19. O'Neal SL, Hong L, Fu S, Jiang W, Jones A, Nie LH, Zheng W. Manganese accumulation in bone following chronic exposure in rats: Steady-state concentration and half-life in bone *Toxicology Letters.* 2014;229: 93-100.
20. Zheng W, Jiang YM, Zhang Y, Wang X, Cwan DM. Chelation therapy of manganese intoxication with para-aminosalicylic acid (PAS) in Sprague-Dawley rats. *Neurotoxicology.* 2009; 30(2): 240-248.

These pages are sponsored by PathCare.