

Manganese neurotoxicity: Connecting the dots along the continuum of dysfunction[☆]

Christopher J. Martin^{*}

Institute of Occupational and Environmental Health, Department of Community Medicine, School of Medicine, West Virginia University, P.O. Box 9190, 3801 Health Sciences Center South, Morgantown, WV 26506-9190, United States

Available online 5 December 2005

Abstract

Three different manifestations of manganese neurotoxicity have been described. The first, and historically most prominent, is often termed manganism: a dramatic extrapyramidal syndrome following acute, overwhelming exposure. While resembling Idiopathic Parkinson's Disease (IPD), most authorities have regarded the two conditions as clinically and pathophysiologically distinct. The second manifestation, reported by several investigators starting in the 1980s, consisted of subclinical and subfunctional declines in the performance of specialized neuropsychological tests. The implication of these cross-sectional findings was that, when superimposed upon age-related attritional effects, increased rates of clinical disease could result. In this decade, it has been proposed that manganese exposure may play a role in the development of IPD itself. Investigating the relationship between these three manifestations should be a priority for future research.

© 2005 Elsevier Inc. All rights reserved.

Keywords: Manganese; Manganism; Neurotoxicity

What, precisely, are the manifestations of manganese neurotoxicity? While seemingly a rather simplistic question, there are three lines of evidence available, in which different effects have been observed.

1. Manganism

It has been known since Couper's first description in 1837 that overexposure to manganese results in a dramatic extrapyramidal syndrome termed manganism (Couper, 1837). The setting for such cases is typically high level, inhalational exposure, chronologically best described as acute. Such cases are now relatively rare in the United States, with the best-studied cohorts including Taiwanese smelter workers (Wang et al., 1989) and Chilean miners (Schuler et al., 1957).

As summarized at the conference by Olanow, manganism is distinct from Idiopathic Parkinson's Disease (IPD). Unlike IPD, manganism patients do not respond to dopamine replacement

and functional imaging studies using fluorodopa-labeled positron emission tomography (PET) scans fail to show the pattern of reduced striatal uptake which is uniformly present in IPD. Clinical features are different too, with manganism patients demonstrating early personality changes (in particular bizarre, compulsive behavior), relatively early postural, gait, and speech abnormalities with relatively less tremor. Animal models in which primates were overexposed to manganese resembled manganism, not IPD (Shinotoh et al., 1995). On the rare occasions when tissue was available, pathological findings were discordant. Finally, in case reports of impaired biliary manganese excretion leading to an overload situation (termed non-Wilsonian hepatolenticular degeneration), patients had clinical features resembling manganism.

Two additional points concerning manganism warrant mentioning. The condition has been noted to progressively deteriorate years following removal from exposure (Huang et al., 1998). Secondly, MRI studies of affected cases show a characteristic increased signal intensity on T1-weighted images of the globus pallidus and midbrain. However, these findings normalize approximately 6 months post-exposure (Nelson et al., 1993). As Roels commented at the conference, all of this lead to the traditional teaching that manganese entered the brain, did damage acutely, and was subsequently cleared by the

[☆] This work was presented at the conference entitled *Health Effects, Clinical Research and Industrial Hygiene Issues in Occupational Exposure to Manganese* held April 17 & 18, 2004 in New Orleans, LA.

* Tel.: +1 304 293 3693; fax: +1 304 293 2629.

E-mail address: cmartin@hsc.wvu.edu.

body. More recently, it has been further noted that MRI findings may not be specific, since over 73% of active, yet asymptomatic, welders in a Korean study have been shown to have similar MRI findings as those reported in cases of manganese-related parkinsonism (Kim et al., 1999).

2. Neuropsychological abnormalities

Several cross-sectional studies in North America and Western Europe have shown that manganese-exposed workers perform poorer on neuropsychological tests compared to unexposed workers (Iregren, 1999). In response to a question on the significance of these findings, Mergler emphasized that they are based on specialized tests, and deficits would not be apparent either to the workers themselves or to the physician performing a routine medical examination.

The concern is based on the concept of a shifting bell curve. In order to understand this argument, it is important to appreciate two related observations concerning the extrapyramidal tract. Firstly, it is well known that extrapyramidal neural tissues have considerable reserve capacity, with PET scans demonstrating that loss of neurons long precedes the development of clinically apparent disease in IPD (Calne et al., 1997). Secondly, it has been established in another setting (MPTP-induced parkinsonism) that an individual can sustain a neurotoxic insult but not manifest symptoms until some latency has passed, during which time additional effects, such as age-related attrition of neurons, exceed the reserve capacity of the tissue (Vingerhoets et al., 1994). This is also consistent with the observation, noted above, that manganism patients continue to worsen even many years after exposure has ceased. Presuming that extrapyramidal function follows a Gaussian distribution, subclinical downward ‘shifts’ in active workers today may mean future symptomatic disease in individuals who would otherwise have remained healthy. Because of the shape of a normal distribution, even relatively small shifts along can lead to substantial increases in the number at the lower tail, in this case, those with disease.

3. IPD and welders

Most recently, the study by Racette et al. of 953 patients newly diagnosed with IPD has created heightened interest in this area (Racette et al., 2001). In 15 of the patients who were career welders, the age of diagnosis was 17 years earlier than non-welders (46 versus 63 years). In all other clinical areas, including response to dopamine replacement, there was no difference between welders and non-welders. Fluorodopa PET scans were available for two of the affected welders and were reported to show abnormal findings typical of IPD.

Clearly, these results are inconsistent with the notion of manganism as a condition distinct from IPD. Racette stated that IPD is a clinically heterogeneous disorder. He invoked an overlapping Venn diagram to account for his findings, in which some cases of manganese-related neurotoxicity were distinct from IPD, whereas others were not. Manganese exposure in the

overlap cases could accelerate the development of a condition indistinguishable from IPD.

Focusing on active welders, Nausieda reported the preliminary findings on a screening program of active US welders in the Gulf region in which he observes an alarmingly high prevalence of clinically apparent movement disorders—in excess of 10%. If confirmed, these findings would represent an extraordinary public health and medical failure, one which should not be dismissed simply as the result of a reluctance of these workers to seek medical attention, as was stated in the panel discussion. Reflective of the unresolved issues in this area, videotaped examinations of several of these patients shown at the conference were described as manganism by Nausieda and IPD by Racette.

4. A continuum of dysfunction

The manifestations of manganese neurotoxicity have been described as ‘a continuum of dysfunction’ (Mergler et al., 1999). Although each line of evidence has been presented separately, the question is begged: Are these all simply different manifestations of the same disease spectrum, at least partially reflective of differences in exposure circumstances? While there is a sound theoretical basis for this argument, exploring the relationships between overt manganism distinct from IPD, subfunctional neuropsychological abnormalities, and IPD in welders has been understudied and should be a priority for future research. The picture has become even less clear with the findings of a recent large, cross-sectional study of a South African occupational cohort with a wide range of exposure levels to manganese, which failed to document a continuum of effects (Myers et al., 2003).

Firstly, the idea of a shifting bell curve is a readily testable hypothesis. What is needed are further long-term, prospective studies of groups of manganese-exposed workers with documented neuropsychological abnormalities to determine if they develop clinically apparent disease in the future. One such study yielded mixed results with respect to neuropsychological test outcomes (two parameters failed to recover, one showed a partial recovery) (Roels et al., 1999). Although time-consuming, these studies are warranted in view of the enormous public health significance of the results, especially if it can be shown that subclinical effects can progress over time to overt disease.

Secondly, the issue of welding and either IPD or manganism (or both) must be further explored. The study of Racette et al. (2001) urgently needs to be repeated in other populations, preferably with larger sample sizes. These findings are inconsistent with a large body of literature, which suggests that manganism is distinct from IPD. Welding is a common occupation and IPD a relatively common neurological disease, we need to replicate these findings before we rethink the paradigm. Fluorodopa-labeled PET scans should be performed on all affected welders.

By its very design, any such studies will identify only the overlap cases, that is, those in which manganese exposure is presumed to have accelerated the development of IPD.

Therefore, additional studies are needed based on exposure status as a welder rather than disease status. Although large-scale screening studies have the merit of identifying greater numbers of cases, smaller studies with strict case criteria in which affected workers are more intensively investigated are needed. We do have objective tests that may allow the distinction between the two conditions to be made: PET scans and to a lesser extent, T1-weighted MRI. If the idea of an overlapping Venn diagram is correct, we should be able to identify populations of clinically affected welders with normal PET scans, and for active welders, abnormal MRI's.

5. Conclusion

In the meantime, there is sufficient concern based on available evidence that preventive strategies should not await further research. This need is highlighted by ambiguity concerning the protective value of exposure limits for manganese. Based on modeling, it has been shown that manganese exposures are likely to exceed the previously proposed lowered threshold limit value (TLV[®]) of 0.03 mg/m³ (respirable fraction) for welding in the construction sector (Welch et al., 2004). In 2004, the ACGIH withdrew this intended change and has retained the current TLV of 0.2 mg/m³ based on total dust. However, since 90% of particles produced in most welding fumes are in the respirable range, the appropriateness of this recommendation is uncertain. Clearly, manganese exposures in welding need to be better characterized in order to guide efforts to reduce them.

References

- Calne DB, de la Fuente-Fernandez R, Kishore A. Contributions of positron emission tomography to elucidating the pathogenesis of idiopathic parkinsonism and dopa responsive dystonia. *J Neural Transm Suppl* 1997;50:47–52.
- Couper J. On the effects of black oxide of manganese when inhaled into the lungs. *Br Ann Med Pharmacol* 1837;1:41–2.
- Huang CC, Chu NS, Lu CS, Chen RS, Calne DB. Long-term progression in chronic manganism. Ten years of follow-up. *Neurology* 1998;50:698–700.
- Iregren A. Manganese neurotoxicity in industrial exposures: proof of effects, critical exposure level, and sensitive tests. *Neurotoxicology* 1999;20:315–24.
- Kim Y, Kim KS, Yang JS, Park IJ, Kim E, Jin Y, et al. Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. *Neurotoxicology* 1999;20(6):901–7.
- Mergler D, Baldwin M, Belanger S, Larribe F, Beuter A, Bowler R, et al. Manganese neurotoxicity, a continuum of dysfunction: results from a community based study. *Neurotoxicology* 1999;20(2–3):327–42.
- Myers JE, Thompson ML, Ramushu S, Young T, Jeebhay MF, London L, et al. The nervous system effects of occupational exposure on workers in a South African manganese smelter. *Neurotoxicology* 2003;24(6):885–94.
- Nelson K, Golnick J, Korn T, Angle C. Manganese encephalopathy: utility of early magnetic resonance imaging. *Br J Ind Med* 1993;50(6):510–3.
- Racette BA, McGee-Minnich L, Moerlein SM, Mink JW, Videen TO, Perlmutter JS. Welding related parkinsonism: clinical features, treatment, and pathophysiology. *Neurology* 2001;56:8–13.
- Roels HA, Ortega Eslava MI, Ceulemans E, Robert A, Lison D. Prospective study on the reversibility of neurobehavioral effects in workers exposed to manganese dioxide. *Neurotoxicology* 1999;20:255–72.
- Schuler P, Oyanguren H, Maturana V, Valenzuela A, Cruz E, Plaza V, et al. Manganese poisoning: environmental and medical study at a Chilean mine. *Ind Med Surg* 1957;26:167–73.
- Shinotoh H, Snow BJ, Hewitt KA, Pate BD, Doudet D, Nugent R, et al. MRI and PET studies of manganese-intoxicated monkeys *Neurology* 1995;45(6):1199–204.
- Vingerhoets FJ, Snow BJ, Tetrud JW, Langston JW, Schulzer M, Calne DB. Positron emission tomographic evidence for progression of human MPTP-induced dopaminergic lesions. *Ann Neurol* 1994;36(5):765–70.
- Wang J-D, Huang C-C, Hwang Y-H, Chiang JR, Lin JM, Chen JS. Manganese induced parkinsonism: an outbreak due to an unrepaired ventilation control system in a ferromanganese smelter. *Br J Ind Med* 1989;46:856–9.
- Welch LS, Rappaport SM, Susi P. Construction welding exposures to manganese likely to exceed proposed TLV. *J Occup Environ Hyg* 2004;1(6):D63–5.