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Review

Manganism in the 21st century: The Hanninen lecture

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ABSTRACT

Since the original description of the health effects of inhaled occupational manganese (Mn) by Couper in 1837, an extensive literature details the clinical syndrome and pathophysiology of what was thought to be a rare condition. In the last decade, conventional wisdom regarding the clinicopathological effects of Mn has been challenged. Past exposures to Mn were an order of magnitude higher than modern exposures in developed countries; therefore, the clinical syndrome seen in the time of Couper is no longer typical of modern Mn exposed workers. Parkinsonism (rigidity, bradykinesia, rest tremor, and postural instability) is present in 15% of Mn-exposed workers in welding industries, and these parkinsonian signs are associated with reduced health status and quality of life. These parkinsonian signs also overlap considerably with the clinical findings seen in early stages of Parkinson's disease (PD); although, molecular imaging suggests that Mn-exposed workers have dopaminergic dysfunction in a pattern unique from PD. Furthermore, geographic information system studies demonstrate that regions of the US with high industrial Mn emissions have an increased incidence of PD and increased PD associated mortality. This review will contrast historical, descriptive human studies in Mn-exposed subjects with more recent data and will suggest a research agenda for the 21st century.

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1. Introduction

In 1837, Couper (1837) described a clinical syndrome in two patients exposed to Mn oxide through a grinding process to make bleaching powder. One subject was described as having "paraplegia" that did not recover. The second subject had festinating gait, hypophonia, and masked facies, consistent with parkinsonism. The clinical syndrome associated with Mn overexposure was subsequently termed "manganism". While Parkinson disease (PD) is the most common degenerative cause of parkinsonism, numerous other diseases can cause parkinsonism including manganism. The clinical description of manganism was further characterized by Rodier in 1955 when he described subjects with a rapidly progressive neurobehavioral syndrome characterized by parkinsonism, dystonia, emotional lability, gait impairment, and psychosis. Exposures were as high as 926,000 μg Mn/m^3 among these subjects. In contrast, modern exposures to Mn, encountered primarily through occupational welding, are several orders of magnitude lower than exposures in the Chilean Mn mines studied by Rodier (Meeker et al., 2007; Rodier, 1955; Rappaport et al., 1999). The clinical syndrome associated with 21st century Mn exposures may be substantially different than previously

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described. Numerous reviews have discussed the distinctions between manganism and PD (Olanow, 2004; Calne et al., 1994; Jankovic, 2005; Perl and Olanow, 2007; Guilarte, 2010), but the data supporting these differences are often based upon very small case series with no reference group for comparison. The primary categories on which this review will focus are clinical symptomatology, imaging, and pathology associated with Mn neurotoxicity.

2. Clinical symptomatology

Clinical characteristics stated to be "typical" of Mn-induced parkinsonism include onset of neurobehavioral manifestations, psychosis, low amplitude, rapid postural tremor, early hypokinetic-/hypophonic dysarthria, early gait and balance abnormality, dystonia, action myoclonus, pyramidal signs, and rapid progression initially with stable long term course (Jankovic, 2005). The data on which these distinctions have been made are mostly the Rodier study and the small study of Taiwanese workers with manganism from a ventilation malfunction (Wang et al., 1989; Rodier, 1955). These studies involved massive exposures to Mn over a relatively short period of time, several orders of magnitude greater than modern welding or mining exposures (Meeker et al., 2007; Myers et al., 2003). Most clinical reports of Mn neurotoxicity in the last 40 years describe a parkinsonian predominant phenotype (Tanaka and Lieben, 1969; Nelson et al., 1993; Cook et al., 1974; Selikhova et al., 2008; Sikk et al., 2010; Stepens et al., 2010). It is important to note that the "specificity" of the manganism clinical phenotype is very much over stated. Cognitive dysfunction, behavioral/mood disorders, psychosis, and dystonia are all within the spectrum of clinical symptomatology in PD (Lucking et al., 2000). Only the presence of pyramidal tract dysfunction distinguishes neurotoxicity from high dose Mn exposure from PD, but these signs are not uniformly present. Moreover, there is almost no longitudinal clinical data on Mn-exposed workers. The largest longitudinal dataset is the study of five Taiwanese smelter workers with massive occupational Mn exposure who had follow-up examinations at four and ten years (Huang et al., 1993, 1998). These workers demonstrated progression in parkinsonism with much of the progression in gait dysfunction and freezing.

To investigate the neurologic signs associated with chronic, low level occupational Mn exposures, we have conducted several clinical studies in welders. Concerns about the neurotoxic effects of welding fumes have increased over recent years (Harris et al., 2005; Meeker et al., 2007). Mn is commonly found in welding fumes, and many welders are regularly overexposed to the American Conference of Governmental Industrial Hygienists threshold limit value (TLV) of 0.2 mg/m^3, which was primarily set in regard to pre-clinical neurological effects (American Conference of Governmental Industrial Hygienists, 1992; Korczynski, 2000). We examined 1423 Alabama Mn-exposed welders for parkinsonism, calculated the age-adjusted prevalence of parkinsonism using Department of Labor statistics, and compared this prevalence to the prevalence of parkinsonism in Copiah County, MS (Schoenberg et al., 1985; Susi et al., 2000; Racette et al., 2005a). We found that the prevalence of parkinsonism was substantially higher in welders (prevalence ratio 10.19; 95% CI 4.43–23.43) and concluded that this study provided evidence that parkinsonism is more common in welders than in the general population. In a recent study, we investigated the dose–response relationship between cumulative welding exposure and parkinsonism among 811 male shipyard welders, mean age 45.9 (±12.3), recruited from the International Brotherhood of Boilermakers (IBB) (Racette et al., 2012). Study subjects were examined by a movement disorders specialist using the Unified Parkinson Disease Rating Scale motor subsection 3 (UPDRS3) (Fahn and Elton, 1987) without knowledge of exposure history. Two reference groups included 59 non-welder trade workers (henceforth termed 'reference workers') and 118 newly diagnosed, untreated idiopathic PD patients. Parkinsonism cases among welders were defined as those with UPDRS3 score ≥15 (Harris et al., 2011). We used this case definition of parkinsonism since most idiopathic PD patients become symptomatic enough to present for medical attention with UPDRS3 scores ≥15 (Parkinson's Study Group, 1989; Parkinson Study Group, 2004; Fahn et al., 2004). Normal was defined as UPDRS3 <6. Exposure was classified as intensity weighted, cumulative years of welding, using a previously validated questionnaire (Hobson et al., 2009). Prevalence ratios (PR) for parkinsonism, adjusted for age, race, smoking, and education, were calculated in relation to quartiles of welding hours. The overall prevalence estimate of parkinsonism was 15.6% in welders compared to 0% in the reference workers. There was a U-shaped dose–response relationship with a modest increase in the prevalence of parkinsonism for the two middle quartiles of total weighted welding years (Racette et al., 2012). The prevalence of parkinsonism in this population-based cohort was even higher than in our previous cross-sectional study of parkinsonism in welders (Racette et al., 2005a). In the shipyard welder study, UPDRS3 scores for most domains on the UPDRS3 were similar between welders with UPDRS3 ≥15 and newly diagnosed PD patients except for higher mean scores for rest tremor and asymmetry in PD patients. This worksite based study of parkinsonism in Mn-exposed welders demonstrated both a high prevalence of parkinsonism compared to reference workers as well as a clinical phenotype that overlaps substantially with PD. However, this cross-sectional study of parkinsonism in Mn-exposed welders does not indicate that these workers have PD. Instead, these findings demonstrate the difficulty in distinguishing occupational parkinsonism from PD in cross-sectional epidemiology studies. Long-term follow-up of these workers will be needed to clarify if the parkinsonian subjects experience progression of their parkinsonism, similar to PD.

Levodopa responsiveness is frequently cited as a distinguishing feature between PD and manganism. Levodopa supplementation replaces dopamine loss from degenerating substantia nigra projections in PD and improvement of symptoms with levodopa is a clinical hallmark of PD. However, any condition in which there is loss of these nigrostriatal projections may improve with levodopa supplementation, and there is no gold standard defining levodopa responsiveness (Constantinescu et al., 2007). Similarly, there is no consensus on the dose of levodopa required to establish that parkinsonism is not responsive to levodopa, but trials of up to 2000 mg/day are often used in clinical practice. A commonly cited study of levodopa in manganism randomized four subjects with severe parkinsonism due to manganism to a single dose of 100 mg, 200 mg, 300 mg or placebo and concluded that there was no improvement in clinical measures of parkinsonism (Lu et al., 1994). A larger study of 13 subjects found no improvement with a longer trial of up to 300 mg of levodopa (Koller et al., 2004). However, we demonstrated improvement in parkinsonism in a patient with manganism due to liver failure with 900 mg levodopa per day. Many other studies report lack of efficacy of levodopa in manganism (Selikhova et al., 2008; Sanotsky et al., 2007; Aggarwal et al., 2006; Sadek et al., 2003), but few provide information on levodopa dose used or quantify clinical signs. Larger (appropriately powered), placebo controlled studies, using higher doses of levodopa are needed to determine degree to which manganism can be distinguished from PD based upon levodopa responsiveness. More importantly, determining levodopa responsiveness has critical clinical implications given the very limited treatment options for parkinsonism associated with Mn exposure.

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