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How Does an Occupational Neurologist Assess Welders and Steelworkers for a Manganese-Induced Movement Disorder? An International Team's Experiences in Guanxi, China, Part I

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In this two-part series, J.S.R and colleagues thoroughly discuss aspects of the evaluation of these 6 workers. Part I focuses on the historical background and literature supporting Parkinsonism and manganese exposure, both from mining and welding. Differential diagnosis including radiological assessment and methods for this evaluation will be discussed. Part II, in a future edition of JOEM, will discuss and analyze results, including blood and urine Mn and results from one MRI. Limitations and conclusions will be presented.

The debate regarding Parkinson's disease (PD) and manganese-induced movement disorder has centered around clinical presentation and the location of the neurologic dysfunction as well as the relationships between various exposures from specific occupations and the clinical findings. Some believe that exposure to manganese in welding fumes can cause parkinsonian neurological disorders, while others suggest that manganese exposure can lead directly to PD at a younger age of onset. This clinical investigation, by examining welders and steel workers with clear movement disorders and history of occupational exposure to manganese, aimed at comparing the differences between manganese-induced movement disorder and PD, and the association of clinical presentations to workers' occupation. With the fast economic growth and ensuing heavy consumption of manganese products in China, manganese exposure has become a significant occupational health risk. Chinese workers were chosen to address the emergence of this problem.

Parkinson's disease (PD) was initially described as a shaking palsy in 1817 by James Parkinson. Parkinsonian syndromes have also been described in manganese ore crushers in 1837 by Couper[1]; manganese miners in 1955 by Rodier,[2] and Schuler[3] in 1957; ferroalloy and battery plants grinders in the 1973 by Smyth[4] and in 1971 by Emara[5]; and welders by Nelson[6] in 1993, Kim[7] in 1998, and Sadek[8] in 2003 among others. Canavan's article in the *Archives of Neurology and Psychiatry*[9] in 1934 outlined characteristics of a millworker with manganese exposure.

The term manganism has been applied to an identifiable atypical parkinsonian syndrome. Characteristics mentioned by Feldman in his textbook, *Occupational and Environmental Neurotoxicity*[10] in 1999 include mood changes, motor disturbances and with continued exposure, psychosis with dystonia. Gait was noted to be different from that in PD patients and the progression was thought to be slower than in patients with PD. Specifically, a manganese-induced movement disorder has been thought to be different from PD in many categories. Jankovic [11] in 2005, has described the condition as an atypical parkinsonian syndrome, with symmetrical findings; poor or no response to levodopa, with related psychiatric symptoms; initial rapid progression followed by stable course; initial and transient elevations in blood, urine, and hair; magnetic resonance imaging with bilateral hyperintensities in the globus pallidus and substantia nigra on T1, which may be transient, and fluorodopa PET scan usually normal, but reduced with raclopride binding technique. Also pathological findings include degeneration and gliosis of the globus pallidus with no Lewy's bodies.

With this in mind, however, manganese had been suspected to be part of an etiologic role for PD[12–15] or in those susceptible, accelerate or initiate the disorder.[13,15] In fact, numerous papers contradict the tenets that are described by Jankovic. Regarding pathology, Lewy bodies were found in the substantia nigra of a patient with manganism as per Bernheimer[16] in 1973. In fact Hughes et al,[17] in 1992, found that of 100 patients with clinically typical PD, only 76 had pathological confirmation with Lewy bodies. Of these 24 "misdiagnosed," 67% of these had marked improvement from an initial response to Levodopa. An article by Weiner[18] concludes that there is no single PD. The discussion pertaining to neuroimaging is similar. Racette,[19] in 2001, reported that 6-(18F) FDOPA PET (18-flouro dopa positron emissions testing) results in 2 of 15 welders with asymmetrical Parkinsonism as having asymmetrically reduced uptake, compared to normal controls, in the striatum, findings typical of PD. In patients with hepatitis-induced elevated blood manganese who presented with symmetrical rigidity, magnetic resonance imaging revealed increased signal in the internal pallidum on T1-weighted images and 18F FDOPA PET revealed a symmetrical reduction of pallidal uptake, findings typical of PD.[20,21] With regard to examination, Racette,[19] in 2001, evaluated 15 welders with Parkinsonism and found that welders had an earlier age of onset of their symptoms but that there was no difference in frequency of tremor, bradykinesia, rigidity, asymmetric onset, postural instability, family history, depression, dementia, or drug-induced psychosis compared to controls. Koller,[22] in 2004, also evaluated 13 welders with Parkinsonism and found no difference in their response to three different doses of levodopa over an 8-week period; 7 of 13 of these were found to have symmetric

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symptoms at onset with progression. There symptoms were "typical" for Parkinsonism but 9 of 13 had a kinetic tremor. Racette and his colleagues,[23] in 2005, assessed nearly 1500 litigant welders and further speculated that the occupation of welding increased the prevalence of Idiopathic Parkinson's disease at all ages and may shift the distribution to a younger age.

Historically, Emara[5] reported a dry battery industry worker with manganese intoxication and hemiparkinsonism in 1971. Smyth,[4] in 1973, also wrote that clinical manganism is indistinguishable from PD and reported 5 cases in ferromanganese alloy production workers, some with unilateral presentations as well as lacking in depression, sleep issues or autonomic dysfunction. Parkinsonism was noted in 6 of 8 welders by Wang et al[24] in 1989 who were "well under the usual age of onset of idiopathic Parkinson's Disease." Details of their examinations were not available. Huang et al[25] in 1989 also noted that patients with chronic manganese intoxication responded to levodopa, and had normal cognitive functions and that the clinical picture of resembled PD. Later Huang et al,[26] in 1993, wrote that chronic manganism may overlap with PD and that it was progressive and response to levodopa was initially positive but that they did not develop dyskinesia. Jiang et al,[27] in 2006, reported a case of chronic manganism patient who initially responded to levodopa, yet the symptoms became aggravated after 1-year treatment.

On the basis of the above six cases, Calne and others[28] highlighted, in 1994, the differences leading to Dr Jankovic's paper most recently.

A number of other population studies have supported an increased prevalence of PD in those exposed to manganese. Gorrell,[29] in 1999, identified a very large odds ratio (OR) close to 10 for those with more than 20 years of manganese exposure. Lucchini,[30] in 2007, found an increased exposure to manganese in a rural community in Italy which was noted to have an increased risk for PD. Although published as no relationship, data presented by Seidler,[31] in 1996, support an OR close to 10 for those with manganese exposure. The same may be said for two other articles. Wechsler,[32] in 1991, reported that he did not calculate odds ratios due to a lack of welders who were controls; however, 16% of those with PD were welders. Smargiassi,[33] in 1998, found 4 patients of 86 with PD who had exposure to heavy metals but none of 86 controls. Zayed,[34] in 1990, found an increased OR of more than 10 for a combination of iron, aluminum, and manganese exposure of more than 30 years. There are many papers that have reported no association between occupational exposure to manganese or welders with Parkinson's disease.[35–39] While some papers suffered from a small number of cases or of no cases with controls, others suffered from a lack of power because of study design or other factors.

In this article, we describe six patients who present with movement disorders and occupational exposure to manganese in China where protection from exposure is a challenge. The spectrum of manganese-induced movement disorders are displayed.

TABLE 1. Chinese Diagnostic Criteria of Occupational Chronic Manganism, June 2002 (English Translation)*

Diagnosis is made based on occupational exposure history and identification of extracorticospinal tractdamages as the main manifestation; along with information from industrial air monitoring;spot air manganese concentrations; analysis of manganese in urine, hair, or blood;and considering other diagnoses such as paralysis agitans; Wilson syndrome; and others.
Subjective symptoms: dizziness, headache, lassitude, dyssomnia, morbid forgetfulness and limb ache, and heavy feeling as well as autonomic symptoms.
Manganese concentration in the urine or hair exceeding top limit of normal.
Examination findings: *Mild poisoning*: *hypermyotonia*, or tremor and tendon hyperreflexia in fingers and mood changes. *Severe poisoning*: Obvious corticospinal tract damage, *parkinsonian appearance*, *four limbs of hypermyotonia*, static tremor, *cogwheel rigidity*, dysdiadokinesia, positive Romberg's sign, gait irregularity, backward progression difficulty. Toxic psychosis.
Diagnosis is made based on occupational exposure history and identification of extracorticospinal tract damages as the main manifestation, along with information from industrial air monitoring, spot air manganese concentrations,analysis of manganese in urine, hair or blood and considering other diagnoses such as paralysis agitans, Wilson syndrome and others.
Subjective symptoms: dizziness, headache, lassitude, dyssomnia, morbid forgetfulness and limb ache, and heavy feeling as well as autonomic symptoms.
Manganese concentration in the urine or hair exceeding top limit of normal.

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METHODS

A team consisting of a physician with American board certifications in neurology and occupational and environmental medicine, a US neurotoxicologist, and two Chinese occupational medicine physicians was assembled to assess six workers with different exposure background to confirm a diagnosis of manganese-induced movement disorder. Each patient had been previously given the diagnosis of "chronic manganism" by Chinese physicians. Chronic manganism in China was defined by a criterion developed by the Chinese government in 1982 initially and then redrafted in 2002 (Table 1).

The patients were interviewed with the help of a Chinese interpreter and given a thorough neurological examination based on a Unified Parkinson's Disease Rating Scale. Scores were compared to criteria used by Racette et al in 2005. Patients were given diagnoses of Parkinsonism when rigidity, tremor, bradykinesia, or postural instability was evident on examination. Occupational and past medical histories were uncovered. Laboratory testing and brainimaging were reviewed.

A synopsis of each of the six cases is presented in the Part II. References for parts I and II are presented in the following reference list.

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