HIGH LIGHT
CME

Searching for a relationship between manganese and welding and Parkinson's disease

Joseph Jankovic, MD

Abstract—Research into the causes of Parkinson disease (PD) has accelerated recently with the discovery of novel gene mutations. The majority of PD cases, however, remain idiopathic and in those cases environmental causes should be considered. Several recent reports have focused on welding and manganese toxicity as potential risk factors for parkinsonism and some have even proposed that welding is a risk factor for PD. The controversy has stimulated this review, the primary aim of which is to critically and objectively examine the evidence or lack of evidence for a relationship among welding, manganese, parkinsonism, and PD.

NEUROLOGY 2005;64:2021–2028

Parkinson disease (PD) is one of the most common neurodegenerative disorders, affecting approximately 1 million Americans and 1 to 2% of those over age 60 worldwide.[1-3] With the lifetime risk of 2% and an increasing incidence with age, coupled with aging of the population, the prevalence of PD is expected to triple over the next 50 years.

Despite the growing number of newly identified genetic causes of parkinsonism,[4,5] in the majority of cases the cause is unknown, hence the enormous interest in the role of environmental factors in various parkinsonian disorders.[6,7] While numerous toxins have been found to produce nigrostriatal degeneration in experimental animals,[8] there is no evidence that any environmental toxin causes PD. A variety of environmental and occupational exposures, however, have been implicated in the etiology of PD. These include exposure to well water, pesticides, herbicides, rural living, certain metals, fuel oil, magnetic fields, and employment in the steel/alloy industry, wood/pulp plants, farming, carpentry, cleaning, orchards, planer mill, forestry, logging, mining, as well as certain occupations such as body and fender repairmen, auto painters, railroad and car shop mechanics, and workers in oil and gas fields.[9-17] In the recent past, several reports have also suggested that welders may be at a higher risk for developing parkinsonism, and some have even proposed that welding is a risk factor for PD.[18,19] These claims have entered the legal system and numerous lawsuits have been filed on behalf of welders alleging that toxic fumes generated by the welding rods have caused not only parkinsonism, but also PD. In this review, we intend to examine the evidence for and against a relationship among welding, manganese, parkinsonism, and PD.

With the discovery of new causes of parkinsonism and with the recognition that the same etiology (e.g., a single gene mutation) can be associated with markedly diverse pathology, the traditional view that pathologic examination is the gold standard in the diagnosis of PD has been recently challenged.[20,21] In this review, unless a specific etiologic cause is identified, we will define PD based on clinical-pathologic criteria.[22] This approach is supported by several studies demonstrating that when PD is diagnosed clinically by expert parkinsonologists, the autopsy confirms the diagnosis in over 90% of the cases.[23,24]

What is the role of manganese in health? Manganese, the 12th most common element in the earth's crust, is abundantly present in our environment and food, including nuts, grains, tea, legumes, and other foods, which provide an average daily

Editorial, see page 2001
See also page 2033

From the Department of Neurology, Baylor College of Medicine, Houston, TX.

Supported by General Electric and National Parkinson Foundation support to the Center of Excellence at Baylor College of Medicine.

Received February 12, 2005. Accepted in final form April 5, 2005.

Address correspondence and reprint requests to Dr. Joseph Jankovic, Professor of Neurology, Director of PD Center and Movement Disorders Clinic, Department of Neurology, 6550 Fannin, Suite 1801, Baylor College of Medicine, Houston, TX 77030; e-mail: josephj@bcm.tmc.edu

intake of about 5 mg/kg. Besides serving as a cofactor for various enzymes including arginase and glutamine synthetase, manganese is an essential constituent of the mitochondrial enzyme manganese-superoxide dismutase, and as such it plays a critical antioxidant role in a wide variety of cells, including neurons of the CNS. Although manganese does not promote the Fenton reaction to form hydroxyl radicals, as a transitional metal it can exist in multiple valence states and thus may promote redox reactions and form cytotoxic free radicals. Thus, there is evidence both for and against antioxidant and cytoprotective effects of manganese. Manganese deficiency may be associated with abnormal carbohydrate and lipid metabolism, impaired bone development, reduced fertility, birth defects, and other disorders, including epilepsy.[25] Therefore, manganese is recommended in dietary intake (2 to 5 mg/day), and manganese is included in parenteral nutrition.[26] Only 2 to 5% of ingested manganese is absorbed while the rest is excreted in feces, and a much smaller proportion is excreted in urine.[27,28] Normal levels of manganese range from 4.2 to 16.5 mcg/L in blood, 0.40 to 0.85 mcg/L in serum, and 1 to 2 mcg/g of dry weight in the brain (with the highest concentration in the globus pallidus).[29] Manganese levels in urine and feces my be used as a marker for exposure to manganese within the previous few hours, whereas manganese can be detected in blood for days to weeks after exposure ceases.[30] Although present occupational standards for exposure levels for manganese in total dust causing neurologic effects have been estimated to be approximately 0.2 mg/m^3, this threshold limit value (TLV) has never been validated by well-designed scientific studies.[31] Manganese-induced neurotoxicity has been reported to occur only after chronic exposure to high levels of manganese,[26] usually above the permissible exposure limit ceiling at 5 mg/m^3 set by the Occupational Safety and Health Administration.[32]

Besides ingestion, inhalation is another means of entry of manganese into the body, but the bioavailability (whether manganese actually gets from the lung to the blood) is dependent on the size, form, and solubility of the particle. About 80% of all inhaled small (0.1 to 2 μm) particles is cleared by exhalation.[33] Larger particles are cleared by expectoration and swallowing. Olfactory nerve is another, yet unproven, entry of manganese in the brain.[34] The concentration of manganese in the body is narrowly controlled by regulating its excretion from liver to bile.[35] Because manganese homeostasis is so effective and because of competition with iron for availability of transferrin to transport manganese across the blood–brain barrier,[25,36] manganese neurotoxicity is quite rare. Patients with compromised liver function, however, particularly when exposed to excessive concentrations of manganese dust or when receiving total parenteral feedings, are potentially vulnerable to manganese toxicity.[37]

What are the manifestations of manganese toxicity? Neurologic consequences of manganese toxicity have been recognized since 1837[38] when five workers in a manganese ore grinding plant in France developed a variety of symptoms such as low-volume speech, drooling, and loss of facial expression. The two patients described in detail had a characteristic unsteady and propulsive gait, without apparent cognitive impairment and no improvement of symptoms even after up to 7 years after removal from the environment. Since that time clusters of toxic manganese exposure have been reported from many regions of the world,[39] but the best studied series have been the Chilean miners[40-42] and Taiwanese manganese alloy smelters.[43-45] In the Taiwanese outbreak in the late 1980s, six workers in the ferromanganese smelting plant developed the typical symptoms of manganese-induced parkinsonism, attributed to malfunctioning ventilating system, raising ambient levels of manganese to toxic levels (in excess of 27 mg/m^3).[43-45] In addition to occupational exposure, as in manganese miners, workers in manganese smelter plants, and those involved in manufacturing of dry batteries, chronic parenteral nutrition and ingestion of potassium permanganate have been reported to cause manganese toxicity. Public health concerns also have been raised about methylcyclopentadienyl manganese tricarbonyl (MMT), increasingly used as an octane-improving additive to unleaded gasoline, as a possible source of manganese neurotoxicity.[26,46] MMT, however, has not yet been documented to cause parkinsonism in humans, although it does produce behavioral, motor, and neuropathologic changes in experimental animals. While exposure to toxic levels of manganese may be associated with parkinsonism, it does not increase the risk of essential tremor,[47] sometimes associated with PD.[48]

Based on documented series and anecdotal reports, a characteristic constellation of clinical features is observed in patients with manganese poisoning. Within a few hours or days after acute exposure to toxic levels of manganese patients may experience cough and shortness of breath and headaches. This early phase is also manifested by nonspecific symptoms such as asthenia, somnolence, insomnia, anorexia, and loss of sexual drive as well as behavioral manifestations, characterized by irritability, impulsiveness, belligerence, obsessive-compulsive behavior, hallucinations, and other psychiatric symptoms ("manganese madness"). Other psychiatric abnormalities include pseudobulbar affect with emotional incontinence manifested by inappropriate laughing and crying. Later, hypomimia, action tremors, dystonia, myoclonus, speech, gait and balance problems, and other parkinsonian features emerge (table). A variety of neuropsychological abnormalities have been reported, even in early stages of manganese poisoning, but no consistent pattern of behavioral or cognitive abnormalities has emerged.[31]

Table *Typical features of manganese-induced parkinsonism*

1. Onset of neurobehavioral manifestations after (weeks or months) and during exposure to toxic levels of manganese
2. Bilaterally simultaneous onset and symmetric impairment
3. Early appearance of personality changes and emotional lability
4. Visual and auditory hallucinations
5. Low amplitude, rapid postural tremor (usually no rest tremor)
6. Early appearance of hypokinetic-hypophonic dysarthria
7. Early appearance of gait and balance abnormalities (with propulsion or retropulsion)
8. "Cock-like" gait (trunk extended and arm flexed, toe walking)
9. Dystonia in limbs (flexion of ankles and toes), trunk, and face (grimace)
10. Action myoclonus
11. Hyperreflexia and extensor plantar responses
12. Poor or no sustained response to levodopa without levodopa-related motor or psychiatric complications
13. Initial rapid progression followed (usually after 2 years) by a stable course with occasional spontaneous partial remission (may be delayed by several years)
14. Initial and transient elevations of levels of manganese in blood, urine, and hair
15. MRI: Bilateral hyperintensities in globus pallidus and substantia nigra on T1-weighted images (may be transient)
16. F-DOPA PET is usually normal, but raclopride uptake is reduced
17. Pathology: degeneration and gliosis of globus pallidus, no Lewy bodies

How is the diagnosis of manganese-induced parkinsonism confirmed? The clinical, imaging, and pathologic features of manganese-induced parkinsonism are so characteristic that the differentiation of this syndrome from PD should pose no problem for an experienced clinician (see table). In addition to the history of exposure to toxic levels and typical clinical features, the diagnosis of manganese-induced parkinsonism is aided by laboratory and imaging studies.[49] These ancillary studies may be helpful during the acute phase of manganese toxicity, but they are not generally useful in confirming the diagnosis in chronic cases. Concentrations of manganese in blood, urine, and hair are usually increased within a few days or weeks after exposure, but the levels may return to normal at the time when the patient comes to medical attention. Provocative test with the chelating agent dimercaptosuccinic acid (DMSA) has negligible effect on manganese in urine and blood.[50]

MRI typically shows increased signal intensity in the globus pallidus on T1-weighted images, but this abnormality may resolve and even be absent at the time the patient still exhibits neurobehavioral symptoms. In one series of workers with alleged occupational exposure to manganese, 46% showed typical signal changes in the globus pallidus, even though there were no observable neurologic symptoms or signs.[51] Other studies suggested that these MRI findings are indicative of striatal-pallidal degeneration correlating with the clinical picture of atypical parkinsonism manifested chiefly by axial features, such as dysarthria, gait and balance problems, absence of rest tremor, and poor or no response to levodopa. Elevated blood manganese levels may also correlate with high signal intensities in the globus pallidus on T1-weighted MRI in patients with liver cirrhosis.[52-54a] Besides atypical parkinsonism and hepatocerebral disease, other disorders associated with T1 pallidal hyperintensity include hyperglycemia, Wilson's disease, abnormal calcium metabolism, neurofibromatosis, hypoxia, and a sequelae of cerebral hemorrhage. Among the Taiwanese smelting plant workers fluorodopa PET remained normal for more than 5 years after they were removed from the toxic environment, suggesting that the nigrostriatal system is spared in manganese-induced parkinsonism.[55] Although previous PET studies have indicated that striatal dopamine transporter density is normal in manganese-induced parkinsonism (whereas it is decreased in PD), Kim et al.[56] showed a severe reduction in [(123)I]-(1r)-2beta-carboxymethoxy-3beta-(4-iodophenyl)tropane(beta-CIT), a ligand for dopamine transporter, by SPECT in two patients with "a long history of occupational manganese exposure." Because of some atypical features, the authors conceded that the two patients may have had idiopathic PD rather than manganese-induced parkinsonism. Using raclopride as a ligand for D2 receptors, PET studies of individuals exposed to manganese showed a reduction of binding, consistent with the loss of postsynaptic striatal dopaminergic projections.[55]

Degeneration of dopamine-producing neurons in the substantia nigra zona compacta, Lewy bodies, intracytoplasmic inclusions that stain for α-synuclein, ubiquitin, and a variety of other proteins, and a loss of striatal dopamine are the pathologic hallmarks of PD. PD is also associated with degeneration and Lewy bodies in other regions including the locus coeruleus, the dorsal motor nucleus of the vagus, the nucleus basalis of Meynert, and selected neurons of the cerebral cortex, spinal cord, and peripheral nervous system.[57] In contrast, postmortem neuropathologic examination of patients with documented manganese-induced parkinsonism usually shows predominant involvement of the basal ganglia with neuronal degeneration and gliosis in the globus pallidus, and to lesser extent putamen, caudate, and thalamus, and degeneration in the substantia nigra pars reticularis, with sparing of the nigrostriatal system and other regions typically affected in PD[58] (see table). At the time of death, which may be years after the exposure, the brain manganese levels may be normal. Similar pathologic changes and preservation of normal striatal dopamine levels have also been demonstrated in experimental animals exposed to toxic concentrations of manganese.[59-62] It is not clear why manganese is most highly concentrated in

the globus pallidus in normal brains and why manganese preferentially accumulates and causes damage in this nucleus following toxic exposure to manganese in humans and animals. The pattern of selective accumulation of metal in the globus pallidus is similar to that in two human diseases: Wilson's disease and neurodegeneration with brain iron degeneration, frequently associated mutations in the pantothenate kinase 2 (*PANK2*) gene.[63]

What is the treatment and outcome of manganese-induced parkinsonism? The most important step in the management of manganese toxicity is to prevent it. If removed from the exposure within few weeks or months, the behavioral and neurologic signs often resolve or improve, and within 2 years stabilize, although in some cases spontaneous, usually partial remission, has been described several years after initial exposure.[64] However, if the exposure continues, the syndrome becomes irreversible. In nearly all the occupational clusters the work environment is described as heavily laden with a manganese-containing dust that coats the workmen's clothes.[65] The degree and duration of exposure in relationship to the risk of manganese-induced parkinsonism has not been well studied, but based on a study of 39 cases, Edsall et al.[66] determined that over 4 months of exposure to 9 to 12% levels of manganese was required to produce "permanent" deficits. The marked decline in reports of manganese neurotoxicity are probably due to improvements in environmental workplace, including enhanced ventilation and a change in mining procedures to wet drilling.

While it would be desirable to remove deposited manganese from the brain, chelation with agents such as edetate calcium disodium (EDTA) is of limited benefit. When used in the early phases of the poisoning EDTA, however, may prevent severe neurologic damage.[36,67] Cotzias, a pioneer in levodopa therapy of PD, attempted to treat the Chilean miners with levodopa, but despite initial short-term benefit, long-term trials of levodopa were disappointing.[68,69] Similar response was noted in the Taiwanese workers. Although initially some of the patients were reported to have subjective improvement, this was later thought to be in part a placebo response and a subsequent double-blind trial of levodopa in the same cohort showed no benefit.[70] The postsynaptic nature of manganese parkinsonism is suggested not only by the lack of benefit of levodopa, but also by the absence of motor and psychiatric complications of levodopa therapy, commonly encountered in patients with PD.[71]

Is manganese a risk factor for PD? Because of the recognized association of manganese toxicity and parkinsonism, many studies have attempted to link manganese exposure to increased risk of PD. For example, a survey of food habits of 250 patients with PD compared with 388 controls found that a high intake of iron, especially in combination with high manganese intake, doubled the risk for PD.[72] This finding, even if confirmed, probably has no relevance to the pathogenesis of PD because, as noted before, the body's effective homeostatic regulation of dietary manganese would not allow for manganese from food diet to ever reach toxic levels in the brain. Furthermore, nearly all epidemiologic studies have failed to establish a cause-effect relationship between manganese and PD. Several studies have suggested that exposures to aluminum, copper, and lead are risk factors for PD,[10,73,74] but no such link has been found for manganese.[10,12,74-80] In one study conducted in southern Quebec (Canada), involving 42 parkinsonian patients compared with a group of 84 matched controls, a slightly increased risk for PD was found to be associated with occupational exposure to manganese, iron, and aluminum, but this association did not reach statistical significance.[81] In a study of WWII Twins Cohort, involving 163 twin pairs, in which a blinded industrial hygienist estimated lifetime occupational manganese exposure intensity and duration, twins with PD were less likely to have ever been exposed to manganese than their control twin (OR = 0.36) and had a shorter average duration of manganese exposure than did controls.[79]

These epidemiologic studies are supported by clinical-pathologic studies. Based on autopsies of 27 brains of patients with PD and 34 controls, Dexter et al.[82] found that manganese levels were similar in case and control substantia nigra, globus pallidus, and other brain structures and that PD brains had 20% lower manganese levels in the striatum than controls. Thus, there is currently no evidence that manganese causes PD.

Can welding cause manganese neurotoxicity? Although invented in the 19th century, welding was first used commercially prior to World War I, and became widely applied during World War II, especially in the shipyards where it replaced riveting as the primary method for joining metals. Since 90% of welding fume particles are less than 2 μm in diameter, approximately 80% of the particles are exhaled and not deposited in the respiratory system.[33] The remaining 20% of inhaled particles may be deposited in the lung alveolar regions and eventually cleared by macrophages. In contrast to relatively low concentrations of manganese in the welding fumes in the breathing zone of the welder (<1 mg/m^3), manganese particles found in manganese dust generated in mining and ore crushing operations are much larger and may reach high concentrations (450 to 900 mg/m^3).[83] These large particles tend to deposit in the nose and upper airways and when swallowed become available to the liver. If this excretion mechanism, however, is overwhelmed because of extreme manganese dust exposure or because of impaired liver function, manganese can be carried into blood and cause brain toxicity. Furthermore, manganese can readily dissociate from these large particles to yield free manganese. In contrast, fumes during welding are formed by the vaporization of metals under conditions of extreme heat (2,000 to 3,000 centigrade temperatures) and the subsequent condensation with iron

results in a tightly bound, non-soluble, iron-manganese amalgam, making transportation of any free manganese across blood–brain barrier unlikely.[84] These and other studies lead to the conclusion that despite attempts linking welding to manganese neurotoxicity, there is little or no evidence that welding fumes contain sufficient amounts of free and soluble manganese to actually enter the blood and brain, strongly arguing against any neurotoxic effects of manganese from welding.

Can welding cause PD? Several epidemiologic studies have attempted to address the question whether welding is a risk factor for PD or other neurologic disorders. A 1947 health survey of 4,650 shipyard workers, three-quarters of whom were welders, found no evidence that these workers had an unusually high occurrence of parkinsonism or any other neurologic disease.[85] Welders, included in the "machine trades" category of the Dictionary of Occupational Titles of the United States Department of Labor and in the "manufacturing" sector of the Standard Industrial Classification (SIC) Manual of the Office of Budget and Management, actually were found to have a slightly lower incidence of PD than the control subjects.[86] In a study involving the World War II Veteran Twins Cohort, in which 142 twin pairs were identified where one twin had PD, welding was not associated with PD.[87] Several mortality surveys of large populations of welders found elevated rates of digestive tract cancer, accidental trauma, stroke, lung cancer, cirrhosis, suicide, and heart disease, but not of PD or any other neurologic disease.[88]

A comparison of welders with other populations using various psychological and neurologic tests has yielded conflicting results. A recent study of 100 male manganese alloy plant workers found no difference in performance of various neuropsychological tests between the workers and controls.[89] One of the most cited studies is that of Bowler et al.,[90] who evaluated 76 welders, with occupational history of 25 years, and compared them to 42 controls. The two groups performed similarly on tests of verbal skills, verbal retention, and auditory spans, but welders performed worse than controls on tests of verbal learning, working memory, cognitive flexibility, visuomotor processing speed, and motor efficiency. Furthermore, welders had more complaints related to emotional and physical well-being. This study, however, has been criticized because of many methodologic problems, including the fact that welders had a lower educational background than controls.[91] Also, no attempt was made to correlate the abnormal neuropsychological findings with dose or duration of exposure. Furthermore, there was an obvious selection bias as the welders were recruited into the study because they filed civil and Workman's Compensation litigation claiming that their symptoms were related to occupational welding. For these and other reasons, there is no justification for the conclusion that "neuropsychological testing is an effective means for assessing manganese toxicity."[90]

The debate about a possible relationship between welding and PD was fueled by the report of Racette et al.,[18] who surveyed 953 parkinsonian patients seen in their neurology specialty clinic between 1996 and 2000 and found that the mean age of 15 welders with PD was 17 years younger (46 years) as compared to PD patients who were not welders (63 years). Although the study did not provide any evidence that welders were more likely to develop PD than the general population, the authors suggested that welding acted to accelerate the onset of PD. There are, however, many methodologic problems with the study, making any interpretation difficult. For example, the patients were not randomly selected and there was no evidence that the welders in the study were representative of all welders. It is not clear whether they were coworkers and how they were referred to the specialty clinic. The study was conducted in a tertiary center specializing in parkinsonian disorders, therefore raising the possibility of a referral bias as patients referred to such specialty clinics are more atypical than the general population of PD patients. The majority (8/15) of the welders in the study had a family history of PD, a rate much higher than the 15% reported in unselected PD patients.[92] The high frequency of family history is similar to young-onset PD cases, many of whom have a *Parkin* mutation.[93] It is likely, therefore, that genetic factors rather than welding were the major risk factor in these relatively young patients with PD who happened to be welders.[94] Therefore, despite the title of the article, "welding-related parkinsonism," the report provides no convincing evidence that welding is a risk factor for PD. In a subsequent report, Racette et al.[19] described their findings in 1,423 welders from Alabama referred by attorneys for medical-legal evaluation. The prevalence of parkinsonism (prevalence ratio of 10.2; 5.8% had a diagnosis of "definite PD") among the welders was significantly higher than the estimated prevalence in the general population, based on published data from a 1985 epidemiologic study of Copiah county.[95] There are, however, many methodologic flaws in this study such as the obvious bias by a study sample consisting entirely of potential litigants, the use of unvalidated video protocol rather than complete neurologic examination to establish the diagnosis, absence of blindness, using historical controls rather than true control population examined by the same methods as the welders, and a claim that part III (motor examination) of the Unified PD Rating Scale was used even though this would require actual physical examination, which was performed in less than 7.9% of a "pseudo-random group" of subjects. Furthermore, although they state that that some of the welders had symptoms "consistent with manganese exposure," the authors provide no evidence for the implied link between welding and manganese exposure.

Despite the lack of evidence, other reports also

attempt to make the association between welding and manganese and parkinsonism. For example, Koller et al.[96] described a group of welders as having "manganese-induced parkinsonism," even though there is no evidence to support the diagnosis. The authors state that "presumptive diagnosis of manganese-induced parkinsonism . . . was based solely on the presence of parkinsonian signs and a history of long-term exposure to manganese in welding rods." They cite lack of response to levodopa (up to 900 mg per day) in 13 welders as evidence for "manganese-induced parkinsonism." The subjects were apparently "randomly selected" for the study, but it is not clear how many welders were actually screened. All patients were still working despite a mean lapse of nearly 8 years since the onset of symptoms. Other atypical features for manganese-induced parkinsonism included asymmetric presentation in six, rest tremor in five, and absence of dystonia (see table). Finally, the authors failed to disclose the source of their support for the study, specifically their relationship to the plaintiff's attorneys, or why the welders were being "examined for possible neurotoxicity." They also failed to respond to questions addressed to them regarding the validity of the diagnosis of manganese-induced parkinsonism and the lack of qualifications of the diagnosing physician.[97,98] Other studies of occupations in PD patients have found no evidence of an increased risk of PD among workers in metal processing plants, construction, machine-related occupations, and other technical workers, which would have included welders.[14,99] These negative findings are consistent with those of a previous study involving 489 mine workers with "medium and low occupational manganese exposures"[100] and 509 workers at a manganese smelter plant.[101]

The studies by Racette and colleagues[18,19] highlight the pitfalls in accepting the notion that coexistence implies a cause-and-effect relationship. This is exemplified by the case of a 48-year-old man who had welded 2 hours per day for 8 years, followed by 10 hours per day for 2 years.[102] While his parkinsonism was attributed to welding, despite unilateral involvement, presence of rest tremor, lack of gait difficulty, and modest improvement with levodopa, reduced fluorodopa uptake on PET in the left putamen, contralateral to his symptoms, was much more consistent with the diagnosis of PD rather than manganese-induced parkinsonism.[102] The only case report suggesting a possible link between welding and manganese and parkinsonism is that by Sadek et al.,[103] in which a young welder presented with a 2-year history of cognitive difficulties, tremor, and propulsive gait with tendency to walk on toes. Although the dosage was not stated, there was apparently no response to levodopa. His T1-weighted MRI showed increased signal in the area of globus pallidus, consistent with deposition of manganese. One month after his last day of work his serum and urine manganese levels were mildly elevated. Besides this case, another single case report, a 17-year-old boy who welded for about 2 years, suggested that myoclonus may be a manifestation of welding-associated manganese poisoning.[104] Although this patient had elevated levels of manganese in the blood and hair, and his MRI showed the typical T1 hyperintensities in the globus pallidus, there were some atypical features including the unilateral nature of the involuntary movement. Chelation with EDTA was associated with resolution of the myoclonus and abnormal MRI.

Epidemiologic, experimental, or other studies, or standard textbooks of PD and of other movement disorders,[16,74] do not provide any convincing evidence that welding is a significant risk factor for PD or for parkinsonism or that manganese-induced parkinsonism shares any pathogenetic mechanisms with PD.

References

1. Bergareche A, De La Puente E, Lopez de Munain A, et al. Prevalence of Parkinson's disease and other types of Parkinsonism. A door-to-door survey in Bidasoa, Spain. J Neurol 2004;251:340–345.
2. Elbaz A, Bower JH, Maraganore DM, et al. Risk tables for parkinsonism and Parkinson's disease. J Clin Epidemiol 2002;55:25–31.
3. Strickland D, Bertoni JM. Parkinson's prevalence estimated by a state registry. Mov Disord 2004;19:318–323.
4. Huang Y, Cheung L, Rowe D, Halliday G. Genetic contributions to Parkinson's disease. Brain Res Brain Res Rev 2004;46:44–70.
5. Nichols WC, Pankratz N, Hernandez D, et al. Genetic screening for a single common LRRK2 mutation in familial Parkinson's disease. Lancet 2005;365:410–412.
6. Hanna P, Jankovic J, Kilkpatrick J. Multiple system atrophy: the putative causative role of environmental toxins. Arch Neurol 1999;56:90–94.
7. Kumar A, Calne SM, Schulzer M, et al. Clustering of Parkinson disease: shared cause or coincidence? Arch Neurol 2004;61:1057–1060.
8. McNaught KS, Perl DP, Brownell AL, et al. Systemic exposure to proteasome inhibitors causes a progressive model of Parkinson's disease. Ann Neurol 2004;56:149–162.
9. Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. Neurology 1993;43:1173–1180.
10. Hertzman C, Wiens M, Snow B, Kelly S, Calne D. A case-control study of Parkinson's disease in a horticultural region of British Columbia. Mov Disord 1994;9:69–75.
11. Schulte PA, Burnett CA, Boeniger MF, Johnson J. Neurodegenerative diseases: occupational occurrence and potential risk factors, 1982 through 1991. Am J Public Health 1996;86:1281–1288.
12. Seidler A, Hellenbrand W, Robra BP, et al. Possible environmental, occupational, and other etiologic factors for Parkinson's disease: a case-control study in Germany. Neurology 1996;46:1275–1284.
13. Smargiassi A, Mutti A, De Rosa A, De Palma G, Negrotti A, Calzetti S. A case-control study of occupational and environmental risk factors for Parkinson's disease in the Emilia-Omagna region of Italy. Neurotoxicology 1998;19:709–712.
14. Fall PA, Fredrikson M, Axelson O, Granerus AK. Nutritional and occupational factors influencing the risk of Parkinson's disease: a case-control study in southeastern Sweden. Mov Disord 1999;14:28–37.
15. Noonan CW, Reif JS, Yost M, Touchstone J. Occupational exposure to magnetic fields in case-referent studies of neurodegenerative diseases. Scand J Work Environ Health 2002;28:42–48.
16. Tanner CM, Goldman SM. The etiology of Parkinson's disease. In: Jankovic J, Tolosa E, eds. Parkinson's disease and movement disorders, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2002;90–103.
17. Gorell JM, Peterson EL, Rybicki BA, Johnson CC. Multiple risk factors for Parkinson's disease. J Neurol Sci 2004;217:169–174.
18. 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.
19. Racette BA, Tabbal SD, Jennings D, Good L, Perlmutter JS, Evanoff B. Prevalence of parkinsonism and relationship to exposure in a large sample of Alabama welders. Neurology 2005;64:230–235.
20. Uitti RJ, Calne DB, Dickson DW, Wszolek ZK. Is the neuropathological 'gold standard' diagnosis dead? Implications of clinicopathological findings in an autosomal dominant neurodegenerative disorder. Parkinsonism Relat Disord 2004;10:461–463.
21. Zimprich A, Biskup S, Leitner P, et al. Mutations in LRRK2 cause autosomal-dominant parkinsonism with pleomorphic pathology. Neuron 2004;44:601–607.

22. Gelb DJ, Oliver E, Gilman S. Diagnostic criteria for Parkinson's disease. Arch Neurol 1999;56:33–39.
23. Jankovic J, Rajput AH, McDermott MP, Perl DP. The evolution of diagnosis in early Parkinson disease. Arch Neurol 2000;57:369–372.
24. Hughes AJ, Daniel SE, Ben-Shlomo Y, Lees AJ. The accuracy of diagnosis of parkinsonian syndromes in a specialist movement disorder service. Brain 2002;125:861–870.
25. Takeda A. Manganese action in brain function. Brain Res Brain Res Rev 2003;41:79–87.
26. Dobson AW, Erikson KM, Aschner M. Manganese neurotoxicity. Ann NY Acad Sci 2004;1012:115–128.
27. Kaji H, Ohsaki Y, Rokujo C, Higashi T, Fujino A, Kamada T. Determination of blood and urine manganese (Mn) concentrations and the application of static sensography as the indices of Mn-exposure among Mn-refinery workers. J UOEH 1993;15:287–296.
28. Barceloux DG. Manganese. J Toxicol Clin Toxicol 1999;37:293–307.
29. Prohaska JR. Functions of trace elements in brain metabolism. Physiol Rev 1987;67:858–910.
30. Lander F, Kristiansen J, Lauritsen J. Manganese exposure in foundry furnacemen and scrap recycling workers. Int Arch Occup Environ Health 1999;72:546–550.
31. Iregren A. Manganese neurotoxicity in industrial exposures: proof of effects, critical exposure level, and sensitive tests. Neurotoxicology 1999;20:315–324.
32. US Department of Labor. Occupational Safety & Health Administration. Available at: http://www.osha.gov/
33. Kim CS. Methods of calculating lung delivery and deposition of aerosol particles. Respir Care 2000;45:695–711.
34. Fechter LD, Johnson DL, Lynch RA. The relationship of particle size to olfactory nerve uptake of a non-soluble form of manganese into brain. Neurotoxicology 2002;23:177–183.
35. Scheuhammer A, Cherian M. The distribution and excretion of manganese: the effects of manganese dose, L-dopa, and pretreatment with zinc. Toxicol Appl Pharmacol 1982;65:203–213.
36. Crossgrove J, Zheng W. Manganese toxicity upon overexposure. NMR Biomed 2004;17:544–553.
37. Fell JM, Reynolds AP, Meadows N, et al. Manganese toxicity in children receiving long term parenteral nutrition. Lancet 1996;347:1218–1221.
38. Couper J. On the effects of black oxide of manganese when inhaled into the lungs. Br Ann Med Pharmacol 1837;1:41–42.
39. Lee J-W. Manganese intoxication. Arch Neurol 2000;57:597–599.
40. Cotzias GC, Horiuchi K, Fuenzalida S, Mena I. Chronic manganese poisoning. Clearance of tissue manganese concentrations with persistence of the neurological picture. Neurology 1968;18:376–382.
41. Mena I, Marin O, Fuenzalida S, Cotzias GC. Chronic manganese poisoning. Clinical picture and manganese turnover. Neurology 1967;17:128–136.
42. Mena I, Horiuchi K, Burke K, Cotzias GC. Chronic manganese poisoning. Individual susceptibility and absorption of iron. Neurology 1969;19:1000–1006.
43. Huang CC, Chu NS, Lu CS, et al. Chronic manganese intoxication. Arch Neurol 1989;46:1104–1106.
44. Huang CC, Chu NS, Lu CS, et al. Long-term progression in chronic manganism: ten years of follow-up. Neurology 1998;50:698–700.
45. Wang JD, Huang CC, Hwang YH, 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;46:856–859.
46. Normandin L, Panisset M, Zayed J. Manganese neurotoxicity: behavioral, pathological, and biochemical effects following various routes of exposure. Rev Environ Health 2002;17:189–217.
47. Louis ED, Applegate LM, Factor-Litvak P, Parides MK, Andrews L. Essential tremor: occupational exposures to manganese and organic solvents. Neurology 2004;63:2162–2164.
48. Jankovic J. Essential tremor: a heterogenous disorder. Mov Disord 2002;17:638–644.
49. Olanow CW. Manganese-induced parkinsonism and Parkinson's disease. Ann NY Acad Sci 2004;1012:209–223.
50. Angle CR. Dimercaptosuccinic acid (DMSA): negligible effect on manganese in urine and blood. Occup Environ Med 1995;52:846.
51. Kim Y, Kim KS, Yang JS, et al. Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. Neurotoxicology 1999;20:901–907.
52. Hauser R, Zesiewicz ATA, et al. Blood manganese correlates with brain magnetic resonance imaging changes in patients with liver disease. Can J Neurol Sci 1996;23:95–98.
53. Burkhard PR, Delavelle J, Du Pasquier R, Spahr L. Chronic parkinsonism associated with cirrhosis: a distinct subset of acquired hepatocerebral degeneration. Arch Neurol 2003;60:521–528.
54. Park NH, Park JK, Choi Y, et al. Whole blood manganese correlates with high signal intensities on T1-weighted MRI in patients with liver cirrhosis. Neurotoxicology 2003;24:909–915.
54a. Racette BA, Antenor JA, McGee-Minnich L, et al. [(18)F]FDOPA PET and clinical features in parkinsonism due to manganism. Mov Disord 2005;20:492–496.
55. Shinotoh H, Snow BJ, Chu NS, et al. Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: a positron emission tomography study. Neurology 1997;48:1053–1056.
56. Kim Y, Kim JM, Kim JW, et al. Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure: what does it mean? Mov Disord 2002;17:568–575.
57. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. Cell Tissue Res 2004;318:121–134.
58. Yamada M, Ohno S, Okayasu I, et al. Chronic manganese poisoning: a neuropathological study with determination of manganese distribution in the brain. Acta Neuropathol (Berl) 1986;70:273–278.
59. Spadoni F, Stefani A, Morello M, et al. Selective vulnerability of pallidal neurons in the early phases of manganese intoxication. Exp Brain Res 2000;135:544–551.
60. Suzuki Y, Mouri Y, Suzuki K, et al. Study of subacute toxicity of manganese dioxide in monkeys. Tokoshima J Exp 1975;22:5–10.
61. Olanow CW, Good PF, Shinotoh H, et al. Manganese intoxication in the rhesus monkey: a clinical, pathologic, and biochemical study. Neurology 1996;46:492–498.
62. Gwiazda RH, Lee D, Sheridan J, Smith DR. Low cumulative manganese exposure affects striatal GABA, but not dopamine. Neurotoxicology 2002;23:69–76.
63. Thomas M, Hayflick SJ, Jankovic J. Clinical heterogeneity of neurodegeneration with iron accumulation–1 (Hallervorden-Spatz syndrome) and pantothenate kinase associated neurodegeneration (PKAN). Mov Disord 2004;19:36–42.
64. Casamajor L. An unusual form of mineral poisoning affecting the nervous system: manganese? JAMA 1913;60:646–649.
65. McNally W. Industrial manganese poisoning—with a review of the literature. Indust Med 1935;4:581–599.
66. Edsall DL, Wilbur FF, Drinker CK. The occurrence, course and prevention of chronic manganese poisoning. J Indust Hyg 1919;1:183–193.
67. Discalzi G, Pira E, Herrero Hernandez E, Valentini C, Turbiglio M, Meliga F. Occupational Mn parkinsonism: magnetic resonance imaging and clinical patterns following CaNa2-EDTA chelation. Neurotoxicology 2000;21:863–866.
68. Mena I, Court J, Fuenzalida S, Papavasiliou PS, Cotzias GC. Modification of chronic manganese poisoning. Treatment with L-dopa or 5-OH tryptophane. N Engl J Med 1970;282:5–10.
69. Cook DG, Fahn S, Brait KA. Chronic manganese intoxication. Arch Neurol 1974;30:59–64.
70. Lu CS, Huang CC, Chu NS, Calne DB. Levodopa failure in chronic manganism. Neurology 1994;44:1600–1602.
71. Jankovic J. Levodopa-related motor fluctuations and dyskinesias: clinical manifestation and classification. Mov Disord 2005 (suppl) (in press).
72. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT Jr., Swanson PD, Checkoway H. Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. Neurology 2003;60:1761–1766.
73. Wechsler LS, Checkoway H, Franklin GM, Costa LG. A pilot study of occupational and environmental risk factors for Parkinson's disease. Neurotoxicology 1991;12:387–392.
74. Gorell JM, Rybicki BA. Environmental risk factors for Parkinson's disease. In: Pahwa R, Lyons KE, Koller WC, eds. Handbook of Parkinson's disease. Third ed. New York: Marcel Dekker, 2003;339–362.
75. Semchuk KM, Love EJ, Lee RG. Parkinson's disease: a test of the multifactorial etiologic hypothesis. Neurology 1993;43:1173–1180.
76. Vieregge P, Heinzow B, Korf G, et al. Long term exposure to manganese in rural well water has no neurological effects. Can J Neurol Sci 1995;22:286–289.
77. McDonnell L, Maginnis C, Lewis S, et al. Occupational exposure to solvents and metals and Parkinson's disease. Neurology 2003;61:716–717.
78. Goldman SM, Field RD, Olanow W, Langston JW, Tanner CM. Occupation and Parkinson's disease (PD) onset age in a movement disorders clinic. Neurology 2004;62(suppl 5):A90a.
79. Goldman SM, Quinlan PJ, Smith AR, Langston J, Tanner CM. Manganese exposure and risk of Parkinson's disease in twins. Mov Disord 2004;19(suppl 9): S162b.
80. Park J, Yoo CI, Sim CS, et al. Occupations and Parkinson's disease: a multi-center case control study in South Korea. NeuroToxicology 2005;26:99–105.
81. Zayed J, Ducic S, Campanella G, et al. [Environmental factors in the etiology of Parkinson's disease.] Can J Neurol Sci 1990;17:286–291.
82. Dexter DT, Carayon A, Javoy-Agid F, et al. Alterations in the levels of iron, ferritin and other trace metals in Parkinson's disease and other neurodegenerative diseases affecting the basal ganglia. Brain 1991;114:1953–1975.
83. Agency for Toxic Substances and Disease Registry. Available at: http://www.atsdr.cdc.gov/
84. Dorman D, Struve M, James R, et al. Influence of particle solubility on the delivery of inhaled manganese to the rat brain: manganese sulfate and manganese tetroxide pharmacokinetics following repeated (14-day) exposure. Toxicol Appl Pharmacol 2001;1700:79–87.
85. Dreessen WC, Brinton HP, Keenan RG, Thomas TR, Place EH, Fuller JE. Health of arc welders in steel ship construction. Public Health

Bulletin No. 298. Washington, DC: U.S. Public Health Service, 1947; 1–200.
86. Kirkey KL, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Gorell JM. Occupational categories at risk for Parkinson's disease. Am J Ind Med 2001;39:564–571.
87. Tanner CM, Goldman SM, Quinlan P, et al. Occupation and risk of Parkinson's disease (PD): a preliminary investigation of Standard Occupational Codes (SOC) in twins discordant for disease. Neurology 2003;60(suppl 1):A415.
88. Coggon D, Inskip H, Winter P, Pannett B. Occupational mortality of men. London: Medical Research Council, 1995;23–61.
89. Pettersen R, Ellingsen DG, Hetland SM, Thomassenn Y. Neuropsychological function in manganese alloy plant workers. Int Arch Occup Environ Health 2004;77:277–287.
90. Bowler RM, Gysens S, Diamond E, et al. Neuropsychological sequelae of exposure to welding fumes in a group of occupationally exposed men. Int J Hyg Environ Health 2003;206:517–529.
91. Lees-Haley PR, Greiffenstein MF, Larrabee GJ, Manning EL. Methodological problems in the neuropsychological assessment of effects of exposure to welding fumes and manganese. Clin Neuropsychol 2005 (in press).
92. Rybicki BA, Johnson CC, Peterson EL, Kortsha GX, Gorell JM. A family history of Parkinson's disease and its effect on other PD risk factors. Neuroepidemiology 1999;18:270–278.
93. Periquet M, Latouche M, Lohmann E, et al. Parkin mutations are frequent in patients with isolated early-onset parkinsonism. Brain 2003;126:1271–1278.
94. Tanner CM, Ottman R, Goldman SM, et al. Parkinson disease in twins: an etiologic study. JAMA 1999;281:341–346.
95. Schoenberg BS, Anderson DW, Haerer AF. Prevalence of Parkinson's disease in the biracial population of Copiah County, Mississippi. Neurology 1985;35:841–845.
96. Koller WC, Lyons KE, Truly W. Effect of levodopa treatment for parkinsonism in welders: a double-blind study. Neurology 2004;62:730–733.
97. Chu NS. Effect of levodopa treatment for parkinsonism in welders: a double-blind study. Neurology 2004;63:1541.
98. Koller WC, Lyons KE. Effect of levodopa treatment for parkinsonism in welders: a double-blind study. Neurology 2004;63:1541.
99. Goldman SM, Smith AR, Quinlan PJ. Welding and risk of Parkinson's disease. Neuroepidemiology 2004;23:154c.
100. Myers JE, teWaterNaude J, Fourie M, et al. Nervous system effects of occupational manganese exposure on South African manganese mine workers. NeuroToxicology 2003;24:649–656a.
101. Myers JE, Thompson ML, Ramushu S, et al. The nervous system effect of occupational exposure on workers in a South African manganese smelter. NeuroToxicology 2003;24:885–894b.
102. Kim Y, Kim JW, Ito K, et al. Idiopathic parkinsonism with superimposed manganese exposure: utility of positron emission tomography. Neurotoxicology 1999;20:249–252.
103. Sadek AH, Rauch R, Schulz PE. Parkinsonism due to manganism in a welder. Int J Toxicol 2003;22:393–401.
104. Ono K, Komai K, Yamada M. Myoclonic involuntary movement associated with chronic manganese poisoning. J Neurol Sci 2002;199:93–96.

Searching for a relationship between manganese and welding and Parkinson's disease

Joseph Jankovic

Neurology 2005;64;2021-2028
DOI 10.1212/01.WNL.0000166916.40902.63