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REVIEW PAPER

From Manganism to Manganese-Induced Parkinsonism: A Conceptual Model Based on the Evolution of Exposure

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Abstract Manganism is a distinct medical condition from Parkinson's disease. Manganese exposure scenarios in the last century generally have changed from the acute, high-level exposure conditions responsible for the occurrence of manganism to chronic exposure to much lower levels. Such chronic exposures may progressively extend the site of manganese deposition and toxicity from the globus pallidus to the entire area of the basal ganglia, including the substantia nigra pars compacta involved in Parkinson's disease. The mechanisms of manganese neurotoxicity from chronic exposure to very low levels are not well understood, but promising information is based on the concept of susceptibility that may place individuals exposed to manganese at a higher risk for developing Parkinsonian disturbances. These conditions include mutations of genes which play important pathogenetic roles in both Parkinsonism and in the regulation of manganese transport and metabolism. Liver function is also important in manganese-related neurotoxicity and sub-clinical impairment may increase the risk of Parkinsonism. The purpose and scope of this report are to explore the literature concerning manganese exposure and potential subclinical effects and biological pathways, impairment, and development of diseases such as Parkinsonism and manganism. Inhalation and ingestion of manganese will be the focus of this report.

Keywords Manganism · Manganese poisoning · Parkinsonian disorders · Occupational exposure · Neurotoxicity

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Introduction

Cases of manganese intoxication have occurred worldwide for almost two centuries, causing a severe, debilitating neurological disease resembling Parkinson's disease referred to as manganism. Manganese is an essential element; in humans, homeostatic mechanisms are present to constantly adjust absorption and excretion rates in order to maintain the physiological ranges and avoid both deficiency and intoxication (Roth 2006). Although manganism, which typically follows acute, high-level exposure, is the most obvious clinical manifestation of manganese neurotoxicity, subclinical and sub-functional declines in neuropsychological tests, mainly related to motor coordination of fine movements, have been documented in the context of lower level exposure. Chronic lifetime exposure to very low levels is currently hypothesized as a possible risk factor for the onset of Parkinson's disease. These three manifestations may be associated with a continuum of dysfunction (Martin 2006).

The purpose and scope of this review article are to explore the literature concerning manganese exposure and potential subclinical effects and biological pathways, impairment, and development of diseases such as

Parkinson's disease and manganism. Inhalation and ingestion of manganese will be the focus of this report.

The Classical Features of "Manganism"

James Couper (1837) is credited with the first clear description of the adverse neurological effects of manganese in five Scottish men employed grinding manganese dioxide ore in 1837. At that time, the industrial use of manganese was limited, and in Couper's case series, the application was to generate 'bleaching powder.' Several of Couper's observations deserve mention. The most prominent and earliest symptom was described as paraplegia, with the lower extremities being markedly more affected than upper extremities. As a result, "the patient staggers, and inclines to run forward when he attempts to walk." Facial expression was vacant, with drooling and difficulty speaking. Couper remarked specifically on the absence of any tremor, any deficiency of intellect or any abnormalities in sensation. The first two cases, for whom exposure was more prolonged, failed to improve even 1 and 7 years following cessation of exposure. The latter three cases, removed promptly from exposure when staggering was noted, were described as having fully recovered.

Although not referenced by Couper, his report was only 20 years after James Parkinson's seminal description of the "shaking palsy" (Parkinson 2002). However, many other movement disorders clearly unrelated to manganese were also described at this time, such as Wilson's Disease in 1883 and Huntington's Chorea in 1842 (Harper 2002; Wexler 2008).

Several decades after Couper's first description, manganese began to be used much more widely in what remains by far its most common application, as a metal essential to the manufacture of steel alloy. In 1901, Von Jaksch (1909) described a case with very similar symptoms, with the exception of a marked tremor in the right hand. He is also credited with coining the term 'cock-walk' for the peculiar gait now closely associated with manganism. However, he was initially unaware of Couper's earlier work, and even though occupational manganese exposure was documented, he misdiagnosed the disease as multiple sclerosis. By 1919, a definitive review of clinical, toxicological, and epidemiological evidence available to date was published which not only clearly and unequivocally implicated manganese as the cause of this neurological disease, but also proposed diagnostic criteria (Edsall et al. 1919).

Later, psychiatric symptoms were described, termed *locura manganica* or 'manganese madness' (Cotzias 1958). Rodier (1955) described three clinical phases in an extensive study of 115 cases among underground miners. A prodromal phase was considered to consist largely of subjective symptoms of general asthenia, anorexia and apathy. There was an initial mental and sexual excitement followed closely by impotence, which was considered the most common symptom in this phase. Patients were aggressive and deranged. Gait could be staggered in this phase and speech slowed. The intermediate phase was characterized by objective neurological symptoms with the earliest symptom being disorders of speech consisting of dysarthria, stuttering and eventual muteness. A loss of facial expression was termed the "masque manganique." Movements became clumsy and subjects exhibited labile moods. A propensity to fall backwards was noted. In the established phase, both subjective and objective symptoms and signs progressed and there were obvious gait abnormalities with the cock-walk present in all cases. Tremor, hypertonicity, and weakness were present. Dystonia of the feet and hands as well as one case of torticollis were described. Psychiatric symptoms were present in all stages.

Since these first works, a large number of additional case reports and series of an extrapyramidal syndrome now termed *manganism* have been described, with an estimated 400 published cumulative cases by 1973 (Smyth et al. 1973). Among the most closely studied cohorts are smelter workers in Taiwan (Wang et al. 1989) and miners in Chile (Schuler et al. 1957). Manganism has now been described or suspected in a great variety of settings, both occupational and non-occupational, a spectrum summarized in Table 1. The exposure absorption routes by the stages of development are illustrated. Inhalational occupational exposure is an important absorption route in adulthood.

Most frequently (as in Couper's report), the exposures implicated involve estimated high, occupational inhalational exposure to the dust or fumes of manganese dioxide ores. Some of these reports must be read critically. In some instances, patients were exposed to several neurotoxic agents. External measurements are generally unavailable and therefore the level of exposure to manganese is not known. Measurements of manganese in blood or urine bear a complex and poorly understood relationship to external measurements and are of little value in determining exposure levels (Smith et al. 2007). Unlike other neurotoxic metals, such as mercury and lead, manganese is an essential element. Therefore, homeostatic mechanisms exist which regulate levels within a narrow range and preclude a direct inference between external exposure and levels within the body. Most recently, the blood manganese–iron ratio has been reported to more closely correlate with airborne manganese levels (Cowan et al. 2009). However, anemia unrelated to exposure may substantially influence this biomarker and diminish its predictive power.

A second tool used to establish manganese overexposure is the MRI, with the characteristic finding being a markedly increased signal intensity on T1-weighted images of the

Table 1 Spectrum of case reports of manganism by exposure source and route

Exposure source	Route of exposure	Reference
Manganese fumes in a smelter with malfunctioning ventilation	Inhalational	Wang et al. (1989)
Dust of fungicide maneb (manganese ethylene-bis-dithiocarbamate)	Inhalational	Meco et al. (1994)
Welding in confined space without respiratory protection	Inhalational	Kenangil et al. (2006)
Potassium permanganate ($KMnO_4$) used in manufacture of the recreational drug methcathinone	Intravenous	Stepens et al. (2008)
Increased dietary manganese absorption from sideropenia secondary to polcythemia vera	Gastrointestinal	Pratesi et al. (2008)
Excess manganese supplementation in patients receiving long-term total parenteral nutrition	Gastrointestinal	Fell et al. (1996)
Chronic liver failure	Impaired clearance	Klos et al. (2005)
Manganese powder in a worker with hepatic dysfunction from hepatitis C infection	Both inhalational and impaired clearance	Schaumburg et al. (2006)

globus pallidus and midbrain. However, even though clinical symptoms of manganism persist or progress, these imaging findings normalize approximately 6 months after cessation of exposure (Nelson et al. 1993). Moreover, MRI findings appear to be non-specific with respect to clinical manganism, being present in over 73% of active, yet asymptomatic, welders in a Korean study (Kim et al. 1999a). The same MRI findings have also been observed in the absence of clinical manganism in patients undergoing hemodialysis (da Silva et al. 2007) and after surgery to correct biliary atresia (Agarwal et al. 2008). Nevertheless, with these caveats in mind, several themes emerge.

Firstly, there is striking variability in the clinical presentation of manganism. The onset of symptoms from the time of exposure can vary from only a few months to over a decade within the same occupational cohort. Psychiatric symptoms are variably described, in some reports (such as those of Couper) they are not mentioned at all, whereas in later descriptions, they are prominent and early features. When present, psychiatric and neurological components are present in all phases of disease, with psychiatric symptoms dominating in earlier and neurological symptoms in later stages.

Secondly, although symptoms may overlap, manganism is a distinct entity from Parkinson's disease at many levels (Calne et al. 1994). Shared features include generalized rigidity and bradykinesia. However, unlike the festinating gait in Parkinson's disease, the gait abnormality of manganism is a cock-walk with an associated foot dystonia, such that patients walk on the balls of the feet with the heels elevated above the ground. Dystonia has also been documented in other locations, unlike Parkinson's disease. In manganism, tremor is less prominent, postural, of higher frequency and lower amplitude. Manganism patients are more prone to fall backward.

Thirdly, the differences extend beyond signs and symptoms. Manganism patients do not show a sustained response 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 Parkinson's disease. In primate studies of overexposure to manganese, the disease resembles manganism, not Parkinson's disease (Shinotoh et al. 1995). On the rare occasions when tissue was available from humans, pathological findings are also discordant (Yamada et al. 1986).

Fourthly, based on a small series of four cases from the Taiwanese cohort, the condition has been noted to progressively deteriorate for 10 years following removal from exposure, followed by a plateau in the second decade (Huang et al. 2007).

From Historical High Manganese Levels to Lifetime Exposure: An Alternative Situation

From the time of Couper's report, changes in exposure have taken place all over the world although differences persist between individual countries and among the developed and the developing regions. From high exposures for relatively short periods of time (mainly confined to the workplace), exposure to hazardous substances like manganese has progressively extended to the general environment outside the workplace, although at much lower levels. In occupational settings, airborne concentrations of manganese in inhalable particles were easily above a full-shift time-weighted average of 1 mg/m^3, considered as the minimum level able to cause manganism in susceptible individuals (WHO 1981). Today, the exposure levels are generally around a time-weighted average value of 200 $\mu g/m^3$ adopted by ACGIH® (2009) in most ferroalloy and mining operations (IEH/IOM 2004). In the general environment, outdoor manganese concentrations are approximately 40 ng/m^3 in urban areas (EPA 2003) but can

reach 300 ng/m^3 in the vicinity of sources such as ferro-alloy facilities, coke ovens, and power plants (WHO 2004).

Concern has also been raised regarding the content of manganese in drinking water and the associated neurobehavioral impairment in children (Wasserman et al. 2006; Wright et al. 2006; Bouchard et al. 2007). Manganese concentrations in Swedish groundwater used for drinking water are on average 150 ± 510 μg/l, with maximum values as high as 30,000 μg/l. Around 20% of the 12,000 sampled wells had manganese concentrations exceeding the Swedish recommended guideline value of 300 μg/l (Ljung and Vahter 2007). In urban areas of the United States, the median groundwater concentration of manganese was found to be 150 μg/l, with the 99th percentile at 5600 μg/l. In public water systems supplied by groundwater, approximately 3% of the 982 sampled sources exceed the U.S. health reference level of 300 μg/l (EPA 2003).

In addition to exposure intensity, health effects also depend on lifetime exposure duration, which is constantly increasing both due to increases in life expectancy and the proportion of life spent working. In addition, health effects depend upon exposure timing, the period of life *when* exposure occurs, especially when the nervous system is the target organ of toxicity (Grandjean and Landrigan 2006). The brain needs manganese during the early phases of development, as a constituent of important metalloenzymes such as arginase, glutamine synthetase, pyruvate carboxylase, and superoxide dismutase. Manganese exposure can start before birth from the maternal exposure through inhalation and ingestion of food items that may contain higher manganese concentration from environmental pollution. Therefore, excessive concentration of manganese may cause an overload that is potentially harmful for the fetus (Zota et al. 2009). Post-natal exposure can also be relevant due to a relatively high concentration of manganese in formulas (Aschner and Aschner 2005), with one small primate study reporting an association with differences in neurobehavioral outcomes (Golub et al. 2005). In order to provide manganese to the developing brain, the intestinal absorption of this element is high (Dörner et al. 1989), whereas the excretion rate is low due to the incomplete development of the biliary pathway, responsible for manganese elimination (Lönnerdal 1994). However, reassuring results were found in a recent study of 408 women living in an area of Bangladesh with elevated manganese in drinking water, urine, and blood, since corresponding elevations in breast milk were not observed (Ljung et al. 2009). According to the authors, elevated maternal manganese exposure does not necessarily lead to excessive exposure of breast-fed infants, stressing the importance of breast feeding in high manganese areas.

Manganese exposure can continue during childhood and adulthood from both environmental and occupational exposure. According to each life stage, different absorption routes and different potentials for increased exposure may occur, consistently during an entire lifetime or during discreet periods, leading to a final total body burden that may result in neurotoxicity. The concept of lifetime exposure is an important toxicological aspect to be considered for substances like manganese, which are characterized by a cumulative mechanism of action (Lucchini and Zimmerman 2009). Cumulative exposure can result in delayed, long-term toxicity.

According to the principle of "fetal programming" of the brain (Grandjean et al. 2007), prenatal exposure may be of concern for late-onset neurodegenerative effects. The occurrence of delayed effects can be explained by the different mechanisms of transport across the blood–brain barrier. A carrier-mediated brain influx and a diffusion-mediated efflux cause manganese overload in the brain with prolonged excessive exposure and prolonged very low-level exposure (Yokel, this issue).

Cumulative toxicity may also derive from contemporary exposure to multiple agents, a common scenario when manganese exposure may occur together with other known neurotoxicants such as pesticides and lead. According to the "multi-hit" hypothesis, the brain may compensate less efficiently when exposed to multiple neurotoxicants, leading to sustained and cumulative damage (Cory-Slechta 2005).

Taken together, this change in exposure scenario from occupational settings to the general environment represents an important background to be considered when approaching the relationship between current manganese exposure and the subsequent neurotoxic effects. Currently, overt, clinical manganism is a very rare event (Verschoor and Verschoor 2009; Konstantinova et al. 2009), while low-level prolonged manganese exposure remains of concern. Studies of toxicity implicating manganese should be interpreted with these considerations in mind. This is particularly related to inhaled manganese that can be transported directly to the brain through nasal deposition and transport along olfactory neurons (Dorman et al. 2002; Thompson et al. 2007), especially when transported by ultrafine particles, such as welding fumes (Elder et al. 2006). Changes in olfactory threshold and odor identification have been shown in manganese exposed workers (Antunes et al. 2007; Lucchini et al. 1997) and the same tests are recognized as predictive of Parkinson disease (Ponsen et al. 2009).

From Manganism to Manganese-Induced Parkinsonism: The Case of Welders

Manganese deposition takes place in the basal ganglia and the globus pallidus of the brain because of a selective

affinity for such neuromelanin-rich areas (Verity 1999). The deposition is facilitated by the Dopamine Transporter (DAT) (Anderson et al. 2007) and other manganese transporters such as the divalent metal transporter DMT-1 (Roth, this issue), and/or store-operated calcium channels (Yokel, this issue).

This small area is functionally responsible for the control of fine movements and mood state (Newland and Weiss 1992) and thus explains the neuropsychiatric features of classical manganism. The globus pallidus can be considered as the critical target organ for manganese according to a toxicological definition, meaning the site that reaches a critical dose and therefore a critical adverse effect, earlier than any other target organ (IUPAC 1993). Manganism occurs when the inhaled airborne concentration exceeds a threshold, corresponding to at least 1 mg/m^3 of manganese. The duration of exposure required to result in the critical dose to the globus pallidus is not clear and likely varies among individuals (WHO 1981).

As previously noted, the latency from the time of exposure to manganese to first clinical effects can vary from a few months to a decade. Therefore, although the concentration and duration of exposure to manganese are important, individual variability in susceptibility is also relevant. In the context of manganism, other areas of the basal ganglia such as the substantia nigra pars compacta, known to be affected in Parkinson's disease, are generally spared as shown by the post-mortem studies (Perl and Olanow 2007).

Concern about the potential for an additional manifestation of manganese neurotoxicity other than classical manganism was first raised by a study reporting that among 953 newly diagnosed cases of Parkinson's disease, the age at diagnosis was 17 years earlier in 15 career welders than non-welders (Racette et al. 2001). All other clinical features, such as a response to dopamine replacement, were the same between the two groups. Fluorodopa PET scans were available for two of the affected welders and were reported to show the abnormalities typical of Parkinson's disease. These findings extend beyond the concept of manganism as a condition distinct from Parkinson's disease.

Since then, several additional studies, both positive and negative with respect to an association between occupation as a welder and a risk for Parkinson's disease, have been published. One of the largest recent studies of mortality data on over 4 million men included 49,174 deaths attributed to Parkinson's disease (Stampfer 2009). Death certificates were abstracted and no information about exposure, types of welding or materials, respirator use, or engineering controls were available. No association with employment as a welder was seen nor was death as a result of Parkinson's disease observed more frequently in younger male welders. Nevertheless, this study has been criticized for using an insensitive diagnosis for Parkinson's disease, which may be too restrictive for manganese-related Parkinsonism. Other negative studies have been criticized for being based on hospitalization, which is not a common situation for Parkinsonian patients. Therefore, this topic remains controversial, also because of the "healthy worker effect" that may well reduce the incidence of neurodegenerative diseases in the active workforce.

In a recent review, given the strong likelihood that genetic background alters manganese pharmacokinetics and pharmacodynamics and an individual's response to manganese exposure, the incorporation of genetic susceptibility into the risk assessment for inhaled manganese has been recommended to resolve these opposing viewpoints (Curran et al. 2008). Regardless of the uncertainties, the issue of manganese-related Parkinsonism among welders has been important to raise the hypothesis that manganese neurotoxicity may not be limited only to the globus pallidus and the nigro-striatal area.

Parkinsonism in Populations Environmentally Exposed to Manganese

More recently, the hypothesis of an increased risk of Parkinsonian disturbances pointed out by manganese occupational studies (Gorell et al. 1999; Racette et al. 2001; Kim et al. 2002; Racette et al. 2005) has prompted new epidemiological research in environmentally exposed populations. A study was conducted in 1996 in the community of Sauda, Norway, where the world's largest ferroalloy plant was active until 1923. A total number of 15 Parkinson's cases were observed among 5,294 inhabitants, equivalent to a crude prevalence rate of 245.6/100,000 (Øygard et al. 1992), which is higher than the average rates of Scandinavian countries, where a crude rate of 25/100,000 was recently reported by Alves et al. (2009).

An epidemiological study investigated the risk of Parkinsonian disorders in the population of Toronto and Hamilton, Ontario, in relation with industrial emissions of manganese and the use of the organometallic compound formed from manganese, methylcyclopentadienyl manganese tricarbonyl (MMT) as fuel additive. Data sources were represented by physicians' diagnoses registered in the Ministry of Health administrative databases, 1992–1999, and prescriptions for L-Dopa containing medication. Subjects were mapped to residence and homes were assessed in relationship to distance from traffic, markers of traffic-generated air pollution and neighborhood levels of ambient manganese. Results have pointed out that in Hamilton, the odds ratio for a physician's diagnosis was 1.034 (1.00–1.07) per 0.01 mg/m^3 increase in manganese in total suspended particles. The estimate of "doubling exposure" for

a physician's diagnosis was about 0.15 mg/m^3 manganese in the ambient air. According to the authors, this study is consistent with the theory that exposure to manganese may add to the natural loss of neurons attributable to the aging process (Finkelstein and Jerrett 2007).

A third epidemiological observation was based on a study in the Italian province of Brescia, where the crude prevalence of Parkinsonism among the 903,997 residents was 296/100,000 and 407/100,000 when adjusted by age and gender (Lucchini et al. 2007a). The frequency increased to a standardized rate of 492/100,000 among the residents in the vicinity of ferroalloy plants located in Valcamonica, a pre-Alps valley in the North of the province, whereas the plant in the South part of the province had an open geographical setting. The data were also significantly higher compared to both the average crude Italian rate of 157.7/100,000 and the European from 108 to 257/100,000 (Von Campenhausen et al. 2005). The Standardized Morbidity Ratio calculated for Parkinsonism was significantly associated to the level of manganese in deposited dust sampled in the same area.

Taken together, the three community studies support the hypothesis that lifetime exposure to low manganese levels, starting from pre-natal to older age, may be a risk factor for Parkinsonism. Nevertheless, these studies cannot be considered as conclusive, especially because of the lack of genetic assessment, which may be important with possible gene–environment interaction that could explain the existing variability of health outcomes. Therefore, more epidemiological observations should be provided on this matter, considering also co-exposures to other known neurotoxicants for extrapyramidal functions such as pesticides. A number of epidemiological observations are supporting the role of manganese-based fungicides like MANEB and MANCOZEB in the onset of Parkinsonism in rural areas and among product applicators in agriculture (Costello et al. 2009). Unfortunately, none of these studies has assessed the possible role of manganese, although exposure to manganese is known to derive from the use of these products (Canossa et al. 1993). Interestingly, genetic variability in the DAT resulted in an interactive effect with occupational pesticide exposure in increasing the risk of Parkinson's disease (Ritz et al. 2009).

Manganese Neurotoxicity at High Acute Versus Low Chronic Exposure: What Are the Possible Mechanisms?

Taken together, current epidemiological observation indicates that manganism and manganese-related Parkinsonism may stand as two extreme conditions at the opposite sides

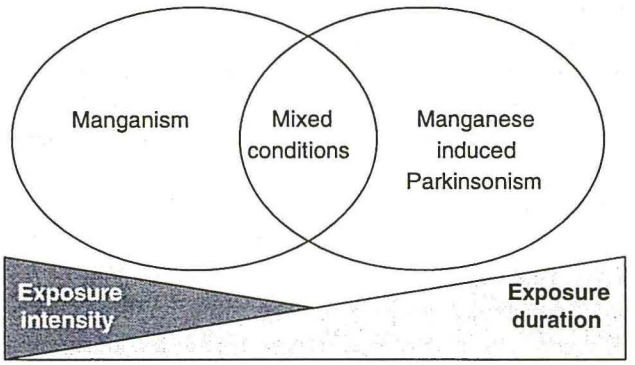

Fig. 1 Venn diagram showing the occurrence of manganism, manganese-induced Parkinsonism, and mixed conditions as a function of exposure intensity and exposure duration

of the interactions between the exposure intensity and the exposure duration. This can be represented by a Venn diagram (Fig. 1), where overlapping conditions are in between the two clinical entities, and with mixed condition observable in populations like the welders. In this context, the idea of a Parkinsonism "coincidentally" superimposed on manganese exposure (Kim et al. 1999b) would be an unlikely occurrence.

The exposure levels responsible for the two conditions of manganism and manganese-related Parkinsonism can be substantially different. As mentioned previously, manganism can occur at manganese airborne concentration above 1 mg/m^3 in inhalable particles (WHO 1981), whereas manganese-related Parkinsonism may occur after lifetime exposure to much lower exposure levels, possibly around 100 ng/m^3 of manganese in respirable particles (Lucchini et al. 2007a; Finkelstein and Jerrett 2007).

The different forms of manganese neurotoxicity likely recognize different underlying mechanism. Several interpretations have been proposed, but they are mostly derived by experimental models based on high exposure levels, equivalent to those able to induce manganism in humans (Gwiazda et al. 2007), and not suitable to reproduce chronic low levels in humans.

Several authors have pointed out that the sites involved in manganism, i.e. the globus pallidus, and Parkinsonism, i.e. the substantia nigra pars compacta, are closely interconnected with other components of the basal ganglia, such as the caudate and putamen, nucleus accumbens and subthalamic nucleus (Weiss 2006). These regions are functionally joined to each other by a complex neurochemical and anatomical network consisting of both excitatory and inhibitory pathways (Roth, this issue) (Fig. 2). Lifetime manganese exposure may affect both the globus pallidus and the subtantia nigra, because of the influx process occurring at very low doses and at relatively slow rate, and with an even slower efflux rate (Yokel, this issue) (Fig. 2).

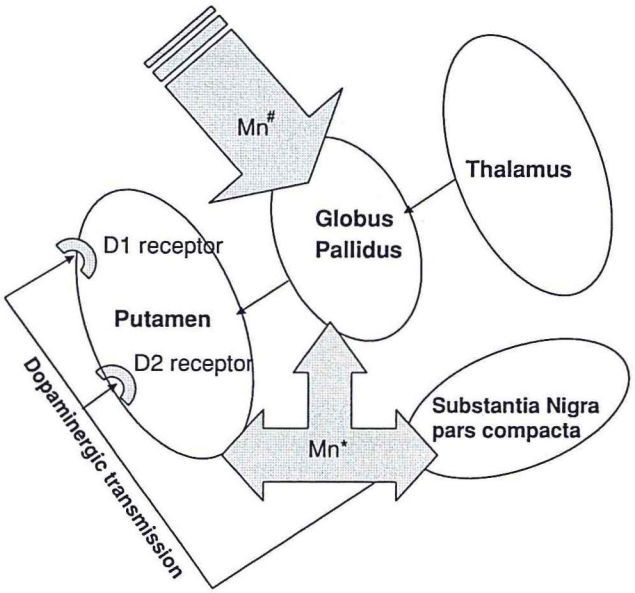

Fig. 2 Diagram showing specific brain regions where the manganism occurs ($Mn^{\#}$: Globus Pallidus) and those where the manganese-related Parkinsonism may occur (Mn*: putamen, Globus Pallidus, Substantia Nigra pars compacta)

In this way, manganese levels in the globus pallidus may not reach the critical concentration required to cause the critical effects of manganism, and the accumulation process may continue, involving all the other sites in the basal ganglia, including the substantia nigra pars compacta (Park et al. 2007).

Nevertheless, several aspects remain unclear. Manganese can cause dopamine auto-oxidation (Verity 1999), but manganese++ is an antioxidant able to inactivate the oxidative properties of dopamine. On the other hand, manganese toxicity in the globus pallidus is mainly directed to the GABAergic neurons (Gwiazda et al. 2007) and the mechanism of toxicity at the globus pallidus probably combines several simultaneous processes including influence on the glutamate transport (Roth, this issue). Selective injuries of the globus palidus result in a reduction of the dopaminergic neurons in the substantia nigra, mediated by an increased activity of the subthalamic nucleus, which is normally under tonic inhibition by the globus pallidus (Wright and Arbuthnott 2007). Future studies are needed to better characterize these interactions.

Individual Susceptibility Factors

Besides the mechanisms of direct toxicity in the basal ganglia, the importance of inter-individual variability is quite evident in all manganese exposure conditions. According to Roth (this issue), genetic mutations of two genes play an important role in rendering some individuals more at risk for Parkinsonism when chronically exposed to manganese. The ubiquitin E3 ligase parkin, which is associated with early onset of Parkinson's disease (Lesage and Brice 2009), can also protect from manganese toxicity (Higashi et al. 2004). A genetic interaction has also been observed between α-synuclein, an important protein for Parkinson's disease, and PARK9, a yeast-ortholog of the human gene ATP13A2, which is also important for Parkinson's disease. Yeast PARK9 protects the cells from manganese toxicity (Gitler et al. 2009). Mutations in these genes may be ultimately important for the expression of DMT1, therefore influencing the transport of manganese.

Other genetic markers of oxidative stress, susceptibility, and disease are suggested by Curran et al. (2008) together with the assessment of DNA methylation arrays. Although these techniques provide a global view of epigenetic changes, the differences in epigenomes across tissues may diminish the predictive power of changes observable in peripheral cells.

Interactions between manganese and iron have been pointed out as important for manganese absorption and transport across biological barriers (Roth and Garrick 2003; Roth, this issue). Anemic condition can increase the manganese uptake and should be considered as a potential cause of hypersensitivity to manganese exposure.

Another condition able to increase the risk of Parkinsonism in manganese-exposed individuals may be represented by sub-clinical impairment of liver function. Manganese is almost totally excreted via the biliary system, and therefore any impairment of this pathway is potentially able to cause manganese overload due to insufficient elimination from the body. This is well known in the case of cirrhotic patients showing manganese related abnormalities, where the "liver encephalopathy" may be partially explained by the excessive manganese in the brain (Rovira et al. 2008). Milder liver abnormalities may become highly important under conditions of lifetime manganese exposure. Compatible results were obtained by a further study on a targeted group of subjects selected from the Italian study of Valcamonica where environmental exposures to manganese are higher. A group of 65 patients and 52 controls from Valcamonica and 28 patients and 14 controls from Brescia (a region of lower manganese exposure) were examined for clinical and biochemical indicators and exposure biomarkers. After adjusting for age, gender, and illness duration, the clinical examination of the Parkinsonian patients resident in the manganese exposed areas showed a more severe phenotypic expression as examined at the Unified Parkinson's Disease Rating Scale testing, together with a more pronounced deterioration of cognitive function as expressed by the Mini Mental State, Token and Trial Making tests examination (Lucchini et al. 2007b).

The Parkinsonian patients resident in the exposed area showed also significantly higher serum levels of Cu, Cu/Zn, and AST/ALT ratios and lower serum Zn compared to Parkinsonian patients resident in other areas and to healthy controls from the same area. Within the Parkinsonian patients, Cu, Cu/Zn ratio, AST/ALT ratio, and the duration of illness correlated with the UDPRS scores. Manganese concentrations in blood and urine were higher among the residents in the exposed area and manganese in blood was associated with both AST/ALT ratio (Lucchini et al. 2008; Squitti et al. 2009) and serum cerulopasmin (Squitti, unpublished).

These observations point out a possible role played by sub-clinical liver impairment that may render manganese exposed individuals at higher risk for Parkinsonism. Inbalance of copper and zinc is also important in manganese exposure and was already observed in exposed workers (Li et al. 2004, 2005) and non-human primates (Guilarte and Chen 2007). These metals are both important in cellular redox reactions; therefore, a dysregulation of their homeostasis may potentiate the cellular damage resulting from reactive oxygen species. Ceruloplasmin was found to influence the disposition and neurotoxicity of manganese (Jursa and Smith 2009). Therefore, underlying impaired liver function likely influences the neurotoxicity of manganese through a number of pathways.

Summary

In conclusion, manganism is a medical condition that differs from Parkinson's disease according to clinical, pathological, and imaging parameters. The dynamic changes of exposure scenarios have led to different situations from the acute high exposure condition that was responsible for the occurrence of manganism to the chronic exposure to much lower levels of manganese is not likely to cause manganism. However, chronic exposure can progressively extend the site of deposition and toxicity from the globus pallidus to the entire area of the basal ganglia, including the substantia nigra pars compacta that is responsible for typical Parkinsonism.

Lifetime exposure to very low levels is now a more common condition, one that can start prenatally and may increase the risk of Parkinsonism in more sensitive subpopulations. This assumption is based on the cumulative mechanism of action of manganese that may entail delayed long-term manifestation of the clinical damage but also on co-exposures to other known neurotoxicants for extrapyramidal functions such as pesticides.

The mechanisms of manganese neurotoxicity at chronic exposure to very low levels are not sufficiently known, but promising information is based on the condition of susceptibility which may render individuals exposed to manganese at a higher risk for developing Parkinsonian disturbances. Such conditions include genetic mutations of genes that play important pathogenetic roles in both Parkinsonism and in the regulation of manganese transport and metabolism. Liver function is also important in manganese-related neurotoxicity and sub-clinical impairment may also increase the risk of Parkinsonism. Future research is needed to understand the development of manganism and the impact manganese exposure in the occupational and community settings.

Disclaimer The findings and conclusions of this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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