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Manganese exposure and neurotoxic effects in children

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ABSTRACT

Manganese (Mn) is the fifth most abundant metal on earth. Although it is a well understood essential trace element, in excess, Mn is neurotoxic. Initial toxic symptoms associated with Mn are of psychiatric nature and are clinically defined as *locura manganica*. Neurological signs of Mn toxicity include dystonia, progressive bradykinesia, and disturbance of gait, slurring, and stuttering of speech with diminished volume. Studies indicate that children who ingested Mn in the drinking water (WMn) at or above a level of 0.241 mg/L for a minimum of three years performed more poorly in school as measured by mastery of language, mathematics, and in their overall grade average. The Mn-exposed children also performed more poorly on a battery of neurobehavioral tests. It was also found a significant association between higher WMn and lower cognitive performance, verbal function, and full-scale intelligence quotient (IQ) scores. Young children appear to make up a vulnerable group in exposed populations. Toxicity of WMn is a problem particularly in areas of industrial waste or where Mn is leaching from the soil into public drinking water. Practical and cost-effective approaches are available to remove Mn from drinking water. It is crucial to protect developing brains against Mn toxicity.

1. Introduction

Manganese (Mn) is the fifth most abundant metal on earth. It is ubiquitous in the environment and is present in water, soil, air, and food. It is a well-established and well understood essential trace element for domestic animals and humans (Underwood, 1977; Hurley and Keen, 1987). Manganese is needed for proper fetal development and growth (Wood, 2009; Zota et al., 2009; Mistry and Williams, 2011) and is crucial throughout the life span of the mammalian organism. It serves as a necessary constituent of metalloproteins, including the mitochondrial enzymes, superoxide dismutase (SOD) and pyruvate carboxylase, the astrocyte-specific enzyme, and glutamine synthetase (GS) (Prohaska, 1987; Wedler, 1993; Aschner, 2000).

Manifest Mn deficiency diseases seem to be much more common in domestic animals than in humans, where overt diseases are extremely rare (Underwood, 1977; Hurley and Keen, 1987). However, there may exist segments of populations who suffer from subclinical Mn deficiency without clinical signs of deficiency, but with suboptimal Mn saturation of the mitochondrial SOD (Mn-SOD).

In non-occupationally exposed individuals, the major route of exposure to Mn is via food. More than 90% of the total dietary intake of Mn comes from plant foods, spices, and plant-derived beverages (Koivistoinen, 1980). The average intake of Mn is between 2 and 9 mg/day (for an average 70-kg person) (Aschner, 2000). Avocados, blueberries, nuts and seeds, seaweed, egg yolks, whole grains, legumes, dried peas, and green leafy vegetables are particularly rich in Mn, as is tea (Aschner, 2000). The Mn concentration in tea is very high (Koivistoinen, 1980), which may at least partly be explained by the growth of tea plants on acid soils, where the Mn/calcium (Ca) and Mn/magnesium (Mg) ratios have significantly increased in recent years, compared to the basic bedrock composition, resulting from excessive chemical weathering. The tea intake appears to account for a greater daily intake of Mn in Great Britain than in the United States (8.8 vs. 2.5–4 mg Mn/day, respectively, in average) (Aschner, 2000). Tobacco smoke also plays a role as a source of Mn, because of high Mn concentrations in all green leaves (Koivistoinen, 1980), and a presumably high Mn absorption in the lungs. Thus when Mn exposure occurs in the workplace, inhalation is the primary mode of uptake (Lucchini et al., 2015). Mothers who smoke have been shown to have reduced Mn concentrations in umbilical cord blood (Jones et al., 2010; Mistry and Williams, 2011).

Although only a small fraction of Mn is distributed to the brain (Cotzias et al., 1968), the brain is the critical organ in cases of excess of

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Mn. Manganese readily crosses the blood-brain barrier (BBB) in the developing fetus and the neonate, and also in the mature mammal (Mena et al., 1974; Aschner and Aschner, 1990; Lucchini et al., 2015). Seizure activity, a hallmark of Mn deficiency, is believed to result from decreased Mn-SOD activity (Critchfield et al., 1993), whereas excessive exposure to Mn also demonstrates a close relationship with central nervous system (CNS) disorders as it is characterized by marked psychological and neurological abnormalities. High exposure to Mn during pregnancy may have toxic effects on the developing fetus (Wood, 2009). Increased MnSOD messenger RNA (mRNA) expression has been found in fetal membranes of women with preterm labor (Than et al., 2009).

Initial symptoms on the neurotoxicity of Mn are of psychiatric nature and are clinically defined (Hurley and Keen, 1987; Lucchini et al., 2015). These so-called *locura manganica* symptoms closely resemble those encountered in people with schizophrenia, including emotional instability, violent or compulsive behavior, and hallucinations. Neurological effects most often start 1–2 months after the presentation of the psychiatric behaviors. The neurological signs include progressive bradykinesia, dystonia, and disturbance of gait. The facial expression is somewhat fixed, and speech difficulties are frequently observed. Over time, individuals progressively develop slurring and stuttering of speech with diminished volume as their voices become monotonous and sink to a whisper. The speech is slow and irregular, at times with a stammer. The clinical picture with dystonia closely resembles several other disorders known collectively as extrapyramidal motor system dysfunction and, in particular, Parkinson's disease (Barbeau et al., 1976; Barbeau, 1984; Calne et al., 1994). At the cellular level, the disorder is associated with increased concentrations of Mn, primarily in CNS regions with high concentrations of non-heme iron (Fe). These areas comprise the subthalamic nuclei, caudate-putamen, substantia nigra, and globus pallidus (Eriksson et al., 1992; Calne et al., 1994; Komura and Sakamoto, 1994). A pallidal index based on Mn-induced signal intensity from the pallidal region in T1-weighed magnetic resonance images (MRI) has been introduced to characterize and describe the cerebral Mn accumulation (Krieger et al., 1995; Kim, 2006). However, in contrast to idiopathic Parkinson's disease, Mn intoxication appears to be associated with preservation of the nigrostriatal dopaminergic pathway despite clinical evidence of Parkinsonian-like deficits (Calne et al., 1994). Further research by neuroimaging is recommended to clarify whether Mn damage in some cases can also extend to the nigrostriatal pathway, as suggested by Racette et al. (2005). In contrast to genuine Parkinson's disease, Lewy bodies are unusual findings in the substantia nigra in manganism (Calne et al., 1994). Advanced manganism appears to happen only in occupational settings with exposure leading to inhalation of large quantities of Mn-rich dust particles, e.g. among workers in Mn mines (Lucchini et al., 2015).

Manganese poisoning in humans caused by high dietary intake is a disease that is insufficiently described, although it presumably occurs as a consequence of substantial over-consumption of Mn as a dietary supplement. In particular, infants can ingest more than the safe and adequate levels of 0.5–1 mg/day for these age groups because of relatively high Mn levels in prepared infants food (Lönnerdal, 1997). Contamination with Mn of public water supplies has long been regarded as posing a toxicological threat to public health. However, in 2011 the World Health Organization (WHO) considered the hazard of Mn overload in the public water supply (drinking water (WMn)) relatively low, and they discontinued the guidelines for the maximum allowable Mn in drinking water (WMn < 400 μg/L) (WHO, 2011; Frisbie et al., 2012). Because “this health-based value is well above concentrations of Mn normally found in drinking water, it is not considered necessary to derive a formal guideline value,” WHO concluded. However, recent studies particularly on developing individuals, indicate that this stance needs to be revisited. The aim of the present review is to summarize research indicating that the WHO threshold guideline was too high to protect against undesired effects in children.

2. Cognitive effects

Studies by He et al. (1994) and Zhang et al. (1995) indicate that children who ingested Mn in the drinking water (≥0.241 mg/L) for a minimum of three years performed more poorly in school as measured by mastery in Chinese, mathematics performance, and in their overall grade average, as compared to non-exposed individuals. The Mn-exposed children also performed more poorly on a battery of neurobehavioral tests. Manganese exposure levels in these students were determined by hair analysis. It is noteworthy that no reference was made in the study (Zhang et al., 1995) to levels of lead (Pb) and mercury (Hg) in the hair, and it is unclear if these or perhaps other xenobiotics in the drinking water may have contributed to the differences in the tests.

Bouchard et al. (2011) studied the relationship between decreased intelligence quotient (IQ) in children and exposure to Mn in public drinking water. The researchers measured the content of Mn both in the drinking water and in the hair of 362 children (hair manganese (HMn)), aged 6–13 years, residing in an area with a specified gradient of WMn. The relationship between IQ score and WMn in a model adjusted for family income, maternal intelligence, and other confounders, demonstrated that elevated WMn was closely related to decreased achievement as well as lower verbal, and full-scale IQ scores. The difference was 6.2 IQ points between subjects in the lowest and highest WMn quintiles. Likewise, higher HMn in the adjusted analysis was associated with lower full-scale IQ scores. It was fond a significant statistical association between Mn in drinking water and HMn. Menezes-Filho et al. (2011) studied the relationship between hair (HMn) and blood manganese (BMn) and blood lead (BPb), with children's IQ. Their study population encompassed 83 children aged 6–12 years, who lived close to a ferromanganese plant in Brazil. Their main findings were that subject's HMn was inversely related to verbal as well as to total IQ scores.

Wasserman et al. (2011) measured the effect of Mn and arsenic (As) exposure on children's intelligence performance. The subject population was comprised of 299 children aged 8–11 years in Bangladesh. This is a nation with high concentrations of As and Mn in well water, which is used for drinking water. The study design stratified both As and Mn concentration levels in public drinking water, and the results indicated that BMn and As in the blood (BAs) were negatively and significantly associated with the scores in Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) when adjusted for each variable. Further adjustments of ferritin and sociodemographic variables revealed an opposite relationship between BMn and the subscales for working memory and perceptual reasoning relative to WISC.

Other investigators considered the potential effects of Mn exposure on children's academic performance in another study in Bangladesh (Khan et al., 2012). This study investigated a subject population of 840 children, 8–11 years of age, and collected data from well water samples from each family home. Their study utilized urinary As (UAs) measurements as independent variable versus academic achievement in the three subject areas of Bangla, English, and Mathematics. Their results showed a significant inverse relationship between WMn and mathematics scores in an adjusted model. Also, they reported an insignificant relationship between WMn and language scores. The biomarkers of As (UAs and As in the drinking water (WAs)) indicated no significant associations to the three test scores in this population.

Meanwhile, Claus Henn et al. (2012) studied the possible association in neurodevelopmental delays and Mn-Pb interaction in early childhood. This study included 455 Mexican children. The Spanish version of the Bayley Scales of Infant Development, 2nd Edition (BSID-IIS) was used to assess the children's development every six months from they were 12–36 months old. The researchers also assessed Pb