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Environmental exposure to manganese in air: Associations with cognitive functions

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A B S T R A C T

Manganese (Mn), an essential element, can be neurotoxic in high doses. This cross-sectional study explored the cognitive function of adults residing in two towns (Marietta and East Liverpool, Ohio, USA) identified as having high levels of environmental airborne Mn from industrial sources.

Air-Mn site surface emissions method modeling for total suspended particulate (TSP) ranged from 0.03 to 1.61 $\mu g/m^3$ in Marietta and 0.01–6.32 $\mu g/m^3$ in East Liverpool. A comprehensive screening test battery of cognitive function, including the domains of abstract thinking, attention/concentration, executive function and memory was administered. The mean age of the participants was 56 years ($\pm$10.8 years). Participants were mostly female (59.1) and primarily white (94.6%). Significant relationships ($p < 0.05$) were found between Mn exposure and performance on working and visuospatial memory (e.g., Rey-O Immediate $\beta = -0.19$, Rey-O Delayed $\beta = -0.16$) and verbal skills (e.g., Similarities $\beta = -0.19$).

Using extensive cognitive testing and computer modeling of 10-plus years of measured air monitoring data, this study suggests that long-term environmental exposure to high levels of air-Mn, the exposure metric of this paper, may result in mild deficits of cognitive function in adult populations.

1. Introduction

1.1. Brief overview on manganese and environmental studies

Manganese (Mn) is an essential element for healthy human functioning, especially for bone health and fat and carbohydrate metabolism (Ehrlich, 2013). However, with overexposure, manganese may be neurotoxic to humans.

Manganese is a byproduct of some industrial processes and is released into the air, soil, and water. Environmental studies have most often included rural and suburban populations living close to industries (Bowler et al., 2011; Menezes-Filho et al., 2011; Mergler et al., 1999; Haynes et al., 2010; Lucchini et al., 2014; Viana et al., 2014), and rural populations exposed through contaminated well water (Khan et al., 2012; Wasserman et al., 2006).

The prominent pathophysiological manifestations of Mn inhalation overexposure in humans are encephalopathy and basal ganglia disturbance (Feldman, 1999). This condition clinically resembles Parkinson's Disease (PD), but responds poorly to dopaminergic medications and typically has an earlier onset of cognitive dysfunction than PD (Feldman, 1999).

The recent use of neuroimaging in studying the effects of Mn on the brain has demonstrated increased T_1 signal intensity (Kim et al., 1999, 2007; Kim, 2004; Shin et al., 2007; Chang et al., 2010a,b,c; Criswell et al., 2011). After high exposure to Mn, higher T_1-weighted signal intensities have been observed in the substantia nigra, globus pallidus, caudate nucleus, red nucleus, and the frontal lobes (Long et al., 2014; Chang et al., 2010c). These localized hyperintensities have been associated with mood, motor

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and tremor disturbances, and also with cognitive deficits (Chang et al., 2010a,b; Long et al., 2014; Kim et al., 1999).

1.2. Published studies of Mn and cognitive effects

1.2.1. Cognitive effects in children using neuropsychological testing

The large majority of studies in the literature that focus on environmental Mn exposure and neuropsychological effects are in children (Wasserman et al., 2006, 2011; Wright et al., 2006; Kim et al., 2009; Riojas-Rodríguez et al., 2010; Bouchard et al., 2011; Menezes-Filho et al., 2011; Khan et al., 2012; Torres-Agustín et al., 2013; He et al., 1994; Lucchini et al., 2012; Haynes et al., 2010, 2012, 2015). These studies have reported decreased verbal, performance, and intellectual ability associated with level of Mn exposure using Mn in hair or blood as a biomarker. Two of these studies investigated the effect of environmental Mn exposure with co-exposure to lead (Pb) (Kim et al., 2009) and arsenic (As) (Wasserman et al., 2011) and found adverse effects on cognitive function from neurotoxicant exposure from air and water. The primary association was with Mn and As, but not Pb. Wright et al. (2006) and Torres-Agustín et al. (2013) reported negative associations between Mn exposure and scores on tests of verbal learning and memory. In a study of children living in a rural village using irrigation and drinking water with highMn content, children from the exposed village had lower scores on tests of attention and concentration, working memory, and visual memory compared to children living in an unexposed village (He et al., 1994). Recently, Haynes et al. (2015) reported associations between hair and blood Mn and both full scale and subscale IQ scores in children from the same Ohio towns as the current study. Because children's brains are developing, they may be more vulnerable than adults (Zoni and Lucchini, 2013).

1.2.2. Few environmental studies for adults using neuropsychological testing

Although Mn effects in exposed workers have been studied frequently with tests of motor function, including tremor, formal neuropsychological testing has been somewhat infrequent. In a sequence of studies of welders, deficits in attention and concentration, memory, visuospatial function, verbal learning, executive and other cognitive functions were reported, and a dose-effect relationship was found between cognitive function and Mn in blood (Bowler et al., 2007; Antunes et al., 2007; Park et al., 2006; Roels et al., 2012). In these occupational Mn exposure studies, where Mn is typically higher than in environmental settings, well-normed standardized tests were also used, including verbal and performance tests (Bowler and Lezak, 2015).

Environmental studies have examined the effects of exposure to Mn in adults by primarily evaluating motor function and tremor symptoms (Kim et al., 2011; Solís-Vivanco et al., 2009; Rodriquez-Agudelo et al., 2006; Baldwin et al., 1999; Beuter et al., 1999; Bowler et al., 1999; Mergler et al., 1999). Most of these studies did not assess cognitive function.

One of the early community studies examining environmental Mn exposures in Quebec (Mergler et al., 1999) used tests of cognitive function. An association between Mn exposure and verbal learning, as well as attention, was reported. Canadian women with higher Mn blood levels had lower scores on a test of visual memory and lower scores on recall of Digit Span forward. For men in the same sample, higher Mn blood levels were associated with poor initial learning and recall of both visual and verbal test scores.

Santos-Burgoa et al. (2001) conducted a pilot study of Mexican residents in two rural mining communities. Mn content in outdoor and indoor air, river water, well water, food, indoor dust, and blood was assessed. These authors assessed cognitive function and found that low-level cognitive function on the Mini Mental State Examination (MMSE) was associated with higher blood Mn levels. Also working in Mexico, Solis-Vivanco et al. (2009) used Digit Span recall and reported an association between Mn levels and poor performance on these tests, including a negative association between Mn levels in air at a participant's residence and Digit Span recall. Menezes-Filho et al. (2011) conducted a study of mothers and children in Brazil and found that Mn in hair was negatively associated with the scores on Raven's Progressive Matrices, a measure of nonverbal cognitive ability and abstract reasoning (Raven and Court, 1995), among mothers exposed to Mn in the environment from a ferro-manganese alloy plant. Two of these published papers contain analyses of data, collected as part of a larger study in a mining district in Mexico, which may be of concern regarding generalizability given the age, low education level and low socioeconomic status of the participants (Riojas-Rodríguez et al., 2010; Solís-Vivanco et al., 2009).

A recent study by Viana et al. (2014) investigated the neuropsychological effects of environmental Mn exposure from industrial emissions in an adult population from Brazil. They found an association between Mn in hair and fingernail concentrations and tests of visual working memory, as well as tests designed to measure intelligence.

1.3. Objectives

With few reports available from environmental epidemiologic studies of Mn exposed adults, the current study examined Mn exposed adult residents of two Ohio, USA, towns (East Liverpool and Marietta). Both towns have previously been identified as having high levels of air-Mn from industrial sources (ATSDR, 2007, 2009, 2010). The objectives of this study are to (1) evaluate cognitive function and to (2) determine whether Mn exposure through long-term inhalation is associated with cognitive dysfunction.

2. Methods

2.1. Study design and participant selection

A cross-sectional study design was used to examine the potential effects of exposure to air-Mn from industrial sources on the cognitive function of residents of two exposed towns. This approach was made possible by the availability of residents living near a ferromanganese smelter and an open-air Mn storage and packaging facility. In the present study, the data from both exposed towns were combined to achieve greater statistical power.

The recruitment and selection of participants from Marietta are described in detail by Bowler et al. (2012) and Kim et al. (2011). Similar recruitment procedures were followed in East Liverpool. The recruitment zone in Marietta was within 12 miles from the emission source. Due to the larger particle size and reduced dispersion range of the Mn emissions in East Liverpool, the participant recruitment zone in East Liverpool was limited to two air-miles downwind of the emissions site.

Based on power analyses, the goal was to recruit 100 participants from each town. Because Ohio has areas with naturally occurring Mn and iron in groundwater, only households served by public water companies, which are required to reduce Mn and iron levels to national secondary maximum contaminant levels, were eligible for participation (Bowler et al., 2012). For Marietta residents, a random sample of parcels was drawn from December 2008 property tax records within the ZIP code of the pre-defined Mn exposure zone of 0.04 $\mu g/m^3$ or higher. In East Liverpool, a sample of single family units, multifamily units, and trailer addresses located within two air-miles west-northwest of the S.H. Bell Stateline facility was purchased from a commercial