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Associations among environmental exposure to manganese, neuropsychological performance, oxidative damage and kidney biomarkers in children

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ABSTRACT

Environmental exposure to manganese (Mn) results in several toxic effects, mainly neurotoxicity. This study investigated associations among Mn exposure, neuropsychological performance, biomarkers of oxidative damage and early kidney dysfunction in children aged 6–12 years old. Sixty-three children were enrolled in this study, being 43 from a rural area and 20 from an urban area. Manganese was quantified in blood (B-Mn), hair (H-Mn) and drinking water using inductively coupled plasma mass spectrometry (ICP-MS). The neuropsychological functions assessed were attention, perception, working memory, phonological awareness and executive functions – inhibition. The Intelligence quotient (IQ) was also evaluated. The biomarkers malondialdehyde (MDA), protein carbonyls (PCO), δ-aminolevulinate dehydratase (ALA-D), reactivation indexes with dithiothreitol (ALA-RE/DTT) and $ZnCl_2$ (ALA-RE/$ZnCl_2$), non-protein thiol groups, as well as microalbuminuria (mALB) level and N-acetyl-β-D-glucosaminidase (NAG) activity were assessed. The results demonstrated that Mn levels in blood, hair and drinking water were higher in rural children than in urban children ($p<0.01$). Adjusted for potential confounding factors, IQ, age, gender and parents' education, significant associations were observed mainly between B-Mn and visual attention ($\beta=0.649$; $p<0.001$). Moreover, B-Mn was negatively associated with visual perception and phonological awareness. H-Mn was inversely associated with working memory, and Mn levels from drinking water with written language and executive functions – inhibition. Rural children showed a significant increase in oxidative damage to proteins and lipids, as well as alteration in kidney function biomarkers ($p<0.05$). Moreover, significant associations were found between B-Mn, H-Mn and Mn levels in drinking water and biomarkers of oxidative damage and kidney function, besides between some oxidative stress biomarkers and neuropsychological tasks ($p<0.05$). The findings of this study suggest an important association between environmental exposure to Mn and toxic effects on neuropsychological function, oxidative damage and kidney function in children.

1. Introduction

Manganese (Mn) is a naturally occurring element found in the environment, being a normal constituent of air, water, soil and food (ATSDR, 2012). The primary source of Mn exposure in the general population is the diet (nuts, grains, fruits, tea, vegetables, infant formulas, and some meat and fish) (EPA, 2003).

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Furthermore, additional Mn can be found in the environment after release from the manufacture, use, and disposal of manganese-based products (ATSDR, 2012). Mn is used in a wide variety of products including paints, dry-cell batteries, cosmetics, disinfectants, gasoline anti-knock additives, and in the composition of two extensively applied agricultural fungicides – maneb and mancozeb (ATSDR, 2012; Farina et al., 2013; Sanders et al., 2015). Therefore, excess exposure may occurs from elevated Mn levels in drinking water or in air as a result of anthropogenic sources from industrial, welding, mining, and agricultural activities (Sanders et al., 2015).

Annually, 2.5 million tons of pesticides are used in the world, and 130,000 t of them are consumed by Brazil, being one the major consumers of pesticides. This consume varies in the different regions of Brazil. The Southern region consumes 31% of the pesticides, where several traditional and intensive agricultural activities are performed (EMBRAPA, 2015). Dithiocarbamates are pesticides widely used around the world, including Brazil, where some compounds are registered by the Agência Nacional de Vigilância Sanitária (ANVISA), such as mancozeb (ANVISA, 2015; Caldas et al., 2006). Mancozeb is an ethylene bisdithiocarbamate (EBDC) fungicide containing approximately 20% manganese by weight, which represent a potential source of exposure to Mn to human (Mora et al., 2014).

Manganese, an essential metal required for a variety of physiological processes in the human organism, is neurotoxic at high concentrations (Aschner et al., 2007). Chronic Mn exposure from occupational and environmental sources is associated with a range of neurologic health effects (Khan et al., 2011). Several studies have reported that high Mn concentrations in blood and hair from children is associated with lower scores in IQ tests (Wright et al., 2006; Kim et al., 2009; Riojas-Rodríguez et al., 2010; Bouchard et al., 2011; Menezes-Filho et al., 2011; Betancourt et al., 2015). Moreover, Mn exposure in childhood has been associated with lower cognitive function scores, such as memory and learning disorders (Torres-Agustín et al., 2013), attention and non-verbal memory deficits (Takser et al., 2003), and lower performance in executive function of verbal working memory tests (Carvalho et al., 2014), besides behavioral problems (Bouchard et al., 2007; Menezes-Filho et al., 2014). Furthermore, there are growing evidences that Mn exposure from drinking water leads to adverse neurologic effects in children (Khan et al., 2011; Bouchard et al., 2011; Wasserman et al., 2007, 2011; Khan et al., 2012; Oulhote et al., 2014a).

Currently, there is no consensus regarding to the best biomarker of exposure to Mn (Bouchard et al., 2011; Gunier et al., 2014). Blood is one of the most common samples used for biomonitoring metal exposure (Molina-Villalba et al., 2015). Hair Mn has been used in epidemiological studies, since reflects environmental exposures (Gunier et al., 2014). In addition, hair is considered a promise as a biomarker of metal exposure in studies with children because is a simple and noninvasive sample (Kordas et al., 2010). Besides, this sample is an attractive choice for environmental health studies since metal cations bind to the sulfur atoms of the keratin present in hair, representing exposure over several months (Kordas et al., 2010; Molina-Villalba et al., 2015). Therefore, in contrast to blood concentrations that reflect recent exposures, hair levels reflect long-term exposure (Kordas et al., 2010).

At physiological levels, Mn protects against oxidative stress (OS), however the excessive Mn accumulation enhances OS (Komatsu et al., 2009) because high Mn levels itself acts as an oxidant (Roels et al., 2012). Therefore, OS is reported as a contributing mechanism by which Mn can be a neurotoxic compound, potentially via oxidation of dopamine and other catecholamines (Erikson et al., 2004). Dopamine oxidation in the brain by Mn has been associated with oxidation of thiol (–SH) groups in important biological molecules. Subsequently, this oxidation can lead, for example, to inhibition of some sulphydryl-containing enzymes as the δ-aminolevulinate dehydratase (ALA-D), an enzyme involved in the heme biosynthesis pathway, whose –SH groups are essential for their optimal activity. Given its sensitivity to cellular redox status, this enzyme has been commonly used as a biomarker of effect in metal exposures (Avila et al., 2008).

Moreover, ALA-D has been suggested as a marker for OS due to high sensitivity to –SH oxidation by pro-oxidant elements (Valentini et al., 2007; Avila et al., 2008). Additionally, ALA-D inhibition results in the accumulation of the substrate δ-aminolevulinic acid (ALA), a pro-oxidant and neurotoxic compound (Rocha et al., 2012). However, the exact mechanism of neurotoxicity is still controversial (Baierle et al., 2014). The brain is especially susceptible to OS due to particular factors that can lead to increase in production of reactive oxygen species (ROS) such as its high oxygen consumption, high concentration of polyunsaturated fatty acids that are highly vulnerable to lipid peroxidation, and low antioxidant levels in relation to other organs (Brucker et al., 2013; Baierle et al., 2014). The measurement of OS biomarkers in peripheral blood samples may reflect what is occurring in brain (Liu et al., 2004).

The major objectives of this study were to characterize Mn exposures in both rural and urban children and find the correlations between different exposure markers of Mn in these two groups of children. Furthermore, we also examined the associations between Mn exposure and a set of neuropsychological functions in the children after accounting for potential confounders. An additional objective of this study was to explore the oxidative damage and kidney function biomarkers among the participants and its possible association with Mn exposure. Recently, we reported elevated Mn levels in hair of children living in a rural area of Southern Brazil (Nascimento et al., 2015); and its concentrations were significantly associated with IQ deficits. However, this previous study was performed in a period before pesticide application. In this line, the collection of the samples from children in the current study was performed in a period after pesticide application in this rural area.

2. Material and methods

2.1. Study population

School children from two different areas of central region of Rio Grande do Sul, Southern Brazil, were enrolled in this study. The school principals had greater contact with children, thus they helped us with a formal invitation for all children aged 6–12 years old, since the neuropsychological tests are appropriate for this age range. A total of 90 children from the rural and urban area fulfilled the inclusion criteria. Of these, the parents of 66 (73%) consented with the participation of their children in the study. Three children were excluded because they refused to provide biological samples. The final study population was composed of 63 children, 70% of all children invited to participate. The first group consisted of 43 children from a rural area (rural children), where the main agricultural activities were tobacco and rice cultures, and the second group was composed by 20 children from an urban area regarded as a college town (urban children) about 70 km far from the rural area. In the rural area, biological samples collection was performed after the period of pesticides application in order to evaluate the potential influence of environmental Mn contamination on children's health, after the use of these chemical products.

All parents provided written consent, and answered a questionnaire to assess general children's health, lifestyle and parents' education data. The study was approved by the Research Ethics