Environment International 84 (2015) 39–54

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Prenatal and postnatal manganese teeth levels and neurodevelopment at 7, 9, and 10.5 years in the CHAMACOS cohort

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ARTICLE INFO

Article history:
Received 22 April 2015
Received in revised form 16 June 2015
Accepted 5 July 2015
Available online xxxx

Keywords:
Manganese
Teeth
Neurodevelopment
Children
California

ABSTRACT

Background: Numerous cross-sectional studies of school-age children have observed that exposure to manganese (Mn) adversely affects neurodevelopment. However, few prospective studies have looked at the effects of both prenatal and postnatal Mn exposure on child neurodevelopment.
Methods: We measured Mn levels in prenatal and early postnatal dentine of shed teeth and examined their association with behavior, cognition, memory, and motor functioning in 248 children aged 7, 9, and/or 10.5 years living near agricultural fields treated with Mn-containing fungicides in California. We used generalized linear models and generalized additive models to test for linear and nonlinear associations, and generalized estimating equation models to assess longitudinal effects.
Results: We observed that higher prenatal and early postnatal Mn levels in dentine of deciduous teeth were adversely associated with behavioral outcomes, namely internalizing, externalizing, and hyperactivity problems, in boys and girls at 7 and 10.5 years. In contrast, higher Mn levels in prenatal and postnatal dentine were associated with better memory abilities at ages 9 and 10.5, and better cognitive and motor outcomes at ages 7 and 10.5 years, among boys only. Higher prenatal dentine Mn levels were also associated with poorer visuospatial memory outcomes at 9 years and worse cognitive scores at 7 and 10.5 years in children with higher prenatal lead levels (≥0.8 μg/dL). All these associations were linear and were consistent with findings from longitudinal analyses.
Conclusions: We observed that higher prenatal and early postnatal Mn levels measured in dentine of deciduous teeth, a novel biomarker that provides reliable information on the developmental timing of exposures to Mn, were associated with poorer behavioral outcomes in school-age boys and girls and better motor function, memory, and/or cognitive abilities in school-age boys. Additional research is needed to understand the inconsistencies in the neurodevelopmental findings across studies and the degree to which differences may be associated with different Mn exposure pathways and biomarkers.

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; AUC, Area Under the Curve; BASC-2, Behavior Assessment Scale for Children, 2nd edition; CADS, Conners' ADHD/DSM-IV Scales, Parent and Teacher versions; CAVLT-2, Children's Auditory Verbal Learning Test, 2nd edition; CES-D, Center for Epidemiologic Studies Depression Scale; CHAM1, Initial CHAMACOS cohort (recruited 1999–2000 during pregnancy); CHAM2, Second CHAMACOS cohort (recruited 2009–2011 at child age 9); CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, Confidence Interval; CPT-II, Conners' Continuous Performance Test II, Version 5; DAP, Dialkyl Phosphate; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; GEE, Generalized Estimating Equations; GM, Geometric Mean; HOME, Home Observation for Measurement of the Environment; IQ, Intelligence Quotient; LOD, Limit of Detection; Mn, Manganese; NEPSY-II, A Developmental Neuropsychological Assessment, 2nd edition; OP, Organophosphate; PBDE, Polybrominated Diphenyl Ether; PPVT, Peabody Picture Vocabulary Test; TVIP, Test de Vocabulario en Imágenes Peabody; SD, Standard Deviation; SE, Standard Error; WISC-IV, Wechsler Intelligence Scale for Children, 4th edition; WRAVMA, Wide Range Assessment of Visual Motor Ability.

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http://dx.doi.org/10.1016/j.envint.2015.07.009
0160-4120/

1. Introduction

Manganese (Mn) is an essential element involved in important enzymatic reactions (Aschner, 2000; Gwiazda et al., 2002), but in excess, it is a potent neurotoxicant (Menezes-Filho et al., 2009a; Mergler and Baldwin, 1997; Roels et al., 2012). Food is the main source of Mn for the general population (ATDSR, 2012), but environmental exposure to Mn can occur from water naturally high in Mn or contaminated by industrial waste (Bouchard et al., 2007; Bouchard et al., 2011b; He et al., 1994; Kondakis et al., 1989), combustion of anti-knock additives in gasoline (Zayed et al., 1999), Mn mining operations (Riojas-Rodriguez et al., 2010), ferromanganese production facilities (Haynes et al., 2010; Menezes-Filho et al., 2009b), and spraying of Mn-containing fungicides (Gunier et al., 2013; Mora et al., 2014). Absorption and distribution of ingested Mn are closely regulated through homeostatic mechanisms (Papavasiliou et al., 1966; Roth, 2006). However, inhaled Mn can directly enter the systemic circulation through the lungs (Vitarella et al., 2000) and access the brain directly through the olfactory bulb (Dorman et al., 2002; Elder et al., 2006; Leavens et al., 2007), bypassing biliary excretion mechanisms.

Children and infants may be particularly susceptible to the neurotoxic effects of Mn exposure as their Mn homeostatic mechanisms are poorly developed (Aschner, 2000; Ljung and Vahter, 2007; Yoon et al., 2009) and Mn can enter their developing brains by crossing the blood–brain barrier (Aschner, 2000; Aschner and Dorman, 2006). Multiple studies have reported associations between exposure to Mn and neurodevelopmental problems in children. Higher in utero Mn levels measured in blood and teeth have been associated with attention problems (Ericson et al., 2007; Takser et al., 2003), behavioral disinhibition (Ericson et al., 2007), impaired non-verbal memory (Takser et al., 2003), and poor cognitive and language development (Lin et al., 2013) in toddlers and preschoolers, and with externalizing behavior and attention problems (Ericson et al., 2007) in school-aged children. Postnatal Mn exposure has been associated with poor language development in toddler boys (Rink et al., 2014), and behavioral problems in school-aged boys and girls (Ericson et al., 2007). Studies of school-aged children and adolescents (6–14 year olds) have linked elevated Mn levels in drinking water, blood, and hair samples with oppositional behavior and hyperactivity (Bouchard et al., 2007), impaired cognitive abilities (Bouchard et al., 2011b; Kim et al., 2009; Menezes-Filho et al., 2011; Riojas-Rodriguez et al., 2010; Wasserman et al., 2006), and poor memory (He et al., 1994; Torres-Agustin et al., 2013), motor coordination (He et al., 1994; Hernandez-Bonilla et al., 2011; Lucchini et al., 2012), and visuoperceptive speed (He et al., 1994; Zhang et al., 1995). To date, only one epidemiologic study has assessed exposure to Mn both prenatally and postnatally (Ericson et al., 2007).

Blood Mn has typically been used as a biomarker of exposure to Mn in occupational and population-based studies of adults and children (Mergler et al., 1999; Takser et al., 2003), while studies in environmentally-exposed children have also measured Mn levels in hair (Bouchard et al., 2007; Bouchard et al., 2011b; Eastman et al., 2013; Menezes-Filho et al., 2011; Riojas-Rodriguez et al., 2010; Wright et al., 2006), in the exposure medium (e.g., water) (Bouchard et al., 2011b; Khan et al., 2012; Wasserman et al., 2006), or in teeth (Arora et al., 2012; Ericson et al., 2007). Studies on Mn toxicokinetics suggest that blood may best reflect recent exposures (i.e., days), while teeth may integrate longer-term exposures (e.g., months or longer) (Arora et al., 2011; Arora et al., 2012; Ericson et al., 2007; Smith et al., 2007). Deciduous teeth incorporate Mn in an incremental pattern and dentine, unlike enamel, can provide reliable information on the developmental timing of exposures to Mn that occur between the second trimester of pregnancy (starting at 13–16 weeks gestation, when incisors begin forming) and 10–11 months after birth (when molars stop developing) (Arora et al., 2012).

In this study, we measured prenatal and early postnatal dentine Mn levels in children's deciduous teeth, and examined the association of Mn levels with behavior, cognition, memory, and motor development in 7-, 9-, and 10.5-year-old children living in an agricultural community in California where large amounts of Mn-containing fungicides are applied.

2. Methods

2.1. Study population

The Center for the Health Assessment of Mother and Children of Salinas (CHAMACOS) is a birth cohort study examining the health effects of pesticide and other environmental exposures in Mexican-American children living in the Salinas Valley, California. Common crops in this agricultural region include lettuce, strawberries, grapes, and broccoli. About 110,000 kg of Mn-containing fungicides, mancozeb and maneb (20% Mn by weight) (FAO, 1980), were used in Monterey County in 2012 (CDPR, 2014), but almost 160,000 kg were applied in 1999–2000, when study participants were pregnant (CDPR, 2001).

Detailed methods for the CHAMACOS study have been described elsewhere (Eskenazi et al., 2004; Eskenazi et al., 2006). Briefly, eligible pregnant women (≥18 years old, <20 weeks of gestation, Spanish- or English-speaking, qualified for low-income health insurance, and planning to deliver at the county hospital) were recruited in community clinics between September 1999 and December 2000. Six hundred and one pregnant women were enrolled and 526 of them delivered live-born singletons (referred to henceforth as the CHAM1 cohort).

A second cohort of 300 9 year-olds (referred to henceforth as the CHAM2 cohort) was recruited between September 2009 and August 2011. CHAM2 children were born between February 2000 and August 2002 to approximately match the birth dates of CHAM1 children. Children were eligible to participate if their mother, when pregnant, was ≥18 years old, Spanish- or English-speaking, qualified for low-income health insurance, and received prenatal care at any low-income provider in the Salinas Valley.

Because CHAM2 enrollment began at age 9, only CHAM1 children completed the neurobehavioral test battery at age 7 ($n = 339$). CHAM1 and CHAM2 children completed identical neurobehavioral assessments at ages 9 ($n = 634$) and 10.5 ($n = 615$). Standardized assessments were conducted by bilingual psychometricians who were trained and supervised by a pediatric neuropsychologist. Subtests were administered in the dominant language of the child, which was determined through administration of the Oral Vocabulary subtest of the Woodcock–Johnson/Woodcock–Muñoz Tests of Cognitive Ability in both English and Spanish (Woodcock and Johnson, 1990).

Teeth were collected for 282 CHAM1 and 173 CHAM2 children, but due to financial and logistical constraints, only teeth for 227 CHAM1 children and 70 CHAM2 children were analyzed. For this study, we excluded 39 children who provided a shed molar instead of an incisor, four children with a medical condition that would affect the neurobehavioral assessment (i.e., one with autism, and three with history of seizures), three children who were twins, and three children missing all neurobehavioral assessments. Children included in these analyses ($n = 248$) did not differ significantly from the full sample of CHAM1 ($n = 335$) and CHAM2 ($n = 309$) children on most attributes, including maternal marital status, poverty category at age 9, and child's birth weight. However, children included in these analyses had older mothers (mean age = 26.8 vs. 25.6 years, $p < 0.01$) with poorer cognitive abilities [mean maternal Peabody Picture Vocabulary Test (PPVT) score = 88.9 vs. 93.2 points, $p < 0.01$] than the full sample of CHAM1 and CHAM2 children.

All study activities were approved by the University of California at Berkeley Committee for the Protection of Human Subjects, and written informed consent was obtained from all mothers. Child verbal assent was obtained at 7, 9, and 10.5 years of age.