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Manganese in teeth and neurodevelopment in young Mexican–American children

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ABSTRACT

Introduction: Manganese (Mn) is an essential nutrient but higher exposure has been associated with poorer neurodevelopment in children.
Methods: We measured Mn levels in prenatal (Mn_{pre}) ($n=197$) and postnatal (Mn_{post}) dentin ($n=193$) from children's shed teeth using laser ablation inductively coupled plasma mass spectroscopy and examined the relationship with children's scores on the Mental Development Index (MDI) and Psychomotor Development Index (PDI) on the Bayley Scales of Infant Development at 6, 12, and 24-months. We explored non-linear associations and interactions by sex, blood lead concentrations and maternal iron status during pregnancy.
Results: A two-fold increase of Mn_{post} levels in dentin was associated with small decreases in MDI at 6-months and 12-months of age. We also observed a non-linear relationship between Mn_{post} levels and PDI at 6-months. We found effect modification by sex for Mn_{post} levels and neurodevelopment at 6-months with stronger effects among girls for both MDI (−1.5 points; 95% Confidence Interval (CI): −2.4, −0.6) and PDI (−1.8 points; 95% CI: −3.3, −0.3). Girls whose mothers had lower hemoglobin levels experienced larger decreases in MDI and PDI associated with Mn_{pre} levels than girls whose mothers had higher hemoglobin levels ($p_{interaction}=0.007$ and 0.09, respectively). We did not observe interactions with blood lead concentrations or any relationships with neurodevelopment at 24-months.
Conclusions: Using Mn measurements in tooth dentin, a novel biomarker that provides prenatal and early postnatal levels, we observed negative transient associations between postnatal Mn levels and early neurodevelopment with effect modification by sex and interactions with prenatal hemoglobin.

1. Introduction

Manganese (Mn) is an essential nutrient but can be neurotoxic at high levels (Menezes-Filho et al., 2009; Roels et al., 2012). Inhalation exposures bypass intestinal and hepatic Mn control processes (Teeguarden et al., 2007). Fetuses and infants might be more vulnerable to the negative effects of high Mn concentrations due to the ability of Mn to cross the placenta and differences in Mn homeostatic mechanisms in young children, who absorb and retain a larger fraction of ingested Mn than adults (Aschner and Aschner, 2005; Yoon et al., 2011).

Previous studies have reported associations between Mn exposure and cognitive and behavioral problems in children (Rodríguez-Barranco et al., 2013) with adverse associations sometimes noted at both highest and lowest exposure levels. A cross-sectional study of 448 infants and toddlers observed an inverted U-shaped relationship between Mn blood concentrations at 12-

Abbreviations: AUC, area under the curve; CES-D, Center for Epidemiologic Studies Depression Scale; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CI, confidence interval; DAP, dialkyl phosphate; DDE, *p,p*′-dichlorodiphenyldichloroethylene; DDT, *p,p*′-dichlorodiphenyltrichloroethylene; GEE, generalized estimating equations; HOME, Home Observation for Measurement of the Environment; LOD, limit of detection; MDI, mental development index; Mn, manganese; Mn_{pre}, manganese in prenatal dentin; Mn_{post}, manganese in prenatal dentin; PDI, psychomotor development index; PPVT, Peabody Picture Vocabulary Test

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months and concurrent mental development, with deficits at the lowest and highest quintiles (Claus Henn et al., 2010). In cross-sectional studies of school-aged children, higher Mn levels in hair, blood and drinking water have been associated with lower full-scale and verbal intelligence quotients (Kim et al., 2009; Riojas-Rodriguez et al., 2010; Bouchard et al., 2011; Menezes-Filho et al., 2011; Wasserman et al., 2011); lower verbal learning and memory scores (Torres-Agustin et al., 2013); and poorer motor coordination (Lucchini et al., 2012). In prospective studies, higher cord blood Mn levels have been associated with poorer neonatal behavior in a non-linear fashion (Yu et al., 2014); poorer cognition and language in 2-year-olds (Lin et al., 2013); and poorer attention, non-verbal memory, and hand skills in 3-year-olds (Takser et al., 2003). A recent study reported an inverted U-shaped association between maternal prenatal blood Mn and both mental and psychomotor development in 6-month-olds (Chung et al., 2015). Only one previous small study ($n=27$) measured Mn levels in enamel of deciduous teeth and reported positive correlations with behavioral disinhibition in 3-year-olds (Ericson et al., 2007).

Several studies have observed stronger adverse associations in girls than boys (Riojas-Rodriguez et al., 2010; Torres-Agustin et al., 2013; Roels et al., 2012; Menezes-Filho et al., 2014). In addition, steeper negative slopes have been reported for children with high exposure to both lead and Mn (Claus Henn et al., 2012; Lin et al., 2013; Kim et al., 2009). Iron status may also modify the relationship between Mn exposure and neurodevelopment; Mn and iron share the same absorption pathways (Park et al., 2013; Smith et al., 2013), blood Mn levels in pregnant women at delivery have been related to iron metabolizing genes (Claus Henn et al., 2011), and higher blood Mn concentrations have been reported among iron deficient infants and children (Smith et al., 2013; Kim and Park, 2014), who are at risk of poorer cognitive development with iron deficiency (Chang et al., 2013; Radlowski and Johnson, 2013).

Though blood is the most common matrix in which Mn exposure is quantified (Rodríguez-Barranco et al., 2013), the short half-life (<30 days) in blood means measurements reflect only recent exposures (Smith et al., 2007). Maternal Mn concentrations may not accurately reflect fetal exposure: Mn concentrations are typically two-fold higher in cord than in maternal delivery blood (Takser et al., 2004; Zota et al., 2009; Gunier et al., 2014). Another biomarker, Mn in hair, is only representative of exposure during hair growth, and measurements can be compromised by exogenous contamination (Eastman et al., 2013).

In this study, we use a novel exposure matrix, Mn levels in prenatal and postnatal dentin from children's shed teeth (Arora et al., 2012), to examine perinatal Mn in association with infant neurodevelopment in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study, a prospective birth cohort of children. Measurement of Mn in dentin offers a promising biomarker of early life exposure that provides integrated measures of exposure over the prenatal and postnatal periods of tooth development, which reflect longer term exposure than a single measurement in blood or hair, and may better reflect fetal Mn levels than Mn in maternal blood (Gunier et al., 2014). We previously reported that higher Mn levels in prenatal dentin were associated with residential proximity to use of Mn-containing fungicides and storage of farmworkers' clothing and shoes inside the home (Gunier et al., 2013).

2. Materials and methods

2.1. Study population

In 1999–2000, we enrolled 601 pregnant women receiving prenatal care at clinics serving the Salinas Valley. Women who were ≥ 18 years of age and <20 weeks gestational age, qualified for California's low-income health insurance program, spoke English or Spanish, and planned to deliver at the county hospital were eligible to participate. Of 536 live born children whose mothers remained enrolled at delivery, we included those with neurodevelopmental assessments at 6, 12, and/or 24-months who provided a shed incisor at or after age 7 ($n=204$). We excluded 4 children with medical conditions that could affect performance (e.g. seizures, autism) and 3 twins, yielding a final sample of 197 children. Neurodevelopmental assessments included 182, 188, and 186 children at 6, 12 and 24-months, respectively. Mothers of children included in analyses were older at delivery (mean$=$26.7 years) than mothers of excluded children (mean$=$24.7 years); otherwise; the two populations were similar. Written informed consent was obtained from all women and protocols were approved by the University of California, Berkeley Institutional Review Board.

2.2. Neurodevelopmental outcomes

We used the Bayley Scales of Infant Development-Second Edition to assess children's development at 6, 12, and 24-months (Bayley, 1993). The Mental Developmental Index (MDI) characterizes cognitive abilities and the Psychomotor Developmental Index (PDI) characterizes fine and gross motor coordination. Trained psychometricians who were blind to Mn exposure administered scales in children's dominant home language (Spanish or English) at the CHAMACOS research office or in a mobile testing facility. We assessed the children on average (mean $\pm$ SD) at 6.6 ± 0.9 months, 12.8 ± 1.6-months and 24.6 ± 1.0 months of age. Both MDI and PDI scores were age-standardized to a mean of 100 with a SD of 15. We excluded scores that were more than 4 SD from the mean (<5 scores per scale per age point).

2.3. Manganese exposure measurements

Beginning at age 7, participants were asked to mail or bring in teeth as they were shed. We analyzed incisors that were free of obvious defects such as caries and extensive tooth wear. Analysis methods have been described in detail elsewhere (Arora et al., 2012). Briefly, teeth were sectioned in a vertical plane and microscopy was used to visualize the neonatal line in sectioned teeth samples. The neonatal line is formed by changes in the direction and degree of tooth mineralization occasioned by the transition from intrauterine to extra uterine life and can be used to distinguish between tooth formation during the prenatal and postnatal periods (Sabel et al., 2008). Formation of prenatal dentin of incisors begins at approximately 3 months gestation and continues until birth; postnatal dentin formation of incisors occurs from birth until approximately 2.5 months of age (Ash and Nelson, 2003). We determined the concentrations and spatial distribution of Mn using laser ablation inductively coupled plasma mass spectroscopy. Because multiple measurements were taken in prenatal and postnatal dentin, we calculated the area under the curve (AUC) of Mn levels across all sampling points to estimate cumulative Mn exposure during the prenatal and postnatal periods. Tooth Mn levels were normalized to measured tooth calcium levels (^{55}Mn:^{43}Ca ratio) to provide a measure independent of variations in tooth mineral density. Our final Mn exposure values are ^{55}Mn:^{43}Ca AUC $\times$ 10,000 for points measured during the prenatal (Mn_{pre}) and postnatal (Mn_{post}) periods separately. The coefficient of variation for five teeth measured on three different days ranged from 4.5% to 9.5% indicating good reproducibility of ^{55}Mn:^{43}Ca dentin measurements. The limit of detection (LOD) was 0.001 ^{55}Mn:^{43}Ca. Values below the LOD ($n=4$ postnatal measurements) were assigned the LOD/2. In addition, there were four