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Prenatal co-exposure to neurotoxic metals and neurodevelopment in preschool children: The Environment and Childhood (INMA) Project

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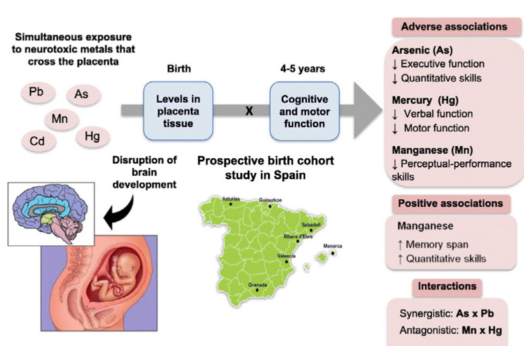
HIGHLIGHTS

- Few studies have examined the effects of early co-exposure to neurotoxic metals.
- As, Cd, Hg, Mn and Pb placental levels were explored in relation to neurodevelopment.
- Exposure to As and Hg was associated with cognitive impairment in preschoolers.
- The effects of Cd and Mn on neurodevelopment appear to be less clear.

GRAPHICAL ABSTRACT



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ABSTRACT

We sought to determine whether prenatal co-exposure to As, Cd, Hg, Mn, and Pb was associated with impaired neurodevelopment in preschool children from the Spanish Environment and Childhood (INMA) Project, using the placenta as exposure matrix. We measured metal levels in placenta tissue samples randomly selected from five of the seven population-based birth cohorts participating in the INMA Project, collected between 2000 and 2008. Neuropsychological assessment of cognitive and motor function was carried through the use of the McCarthy Scales of Children's Abilities (MSCA) at the age of 4–5 years. Data on placental metal levels, MSCA

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scores, and relevant covariates was available for 302 children. Mn was detected in all placental samples, Cd in nearly all placentas (99%) and As, Hg, and Pb in 22%, 58%, and 17% of the placentas, respectively. After adjusting for potential confounders, detectable As levels were associated with decrements in global and verbal executive functions and quantitative abilities; detectable Hg was associated with lower scores on the verbal function of posterior cortex in a dose-response manner, and non-linearly related to poorer motor function and gross motor skills; and Mn levels were associated with decrement in perceptual-performance skills in a dose-response manner but with better memory span and quantitative skills. A synergistic interactive effect was found between As and Pb with respect to the general cognitive score, whereas an antagonistic interaction was found between Mn and Hg. Prenatal exposure to As and Hg may be a risk factor for cognitive and motor impairment in children, while the effects of Cd and Mn on neurodevelopment are less clear. Future studies should examine combined and interactive effects of exposure to multiple metals during vulnerable periods of brain development prospectively.

1. Introduction

Concerns have been growing over the past few decades about developmental neurotoxicity due to early-life exposure to lead (Pb), mercury (Hg), cadmium (Cd), and other ubiquitous metallic trace elements, such as arsenic (As) and manganese (Mn) (Counter and Buchanan, 2004). Numerous studies have demonstrated that both Pb and Hg are highly neurotoxic to the developing brain and nervous system at much lower doses than those known to impair adult brain function (Grandjean and Landrigan, 2006; Jakubowski, 2011; Schoeman et al., 2009). Early exposure to As, Cd, and Mn has also been implicated in neurodevelopmental disorders in humans, but few data are available on the neurodevelopmental effects of exposure to environmentally-relevant levels of these metals (Rodríguez-Barranco et al., 2013; Sanders et al., 2015).

The central nervous system is a common target organ for many environmental metals, whose action can affect different functional domains according to the metal in question, although some areas (*e.g.*, auditory, visual system, motor and memory deficits, and externalizing behavior) may be impaired by all of the aforementioned metallic elements (Riccio et al., 2010). In this regard, several epidemiological studies have associated early (prenatal, postnatal or childhood) exposure to Pb and Hg, especially methyl-Hg, with neurodevelopmental impairment among infants and children (Axelrad et al., 2007; Jakubowski, 2011; Lanphear et al., 2005; Schoeman et al., 2009). However, the effects on neurodevelopment of moderate-to-high dose prenatal Hg exposure have been described as less clear than the effects of Pb (Llop et al., 2017; Myers et al., 2003; Davidson et al., 2008). There is increasing evidence of the neurotoxic effects of As, Cd, and Mn, especially As (Tyler and Allan, 2014), although these compounds have been less well studied (Rodríguez-Barranco et al., 2013; Sanders et al., 2015). Furthermore, although the degree of neurodevelopmental toxicity has been shown to be dependent on co-exposure to multiple neurotoxicants (Bellinger, 2008b; Cory-Slechta et al., 2008), there has been little research on co-exposure to potentially toxic metals (Sanders et al., 2015).

The placenta is a complex tissue consisting mainly of the chorionic villi and amniotic membranes and is highly vascularized by maternal and fetal blood vessels (Iyengar and Rapp, 2001a). Trace metallic elements, including heavy metals such as Pb and Hg, can be mobilized during pregnancy and cross the placental barrier, posing a health risk to the fetus (ATSDR, 2007). This coupled with the fact that the placenta can be collected without invasive procedures, makes placenta tissue an appropriate biological matrix for assessment of both fetal and maternal exposure to metallic elements (Esteban and Castaño, 2009; Esteban-Vasallo et al., 2012; Iyengar and Rapp, 2001b).

Food and drinking water are the most common sources of exposure to toxic metals in the general human population (Tchounwou et al., 2012), although cigarette smoke is also an important source of exposure to several metals (ATSDR, 2008). In Spain, the Environment and Childhood (INMA) Project reported that a higher intake of large oily fish during pregnancy was related to increased umbilical cord blood Hg levels, finding concentrations at or above the current US-EPA reference dose in 64% of newborns studied from different Spanish regions (Ramon et al., 2011); however, cord blood Pb levels were low in the same study population (Llop et al., 2011). In subsequent follow ups of INMA cohorts, cord blood Hg was marginally associated with poorer psychomotor development at 14 months of age among girls (Llop et al., 2012) but was associated with improved child neurodevelopmental scores at the age of 4–5 years (Llop et al., 2017). On the other hand, higher Hg levels in the hair of 4-year-old children from the INMA-Granada cohort were associated with cognitive impairment (Freire et al., 2010), but no association was found between urinary concentrations of As, Cd, or Pb in pregnant women from the INMA-Sabadell cohort and cognitive scores or risk of attention deficit and hyperactivity disorder (ADHD) in the children at age 4 years (Forns et al., 2014). Overall, findings of previous INMA studies have varied according to the exposure biomarker(s) used, while there has been scant research on the neurotoxic effect of prenatal metal exposure using the placenta, which has been proposed as a promising tissue for biomonitoring studies (Esteban-Vasallo et al., 2012). With this background, the objective of the present prospective study was to determine whether prenatal co-exposure to As, Cd, Hg, Mn, and Pb was associated with impaired neurodevelopment in preschool children from the INMA cohorts, using the placenta as biological exposure matrix.

2. Methods

2.1. Population and study design

The INMA Project is a multicenter population-based birth cohort study designed to investigate the effect of environmental exposures and diet during pregnancy on fetal and child development in different geographic areas of Spain (http://www.proyectoinma.org). Five out of the seven INMA cohorts collected placentas at birth and were included in the present study, namely: Asturias, Gipuzkoa (Basque Country), Granada (Andalusia), Sabadell (Catalonia), and Valencia. Cohorts were recruited during the first prenatal visit (10–13 weeks of gestation) (2003–2008) in Asturias, Gipuzkoa, Sabadell, and Valencia but at birth in Granada (2000 − 2002). Details on recruitment strategies and general characteristics of the cohorts are described elsewhere (Guxens et al., 2012). All INMA cohorts included boys and girls except for the INMA-Granada cohort, which contained boys alone. Out of the 490 placentas (approximately one out of five births, 19.5% of the study population) randomly collected at delivery (Vilahur et al., 2013), 366 were randomly selected for metal content analysis. Out of the 3294 babies born to women in the five cohorts under study, 2085 (63%) underwent neuropsychological assessment at 4–5 years of age. Sociodemographic, lifestyle, and dietary data, among others, were gathered from questionnaires administered to the parents during pregnancy, after delivery, and at follow-up visits. The present study included 302 children for whom data were available on placental metal content and on neurodevelopment at the age of 4–5 years. Informed consent was obtained from all participants for each phase, and the study was approved by the hospital ethics committees in the participating regions.