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Cadmium exposure and neuropsychological development in school children in southwestern Spain

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ABSTRACT

This study assessed the association between cadmium exposure and neuropsychological development in children from a region with high industrial and mining activities in southwestern Spain. We conducted a cross-sectional study with 261 children aged 6–9 years between January and March 2012. Cadmium exposure was measured in urine and hair of children, and neuropsychological development was assessed with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV) and with three computerized tests from the Behavioral Assessment and Research System (BARS): Reaction Time Test (RTT), Continuous Performance Test (CPT) and Selective Attention Test (SAT). Multivariate linear regression models, adjusted for potential confounders, were used to estimate the association between neuropsychological development and cadmium exposure measured in urine and hair samples. Geometric means of urine and hair cadmium levels were 0.75 μg/g creatinine and 0.01 μg/g, respectively. We observed that doubling of levels of cadmium in urine was associated with a reduction of two points (95% CI: −3.8 to −0.4) in the Full-Scale intelligence quotient (IQ) in boys. By domains, association was statistically significant for Verbal Comprehension ($\beta = -2.0$; $p = 0.04$) and close to the significance level for Perceptual Reasoning ($\beta = -1.8$; $p = 0.06$). Among girls, only Verbal Comprehension showed suggestive associations with cadmium exposure ($\beta = -1.7$; $p = 0.06$). Cadmium exposure is associated with cognitive delays in boys in our region. Our results provide additional evidence of the neurotoxic effect of low-level postnatal cadmium exposure among children, and support the hypothesis of differences between sexes in the neurotoxic effect of metals on children.

1. Introduction

Over the past decades concern has risen about the potential effect of low-level exposure to toxic metallic compounds (including cadmium) among environmentally exposed populations, especially pregnant women and children (Grandjean and Landrigan, 2006). As reported by Landrigan et al. "children are not small adults", and they present striking differences versus adults in both routes and magnitude of exposure (Landrigan et al., 2004). This makes children the preferred target group for the study of health effects of environmental xenobiotics.

Cadmium (Cd) is a natural element present in Earth's crust in concentrations ranging from 0.1 to 5 μg/g. Nonferrous metal mining and refining, manufacture and application of phosphate fertilizers, fossil fuel combustion, and waste incineration and disposal are the main anthropogenic sources of cadmium in the environment (ATSDR, 2012). Cadmium ranks seventh in the ATSDR list of elements posing the most significant potential threat to human health in the environment, and it ranks third in the heavy

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metals subdivision of the same list, behind lead and mercury (ATSDR, 2011). Cadmium is a Group 1 IARC carcinogen and it is neurotoxic (Cao et al., 2009; ATSDR, 2012).

During pregnancy the placenta acts as a barrier for cadmium, and only a small amount ($<10\%$) is transferred to the fetus (Osman et al., 2000). A similar proportion is transferred to human milk (Hallen et al., 1995). Thus, the fetus and the newborn are protected against cadmium. However, cadmium exposure starts at a very young age through food, environmental tobacco smoke and household dust (Cao et al., 2009). Diet is the main source of environmental exposure to cadmium among non-occupationally exposed and non-smoker population and it has been reported that more than 80% of food-based cadmium comes from cereals and vegetables (Cho et al., 2013). While cadmium in blood reveals recent exposure status, cadmium in urine and hair reflects the body burden and is an indicator for cumulative long term exposure (Adams and Newcomb, 2014).

Although there is evidence of neurotoxic effects of cadmium from experimental studies in animals (Jin et al., 1998; Shagirtha et al., 2011; ATSDR, 2012), a few studies have evaluated the effect of cadmium exposure on child neuropsychological development, and their results are mostly inconclusive (Rodríguez-Barranco et al., 2013). Some studies have found association between prenatal cadmium exposure and neuropsychological development (Tian et al., 2009; Kippler et al., 2012), but there are not enough evidence related to postnatal exposure. Most studies that have evaluated postnatal exposure to cadmium do not observe a significant association with neuropsychological development in children (Torrente et al., 2005; Wright et al., 2006; Cao et al., 2009). In contrast, a recent study found a significant association between postnatal cadmium exposure and learning disability in U.S. children (Ciesielski et al., 2012).

Cadmium exposure can reach high levels in areas close to cadmium-emitting industries (Bao et al., 2009; Blasco et al., 2010), exceeding the 5 ng/m^3 safety threshold limit value recommended by the World Health Organization (WHO, 2004). The levels of cadmium in emission plumes in the proximity of the copper smelter factory in the Huelva area were 6.71 ng/m^3 in August 2005, though the average daily mean in the downtown area between 2001 and 2008 was below 1 ng/m^3 (Sánchez de la Campa et al., 2011).

The aim of this study was to assess the association between postnatal cadmium exposure and neuropsychological development in children living in a coastal industrialized region in southwestern Spain. This area has been dominated for decades by extensive chemical industrial and mining activities, and is crossed by an ecosystem named Ria de Huelva, a complex system of drainage channels that separate several areas of salt marshes. This ecosystem is controlled by the tidal regime and the inputs of the Odiel and Tinto rivers, as well as two channels which exchange water directly with the open sea. Ria of Huelva has high levels of metallic elements such as copper, zinc, iron, cadmium and manganese from three main sources of contamination: the industrial sewage from over 40 neighboring chemical industries, the urban sewage of the city of Huelva, and fluvial inputs from the Odiel and Tinto rivers, which have acidic waters and high levels of metallic trace elements (Blasco et al., 2010).

2. Methods

2.1. Design and study population

A cross-sectional study was conducted between January and March 2012 in a region in southwestern Spain (Huelva, Andalusia). Thirteen schools were randomly selected from a total of 38 public schools in seven municipalities within the Ria of Huelva area (Aljaraque, Huelva, Palos de la Frontera, Punta Umbría, San Juan del Puerto, Tharsis and Valdelamusa). A total of 2199 parents of the selected schools were invited to participate in the study, and 315 of them agreed to participate. A subset of 203 parents among those that declined to participate completed a brief non-participation questionnaire.

Finally, a sample of 261 children aged 6–9 years was randomly selected from those who met the inclusion criteria and whose parents gave signed informed consent. Inclusion criteria included uninterrupted residence in the study area for at least one year, and having one parent or guardian fluent in Spanish. Exclusion criteria included pre-and peri-natal problems, diabetes, neurological disorders, brain trauma, surgery under general anesthesia, and liver or kidney disease. No children were excluded from the study.

The sample size of 261 children was calculated a priori to provide a power of 80% at 0.05 of significance level in order to detect a decrease of -4 points in WISC Full-Scale intelligence quotient (IQ) due to a doubling of lead exposure, based on the results found by Tong et al. (1996).

2.2. Data collection

The day before the neuropsychological assessment, children were provided with a polypropylene container to collect a first morning spot urine sample. Before being used all polypropylene materials were cleaned by soaking in 10% (v/v) HNO_3 for 24 h. They were finally rinsed with several washes of Milli-Q® water and dried in a polypropylene container. Urine samples were collected by the field team in schools at the beginning of classes next day. Samples were refrigerated at -4 °C until transported to the laboratory, and stored at -20 °C until analysis. The same day a minimum of 100 mg of hair was collected from the scalp by a trained personal. Hair samples were cut from the back of the head as close as possible to the scalp and were transported and stored in plastic bags until analysis. Children were also weighed and measured in order to calculate body mass index (BMI).

Two questionnaires (one self-administrated and another by phone interview) were completed by the mother, father or guardian to obtain information about demographic and socioeconomic characteristics, environmental and home exposures, parent's occupational history, birth characteristics and lifetime residential history. Children's diet was assessed by means of a validated semi-quantitative food frequency questionnaire (FFQ) (Vioque et al., 2013). Number of servings per week of vegetables and cereals were calculated from the FFQ. We included pulses in the group of vegetables, and bread and pasta in the group of cereals.

In addition, a psychologist visited each family to assess the maternal intellectual quotient by the Kaufman Brief Intelligence Test (Kaufman and Kaufman, 1990).

2.3. Assessment of children's neuropsychological development

The Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; Wechsler, 2003) was individually administered to assess intellectual function in children and administered in standard form. This scale provides measures of general intellectual ability by the Full-Scale IQ, and for four specific cognitive domains: Verbal Comprehension (with subtest of similarities, vocabulary, comprehension and information); Perceptual Reasoning (block design, matrix completion and picture completion); Working Memory (digit span, letter–number sequencing and arithmetic); and Processing Speed (digit symbol-coding and symbol search). In the event of any of the subtests being suspended, it was replaced with an equivalent subtest according to the author's guidelines, this occurred in five cases (Wechsler, 2003).

In addition, three computerized tests from the Behavioral Assessment and Research System (BARS; Rohlman et al., 2003) were used to assess additional attention functions: Reaction Time Test (RTT), Continuous Performance Test (CPT) and Selective Attention Test (SAT).

In the Reaction Time Test (RTT) a stimulus (square) is presented on the screen and the subject is instructed to press a button with their dominant hand as fast as possible to make it disappear. A total of 50 trials are presented. The Interstimulus Interval (ISI) was variable (between 1 and 3 s) and if the subject did not emit the response after 3 s the stimulus presentation screen disappeared. This task is designed to measure the speed of response to a visual stimulus (Lezak, 2004). Response latency in milliseconds (ms) and response latency excluding trials with latencies higher than 1000 ms were calculated from this test.

The Continuous Performance Test (CPT) measures attention, and consists of subjects pressing a button with their dominant hand as fast as they can when a target stimulus (closed circle) preceded by a cue stimulus (plus sign) is presented on the screen. A series of distractions are presented to subjects, specifically downward arrows, triangles, stars and hexagons. A total of 300 trials were presented, with a cue presentation fixed interval of 0.05 s and an ISI of 1 s. Percentage of false alarms, percentage of omission and response latency (ms) were calculated from this test.

The Selective Attention Test (SAT) presents two equidistant boxes on the screen, one on the right of the screen and one on the left. The subject is instructed to press a button whenever a small dot appeared inside the box (with his/her right hand if it appears on the right and with his/her left hand if it appears on the left) and to ignore dots appearing outside of the boxes. The task has a total duration of 600 s, where 80% of the presentations are within the box and 20% are outside the