Environmental Research 126 (2013) 105–110

Contents lists available at ScienceDirect

Environmental Research

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

Lead, mercury, and cadmium exposure and attention deficit hyperactivity disorder in children

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ARTICLE INFO

Article history:
Received 23 April 2013
Received in revised form
7 August 2013
Accepted 19 August 2013
Available online 10 September 2013

Keywords:
Attention deficit hyperactivity disorder
Heavy metals
Lead
Mercury
Cadmium
Case-control study

ABSTRACT

Background: There is limited research examining the relationship between lead (Pb) exposure and medically diagnosed attention deficit hyperactivity disorder (ADHD) in children. The role of mercury (Hg) and cadmium (Cd) exposures in ADHD development is even less clear.
Objectives: To examine the relationship between Pb, Hg, and Cd and ADHD in children living inside and outside a Lead Investigation Area (LIA) of a former lead refinery in Omaha, NE.
Methods: We carried out a case-control study with 71 currently medically diagnosed ADHD cases and 58 controls from a psychiatric clinic and a pediatric clinic inside and outside of the LIA. The participants were matched on age group (5–8, 9–12 years), sex, race (African American or Caucasians and others), and location (inside or outside LIA). We measured whole blood Pb, total Hg, and Cd using inductively coupled plasma mass spectrometry.
Results: Inside the LIA, the 27 cases had blood Pb geometric mean (GM) 1.89 μg/dL and the 41 controls had 1.51 μg/dL. Outside the LIA, the 44 cases had blood Pb GM 1.02 μg/dL while the 17 controls had 0.97 μg/dL. After adjustment for matching variables and maternal smoking, socioeconomic status, and environmental tobacco exposure, each natural log unit blood Pb had an odds ratio of 2.52 with 95% confidence interval of 1.07–5.92. Stratification by the LIA indicated similar point estimate but wider CIs. No associations were observed for Hg or Cd.
Conclusions: Postnatal Pb exposure may be associated with higher risk of clinical ADHD, but not the postnatal exposure to Hg or Cd.

1. Introduction

Attention deficit hyperactivity disorder (ADHD), characterized by inattention, impulsivity, distractibility, and hyperactivity, is the most commonly diagnosed neurobehavioral disorder in children (APA, 2000; CDC, 2010). The American Psychiatric Association (APA) estimates a childhood prevalence of 3 to 7% in the U.S. and these children are more likely to develop antisocial behavior, abuse drugs, and develop conduct disorder problems as adults (APA, 2000). The etiology of ADHD is complicated, and has a strong genetic component (Faraone et al., 2005; Smith et al., 2009). However, genetics cannot account for all ADHD cases and studies within the past decade have indicated that certain environmental factors, including exposure to environmental pollutants, prenatal substance exposure, and lifestyle, can play a role in ADHD etiology (Aguiar et al., 2010; Banerjee et al., 2007; Froehlich et al., 2011; Pennington et al., 2009; Schettler, 2001; Swanson et al., 2007).

Lead (Pb), mercury (Hg), and cadmium (Cd) are heavy metals naturally found in the environment and are also widely proliferated in the environment through human activity. Pb is a well-known neurotoxicant, especially harmful to child neurodevelopment. Many studies have shown the harmful effects of higher blood lead levels (BLL) (> 10 μg/dL), however a growing body of evidence is showing adverse effects at lower BLLs (e.g., ≤ 5 μg/dL), suggesting no

Abbreviations: ADHD, attention deficit hyperactivity disorder; APA, American Psychiatric Association; ASARCO, American Smelting and Refining Company; ATSDR, Agency for Toxic Substances and Disease Registry; BLL, blood lead level; Cd, cadmium; CI, confidence interval; CDC, Centers for Disease Control and Prevention; CHEER, Children's Health and Environment Research; DDW, double deionized water; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; EPA, Environmental Protection Agency; ETS, Environmental Tobacco Smoke; GM, geometric mean; Hg, mercury; ICP-MS, inductively coupled plasma mass spectrometry; LIA, Lead Investigation Area; LOD, limit of detection; NE, Nebraska; NHANES, National Health and Nutrition Examination Survey; NPL, National Priorities List; OR, odds ratio; Pb, lead; ppb, parts per billion; SES, socioeconomic status; SRM, standard reference material

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0013-9351/$ - see front matter © 2013 Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.envres.2013.08.008

threshold of developmental neurotoxicity (Chiodo et al., 2004; Cho et al., 2010; Kim et al., 2010; Lanphear et al., 2005; Nigg et al., 2008; Wang et al., 2008). In early 2012 the Center for Disease Control and Prevention (CDC) Advisory Committee on Childhood Lead Poisoning Prevention recommended replacing the "blood lead level of concern" at 10 μg/dL with "reference value" at 5 μg/dL as a goal for lead exposure prevention in young children (CDC, 2012). Recent studies have associated blood Pb levels with medically diagnosed ADHD in children (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008, 2010; Wang et al., 2008). While the Wang et al. (2008) study was in China and had mean BLL above 5 μg/dL in both ADHD cases and controls, the other studies were in the U.S. and the association between Pb exposure and ADHD diagnosis was observed at or below 2 μg/dL compared with even lower reference groups (Braun et al., 2006; Froehlich et al., 2009; Nigg et al., 2008, 2010). The association at very low-level exposure, while with significant public health implications, needs to be examined in different populations.

Mercury comes in different forms, but children nowadays are mostly exposed to elemental Hg through dental amalgam and organic mercury (mainly methylmercury [MeHg]) through fish consumption(Caldwell et al., 2009; Ozuah, 2000). It has been suggested that contemporary use of dental amalgam may not be associated with adverse neurodevelopmental deficits in children (Bellinger et al., 2006; DeRouen et al., 2006). However, exposure to MeHg during prenatal period was associated with reduced cognitive function in school age children in a longitudinal study from Faroe Islands (Grandjean et al., 1997). Although similar association was not observed in another epidemiologic study from Seychelles Islands (Davidson et al., 2006), two recent studies, from Inuit population in Arctic Québec and New Bedford Massachusetts respectively, suggest an association between prenatal Hg exposure and child ADHD symptom score using behavioral rating scales (Boucher et al., 2012; Sagiv et al., 2012). Postnatal exposure to Hg was not consistently related to adverse neurodevelopment in both Faroese and Seychelles children (Debes et al., 2006; Myers et al., 2009), but a case control study in Hong Kong found a significant association with medically diagnosed ADHD (Cheuk and Wong, 2006). The Hg levels in children of these three studies of postnatal exposure were significantly higher than the U.S. background exposure (geometric mean 0.4 μg/L among 6–11 year olds) (CDC, 2009). It is unclear whether current postnatal Hg exposure level in the U.S. children is related to ADHD.

Cadmium is of particular concern because of its known skeletal toxicity, nephrotoxicity, and carcinogenicity, but uncertainty remains about developmental neurotoxicity. Studies on prenatal and postnatal Cd exposure and child neurodevelopment are still limited and have had opposing results. A study using NHANES 1999–2000 data reported a weak association between blood Cd levels and attention deficit disorder (ADD) but after adjusting for persistent organic pollutants, the association disappeared (Lee et al., 2007). In a meta-analysis, the authors found only two studies from China that found associations between Cd levels and neurodevelopmental effects, but these were at very high levels and may not translate to lower exposures (Rodriguez-Barranco et al., 2013). Analysis of the National Health and Nutrition Examination Survey (NHANES) 1999–2004 data suggested a positive link between child urinary Cd and the prevalence of learning disability and special education among 6–15 year olds, however, a non-significantly lower prevalence of ADHD was related to the exposure (Ciesielski et al., 2012). Clearly more research is needed to examine the association with ADHD in children with postnatal exposure to Cd.

Overall, the U.S is seeing decreasing emission levels of various heavy metals and other chemicals, but the exposure report from the CDC shows low levels of metals and chemicals in biospecimens across the population (CDC, 2009). Across communities in the U.S., exposure to Pb, Hg, and Cd continues to be an important public health issue, in particular, the National Priorities Sites (aka Superfund sites) that have accumulated hazardous wastes from industries (Bellinger, 2004; Jarup, 2003). It is estimated that as of August 2000, 58% of children in the US live in counties with Superfund sites (Browner, 1996; EPA, 2000). In the scenario of Superfund sites, human exposure to a mixture of chemicals is not rare. On the Agency for Toxic Substances & Disease Registry (ATSDR) Substance Priority List of chemicals present at Superfund sites, lead, mercury, and cadmium ranked number 2, 3, and 7, respectively, in 2011. The residents in the Superfund communities are vulnerable to these mixed exposures, however, few studies have examined combined exposures to heavy metals at these sites (Hu et al., 2007). It is becoming more common to investigate the mixture of metal exposures for child neurodevelopmental outcomes such as ADHD behavior score or medical diagnosis (Boucher et al., 2012; Ha et al., 2009; Nicolescu et al., 2010; Szkup-Jablonska et al., 2012; Yousef et al., 2011). Therefore, we conducted a case-control study of ADHD among children who live close to a current Superfund site to examine environmental exposure to Pb, Hg, and Cd.

2. Study subjects and methods

2.1. Study area

We performed a case-control study to investigate the association between heavy metal exposure and ADHD in Omaha, NE from August 2007 to December 2009. Omaha had been the site of a large lead refinery for about a hundred years before it closed in 1997. The plant emitted Pb and other metals into the atmosphere through smokestacks during its period of operation (EPA, 2009). The EPA and ATSDR designated the former refinery site (23 ac) and the surrounding 8840 ac of land on the west bank of the Missouri River as the "Omaha Lead Initial Site Investigation Area", or "Lead Investigation Area" (LIA) for short. The site, which covers a large proportion of downtown Omaha, was listed on the EPA′s National Priorities List (NPL) in 2003 because of increased lead levels in soil and children. Considering the impact of the LIA on the blood lead levels in children, we enrolled ADHD cases and non-ADHD controls from both inside and outside the LIA.

2.2. Subject enrollment

ADHD cases were recruited from two clinics at the Departments of Psychiatry and Pediatrics at Creighton University Medical Center (located within the LIA). The cases met the following inclusion criteria: (1) a medical diagnosis of ADHD by a physician based on Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV standard; (2) between 5- and 12-year old; and (3) living in Omaha city after birth. Children were excluded based on the following criteria: (1) having severe neurological or psychiatric problems such as cerebral palsy, mental retardation, schizophrenia; and/or (2) having severe birth defects such as chromosome disorders, congenital heart disease, and hereditary metabolic disorders. Non-ADHD controls were recruited from one study clinic at the Department of Pediatrics provided they satisfied the same criteria for enrollment barring the ADHD status. The study was designed to frequency match the cases and controls for age group (5–8 years, 9–12 years), sex (male, female), race (African American, White or Others), and residence (inside or outside the LIA). However, during enrollment we realized that we could not reach the residence matching because more children with ADHD living outside the LIA came to the university clinic for treatment than non-ADHD children living outside the site, therefore we relaxed the matching criterion.

After the parent or guardian provided informed consent and the child provided assent (if above age 7 years) to participate, we acquired information on socio-demographic factors, medical history, lead exposure, and prenatal and postnatal tobacco smoke exposure from questionnaires completed by the parents and collected whole blood samples from the child for heavy metal testing. In this study, a total of 71 ADHD cases and 58 non-ADHD controls had completed questionnaires and enough blood samples for Pb, Hg, and Cd testing. The study was initially approved by Institutional Review Board at Creighton University for enrollment and approved at the University of Cincinnati for metal assays and data analysis.

2.3. Heavy metal measurement and analysis

We measured blood Pb, total Hg, and Cd concentrations in the whole blood samples using an Agilent 7700× inductively coupled plasma mass spectrometry