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Associations of prenatal and early childhood mercury exposure with autistic behaviors at 5 years of age: The Mothers and Children's Environmental Health (MOCEH) study

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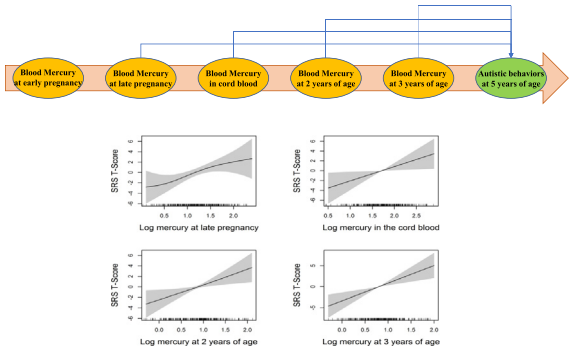
HIGHLIGHTS

- We explored the associations between blood mercury levels and autistic behaviors.
- This study involved an ongoing multicenter prospective birth cohort.
- Blood mercury levels were repeatedly measured from early pregnancy to 3 years.
- Autistic behaviors were assessed at 5 years with the Social Responsiveness Scale.
- Prenatal and early childhood mercury levels were associated with autistic behaviors.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Although mercury is an established neurotoxin, only few longitudinal studies have investigated the association between prenatal and early childhood mercury exposure and autistic behaviors.
Methods: We conducted a longitudinal cohort study using an ongoing prospective birth cohort initiated in 2006, wherein blood mercury levels were measured at early and late pregnancy; in cord blood; and at 2 and 3 years of age. We analyzed 458 mother-child pairs. Autistic behaviors were assessed using the Social Responsiveness Scale (SRS) at 5 years of age. Both continuous SRS T-scores and T-scores dichotomized by a score of ≥60 or <60 were used as outcomes.
Results: The geometric mean of mercury concentrations in cord blood was 5.52 μg/L. In adjusted models, a doubling of blood mercury levels at late pregnancy ($\beta = 1.84$, 95% confidence interval [CI]: 0.39, 3.29), in cord blood ($\beta = 2.24$, 95% CI: 0.22, 4.27), and at 2 years ($\beta = 2.12$, 95% CI: 0.54, 3.70) and 3 years ($\beta = 2.80$, 95% CI: 0.89, 4.72) of age was positively associated with the SRS T-scores. When the SRS T-scores were dichotomized, we

Abbreviations: ASD, autism spectrum disorder; CI, confidence interval; LOD, limit of detection; RR, relative risk; SRS, social responsiveness scale.

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observed positive associations with mercury levels at late pregnancy (relative risk [RR] = 1.31, 95% CI: 1.08, 1.60) and in cord blood (RR = 1.28, 95% CI: 1.01, 1.63).
Conclusion: We found that blood mercury levels at late pregnancy and early childhood were associated with more autistic behaviors in children at 5 years of age. Further study on the long-term effects of mercury exposure is recommended.

1. Introduction

Autism spectrum disorders (ASDs) are neurodevelopmental disorders characterized by impairments in social interaction and communication, repetitive behaviors, and restrictive interests. The prevalence of ASD is estimated to be 1.5% in the U.S. (Christensen et al., 2016) and 2.2% in the Republic of Korea (Kim et al., 2014). Although the etiology of ASD has not been completely established, genetic factors are believed to contribute to ASD in only 30–40% of the total ASD cases (Landrigan et al., 2012), whereas environmental factors may play an important role in ASD development in the remaining cases (Landrigan et al., 2012; Nowack et al., 2015).

Mercury, a widespread heavy metal, can induce harmful effects in the nervous system (Grandjean et al., 2014); however, previous studies' results regarding the neurotoxicity of mercury are inconsistent (Yau et al., 2014). Mercury can efficiently cross the placenta, and hence, cord blood mercury levels–a representative measure of fetal exposure–are usually higher than the blood mercury levels of mothers (Fok et al., 2007). Mercury can also pass through the blood-brain barrier and accumulate in the central nervous system in an organic form (Philbert et al., 2000). It has been reported that mercury exposure at critical neurodevelopmental periods, such as during the prenatal stage and early childhood, can induce persisting motor, sensory, and behavioral impairment (Karagas et al., 2012; Perera and Herbstman, 2011).

However, the results from previous studies investigating the associations between mercury levels measured in blood or hair and ASD diagnosis or symptoms are inconsistent, indicating positive (Lakshmi Priya and Geetha, 2011; Mohamed et al., 2015), null (Hertz-Picciotto et al., 2010; Rahbar et al., 2013), or even inverse associations (Adams et al., 2008; Holmes et al., 2003). The reasons for such inconsistency may include differences in the type and amount of fish consumed (Taylor et al., 2016), genetic predisposition (Ng et al., 2015), mercury levels (Hui et al., 2016; Thomas et al., 2015), and other population characteristics including selenium levels (Ralston and Raymond, 2010). It may also be due to the presence of a susceptible period for mercury exposure and the potential reverse causation as a result of the change in mercury excretion ability with age among autistic children (Majewska et al., 2010). As most previous studies used only a single biomarker measurement, which was recorded concurrently at the time of outcome assessment (reviewed by Kern et al., 2016), longitudinal studies with repeated measurements of mercury exposure are warranted to appropriately investigate the association between mercury exposure and autistic behaviors.

Growing fetuses and children are more vulnerable to mercury exposure than adults, due to their immature detoxification mechanisms and immune system (Ginsberg et al., 2004). Therefore, in the present study, we investigated the association between mercury exposure–repeatedly measured at different time points, including potentially susceptible periods such as early and late pregnancy and early childhood–and autistic behaviors at 5 years of age, using a prospective birth cohort. Our secondary aim was to investigate the potential sex-specific associations between mercury exposure and autistic behaviors, because previous studies have reported that mercury can induce endocrine disruption and ASD is reportedly associated with aberrations in steroid hormones such as androgens and estrogens (Baron-Cohen et al., 2015).

2. Materials and methods

2.1. Study design and participants

We used data from the Mothers and Children's Environmental Health (MOCEH) study, which is an ongoing multi-center prospective birth cohort study conducted to investigate the health effects of environmental risk factors among mothers and children; detailed information regarding the MOCEH study has been described elsewhere (Kim et al., 2009). In brief, a total of 1751 pregnant women (gestational age at enrollment, 7–27 weeks) were recruited from 3 regions (Seoul, Ulsan, and Cheonan) in the Republic of Korea from May 2006 to December 2012. Women > 18 years old who resided in the 3 targeted regions and were pregnant were included in the MOCEH study. Follow-up surveys were performed when the participating children reached 2, 3, and 5 years of age.

In the present study, we restricted the analyses to mother-child pairs with information on blood mercury concentrations in the mother or child and Social Responsiveness Scale (SRS) scores in the child. of the 551 children who were followed up until 5 years of age, responses to the SRS questionnaire were given for 458; each of these children had at least one measurement of blood mercury level obtained either from mother during pregnancy, or after delivery. Thus, 458 mother-child pairs were included in the final analyses. The sample size decreased considerably from the time of recruitment to study end due to follow-up loss by 5 years of age. This might be because as the children grew up they started to attend kindergarten or other educational institutions and to participate in various activities that made attending study follow-up appointments less of a priority.

All study participants provided written informed consent before participation. The study protocol was approved by the Institutional Review Board of Ewha Mokdong Hospital, Dankook University Hospital, and Ulsan University Hospital.

2.2. Data collection

Well-trained researchers interviewed the participants during each survey by using a structured questionnaire that recorded the demographic characteristics, socioeconomic status, occupational and environmental exposure, nutrition, lifestyle characteristics, and medical history. A validated semi-quantitative food frequency questionnaire (Oh et al., 2007) was used to evaluate participants' dietary intake for 1-year period before the survey. The amount of each food item consumed, including fish, was estimated using the Computer Aided Nutritional Analysis Program 3.0 for professionals (CAN-pro 3.0, Korean Society of Nutrition, Seoul, Republic of Korea). Information regarding parity, birth weight, and child's sex was obtained from the medical records at delivery.

2.3. Blood mercury concentrations

Maternal blood samples were collected during early (12–20 gestational weeks) and late pregnancy (28–42 gestational weeks), and cord blood samples were collected at birth. Blood samples were also obtained from the children during follow-up visits at 2 and 3 years of age. All