Neurotoxicology and Teratology 54 (2016) 61–67

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

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

Low-level gestational exposure to mercury and maternal fish consumption: Associations with neurobehavior in early infancy

Yingying Xu [a], Jane C. Khoury [b], Heidi Sucharew [b], Kim Dietrich [c], Kimberly Yolton [a,*]

[a] Cincinnati Children's Hospital Medical Center, Department of Pediatrics, Division of General and Community Pediatrics, Cincinnati, OH, United States
[b] Cincinnati Children's Hospital Medical Center, Department of Pediatrics, Division of Biostatistics and Epidemiology, Cincinnati, OH, United States
[c] University of Cincinnati, College of Medicine, Department of Environmental Health, Cincinnati, OH, United States

ARTICLE INFO

Article history:
Received 18 June 2015
Received in revised form 10 February 2016
Accepted 11 February 2016
Available online 12 February 2016

Keywords:
NNNS
Methylmercury
Fish consumption
Gestational exposure
Neurobehavior
Infancy

ABSTRACT

Background: Studies examining the effects of low-level gestational methylmercury exposure from fish consumption on infant neurobehavioral outcomes in the offspring are limited and inconclusive. Our objective was to examine the effects of low-level gestational exposure to methylmercury on neurobehavioral outcomes in early infancy.
Methods: We assessed neurobehavior of 344 infants at 5-weeks using the NICU Network Neurobehavioral Scale (NNNS). Gestational mercury exposure was measured as whole blood total mercury (WBTHg) in maternal and cord blood. We collected fish consumption information and estimated polyunsaturated fatty acid (PUFA) intake. We examined the association between gestational mercury exposure and NNNS scales using regression, adjusting for covariates.
Results: Geometric mean of maternal and cord WBTHg were 0.64 and 0.72 μg/L, respectively. Most mothers (84%) reported eating fish during pregnancy. Infants with higher prenatal mercury exposure showed increased asymmetric reflexes among girls ($p = 0.04$ for maternal WBTHg and $p = 0.03$ for cord WBTHg), less need for special handling during the assessment ($p = 0.03$ for cord WBTHg) and a trend of better attention ($p = 0.054$ for both maternal WBTHg and cord WBTHg). Similarly, infants born to mothers with higher fish consumption or estimated PUFA intake also had increased asymmetric reflexes and less need for special handling. In models simultaneously adjusted for WBTHg and fish consumption (or PUFA intake), the previously observed WBTHg effects were attenuated; and higher fish consumption (or PUFA intake) was significantly associated with less need for special handling.
Conclusions: In a cohort with low level mercury exposure and reporting low fish consumption, we found minimal evidence of mercury associated detrimental effects on neurobehavioral outcomes during early infancy. Higher prenatal mercury exposure was associated with more frequent asymmetric reflexes in girls. In contrast, infants with higher prenatal mercury exposure and those whose mothers consumed more fish had better attention and needed less special handling, which likely reflect the beneficial nutritional effects of fish consumption.

1. Introduction

Methylmercury (MeHg) is a widespread environmental pollutant to which humans are exposed primarily through the consumption of contaminated seafood. Neurotoxicity, the most sensitive endpoint used to assess the toxic effects of MeHg exposure, has been well recognized since the outbreak of MeHg poisonings in Minamata Bay, Japan and Iraq (Eto, 1997). Because the brain is the main target tissue for MeHg, and given that MeHg effectively crosses both the placenta and the blood-brain barrier (Stern and Smith, 2003), the developing central nervous system of the fetus and young child is especially vulnerable. During the Minamata outbreak, extreme fetal abnormalities and signs of neurotoxicity were even seen in infants born to women with minimal or no MeHg poisoning symptoms (Harada, 1995).

Effects of gestational exposure to MeHg on neurologic outcomes have been evaluated in epidemiological studies conducted typically among populations with a diet consisting of high levels of fish or sea mammal consumption including several large scale cohort studies. The Faroe Island study, using cord whole blood total mercury (geometric mean = 22.9 μg/L) as a biomarker of gestational exposure, reported MeHg associated deficits in language, memory, attention, motor skills, and visual spatial domains assessed at 7 and 14-years of age (Debes et al., 2006; Grandjean et al., 1997). At age 22 years, MeHg associated deficits in cognitive function were still observed in this cohort (Debes et al., 2016). However, the Seychelles study, in which MeHg exposure

* Corresponding author at: Cincinnati Children's Hospital Medical Center, Department of Pediatrics, Division of General and Community Pediatrics, 3333 Burnet Avenue, ML 7035, Cincinnati, OH 45229-3039, United States.
E-mail address: kimberly.yolton@cchmc.org (K. Yolton).

http://dx.doi.org/10.1016/j.ntt.2016.02.002
0892-0362/

was measured as maternal hair mercury (mean = 6.8 ppm, equivalent to a blood mercury concentration of 27.2 μg/L), evaluated children during a follow up from 6 months to 17 years on similar neurocognitive and neurobehavioral functions (using different assessment tools) and found no evidence of adverse effects of gestational MeHg exposure (Davidson et al., 2011; Davidson et al., 1998; Davidson et al., 1995; Myers et al., 2003; Myers et al., 1995). More recently, in a cohort of Inuit infants from the Canadian Arctic, who were exposed to mercury at levels similar to those in Faroes and Seychelles studies, cord blood mercury (mean = 22.5 μg/L) was associated with poorer performance on working memory and school-age assessment of intelligence (IQ) (Boucher et al., 2014; Jacobson et al., 2015). It is important to note that within the Faroe Island and the Canadian Inuit cohorts, the sources of mercury exposure were both marine mammals and fish, whereas the Seychelles cohort was exposed to mercury primarily from consumption of fish. These different sources of exposure could contribute to the disparate outcomes reported.

Compared to most previously published studies, the level of mercury exposure among US women, with a geometric mean of 0.78 μg/L in whole blood (CDC, 2009), is much lower than in populations that rely more on fish for their diets (for example, the Faroe Island cohort, had a cord whole blood total mercury geometric mean = 22.9 μg/L) (Grandjean et al., 1997). Studies conducted at this level of exposure are limited and findings have been inconsistent. Higher maternal mercury exposure was associated with poorer child cognitive performance (Oken et al., 2008; Oken et al., 2005) or delayed neurodevelopment (Jedrychowski et al., 2006), while higher fish consumption during pregnancy was associated with better child neurocognitive development (Daniels et al., 2004; Oken et al., 2008; Oken et al., 2005; Valent et al., 2013). There were also studies that reported no association between higher maternal mercury exposure and adverse child neurodevelopment outcomes (Daniels et al., 2004; Valent et al., 2013).

While fish is a main source of MeHg exposure for the general population, it is also a major dietary source of omega-3 poly-unsaturated fatty acids (PUFA): eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). DHA, an important structural component of the central nervous system, is believed to have important roles in both visual and neural functions (Innis, 2005). Randomized controlled trials have shown that maternal fish oil supplementation during pregnancy may have beneficial effects on children's eye and hand coordination, and on mental and cognitive development (Campoy et al., 2011; Dunstan et al., 2008; Helland et al., 2003). Longitudinal studies have also associated higher maternal or cord DHA concentrations with better attention, superior memory function, and more optimal visual, cognitive, and motor development in childhood (Boucher et al., 2011; Colombo et al., 2004; Jacobson et al., 2008).

Due to concerns about MeHg exposure, fishing advisories and fish intake guidelines have been developed and distributed (USEPA and USFDA, 2004), which may substantially change dietary behavior regarding fish consumption among pregnant women (Oken et al., 2003). Given the well-established neurotoxicity of MeHg and beneficial effects of fish nutrition (PUFA) on neurodevelopment, it is important to elucidate the neurobehavioral effects of low-level prenatal exposure to MeHg that occurs when fish is consumed. However, studies conducted among low fish consumption populations (and hence low level of MeHg exposure) are quite limited. Moreover, studies assessing neurobehavioral outcomes during early infancy are very limited. A Japanese cohort study reported a negative relationship between higher maternal hair total mercury and the quality of muscle tone and movement assessed using the Neonatal Behavioral Assessment Scale (NBAS)·(Suzuki et al., 2010) Another study conducted in China found that among male newborns, higher cord blood total mercury as well as higher maternal hair total mercury were associated with lower scores on a behavioral cluster of items including, habituation to stimuli during sleep, and orienting responses to visual and auditory stimuli (Gao et al., 2007). Thus, the purpose of the current study was to examine the effects of gestational MeHg exposure on neurobehavioral outcomes during early infancy among a cohort of mothers with exposure levels that are representative of US women. In addition, we aimed to examine the potential confounding effects of maternal fish consumption on the relationship between MeHg and neurobehavior.

2. Methods

2.1. Study participants

The current study utilized participants in the Health Outcomes and Measures of the Environment (HOME) Study, an on-going prospective pregnancy and birth cohort study, conducted in Greater Cincinnati, Ohio. The purpose of the HOME Study is to examine the associations between both prenatal and postnatal exposures to common environmental toxicants and health and developmental outcomes through infancy and childhood. Enrollment was conducted between February 2003 and January 2006. Women, at least 18 years of age, and residing in homes built before 1978 (a criterion for a nested study of lead exposure), were contacted at 16 ± 3 weeks of pregnancy. Of the 468 women enrolled, 389 remained in the study to deliver live-born singleton infants. Details of enrollment have been described elsewhere (Yolton et al., 2009). Institutional Review Boards of all involved research institutions, hospitals, and laboratories approved the study protocol. Written informed consent was obtained from each participant.

2.2. Gestational mercury exposure and fish consumption

We measured whole blood total mercury (WBTHg), a commonly used biomarker for MeHg exposure, in maternal samples collected at around 16 and 26 weeks gestation and at delivery, and in infant cord whole blood. The whole blood samples were collected in EDTA vacutainer tubes, and stored at −80 °C until shipment to the Centers for Disease Control and Prevention (CDC) for analysis. Total mercury was quantified using a quadrupole ICP-MS technology based method (CDC, 2003). The limit of detection (LOD) for total mercury was 0.2 μg/L. For results reported as below LOD (16%, 20%, and 14% for 16-week, 26-week and delivery samples, respectively), we imputed a value of LOD divided by square root of 2 (Hornung and Reed, 1990).

We collected maternal fish consumption information during pregnancy with questionnaires at 16 weeks gestation and 5 weeks postpartum. Using a list of fish selected *a priori* based on their popularity and estimated mercury content (salmon, tuna, shellfish, lake trout, mackerel, swordfish, tilefish, shark), we asked women to identify the types of fish they ate during pregnancy and frequency of consumption for each type. We calculated total fish consumption by summing all fish types. We also estimated total intake of poly-unsaturated fatty acids (PUFA) from fish consumption, based on EPA and DHA (two most abundant omega-3 PUFA in fish) content data reported in the USDA National Nutrient Database (USDA).

2.3. Infant neurobehavior assessment

We assessed infant neurobehavior at around 5-weeks of age during a home visit, using the NICU Network Neurobehavioral Scale (NNNS), administered by trained examiners who were blinded to prenatal exposures. The NNNS is a neurobehavioral evaluation that integrates several infant assessment tools with the heaviest influence from the Neonatal Behavioral Assessment Scale (NBAS) (Lester et al., 2004). The NNNS has primarily been used in the assessment of neurobehavior in infants exposed to drugs of abuse, but the potential value of this measure for the detection of effects of gestational exposure to environmental toxicants has also been recognized (Tronick and Lester, 2013; Yolton et al., 2009; Yolton et al., 2013). The predictive validity of the NNNS has been demonstrated in several studies, which reported NNNS scales or profiles predicted childhood neurodevelopmental outcomes, including