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Mercury exposure, serum antinuclear antibodies, and serum cytokine levels in the Long Island Study of Seafood Consumption: A cross-sectional study in NY, USA

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ABSTRACT

Mercury (Hg) is a well-known neurotoxin, and has been more recently studied specifically as an immunotoxin. In experimental and a few epidemiologic studies, Hg has been associated with distinct cytokine profiles and antinuclear antibody (ANA) positivity, though patterns at lower levels of exposure, typical of seafood consumers with a western diet, are not well characterized.

Seafood consumers (n = 287) recruited on Long Island, NY completed food frequency and health questionnaires and provided blood for analysis of Hg, poly-unsaturated fatty acids (omega-3 and omega-6 fatty acids), selenium (Se), ANA, and several cytokines (IL-1β, IL-4, IL-10, TNF-α, IL-17, IFN-γ, and IL-1ra). Logistic and linear regression analyses were conducted to evaluate associations between serum Hg and cytokines and ANA. Adjusted models accounted for gender, age, ethnicity, income, education, smoking, BMI, selenium, omega-3 fatty acids, omega-6 fatty acids, omega-6/omega-3 ratio, and fish intake. Sex-stratified models were also generated with the expectation that immune profiles would differ between women and men.

Median blood Hg was 4.58 μg/L with 90th %ile = 19.8 μg/L. Nine individuals displayed ANA positivity at serum titers above 1:80; many of the cytokines were below detection limits, and the ability to detect was used in the logistic regression analyses. In linear and logistic regression analyses, Hg was not significantly associated with any of the seven investigated cytokines or with ANA-positivity.

Therefore, Hg was not associated with altered immune profiles in this population of seafood consumers.

1. Introduction

Mercury (Hg) is a known toxin with well-studied neurodevelopmental and neurological effects (WHO 2016). It has been more recently studied as an immunotoxin, primarily in susceptible murine models (Sweet, 2001). Bagenstose et al. (1999) demonstrated immunotoxicity of inorganic Hg in mouse models, as susceptible mice injected with subtoxic $HgCl_2$ doses presented with activated autoimmunity and the development of antibodies to nucleolar antigens (ANoA). Similarly, Pollard et al. (2001) found systemic autoimmunity was accelerated by inorganic Hg exposure in lupus-prone mice, and Via et al. (2003) demonstrated exacerbated induced lupus-like graft-versus-host disease in murine models due to pretreatment with subtoxic inorganic Hg. Immune alterations in murine offspring, including differences in cytokine production, are observed after prenatal exposure to both methylmercury (MeHg) and inorganic Hg (Thuvander et al., 1996; Silva et al., 2005, respectively).

Though Hg has been studied more extensively as an immunotoxin in

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experimental studies, a few epidemiologic studies have been conducted in humans, often using cytokines. Cytokines are small immune-acting proteins with a wide cell target range, secreted by many cell types, including helper T cells, B cells, and macrophages (Luu et al., 2014). They impact the communication of other cells through autocrine, paracrine, or endocrine mechanisms, and can have pro-inflammatory and anti-inflammatory effects. Pro-inflammatory cytokines are excitatory, and include interferon (IFN)- γ, interleukin (IL) − 17, IL-1β, and tumor necrosis factor (TNF)-α (Su et al., 2012, Dinarello et al., 2000, Pinto et al., 1999). Anti-inflammatory cytokines work to subdue this response, and include IL-1ra, IL-10, and IL-4 (Su, and Marie et al., 2012, 1996). However, inflammatory effects of cytokines can depend on the cell of origin, target cell, activating signal, timing of their release, and sequence of cytokine pathways, and therefore properties of cytokines can vary within the immune response (Cavaillon, 2001).

Hg, for its hypothesized pro-inflammatory effects, is expected to be directly associated with pro-inflammatory cytokines, (e.g., IFN- γ, IL-17, IL-1β, and TNF-α) and inversely associated with anti-inflammatory cytokines (e.g., IL-1ra, IL-10, IL-4). In in vitro experimental studies of human peripheral blood mononuclear cells (PBMCs) in the presence of the antigenic stimulus lipopolysaccharide, inorganic Hg was associated with an increase in the release of the pro-inflammatory cytokines IL-1β and TNF-α, and concurrent decrease in release of the anti-inflammatory cytokines IL-1Ra and IL-10 (Gardner et al., 2009). In studies with MeHg there was an increase in the release of IL-1β (Gardner et al., 2010a). IL-4, IL-17, and IFN-γ increased in a concentration–response manner. In epidemiologic studies, Gardner et al. (2010b) found an association between urine Hg and elevated IL-1β, TNF-α, and IFN-γ in a population of occupationally-exposed, ANA-detectable gold miners (n = 98). Nyland et al. (2011a) also found elevated IL-4, IFN-γ, and IL-17 (n = 232) with increased blood MeHg, but among ANA-positive participants (n = 14) found decreased IL-1β, TNF-α, IFN-γ, IL-6, and IL-4 with increased blood MeHg. Gardner et al. (2009) found a negative correlation between monocyte inorganic Hg and IL-10. In a study of maternal and fetal blood Hg from 61 mother-child pairs, neither maternal nor fetal blood MeHg was associated with any cytokine (Nyland et al., 2011b). These studies suggest a need for further investigation: results were not always consistent, pro-inflammatory cytokines were not necessarily associated with higher Hg, and anti-inflammatory cytokines were not necessarily associated with lower Hg.

Differences in routes of Hg exposure and differences in Hg compound forms may contribute to the inconsistency of results across recent studies relating blood Hg to circulating cytokines. Differences between elemental and inorganic occupational exposures may impact cytokine proliferation (Nyland et al., 2011a). Occupational gold mining generates waste with high levels of Hg, leading to high total blood Hg levels not only in gold mining populations, but also in non-miners who live near the work sites (de de Andrade Lima et al., 2008; Castilhos et al., 2015). Higher total serum Hg levels in these populations are primarily due to inhalation of Hg vapor, but may also be due to consumption of seafood contaminated with relatively high levels of MeHg due to bioaccumulation in fish. The population in our study consists of avid seafood consumers who are primarily exposed to MeHg (Mahaffey, 2009; UNEP, 2013), as opposed to inorganic or elemental occupational exposure. Differences in males and females may also impact the consistency of Hg immunotoxicity related to cytokines: males and females are known to differ in their immune profiles, most likely due to differences in sex steroids (Pellegrini, 2011; Giefing-Kroll, 2015).

Blood selenium (Se) and fatty acid levels should also be considered when conducting analyses of blood Hg, particularly when relating blood Hg to immune markers. Previous work has suggested opposing influences of Hg and Se (Khan and Wang, 2009; Ralston et al., 2008; Ralston and Raymond, 2010), and experimental and clinical studies have shown effects of Se on immune function (Lemire et al., 2010; Raymond, 2007; Hoffmann and Berry, 2008). Omega-3 and omega-6 fatty acids are known to have anti- and pro-inflammatory effects, respectively, and thus may confound analyses including Hg; ratios of the two are often measured to evaluate potential inflammation (Patterson et al., 2012).

In addition to the aforementioned circulating cytokines, another important immune function marker and immunotoxicity marker is antinuclear antibody (ANA), which is an autoantibody that stimulates inflammation (ACR 2015). Positive ANA tests, particularly at high titers, can indicate the presence of autoimmune disease, including lupus, Sjögren's syndrome, polymyositis, and juvenile rheumatoid arthritis.

Gardner et al. (2010b) and Nyland et al. (2011a) found a positive correlation between mean levels of urine Hg and MeHg and the number of ANA-positive participants. Similarly, Silva et al. (2004) found increased mean blood MeHg correlated with positive ANA test results, specifically in seafood-consuming participants. Somers et al. (2015) found significant associations between total blood Hg (primarily representing MeHg exposure) and ANA-positivity (mean blood Hg = 0.92 μg/L), as well as between hair Hg and ANA-positivity (mean hair Hg = 0.22 ppm), though no association was seen in ANA models with urinary Hg (mean urinary Hg = 0.62 μg/L). Both Gallagher et al. (2013) and Dinse et al. (2016) did not find significant associations between blood Hg and ANA-positive results (Gallagher: mean total blood Hg for ANA-positive = 1.30 μg/L, mean total blood Hg for ANA-negative = 1.47 μg/L; Dinse: mean total/inorganic blood Hg not presented but likely < 2 μg/L). One factor complicating the interpretation of these results is that the criteria for defining ANA positivity differs across many of these studies. Our measure of ANA positivity (1:80 titer cutoff) is the same as that used in Somers et al. (2015).

We tested the hypothesis that increased blood levels of total Hg, primarily as a result of MeHg exposure from seafood consumption, are correlated with increased pro-inflammatory cytokines, decreased anti-inflammatory cytokines, and increased positive ANA in a population of avid seafood consumers from Long Island, NY, USA.

2. Methods

2.1. Participant recruitment

Stony Brook University's Committee on Research Involving Human Research Subjects (CORIHS) approved the study (IRB #2010-1179). From the general Long Island population, 290 avid seafood consumers were recruited between 2011 and 2012. Participants were recruited in person and through posted flyers at seafood markets and restaurants, gyms, libraries, university bulletin boards, and fishing piers. Three advertisements and an article also ran in a newspaper (Newsday) about the study.

Those interested (996 individuals) were informed that the study was being conducted as a risk-benefit analysis of seafood intake. Each person filled out an online survey to estimate blood Hg levels based on his/her reported seafood consumption, using seafood Hg concentrations reported in Karimi et al., 2012. An estimated whole blood Hg level of 5.8 μg/L (corresponding to the USEPA reference dose of 0.1 $\mu g\, kg^{-1}\, day^{-1}$) was used as a cutoff for study eligibility to ensure adequate power to examine risks as well as benefits. Of the 746 eligible, 290 participants chose to enroll.

2.2. Questionnaires

Participants filled out a semi-quantitative Block food frequency questionnaire (FFQ), a semi-quantitative FFQ supplement, and a health questionnaire. The FFQ included questions regarding type, quantity, and frequency of food consumption, and the FFQ supplement included questions regarding the type, quantity, and frequency of different types of seafood. Answers to the seafood questionnaire were converted into cups/week of total seafood intake for these analyses. The health