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Methylmercury and neurodevelopment: Longitudinal analysis of the Seychelles child development cohort☆

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Abstract

Background: The Seychelles Child Development Study (SCDS) has been longitudinally following a cohort of over 700 children enrolled in 1989. Their mothers consumed a diet high in fish during pregnancy. Repeated examination of the SCDS cohort at six different ages through age 11 years has shown no pattern of adverse effects. Some early appearing beneficial associations between both prenatal and postnatal hair MeHg and several child development endpoints were noted. We hypothesized these might be related to micronutrients in the fish, but they were not found when the children reached middle school age. These findings suggest that the associations observed between MeHg and developmental outcomes may vary with developmental stage. *Method*: We examined the main cohort of the SCDS to determine if this might be true using a longitudinal multiple regression analysis design that focused on those endpoints that were repeatedly measured at different ages. The primary endpoint analyzed was global cognition, involving a measure of developmental quotient or IQ. Secondary analyses included other domains such as Reading and Mathematics scholastic achievement, social behavior, and memory. Analyses involved two different approaches, one including incorporation of a passage of time variable, the other including a difference of scores across time points. *Results*: No significant associations were found between prenatal MeHg exposure and any of the repeatedly measured endpoints. *Conclusions*: These results suggest that even when individual subject variance is controlled there was no consistent pattern of associations between child development outcomes and prenatal exposures to MeHg from maternal consumption of a diet high in fish. The Seychellois diet contains about 10 times more ocean fish than is typically consumed by US citizens. Our primary focus on IQ should further inform growing scientific interest in the analysis of the risks and benefits of fish consumption on overall cognitive ability.

Keywords: Child development; Methylmercury; Longitudinal analysis

1. Introduction

Mercury is ubiquitous in the global environment, ensuring universal exposure to small amounts [24,33]. Fish the world over contain small amounts of methylmercury (MeHg). In aquatic environments, microorganisms methylate mercury and it is then bioaccummulated and bioconcentrated up the food chain [34]. The concentrations in fish and sea mammals vary according to

☆ See Verbeke and Molenberghs [30] or Diggle et al. [10] for a detailed discussion of mixed model approaches to longitudinal data. In the context of effects of blood–lead concentrations on cognitive development, see Waternaux et al. [31].

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species, age and size of the animal. In high doses, human MeHg exposure is known to cause intellectual deficiency, cerebral palsy and microcephaly [13,18,24,28]. Whether exposure to smaller doses of MeHg adversely affects neurodevelopment is unclear but of considerable contemporary scientific and public health concern.

Following an outbreak of methylmercury poisoning in Iraq in the mid-1970s, data suggested that the threshold for neurodevelopmental sequelae might be as low as 10 ppm of MeHg as measured in maternal hair [7]. Pregnant women who consume fish can achieve hair levels of 10 ppm. Indeed, maternal hair levels around the globe often exceed this level. In the Seychelles Child Development Study and also in a Japanese survey [36] the highest hair level was 27 ppm while in the Faeroe Islands study it reached approximately 80 ppm [12].

Cross-sectional epidemiological research from Canada [21] and New Zealand [16,17] has suggested that exposures below 10 ppm might cause subtle neurodevelopmental abnormalities in prenatally exposed children. This finding also resulted from a cross-sectional analysis of data from the longitudinal study being conducted in the Faeroe Islands [12]. However, data from Peru [19] and cross-sectional analysis of data from the Seychelles Child Development Study (SCDS: a longitudinal study taking place in the Republic of Seychelles where the range of exposures was similar or higher than that reported by other studies) have not confirmed these findings [8,9,23,22]. Repeated examination of the SCDS cohort at six different ages through 11 years has shown no pattern of adverse effects. Indeed, the study found some early appearing beneficial associations between maternal and child hair MeHg and several child development endpoints that we hypothesized might be related to micronutrients in the fish. These beneficial associations were not present when the children reached middle school age, suggesting that associations between MeHg and developmental outcomes may vary with developmental stage. This question is best studied using a longitudinal analysis. Such analyses afford precision in accounting for within-subject effects that may change over time as a result of many factors including chronic exposure, social factors, and developmental differences. Modeling data from multiple time points simultaneously also provides greater power for the detection of an effect of prenatal exposure than cross-sectional analyses [30].

The SCDS has been following a cohort of over 700 children enrolled in 1989. Their mothers reported consuming an average of 12 fish meals per week during pregnancy. We report here the results of a longitudinal analysis of our data. To our knowledge it is the first longitudinal analysis undertaken in the literature on human prenatal MeHg exposure.

2. Method

2.1. Subjects

The study cohort of 779 initially enrolled mother–infant pairs represented 50% of live births in the Republic of the Seychelles during the enrollment period (February 1989 to January 1990). A total of 39 pairs were omitted from the original cohort: 15 had inadequate maternal hair samples to assess exposure, six were twins, and 18 met *a priori* exclusion criteria described elsewhere [19]. Of the remaining 740 pairs, the final cohort examined initially at 6 months, 738 pairs were available for follow-up at 19 months, and 736 at 29 months. At 66 months there were 735 eligible and at 107 months there were 717 eligible. From those there were 711 seen at 66 months and 643 seen at 107 months.

2.2. Informed consent and protection of human subjects

The study protocol was reviewed and regularly re-approved by the Human Subject Review Boards both at the University of Rochester and in the Republic of Seychelles. Informed consent was obtained from a parent or guardian before their child initially participated in the study and re-consenting took place at each subsequent examination. Families were never informed of the mother's hair Hg level.

2.3. Mercury exposure

Prenatal exposure was assessed using the mean of the total mercury (THg) concentration in the longest available segment of maternal hair representing growth during pregnancy as described previously [4]. Total Hg was used as the measure of exposure because 80% of THg in hair samples collected from fish eating populations is methylmercury [4,25]. The THg in maternal hair also correlates well with the concentration of organic mercury levels in maternal hair and blood [34]. Mercury in maternal hair and blood has been compared to levels of mercury in the brain [4]. In this study, autopsy brains were available from infants dying of natural causes within a few weeks of birth. The mercury concentration in samples of maternal blood and hair mercury was measured. The correlation coefficients of the mercury levels in these samples with levels in six anatomical regions of the infant brain were similar, indicating that maternal blood was no better predictor of brain levels of mercury than maternal hair levels.

The mean of the available maternal hair levels representing prenatal exposure was 6.8 ppm (SD=4.5, range=0.5 to 26.7 ppm). Recent postnatal exposure was assessed using a 1 cm segment (representing approximately 1 month of exposure) of the child's hair closest to the scalp at the time of the 66 month and 107 month evaluations only. The mean postnatal hair level at 66 months was 6.5 ppm (SD=3.3, range=0.9 to 25.8 ppm) and 6.1 ppm at 107 months (SD=3.5, range=0.5 to 24.8 ppm). Prenatal and postnatal concentrations were not highly correlated at either 66 months (Pearson $r=0.15$) or 107 months (Pearson $r=-0.08$). The Pearson r between THg concentrations at 66 and 107 months was 0.44. At 107 months, 143 males out of the 643 cohort children had shaved their heads for stylistic purposes. For these missing values, we substituted a hair sample gathered at 66 months for 129 subjects and at 48 months for 14 subjects.

2.4. Study design and test battery

The test battery measured developmental functions or domains hypothesized to be affected by prenatal exposure to MeHg and is