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ScienceDirect
NeuroToxicology 27 (2006) 1106–1109
NeuroToxicology

Commentary

Prenatal methyl mercury exposure from fish consumption and child development: A review of evidence and perspectives from the Seychelles Child Development Study☆

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Received 12 December 2005; accepted 29 March 2006
Available online 15 April 2006

Abstract

Evidence from an outbreak of methyl mercury (MeHg) poisoning in Iraq suggested that adverse effects of prenatal exposure on child development begin to appear at or above 10 ppm measured in maternal hair. To test this hypothesis in a fish-eating population, we enrolled a cohort of 779 children (the main cohort) in the Seychelles Child Development Study (SCDS). The cohort was prenatally exposed to MeHg from maternal fish consumption, and the children started consuming fish products at about 1 year of age. Prenatal exposure was measured in maternal hair and recent postnatal exposure in the child's hair. The cohort has been examined six times over 11 years using extensive batteries of age-appropriate developmental tests. Analyses of a large number of developmental outcomes have identified frequent significant associations in the appropriate direction with numerous covariates known to affect child development, but only one adverse association between prenatal MeHg exposure and a developmental endpoint. Because such results could be ascribed to chance, there is no convincing evidence for an association between prenatal exposure and child development in this fish-eating population. Secondary analyses have generally supported the primary analyses, but more recently have suggested that latent or delayed adverse effects might be emerging at exposure above 10–12 ppm as the children mature. This suggests that the association between prenatal exposure and child development may be more complex than originally believed. This paper reviews the SCDS main cohort study results and presents our current interpretations.

Keywords: Methyl mercury; Developmental neurotoxicity; Child development; Delayed neurotoxicity

The Seychelles Child Development Study (SCDS) was designed to study the developmental effects of prenatal MeHg exposure in a fish-eating population. A number of social, dietary and economic factors make the Seychelles Islands an optimum environment for studying the effects of prenatal exposure to MeHg arising from fish consumption. The Seychellois consume large quantities of fish and the ocean fish consumed there are similar in species and MeHg content to commercially available fish in the US. They do not consume sea mammals. The Seychelles is westernized and health care for children and mothers emphasizes prevention and is free and readily available. Infant mortality, childhood infectious diseases, maternal antenatal care and preventive pediatric care are all comparable to those in the US (Govinden et al., 2004). Education starts with Créche (preschool) at age 3.5 years and is free, readily available and compulsory through age 16 years. Exposure to other neurotoxicants is minimal: no cases of lead poisoning have been reported, PCB levels measured in a subset of the main cohort were undetectable, and pesticide levels fall within acceptable WHO limits.

In 1989 and 1990, 779 infant–mother pairs were enrolled in the main study. The Rochester mercury laboratory measured prenatal exposure in maternal scalp hair growing during pregnancy. Since enrollment, we have evaluated a wide range of neurodevelopmental endpoints during six separate testing sessions when the children were 6.5 months to 10.5 years of

☆ Parts of this paper were presented at the 21st International Neurotoxicology Conference, Honolulu, Hawaii, February 12–14, 2004.

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doi:10.1016/j.neuro.2006.03.024

age. Covariates known to be associated with child development have shown anticipated effects at each testing age, suggesting that our tests were appropriate for the Seychelles setting (Myers et al., 2003; Sloan-Reeves et al., 2004). At enrollment, the mothers averaged 12 fish meals each week.

The primary analysis plan was predetermined and designed to test the hypothesis that *prenatal exposure* to MeHg from fish consumption would be associated with adverse neurodevelopmental outcomes in children. Multiple linear regression models were used at each testing age to determine the presence of an association between prenatal exposure and each endpoint. Starting at 5.5 years of age we also included recent postnatal exposure in the analyses[1]. This was determined by measuring Hg in the proximal 1-cm of the child's hair taken at the evaluation.

1. Results to date

Our primary analyses have so far identified only one adverse association with prenatal exposure: at 9 years of age, performance on the grooved pegboard, a test of motor speed and coordination, declined in the non-dominant hand with increasing prenatal exposure (Myers et al., 2003). We also reported one association with prenatal exposure indicating performance improvement as exposure increased (the preschool language scale total language score at 66 months) and one association that was indeterminate (boys' activity level on an observer rating scale at 29 months decreased with increasing prenatal MeHg exposure, but we cannot be sure this was either adverse or beneficial).

Beginning with the 66-month evaluations, we used non-linear modeling as a part of a secondary analysis. The rationale for this approach stemmed from the assumption that subtle changes in the association between any endpoint and increasing exposure levels might escape detection by assuming linear relationships (Axtell et al., 2000). Other toxicologists have also suggested such a possibility (Melnick et al., 2002). At 66 months, the non-linear models for the CBCL Total score and the PLS Language score hinted at better performance with exposures above about 10 ppm (Axtell et al., 2000). This apparently *beneficial* association was similar to the results obtained using multiple linear regressions when the cohort children were 66 months old which were interpreted as most likely due to the influence of micronutrients in fish (Davidson et al., 1998).

Huang et al. (2005) also conducted a secondary analysis on six of the 9-year endpoints using non-linear models. One of these six endpoints, the grooved pegboard using the dominant hand, suggested an adverse association at the upper end of the exposures in our cohort. This endpoint was not significantly influenced by exposure when the analysis was performed using multiple linear regression. The test was not given at earlier

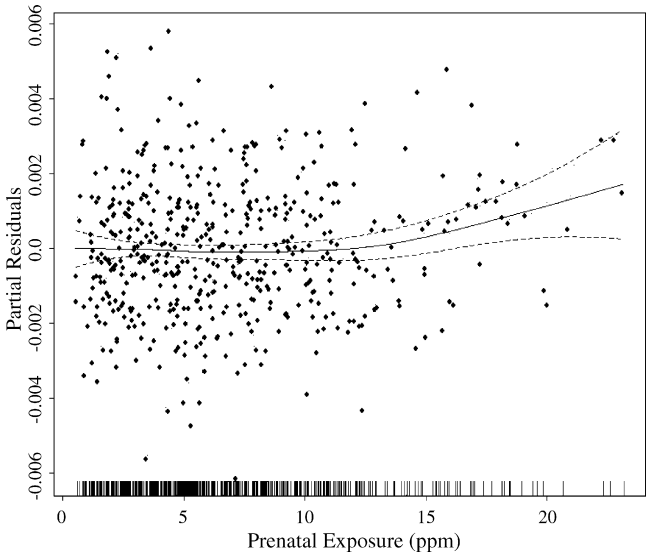

Fig. 1. Generalized additive model analysis of grooved pegboard, preferred hand data from 9 years. Partial residuals represent individual subject scores adjusted for all covariates except prenatal exposure (from Huang et al., 2005).

ages. Fig. 1, adapted from Huang et al. (2005) illustrates this finding. The curve shows no perceptible trend at the lower MeHg levels but an upward trend when maternal hair levels exceed approximately 10–12 ppm. Although data above 10–12 ppm are limited, as is apparent from the rug plots along the *x*-axis, a slightly elevated risk of adverse effects at the upper range of the observed MeHg levels may exist. This plot resembles the one reported by Cox et al. (1989) (shown in Fig. 2) following the mass poisoning episode in Iraq in 1971–1972 initially described by Bakir et al. (1973).

These non-linear analyses suggest that the SCDS must consider the potential for adverse effects of prenatal MeHg exposure at maternal hair levels above 10–12 ppm, but the numbers of observations in that exposure range are limited. One possible interpretation of these results is that adverse effects may be emerging as the children enter adolescence.

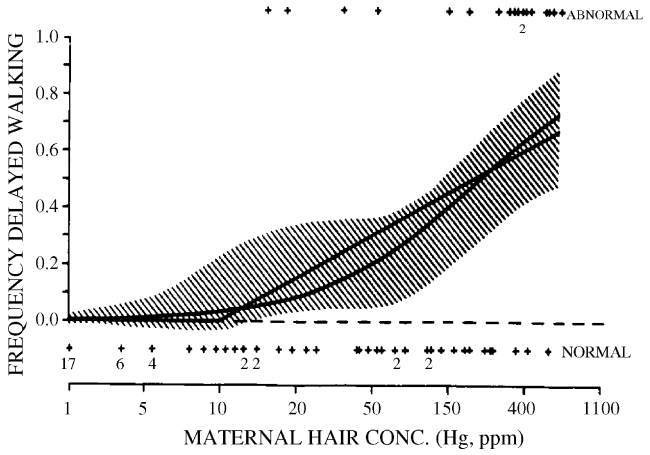

Fig. 2. Hockey stick dose–response curve depicting adverse association between prenatal exposure to MeHg and onset of walking in Iraqi children. Presence or absence of walking was ascertained by parent recall and dichotomized at 18 months (from Cox et al., 1989).

[1] The Pearson correlations between prenatal and postnatal exposure measures were very low at both 66 months ($r = 0.15$, Davidson et al., 1998), and at 107 months ($r = -0.08$, Myers et al., 2003).