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Neurotoxicity from prenatal and postnatal exposure to methylmercury

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ABSTRACT

The extent to which postnatal methylmercury exposure contributes to neurobehavioral delays is uncertain. Confounding may occur because the child's dietary exposure likely correlates with the mother's. This conundrum was examined in the Faroese birth cohort 1 born in 1986–1987. Exposure parameters included mercury concentrations in maternal hair at parturition, cord blood, and child blood and hair at the age-7 clinical examination ($N = 923$). In regression analyses, the child's current blood-mercury at age 7 ($N = 694$) showed only weak associations with the neuropsychological test variables, but visuospatial memory revealed a significant negative association. Mutual adjustment caused decreases of the apparent effect of the prenatal exposure. However, such adjustment may lead to underestimations due to the presence of correlated, error-prone exposure variables. In structural equation models, all methylmercury exposure parameters were instead entered into a latent exposure variable that reflected the total methylmercury load. This latent exposure showed significant associations with neurodevelopmental deficits, with prenatal exposure providing the main information. However, postnatal methylmercury exposure appeared to contribute to neurotoxic effects, in particular in regard to visuospatial processing and memory. Thus, addition in the regression analysis of exposure information obtained at a different point in time was not informative and should be avoided. Further studies with better information on exposure profiles are needed to characterize the effects of postnatal methylmercury exposure.

1. Introduction

While methylmercury is a proven developmental neurotoxicant, most of the evidence regards prenatal exposures (Grandjean et al., 2010; Karagas et al., 2012). From documented poisoning episodes, neurotoxicity is well described in children who have consumed contaminated fish (Harada, 1995; Takeuchi and Eto, 1999). Thus, adverse effects on brain development should be considered a risk associated with postnatal exposures as well. However, due to the low methylmercury concentration in human milk (Grandjean et al., 1995), any such effects would likely occur only after a weaned child has started consuming seafood. Several studies document that exposures at preschool or early school age are much lower than those associated with the mother's seafood intake during pregnancy (Debes et al., 2006; Karagas et al., 2012). Thus, the challenge is to separate possible postnatal neurotoxicity from adverse effects due to much higher prenatal exposures. As only recent exposure is reflected by mercury concentrations in hair and blood, studies of postnatal mercury exposures in young children have produced mixed results (Karagas et al., 2012; Myers et al., 2009).

Most published studies of school-age children include mercury biomarkers that indicate current exposure levels, rather than long-term exposures. In addition, confounding may occur due to prenatal methylmercury exposure and benefits from fish consumption. For example, 72 Spanish children were assessed by the McCarthy Scales of Children's Abilities; those with a hair-mercury concentration of 1 μg/g (corresponding to the US EPA Reference Dose) showed lower scores on general cognitive, memory, and verbal abilities (Freire et al., 2010). Of note, each child's fish consumption, as reflected by their hair mercury, rather than prenatal fish consumption by their mothers, was associated with the deficits. However, the lack of information on fish intake and prenatal exposure makes it difficult to draw conclusions from such evidence. In a study of Canadian Inuit children, neither prenatal nor concurrent mercury exposure was associated with child behavior ratings at 4–6 years of age (Plusquellec et al., 2010).

Using neurophysiological tests of gross and fine motor skill, current, but not prenatal, mercury was associated with increased action tremor amplitude at 4–6 years of age (Despres et al., 2005). In addition, prenatal mercury exposure was associated with longer latencies in visual evoked potentials (VEPs), whereas concurrent mercury was associated

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with shorter VEP latencies (Saint-Amour et al., 2006). The most recent follow-up of this population assessed performance on auditory event-related potentials (ERPs) at ages 10–13 years. Cord blood mercury was associated with both adverse and potentially beneficial effects on early auditory information processing, with increased reaction time and increased latency but fewer false alarms (i.e., false-positive errors) and greater amplitude of response on the auditory ERP task (Boucher et al., 2010). Of note, the concurrent blood mercury (median, 2.8 μg/L) was not associated with auditory ERP performance. In the Faroes, delays in transmission of auditory brain signals in 14-year-old birth cohort members were associated with each child's recent mercury exposure from fish in their own diets, not with their prenatal mercury exposures (Murata et al., 2004). Perhaps the neurophysiological outcomes are more robust than neuropsychological test results and thus more likely to reveal effects of postnatal methylmercury exposure.

The concern that postnatal methylmercury exposure might influence neurobehavioral outcomes affected by prenatal exposure has inspired some investigators to include routine adjustment for postnatal exposure in reports on prenatal methylmercury neurotoxicity (Myers et al., 2003). Similarly, when examining the possible effects of postnatal methylmercury exposure from fish consumption, the researchers adjusted for prenatal exposure in their models (Myers et al., 2009). Such adjustment may represent an imperfect solution to a common problem.

Three challenges complicate the identification of neurobehavioral effects from postnatal methylmercury exposure. The exposure during childhood may vary over time, and exposure assessment at any particular point in time may be an imprecise indicator of the postnatal exposure trajectory. Further, postnatal exposures are lower than prenatal levels (Budtz-Jorgensen et al., 2004a; Karagas et al., 2012), and a decreased postnatal susceptibility will make it difficult to identify effects associated with childhood exposures, unless particular outcome variables are more sensitive to exposures during postnatal development. Finally, postnatal exposures are likely to be associated with the prenatal levels, thereby complicating statistical adjustments. Covariates, such as essential nutrient intakes from seafood, may vary as well over time, thereby further complicating attribution of adverse effects to methylmercury exposures at specific ages. Given the substantial data base available on the first Faroese birth cohort (Budtz-Jorgensen et al., 2007; Grandjean et al., 1997, 2012), we have now applied more advanced statistical models to determine the possible significance of postnatal exposures to methylmercury in regard to neurobehavioral performance.

2. Materials and methods

2.1. Cohort establishment and exposure assessment

A birth cohort was generated in 1986–1987 at the three hospitals in the Faroe Islands (Grandjean et al., 1992). In connection with each singleton birth, cord blood and maternal hair were collected for subsequent analysis. At age 7 years, 923 (90%) of the cohort members participated in a thorough clinical examination with a focus on nervous system function. Methylmercury exposure at age 7 was based on analysis of the child's hair, which was obtained from almost all children, and blood-mercury concentrations were available for 672 cohort members at this age (Grandjean et al., 1999). The number of blood-mercury results has now been increased to 694 by utilizing an improved analytical method that required a smaller blood volume (Petersen et al., 2008). Quality assurance data suggest that laboratory variance was very small and contributed very little to the total imprecision (Budtz-Jorgensen et al., 2007). Both prenatal and postnatal exposures may be a reflection of household dietary habits and availability of seafood, including pilot whale meat, the main source of methylmercury in this community at the time (Fig. 1) (Weihe et al., 1996).

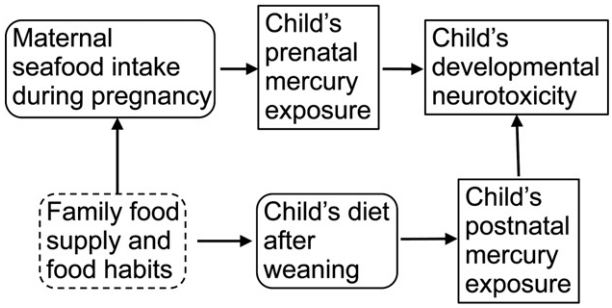

Fig. 1. Directional acyclic graph showing the relationship between diet and developmental exposures to methylmercury and the possible impact of household dietary habits and seafood supply.

2.2. Neuropsychological tests

The individual tests have been previously described (Grandjean et al., 1997) and are briefly outlined here. We used the Neurobehavioral Evaluation System (NES2) Finger Tapping Test (Dahl et al., 1996; Letz and Baker, 1988), where the scores were the maximum number of taps with the preferred hand, the non-preferred hand, and both hands. In the NES2 Hand-Eye Coordination Test, the score was the average deviation from the stimulus in the best two trials. The third computer-assisted test, the NES2 Continuous Performance Test (CPT) is a 4-min attention test using a series of animal silhouettes flashed on the computer screen, where the scores were the total number of missed responses and the average reaction time during the last 3 min. Only the supervised CPT data from the first year were used. All of these outcomes were considered motor tests.

In the Bender Visual Motor Gestalt Test (Schlange et al., 1977), a visuospatial test, we scored the errors in the copying condition using the Göttingen system, while, in the recall condition, we summed the number of recognizable figures.

Among the verbally mediated tests, we used three Wechsler Intelligence Scale for Children—Revised (WISC-R) subtests (Wechsler, 1974), i.e., the Digit Spans number of correct trials in the forward condition, the Similarities raw scores, and the Block Designs scored according to WISC-R criteria based on correct design with bonus points for quick performance. We also used a Faroese translation of the California Verbal Learning Test (Children) (Delis et al., 1994), where we scored the total number of correct responses during five learning trials, the spontaneous recall after an interference list (short recall), and the spontaneous recall of the initial 20 min later (long delay) and the number correctly recognized. In the Boston Naming Test (Kaplan et al., 1983), we scored the number of objects correctly named, both spontaneously and after semantic and phonemic cueing.

2.3. Statistical analysis

We used data from subjects with complete prenatal and postnatal exposure information only. In addition to age and sex as obligatory covariates for all outcomes, we also included adjustment for the maternal score on Raven's Progressive Matrices (Raven, 1958), medical risk for neurobehavioral deficit, maternal and paternal education level, paternal employment, and day care (Grandjean et al., 1997, 2012). The computer-assisted tests were further adjusted for the child's acquaintance with computers and computer games. Because the Similarities test was administered by two different examiners, adjustment for examiner was included. While seafood nutrients may cause negative or reverse confounding of methylmercury neurotoxicity (Choi et al., 2014), we have access only to the number of fish dinners per month and did not attempt to include this parameter in the analysis (Budtz-Jorgensen et al., 2007).

Two neuropsychological outcomes were transformed for the residuals to approach a Gaussian distribution of the residuals, i.e., the