DELAYED NEUROTOXICITY DUE TO DEVELOPMENTAL EXPOSURE TO METHYLMERCURY

Philippe Grandjean, Pal Weihe, Roberta F. White (University of Southern Denmark, Odense, Denmark; Boston University Schools of Medicine and Public Health, Boston, MA 02118, USA; Faroese Hospital System, Torshavn, Faroe Islands) Email: pgrandjean@health.sdu.dk

Abstract

The main concern regarding methylmercury toxicity is CNS damage during fetal development. In carrying out a definitive epidemiological study, the major challenges include the proper consideration of toxicokinetic factors in exposure assessment and of psychometric properties and sensitivity in outcome assessment. We have conducted studies in school children from three different settings. In the Faroe Islands, where mercury exposure mainly comes from pilot whale meat, the main neuropsychological dysfunctions affected were attention, language and memory. In addition, delays were seen on evoked potentials. A small cross-sectional study on the island of Madeira offered limited support of these findings, especially regarding delayed latencies of evoked potentials. Children from the Brazilian Amazon showed mercury-associated decrements on neuropsychological tests of motor function, attention, and visuospatial performance (language function could not be tested). In concert, these studies demonstrate that widespread effects on nervous system function are associated with developmental methylmercury exposure, even at exposure levels previously considered safe.

Introduction

Neurotoxicity may occur in children exposed to methylmercury during early life, but the dose-response relationships have been controversial, in part because of uncertainties associated with observational studies (Grandjean, 1999). The likelihood of an epidemiological study showing a significant association between mercury exposure and neurobehavioral decrement depends on several factors, including the statistical power. The exposure assessment must be designed in accordance with the toxicokinetic fate of methylmercury in the body, and the timing of specimen sampling must reflect the susceptible period(s) of brain development. In choosing and evaluating outcome variables, their psychometric properties and their sensitivity to anticipated effects in the age group examined must be taken into account. Because other factors may affect nervous system development, covariates must be carefully evaluated as to their possible confounding effects, and other potential sources of bias must be taken into account.

We have conducted studies in three different settings with different dietary sources of methylmercury (Grandjean et al., 1997; Grandjean et al., 1999a; Murata et al., 1999). In the Faroe Islands, methylmercury exposure mainly originates from pilot whale meat which is regularly eaten as thin slices of cured meat or, occasionally, as steaks. In Madeira, mercury exposure originates from ocean fish, particularly black scabbard. In the Brazilian Amazon, release of mercury from gold mining results in contamination of freshwater fish downstream with methylmercury. Subjects in these communities who eat contaminated food only rarely or not at all constitute a built-in control group.

Methods

In the Faroes, we are currently studying two birth cohorts prospectively (Grandjean et al., 1997;

Steuerwald et al., 2000). Cohort 1 was born in 1986-1987, and 917 children (90% of the cohort) were first examined at age 7 years. Cohort 2 (182 children) was born in 1994 and is being examined annually. At the two other locations, cross-sectional studies were carried out. relatively stable. On Madeira, we examined 149 first-grade children. We also examined 351 children aged 7-12 years in four Amazonian villages.

Methylmercury exposure was assessed in the Faroes from the mercury concentration in cord blood. In addition, the maternal hair mercury concentration at parturition was assessed. In Madeira, the current maternal hair-mercury level was used as a proxy for the child's exposure *in utero*. However, as maternal hair samples were unavailable for one-third of the Amazonian children and because household mercury levels were closely correlated, the child's own hair-mercury level was applied as a developmental exposure marker.

Detailed physical examinations were carried out using standardized protocols. In Faroese Cohort 2, we applied the Neurological Optimality Score as the most advanced schedule. Blood pressure and heart rate variability were measured in Cohort 1 at age 7 years.

Psychological tests were selected for all studies according to strict criteria (White et al., 1994). While crude developmental tests feasible in small children may not be very sensitive to subtle neurotoxicant effects, neuropsychological tests applicable at school age may be more likely to reveal dysfunctions. Tests were selected to reflect functional domains thought to be vulnerable to prenatal methylmercury exposure. In addition to psychometric properties and sensitivity, cultural differences also have to be considered in selecting the tests and in evaluating the results. In Madeira, the tests had to be administered with the help of an interpreter in the school gymnasium, and the results must therefore be considered less reliable. In the Amazon, language tests were not feasible, and only simple tests were administered that required a minimum amount of instruction.

We also applied neurophysiological tests to assess latencies for evoked potentials following visual and auditory stimuli in the Faroes and Madeira. In addition, we examined vision and hearing functions.

Results and Discussion

In the largest study, the Faroese Cohort 1, mercury-related neuropsychological dysfunctions were observed, especially in attention, language and verbal memory (Grandjean et al., 1997). Motor speed was better related to mercury concentrations in the maternal hair than to cord blood concentrations, possibly reflecting vulnerability to exposures earlier in gestation, perhaps during the second semester (Grandjean et al., 1998). However, visuospatial function was particularly associated with postnatal exposures (Grandjean et al., 1999b). While vision and hearing appeared unaffected, delays were seen the auditory brainstem evoked potentials. However, physical examination revealed only questionable findings. The neuropsychological outcomes remained significantly associated with mercury after confounder adjustments and exclusion of children with high exposures to mercury or increased concomitant exposures to PCB (Grandjean et al., 1997; Budtz-Jørgensen et al., 1999).

In the cross-sectional study on Madeira, peak latencies of evoked potentials showed delays at increased levels of maternal hair-mercury concentrations. Results of the neuropsychological tests using an interpreter showed weak tendencies of a mercury effect. Although the maternal hair mercury concentration is probably an imprecise indicator of the causative exposure, the evoked potential measure is considered reasonably independent of confounders (Murata et al., 1999).

The Brazilian children showed mercury-associated decrements on neuropsychological tests of motor function, attention, visuospatial performance and memory for designs (Grandjean et al., 1999a). Again, although the current hair-mercury concentration may not necessarily reflect the developmental exposure level, the Amazon villages are remarkably homogeneous, and confounding was thought to be limited.

Blood pressure showed a surprising dose-response relationship, where an increase in blood pressure occurred up to a cord blood mercury concentration of about 10 µg/l (corresponding to about 2 µg/g maternal hair) and then increased no further (Sørensen et al., 1999). Whether compensatory mechanisms play a role is not known, but a decrease in heart rate variability seemed not to level off completely at high exposures. These findings could possibly be explained by mercury effects on the autonomic nervous system.

In concert, these studies demonstrate that widespread effects on nervous system functions are associated with developmental methylmercury exposure. The cognitive effects are not associated with detectable sensory impairment, but delays in evoked potential latencies occur. Although clinical effects appear minimal on physical examination, slight effects are seen neonatally on the optimality scale. Notably, adverse effects appear to occur at exposure levels previously considered safe.

Although the mercury-associated effects may seem subtle, each doubling in prenatal mercury exposure corresponds to a delay of one or two months in mental development at age 7 years (Grandjean et al., 1997). Because rapid development occurs at that age, such delays may be important. The delays corresponded to 5-10% of the standard deviations (Grandjean et al., 1999). Although we did not attempt to assess IQ, which has a standard deviation of 15, a similar effect on this measure would have been approximately 1 IQ point for each doubling of the exposure. This calculation is presented only for comparison purposes, as IQs are unavailable.

The mercury effects may be overestimated if some other neurotoxicant associated with mercury is the true cause of the effects. However, although exposures to methylmercury and PCB are associated, the latter is less clearly or only poorly associated with the outcomes. Exposure to dioxins is not increased in the Faroes (Grandjean et al., 1995) and is thought to be low in Madeira and Brazil.

However, for several reasons, the mercury effects may well have been underestimated even in the Faroes study. In particular, a bias toward the null hypothesis is likely to occur as a result of random misclassification from imprecisions of exposure assessment and outcome measurement.

Many questions remain to be considered, including the significance of peak exposures, the timing of vulnerable periods during brain maturation, differences in individual susceptibility, and the protective effects of essential substances in seafood and freshwater fish. In addition, it is not yet known whether the developmental delays observed are permanent and what the long-term consequences may be. The experience with lead neurotoxicity suggests that such effects are likely to remain and may even become more apparent with time.

The public-health importance of these findings must be considered in this light. While the overall mercury-associated deficits seem limited, the long-term health implications should not be disregarded. Also, even small shifts in the average performance of children may be associated with large changes in the tails of the distribution.

Given the intriguing research issues and the public-health relevance, this field of metal toxicology is likely to continue drawing attention.

References

Budtz-Jørgensen E, Keiding N, Grandjean P, White RF, Weihe P (1999). Methylmercury neurotoxicity independent of PCB exposure (letter). Environ Health Perspect 1999; 107: A236-237.

Grandjean P, Weihe P, Needham LL, Burse VW, Patterson DG Jr, Sampson EJ, Jørgensen PJ, Vahter M (1995). Effect of a seafood diet on mercury, selenium, arsenic, and PCBs and other organochlorines in human milk. Environ. Res. 71: 29-38.

Grandjean P, Weihe P, White RF, Debes F, Araki S, Murata K, Sørensen N, Dahl D, Yokoyama K, Jørgensen PJ (1997). Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol. Teratol. 19: 417-428.

Grandjean P, Weihe P, White RF, Debes F (1998). Cognitive performance of children prenatally exposed to 'safe' levels of methylmercury. Environ. Res. 77: 165-172.

Grandjean P (1999). Mercury Risks: Controversy or Just Uncertainty? Publ. Health Rep. 114: 512-515.

Grandjean P, White RF, Nielsen A, Cleary D, de Oliveira Santos EC (1999a). Mercury neurotoxicity in Amazonian children downstream from gold mining. Environ. Health Perspect. 107: 587-591.

Grandjean P, Budtz-Jørgensen E, White RF, Jørgensen PJ, Weihe P, Debes F, Keiding N (1999b). Methylmercury exposure biomarkers as indicators of neurotoxicity in 7-year-old children. Am. J. Epidemiol. 150: 301-305.

Murata K, Weihe P, Renzoni A, Debes F, Vasconcelos R, Zino F, Araki S, Jørgensen PJ, White RF, Grandjean P (1999). Delayed evoked potentials in Madeiran children exposed to methylmercury from seafood. Neurotoxicol. Teratol. 21: 343-348.

Sørensen N, Murata K, Budtz-Jørgensen E, Weihe P, Grandjean P (1999). Blood pressure and heart rate in 7-year-old children with prenatal exposure to methylmercury. Epidemiol 10: 370-375.

Steuerwald U, Weihe P, Jørgensen PJ, Bjerve K, Brock J, Heinzow B, Budtz-Jørgensen E, Grandjean P (2000). Maternal seafood diet, methylmercury exposure, and neonatal neurological function. J. Pediatr. 136: 599-605.

White RF, Debes F, Dahl R, Grandjean P (1994). Development and field testing of a neuropsychological test battery to assess the effects of methylmercury exposure in the Faroe Islands. Proceedings of the international symposium on assessment of environmental pollution and health effects of methylmercury, Kumamoto, pp. 127-140.