

Developmental Neurotoxicity Following Prenatal Exposures to Methylmercury and PCBs in Humans from Epidemiological Studies

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NAKAI, K. and SATOH, H. *Developmental Neurotoxicity Following Prenatal Exposures to Methylmercury and PCBs in Humans from Epidemiological Studies* Tohoku J. Exp. Med., 2002, **196** (2), 89–98 — Adverse health effects following prenatal exposures to methylmercury (MeHg) have been apparent from several prospective cohort studies conducted in a fish-eating population. A prospective study in a Faroese birth cohort documented subtle deficits of several functional domains at prenatal MeHg exposure levels previously thought to be safe. Recent additional studies also showed neurobehavioral deficits associated with exposures to polychlorinated biphenyls (PCBs) with concomitant MeHg poisoning. In contrast, a prospective study in the Seychelles did not detect a similar association between MeHg exposure and neurodevelopmental deficits; children of the highest MeHg exposure group showed better scores in some developmental tests than those of the lower exposure groups for both prenatal and postnatal MeHg exposures. This paradoxical difference between both studies is summarized herein. The primary source of human exposure to MeHg is fish. Since a considerable number of pollutants, including polychlorinated biphenyls (PCBs) and pesticides, are also present in fish, and since some organochemical substances including PCBs are also well documented to be neurotoxic to the developing brain from epidemiological studies, the combined effects of these pollutants should be considered in discussing the neurotoxicity of MeHg. In this article, therefore, major prospective cohort studies focusing on the exposures to PCBs were reviewed. ——— brain development; epidemiology; methylmercury; neurotoxicology; polychlorinated biphenyls; prenatal exposure

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The neurotoxicity of high levels of methylmercury (MeHg) was well documented from the severe epidemic in the small Japanese fishing community, Minamata. Since the developing fetal brain is highly susceptible to MeHg, severe neurotoxicity had been observed in the children of mothers exposed to MeHg during pregnancy, although the mothers themselves did not show clinically evident symptoms of MeHg poisoning. Until recently, public health workers have considered that such high-level exposures to MeHg which cause clinically apparent disease are only the range of adverse health effects of MeHg poisoning. However, in the 1990s, a new understanding has emerged regarding the adverse neurodevelopmental effects of MeHg that may be detectable at the prenatal exposure levels currently considered to be safe (Grandjean et al. 1998). Such adverse effects can be recognized only when a group of individuals are examined in a large cohort study. In this context, several prospective studies have been conducted in fish-eating populations, but the data obtained so far are not consistent. The differences between these studies are summarized in this article. In addition, polychlorinated biphenyls (PCBs) have also been recognized to be potent neurotoxins when children were prenatally exposed, and to cause a delay in neurodevelopment. The primary source of human exposure to MeHg is fish. Considering that significant amounts of PCBs and related halogenated aromatic hydrocarbons are also ingested through fish consumption, the effects of concomitant exposures to several pollutants should be considered. Several major prospective studies regarding the hazardous effects of PCBs on human health are also reviewed.

Neurotoxicity of MeHg

The Faroese birth cohort

Two large prospective cohort studies have been conducted in fish-eating communities; the Faroese birth cohort and the Seychelles Child Development Study.

The Faroese birth cohort was initially generated in 1986–1987 at three hospitals in the Faeroes Islands (Grandjean et al. 1992). This consisted of 1022 consecutive singleton births, and MeHg exposures mainly originated from pilot whale consumption. At approximately seven years of age, 917 of the children underwent detailed neurobehavioral examination. Clinical examination did not reveal any clear-cut MeHg-related abnormalities. However, when a subgroup of 112 children whose mothers had hair mercury concentrations of 10–20 ppm was compared with a subgroup of children whose mothers had lower (<3 ppm) hair mercury concentrations, mild decrements were observed, especially in the domains of motor function, language, and memory (Grandjean et al. 1997; Grandjean et al. 1998). Among the motor function tests, one finger tapping condition and the overall hand-eye coordination average showed a deficit in the exposed group. A small visuospatial deficit was apparent in block designs in the revised version of Wechsler Intelligence Scale for Children. With regard to language, results of the Boston Naming Test were lower in the exposed children than in the nonexposed ones. On the long-term delayed reproduction of the California Verbal Learning Test, increased MeHg exposure was associated with a deficit. Neurophysiological tests also showed significant MeHg-associated delays of the peak III latency and the I-III interpeak latency of the auditory brainstem evoked potentials (Murata et al. 1999)

In this cohort, prenatal exposure to PCBs was re-examined by analysing cord tissues from 435 children (Grandjean et al. 2001b). Maternal exposure to MeHg was through consumption of fish and intermittent higher level exposure, through consumption of pilot whale meat, while consumption of pilot whale blubber resulted in maternal exposure to PCBs. Among 17 neuropsychological outcomes determined at seven years of age, the cord PCB concentration was associated with deficits in the three outcomes,

namely, the Boston Naming Test, the Continuous Performance test reaction time, and possibly, the long-term reproduction of the California Verbal Learning Test. However, the cord blood mercury concentration was associated with seven outcomes in the 17 measures. This suggests that in the Faroese population, MeHg neurotoxicity may be a greater hazard than that associated with PCBs.

In the next cohort, generated from 1994–1995, 182 singleton births were newly evaluated at two weeks of age (Steuerwald et al. 2000). PCBs were determined in maternal serum and breast milk samples, and mercury was determined in cord blood, cord serum, and maternal hair. Infant's neurological optimality score in the Prechtle Neurological Examination was determined with the age adjusted for gestational age. Only cord blood mercury concentration was significantly associated with the neurological optimality score, while PCB, w3 fatty acid, and selenium had no effect on this outcome. Thyroid function was normal. These findings also support the idea that MeHg is the major hazardous material responsible for transplacental neurotoxicity in this fishing community.

The Seychelles Child Development Study

The most direct comparison with the Faroese cohort is the longitudinal assessment of children from a fish-consuming population that has been conducted in the Republic of Seychelles in the Indian Ocean, where 85% of the population daily consumes ocean fish daily (Myers et al. 1997; Davidson et al. 1998). This cohort consisted of 711 mother-child pairs. The prenatal exposure to MeHg was estimated by determining the total mercury level in the mother's hair; the mean maternal hair total mercury level was 6.8 ppm. Postnatal exposure to MeHg was estimated by determining the mercury level in the children's hair; the mean mercury level was 6.5 ppm. Children were assessed at 66 months of age by administering

six neurodevelopmental tests: McCarthy Scales of Children's Abilities (MS), the Preschool Language Scale, the Woodcock-Johnson Applied Problems, Letter and Word Recognition Tests of Achievement, the Bender Gestalt test, and the Child Behavior Checklist. No adverse outcomes were associated with prenatal MeHg exposure. Furthermore, a subgroup of children with higher prenatal and postnatal exposures to MeHg had statistically significant increases in test scores on several developmental outcomes compared with other subgroups of lower MeHg exposures. When children were re-examined at 108 months of age, similar results were obtained; enhanced performance in males in the Boston Naming Test and two tests of visual motor coordination was associated with increased prenatal MeHg exposure (Davidson et al. 2000). The authors discussed these paradoxical findings in terms of the beneficial nutritive factors closely associated with fish consumption other than the intake of MeHg.

Differences between the Faroese birth cohort and the Seychelles Child Development Study

One possible difference is that the Seychellois population is in some way buffered from the adverse effects of prenatal exposure to low levels of MeHg and benefits from a high level of fish consumption (Davidson et al. 1998). One possible candidate for the beneficial nutrition is the essential fatty acids present in seafood since docosahexaenoic acid is known to be essential for early neurodevelopment. However, this point is contradicted by a report showing that an increased intake of marine fat appeared to decrease the birthweight adjusted for gestational age (Grandjean et al. 2001a). Potential differences in the kinds of seafood between the two communities may also be related to the difference in the exposures to other neurotoxicants; this may be the case for the mothers in the Faroese Islands because they may ingest more PCBs by consuming whale blubber. However, in the recent cohorts in the

Faroese Islands, MeHg neurotoxicity has been shown to be more potent than PCB neurotoxicity (Steuerwald et al. 2000; Grandjean et al. 2001b). Other possible differences include the age of the children at the time of testing, differences in the test batteries, genetic/ethnic differences in the populations studied, and potential differences in timing, magnitude, and duration of MeHg exposure (Mahaffey 1998).

Exposure reference dose for MeHg

Fetuses are considered to be the most sensitive subpopulation because of the vulnerability of the developing brain. However, still unknown is the lowest dose that impairs neurodevelopment. A reference dose (RfD) of 0.1 mg MeHg/kg/day had been established by the U.S. Environmental Protection Agency based on a study on Iraqi children exposed to MeHg in utero (Marsh et al. 1987). The RfD is an estimate of the daily exposure to the human population that is likely to be without appreciable risk of deleterious effects during a lifetime. However, the exposure in Iraqi occurred at high levels for a limited period of time, and consequently were not typical of chronic lower exposure levels associated with fish consumption. Major obstacles for understanding such a low-level chronic MeHg exposure include the delayed appearance of the neurodevelopmental effects following prenatal exposure and limited knowledge of cellular and molecular processes underlying these neurological changes. In this context, the National Research Council had started evaluating new epidemiological data that were not available to USEPA at the time it derived the RfD, and finally concluded that the Faroese study was the most appropriate study for discussing the MeHg exposure among sensitive subpopulations (National Research Council 2000). Using a technique called benchmark dose (BMD) analysis (Mahaffey 2000), based on cord blood mercury concentrations, the lowest BMD for a neurobehavioral endpoint that the committee considered to be sufficiently reliable

was 58 ppb of mercury in cord blood, which corresponds to a maternal hair mercury concentration of approximately 12 ppm. A daily intake of 1 mg MeHg/kg/day would result in a maternal hair mercury concentration of 10 ppm. Assuming that an uncertainty factor of 10 was applied, 0.1 mg MeHg/kg body weight per day would be a scientifically justified exposure RfD. Consequently, the NRC Mercury Committee found that USEPA's current RfD for MeHg was a justifiable level for protection of public health.

Neurotoxicity of PCBs and related halogenated aromatic hydrocarbons

The polychlorinated biphenyls (PCBs) and related halogenated aromatic hydrocarbons such as the chlorinated dibenzodioxins (PCDDs) and dibenzofurans (PCDFs) are a family of widely dispersed, environmentally persistent organic compounds. The potential neurotoxicity of PCBs was first recognized in 1968 when a number of Japanese people became ill after ingesting rice oil that was contaminated with PCBs (Yusho). Later, a similar exposure occurred in Taiwan (Yu-Cheng). Children born to Taiwanese mothers who consumed PCB-contaminated rice oil were examined and a number of neurodevelopmental abnormalities, including behavioral problems and lower intelligence quotient (IQ) scores, were observed (Chen et al. 1992).

The Michigan Cohort

Since the Yusho and Yu-Cheng incidents, several cohort studies have been initiated to assess the potential neurobehavioral effects of in utero and lactational exposure to low levels of PCBs in the environment. One of the biggest cohort studies was a longitudinal prospective study of maternal PCB exposure from the food chain (Lake Michigan fish) and its effects on the developmental outcomes in the children. This study was generated by screening more than 800 women who delivered babies in 1980–1981.

The final samples consisted of 313 women. The children were evaluated at birth, five months, seven months, and four years of age. Neonatal behavioral function was assessed using the Brazelton Neonatal Behavioral Assessment Scale (NBAS) (Jacobson et al. 1984). PCB exposure, measured by maternal fish consumption, was associated with several adverse outcomes on the NBAS. However, a more direct measure of exposure, umbilical cord serum PCB level, was not related to any adverse behavioral scores. Infant cognitive function was assessed at five and seven months of age (Jacobson et al. 1985, 1986). The Bayley Scales of Infant Development (BSID) was administered at five months of age, and Fagan Test of Infant Intelligence (FTII) was administered at seven months of age. Neither maternal fish consumption nor umbilical cord serum PCB level was related to scores on BSID. In contrast, both exposure indices were associated with less preference for the novel stimulus on the FTII. Postnatal PCB exposure, determined by measuring PCB level in breast milk, was not related to the scores in FTII. Children were also assessed at four years of age (Jacobson et al. 1990). Higher levels of prenatal PCB exposure, determined by measuring umbilical cord serum PCB levels, were associated with poorer scores on two subtests of the MS that measure verbal and numerical memory. In contrast, neither the quantity of breast milk consumed nor the child's current serum PCB concentrations were related to any of the outcomes. Children were finally reassessed at 11 years of age (Jacobson and Jacobson 1996). Prenatal exposure to PCBs was still associated with lower full-scale and verbal IQ scores, while postnatal exposure to PCB had no impact on the IQ scores.

Development after exposure to PCBs and dichlorodiphenyl dichloroethane transplacentally and through human milk

The North Carolina Cohort

Another important cohort study was car-

ried out in North Carolina. This cohort consisted of 880 pregnant women, and these subjects differed from those in the Michigan cohort in that they were selected from the general population and had not been exposed to any known dietary source of PCBs other than the background levels that contaminate the general food supply. The PCB levels in umbilical cord blood were nearly all below the detection limit, and therefore, the investigators used the PCB level in maternal milk at birth as an indicator of the child's prenatal exposure. In addition, the investigators examined the decline in maternal milk PCB levels at birth and with time, and obtained a rationale to estimate and adjust the maternal milk PCB levels of mothers who did not provide milk samples at birth.

PCB exposure was associated with several adverse outcomes on the NBAS (Rogan et al. 1986). Infants whose mothers had the highest PCB concentrations in their milk had less muscle tone and lower activity levels, and were hyporeflexive. Infant cognitive and motor development was assessed by administering BSID at six, 12, 18, and 24 months of age (Gladden et al. 1988; Rogan and Gladden 1991). Higher transplacental exposure to PCBs was associated with lower psychomotor scores at six, 12, and 24 months of age. There was no relationship between transplacental PCB exposure and scores on the Mental Development Scale, and postnatal exposure through breast feeding was unrelated to performance on either scale. The children were later assessed on the MS at three, four, and five years of age, and neither transplacental nor breast-feeding exposure was related to the scores (Gladden and Rogan 1991).

Other PCB prospective cohorts

A number of additional prospective longitudinal cohort studies are now under way in the United States and Europe. In a cohort study conducted in Oswego in the United States, women who consume sports-caught Great

Lakes fish were recruited. Their infants were assessed at birth by administering NBAS and at six and 12 months of age by administering FTII. The investigators found that heavily (Cl 7 to 9) chlorinated PCB levels were highly associated with poorer performance on the habituation and autonomic clusters of the NBAS, while lightly chlorinated PCB levels were unrelated to NBAS performance (Stewart et al. 2000). A similar relationship was observed between the total umbilical cord blood PCB levels and poorer FTII performance, while there was no significant relationship between total PCBs in breast milk and FTII performance (Darvill et al. 2000).

The relationship between in utero and lactational PCB exposure and later neuropsychological function of children is also being studied in a Dutch cohort. This study consisted of approximately 400 children. They were assessed at birth by administering the Prechtle Neurological Examination (Huisman et al. 1995a). The umbilical cord plasma and maternal plasma PCB levels were not related to neurological function. In contrast, higher levels of planar PCBs, PCDDs, and PCDFs in human breast milk were related to reduced neonatal neurological optimality. The children were assessed at three, seven, and 18 months of age by administering BSID (Koopman-Esseboom et al. 1996). Higher transplacental exposure to PCBs was associated with lower psychomotor scores at three months. Another neurological examination also showed a negative relationship with the level of transplacental exposure to PCBs (Huisman et al. 1995b). A similar phenomenon was observed when the children were assessed at 42 months of age by administering the Kaufman Assessment Battery for Children (Patandin et al. 1999). In utero exposure to PCBs was associated with poorer cognitive function, while lactational exposure to PCB and dioxins was not related to the performance. The investigators, therefore, suggest a beneficial effect of breast-feeding on the fluency of movements.

Implications of cohort studies on the perinatal MeHg and PCBs

These cohort studies presented evidence of a delay in psychomotor development in children who were exposed to MeHg and PCBs during the perinatal periods. MeHg is mainly transferred to the children through the transplacental passage (Sakamoto et al. 2001). In contrast, the absolute quantity of PCBs transferred via breast milk is substantially higher than the quantities transferred via the placenta, and therefore the postnatal exposure would pose a greater threat to the infants. However, the findings from the PCB cohort studies appear to contradict this prediction, suggesting that the exposure during the prenatal period poses the primary threat. These suggest that the prenatal exposures to MeHg and PCBs are most hazardous for the neurodevelopment of the human fetus.

One may debate that although the prenatal exposures to those pollutants are essential in affecting the neurodevelopment in the children, the magnitude of the effects is small. For example, in the North Carolina PCB cohort, the difference in BSID between the lowest and highest PCB exposure groups was only 4–9 points depending on the age of assessment (Rogan and Gladen 1991). Nevertheless, the public health implications of an effect of this magnitude could potentially be very significant. Perinatal lead exposure has been shown to cause lead-associated intellectual deficits. In the lead cohorts, the similar viewpoint has been emphasized (Needleman et al. 1982). At the population level, it was evident that a shift of 4 points in the mean of the normal distribution of IQ had marked effects on the properties of the tails of the distribution; children with elevated lead levels were three times more likely to have a verbal IQ below 80. Although 5% of those with low lead level had IQ in the superior range (>125), no child with an elevated lead level had scored in this range. A shift in mean performance on the BSID of only 4 points would result

TABLE 1. Perinatal PCB exposure and outcomes of neurological and cognitive tests

Test	Major finding	Correlation			Reference
		Fish intake	Prenatal PCB ¹	Postnatal PCB ¹	
The Michigan Cohort					
NBAS (60 hours)	Motor immaturity, Poorer lability of states A greater amount of startle, Hypoactive reflexes	Relate	None		Jacobson et al. 1984
BSID (5, 7 mo)	No relation	None	None		Jacobson et al. 1986
FTII (5, 7 mo)	Less performance	Relate	Relate	None	Jacobson et al. 1985
MS (4 years)	Poorer scores in verbal and numerical memory	Relate	Relate	Relate	Jacobson et al. 1990
IQ test (11 years)	Intellectual impairment	Relate	Relate	None	Jacobson and Jacobson 1996
The North Carolina Cohort					
NBAS (72 hours)	Less muscle tone, Lower activity levels, hyporeflexive		Relate ²		Rogan et al. 1986
BSID (2 years)	Lower psychomotor scores		Relate ²		Gladen 1988, Rogan and Gladen 1991
MDS (2 years)	No relation		None ²		Rogan and Gladen 1991
MN (3-5 years)	No relation		None		Gladen and Rogan 1991
The Oswego Study					
NBAS (48 hours)	Lower scores in habituation, autonomic and reflex	Relate	Relate	None	Stewart et al. 2000
FTII (6 and 12 mo)	Less performance		Relate	None	Darvill et al. 2000
The Dutch Study					
PNE (10-21 days)	Less muscle tone, Reduced neurological optimality		None	Relate	Huisman et al. 1995a
BSID (3 mo)	Lower psychomotor scores		Relate	None	Koopman-Esseboom et al. 1996
BSID (7 mo)	Lower psychomotor scores		None	Relate	Koopman-Esseboom et al. 1996
Neurological examination (18 mo)	Lower optimality		Relate	None	Huisman et al. 1995b
Neurological examination (42 mo)	No relation		None	None	Lanting et al. 1998
K-ABC (42 mo)	Intellectual impairment		Relate ³	None	Patandin et al. 1999

¹Cord blood PCB level for prenatal exposure and maternal milk PCB level for postnatal exposure.

²Prenatal PCB exposure was estimated based on the maternal milk PCB level obtained at birth.

³Maternal blood PCB level.

Neurological and cognitive tests are abbreviated as follows: Neonatal Behavioral Assessment Scale (NBAS), Bayley Scales of Infant Development (BSID), Fagan's Test of Infant Intelligence (FTII), McCarthy Scales (MS), Mental Development Scales (MDS), the Prechtle Neurological Examination (PNE), Kaufman Assessment Battery for Children (K-ABC).
mo, months.

in a 50% increase in the number of children with subnormal scores (Schantz 1996). The costs to society to solve this problem would be large.

The exposures to MeHg and PCBs occur mainly through the intake of foods, especially through fish-eating. The Japanese population like eating fish. USEPA's public health guidance on MeHg intake, as mentioned above, has issued several proposals to the Japanese society to avoid the possible health hazards in high-risk populations such as young females and children (Mahaffey 2001). Fish consumption is widely recognized as a good source of important nutrients, but simultaneously it should be acknowledged that some species and sizes of fish contain MeHg at levels associated with adverse developmental effects. Since the Japanese food culture has characteristics different from those of other countries, the Japanese society should have its own evidence to discuss the hazardous effects of perinatal and low-dose exposures to MeHg, PCBs, and other pollutants.

Finally, one possible confounding factor should be mentioned. Japanese people like rice. Since cadmium (Cd) concentration in Japanese rice is high, the Japanese are known to be exposed to high levels of Cd. Although the typical target organ of Cd exposure has been considered to be the kidney, a recent epidemiological study on exposure to a toxic waste incineration plant revealed that blood Cd concentration was associated with an increase in TSH and a decrease in free T4 (Osius et al. 1999). Considering that one of the possible mechanisms by which PCB disturbs the normal development of fetal brain is suspected to be the disruption of the pituitary thyroid feedback regulation (Porterfield 2000), the exposure to Cd is likely an important confounding factor. In Japan, we must consider these confounding factors including food intake to elucidate the exact effects of neurotoxicity of MeHg and PCBs.

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