ASSOCIATIONS OF NEONATAL NEUROBEHAVIORAL STATUS WITH CORD BLOOD PCB, MATERNAL HAIR MERCURY, AND MATERNAL FISH INTAKE IN THE TOHOKU STUDY OF CHILD DEVELOPMENT

Suzuki K[2,1], Nakai K[1], Nakamura T[1], Hosokawa T[2], Okamura K[3], Sakai T[4], Murata K[5], and Satoh H[1]

[1]Environmental Health Sciences, Tohoku University Graduate School of Medicine, Sendai, 980-8575, Japan; [2]Human Development and Disabilities, Tohoku University Graduate School of Education, Sendai, 980-8576, Japan; [3]Department of Obstetrics, Tohoku University Graduate School of Medicine, Sendai, 980-8575, Japan; [4]Miyagi Children's Hospital, Sendai, 989-3126, Japan; [5]Department of Environmental Health Sciences, Akita University School of Medicine, 010-8543, Japan

Abstract

We have been performing a prospective cohort study, the Tohoku Study of Child Development (TSCD), to examine the effects of perinatal exposures to environmentally persistent organic pollutants and heavy metals on neurobehavioral development of offspring. In the present study, we examined the associations of the Neonatal Behavioral Assessment Scale (NBAS) with the total PCB concentrations in cord blood, maternal hair mercury (hair Hg), and maternal fish intake. Multiple regression analyses indicated some significant associations of the NBAS clusters with hair Hg, but there were no significant associations between total PCBs and any cluster of NBAS. These findings suggest that prenatal methylmercury exposure adversely affects neonatal neurobehavioral status.

Introduction

Several epidemiological studies have indicated some associations of perinatal exposure to polychlorinated biphenyls (PCBs) and methylmercury (MeHg) with developmental deficits such as postnatal growth delay and poor cognitive functions. A common form of perinatal exposure is maternal fish intake; however, fish also contain some nutritive factors such as n-3 polyunsaturated fatty acids (n-3 PUFA) essential for normal brain development in the fetus and infant. From the perspective of risk assessment, these health hazard issues are important for fish-eating populations.

We have been performing a prospective cohort study, the Tohoku Study of Child Development (TSCD), to examine the effects of perinatal exposure to PCBs and MeHg on neurobehavioral development in Japanese children[1]. Previously[2], we reported some preliminary data about the associations of neonatal neurobehavioral status with total PCBs in cord blood and maternal fish intake. Since additional data on PCBs in cord blood have recently become available, in the present study we reexamined the associations of neonatal

neurobehavioral status with total PCBs in cord blood, maternal hair mercury (hair Hg), and maternal fish intake.

Materials and Methods

The subjects were 392 mother-infant pairs whose variables including the PCB concentration in cord blood, the NBAS, and other covariates were available. The mean maternal age at delivery was 31.9 (SD4.2) years. The infants consisted of 203 boys and 189 girls, and they were all singletons from full-term (36-42 weeks) gestation without congenital anomalies or diseases. Birth weight was 2400g or more. Information was obtained about pregnancy, delivery and infant characteristics from medical records.

The PCB concentration was measured from whole cord blood collected immediately after delivery. All 209 congeners were analyzed using HR-GC/MS (IDEA Consultants, Inc, Tokyo, Japan). The total PCB concentration represented the sum of the all measured congeners, expressed as ng/g-fat.

The hair Hg concentration was analyzed from maternal hair samples taken two days after delivery. The total hair Hg concentration was measured by cold vapor atomic absorption[4] at the National Institute for Minamata Disease (Minamata, Japan).

Maternal fish intake was estimated using a semiquantitative food frequency questionnaire (FFQ) for 122 individual foods and recipes[3] and 13 additional items regarding fish and shellfish. The FFQ was administered four days after delivery. Trained investigators showed life-size photographs of each food to the mothers, after which they were asked to answer questions about the frequency and the amount of intake per meal.

Thyroid hormones, including thyroid-stimulating hormone (TSH), total thyroxine (T4), triiodothyromine (T3), free T4 and free T3, were measured from plasma of cord blood by SRL, Inc. (Tokyo, Japan).

The NBAS was administered three days after delivery. Examiners of the NBAS were trained and certified at the training center for NBAS in Nagasaki University School of Medicine, Japan. Reliability checks were conducted throughout the data collection to maintain a 90% level of agreement.

In the statistical analysis, multiple regression analyses were performed for adjustment of covariates. The potential covariates were as follows: maternal age at delivery, maternal alcohol drinking during pregnancy, maternal smoking habit, maternal total energy intake, delivery type, parity, gestational age, sex, birth weight, Apgar score 1 min after delivery, TSH, T4 and T3 concentrations in cord blood, and the NBAS examiners. The significance level was set at 5%.

Results and Discussion

The mean total PCB concentration in cord blood was 55.9 ng/g-fat (SD 35.3) (median 48.4), the mean total hair Hg level was 2.2 μg/g (SD 1.1) (median 2.0), and total fish intake was 25.9 kg/year (SD 17.8) (median 22.7). Table 1 shows the results of multiple regression

analyses. The total PCBs in cord blood and the total fish intake were not significantly associated with any seven clusters of the NBAS. The total hair Hg was negatively associated with the motor score, and positively associated with the range of state and the reflex scores. For the motor and the range of state, higher scores mean more optimal behavioral status, and for the reflex, lower scores mean more optimal status because the reflex score indicates the number of unusual reflexes. Thus, the results suggested that prenatal MeHg exposure adversely affected neonatal neurobehavioral status. In early studies, an adverse effect of prenatal MeHg exposure on neurodevelopment was found in the Faroe Islands[5] and Boston[6], but not in the Seychelles[7]. Our findings are in line with the former two, although the types of examination were different.

Regarding the effects of PCB exposure, early studies demonstrated adverse effects of prenatal PCB exposure on neurodevelopment[8,9]. However, our findings do not agree with those studies. Several possibilities may account for this discrepancy. First, the levels of PCB exposure in Japanese pregnant women have decreased during the past several decades[10]. It is plausible that the level of PCB exposure in our cohort was too low to induce adverse effects on neonatal neurobehavioral status. Second, we used the value of the total PCB concentration as the exposure value. In the Oswego study, highly chlorinated PCBs (Cl7-9) were strongly associated with lower scores of the NBAS, but the total PCB level was not[7]. Therefore, we examined the associations of the NBAS with highly chlorinated PCBs, but found no significance (data not shown). Third, levels of toxicants such as PCB and MeHg and nutritive factors, including n-3 PUFA, vary among different fish types. The Japanese diet relies heavily on steamed rice, fish and vegetables. Indeed, the Japanese eat great amounts of fish, and they also eat many kinds of fish. This food lifestyle may contribute to the differences in the consequences of cohort studies. Further studies will require consideration of the potential risks of fish intake in the context of potential benefits. Since the TSCD study is a prospective cohort study, we will readdress these health issues when the children become older.

Acknowledgments

We thank all the families who participated in the cohort study. The study protocol was approved by the Medical Ethics Committee of the Tohoku University Graduate School of Medicine. This research was funded by the Japan Ministry of Health, Labour, and Welfare, Research on Risks of Chemical Substances.

Table 1. Results of multiple regression analyses

	Total PCBs (ng/g fat)[1]		Total hair Hg (μg/g)[1]		Total fish intake (kg/year)[1]		R^2 of the model
	Standardized beta	F	Standardized beta	F	Standardized beta	F	
Habituation	0.10	0.15	0.37	3.48	-0.31	1.14	0.12
Orientation	0.08	0.21	0.06	0.10	0.17	0.65	0.26
Motor	0.01	0.01	-0.28	5.60*	0.18	2.10	0.16
Range of state	-0.02	0.02	0.38	6.85**	-0.08	0.28	0.11
Regulation of state	0.22	1.27	-0.29	1.70	0.27	1.39	0.08
Autonomic stability	0.02	0.02	0.19	1.07	-0.23	1.38	0.12
Reflex	-0.26	0.72	0.74	4.52*	-0.11	0.09	0.17

* $p < 0.05$ ** $p < 0.01$

[1] Log translations, $Log_{10}X$, were used on values of total PCBs, hair Hg, and total fish intake.

References

1. Nakai K, Suzuki K, Oka T, Murata K, Sakamoto M, Okamura K, Hosokawa T, Sakai T, Nakamura T, Saito Y, Kurokawa N, Kameo S, Satoh H. *Tohoku J Exp Med* 2004; 202: 227-237.
2. Suzuki K, Nakai K, Nakamura T, Hosokawa T, Okamura K, Sakai T, Kurokawa N, Kameo S, Murata K, and Satoh H. *Organohalogen Compounds*. 2006; 68: 1201-1204.
3. Date C, Yamaguchi M, Tanaka H. *J Epidemiol* 1996; 6: S131-S136.
4. Akagi H, Nishimura H. In: *Advances in Mercury Toxicology*, Suzuki T, Nobumasa I, Clarkson T. (ed.), Plenum, New York, 1991: 53-76.
5. Grandjean P, Weihe P, White R, Debes F, Araki S, Yokoyama K, Murata K, Sorensen N, Dahl R, and Jorgensen P. *Neurotoxicol Teratol*. 1997; 19: 417-428.
6. Oken E, Wright R, Kleinman K, Bellinger D, Amarasiriwardena C. Hu H, Rich-Edwards J, and Gillman M. *Environ Health Perspect*. 2005; 113: 1376-1380.
7. Myers G, Davidson P, Cox C, Shamlaye C, Palumbo D, Cernichiari E, Sloane-Reeves J, Wilding G, Kost J, Huang L, and Clarkson T. *Lancet*. 2003; 361: 1686-1692.
8. Stewart P, Reihman J, Lonkey E, Darvill T and Pagano J. *Nurotoxicol and Teratol*. 2000; 22: 21-29.
9. Vreugdenhil H, Van Zanten G, Mulder P, Weisglas-Kuperus N. *Dev Med Child Neurol*. 2004; 46; 398-405.
10. Konishi Y, Kuwabara K, and Hori S. *Arch Environ. Toxicol*. 2001; 40: 571-578.