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Difference in Methylmercury Exposure to Fetus and Breast-feeding Offspring: A Mini-Review

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Abstract : The purpose of this paper was to concisely review the practical changes in MeHg concentrations in fetus and offspring throughout gestation and suckling from our recent animal and human studies. In the animal study, adult female rats were given a diet containing 5 μg/g Hg (as MeHg) for 8 weeks. Then they were mated and subsequently given the same diet throughout gestation and suckling. On embryonic days 18, 20, 22 and at parturition, the concentrations of Hg in the brains of fetus were approximately 1.5-2.0 times higher than those in the mothers. However, during the suckling period Hg concentrations in the brain rapidly declined to about 1/10 of that during late pregnancy. Hg concentrations in blood also decreased rapidly after birth. In human study, Hg concentrations in red blood cells (RBC-Hg) in 16 pairs of maternal and umbilical cord blood samples were compared at birth and 3 months of age after parturition. RBC-Hg in the umbilical cords was about 1.6 times higher than those in the mothers at parturition. However, all the infants showed declines in Hg concentrations throughout the breast-feeding period. RBC-Hg at 3 months of age was about half that at birth. Both the animal and human studies indicated that MeHg exposure to the fetus might be especially high but it dramatically decreases during the suckling period. Therefore, close attention should be paid to the gestation rather than the breast-feeding period to avoid the risk of MeHg to human infants.

Keywords : methylmercury, fetus, pregnant, breast-feeding

Introduction

Methylmercury (MeHg) is a well-known and widespread environmental neurotoxicant. In the natural course of events, most humans are exposed to MeHg through fish and sea mammal consumption. Generally, the larger fish and sea mammals at the top of the food chain, such as whale, shark, sword fish, and tuna, contain higher levels of MeHg than smaller ones (NRC, 2000). Susceptibility of the developing brain during both gestation and suckling might be high (Sakamoto *et al.*, 2002a; Rice and Barone, 2000; Sakamoto *et al.*, 1998; WHO, 1991; Burbacher *et al.*, 1990; Choi, 1989). MeHg can be transferred from mothers to offspring through breast milk, in addition to its passage through the placenta during intrauterine life (Sakamoto *et al.*, 2004; Grandjean, 1994; Kosta *et al.*, 1982; Skerfving, 1988; Amin-Zaki *et al.*, 1974) according to their nutrition demands. Therefore, the effects of MeHg exposure on pregnant and breast-feeding women remain an important issue for elucidation, especially those of continuous uptake in high-fish-consumption populations (NRC, 2000; WHO, 1990; Galster, 1976). Some countries, such as Australia, Canada, Norway, Sweden, the United Kingdom, the United States and Japan, have issued fish consumption advisories to pregnant women and/or women of child-bearing ages concerning the fish and sea mammals that are known to contain high MeHg concentrations (UNEP, 2002; Japanese Government, 2003). Even though the Hg concentration in breast milk is known to be very low (Sakamoto, 2002; Okarsson, 1996; Okarsson, 1995; Skerfving, 1988), some recent studies have still suggested that infants reared on breast milk for a long period might have increased risk (Nunes and Ferreira, 2000; Grandjean *et al.*, 1994). The higher MeHg accumulation at parturition in the fetal brain than that in the mother

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is well established (Sakamoto, 2004; Sakamoto, 2002; WHO, 1990). However, to what extent MeHg in breast milk contributes to the child MeHg concentration is not clear. Therefore, the difference in MeHg exposure to fetus and offspring throughout gestation and suckling must be established under the natural course of MeHg exposure to mother.

Though the MeHg exposure is through fish, an important source of protein especially for Japanese and Asian people, fish consumption also derives some other nutrients (Furst A, 2002; Clarkson and Strain, 2003) and n-3 polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are important for human health and normal brain development and function. Breast-feeding has many benefits and breast milk is the best nutrition source for infants. Therefore, we need an appropriate evaluation of MeHg exposure to fetus and infant through the mother during gestation and lactation to prevent excess avoidance of fish consumption and breast-feeding. The purpose of this paper was to emphasize the difference of methylmercury exposure to offspring during gestation and lactation by showing our own animal and human studies (Pan *et al.*, 2004; Sakamoto *et al.*, 2002b) at the same time. The sample number increased to 16 in comparison with 7 in the last paper (Sakamoto *et al.*, 2002b).

Materials and Methods

Animal Study

Animals and Administrative Procedure: Thirty 4-week-old female Wistar rats were supplied by CLEA Japan, and housed in a room under a 12-h light/12-h dark cycle at 23°C. The rats were maintained with free access to γ-ray-sterilized CE-2 laboratory powdered chow (CLEA Japan) containing MeHg (5 *u*g/g of Hg). This level of MeHg caused no decrease in body weight or apparent toxicity symptoms in our previous experiment (Eto *et al.*, 1997). In the previous experiment, the daily uptake of the diet was restricted to 16 g per rat until mating, but this time we maintained the rats with free access to the diet. The MeHg exposure level was monitored by measuring Hg concentration in blood (described in the next subsection) and, when the level had almost reached a plateau, the females were mated with males. The pregnant females were then continued on the same diet, with access *ad libitum*, throughout the gestation and suckling periods until postnatal day 20 (P20). The MeHg exposure level in the mothers and offspring were also monitored throughout late gestation and after parturition by measuring Hg concentrations in the blood and brain.

Samples: About 5-10 μ*l* of blood was withdrawn from the tail vein of 4 randomly-chosen females from 30, fed on the MeHg-containing diet every two weeks until mating, to monitor the MeHg exposure level at various stages before mating, during gestation and late gestation. On embryonic days 18, 20, 22 (E18, E20, E22), 3 mothers and 6 fetuses (two fetuses from each litter) were randomly chosen to be sacrificed to determine the tissue concentration of Hg. Another randomly-chosen group of 3 mothers and 6 infants (2 females and 2 males each from each litter) were sacrificed on the day of parturition and postnatal days 10 and 20 (P10, P20). On postnatal days 5 and 15 (P5, P15), 8 infants (4 male and 4 female offspring) were also sacrificed to determine tissue Hg concentrations. For tissue sampling, rats were deeply anesthetized by an intraperitoneal injection of pentobarbital. Blood samples were collected by cardiac puncture, and the rats were then killed by transcardiac perfusion with physiological saline for 5 min to flush out blood from the brain. Hg concentrations in the samples were measured according to the method described elsewhere (Sakamoto, 2002a).

Human Study

Subjects: In the previous study (Sakamoto *et al.*, 2002b) the number of the subjects was 7. We added another 9 subjects. In total sixteen healthy Japanese pregnant women, ranging in age from 22 to 36 yr (average 30.4 ± 4.3 yr), planning to deliver in Munakata Suikokai General Hospital, Munakata City, Fukuoka, Japan, gave informed consent to take part in the present trial. Among all infants, five were males. The average body weights at birth and the age of 3 months were 3.3 ± 0.32 and 6.36 ± 0.62 kg, respectively. During the study, five mothers had delivered their first child, three their second, and eight their third. Two mothers consumed fish everyday, and the others two or three times

per week. Fifteen of the infants were reared on breast milk. Only one was reared mainly on breast milk and additional milk formula beginning at 4 and 6 weeks of age.

Samples: Blood samples were collected from sixteen pairs of mothers and infants. The samples included 13 m*l* of venous umbilical cord blood at birth and 10 m*l* of venous maternal blood 1 day after parturition before breakfast, and 2 m*l* of each infant's blood at 3 months of age. All blood samples were obtained by venipuncture with a small amount of heparin-Na and centrifuged at 3000 rpm for 10 min to separate into red blood cells (RBC). Samples were stored at –80°C until analysis. Hg concentrations in the samples were measured according to the method described elsewhere (Sakamoto, 2002b).

Ethics and Informed Consent: Human study was approved by the Ethics Committee of NIMD (National Institute for Minamata Disease). Sixteen normal Japanese pregnant women without any special exposure to mercury, and living in Munakata City, Fukuoka, Japan, gave their informed consent to take part in the trial.

Statistical Analysis

Hg concentrations were represented by means ± SD. The differences between samples were determined by paired *t*-test. The association between the samples was studied by Pearson and Spearman correlation analysis. A *P* value less than or equal to 0.01 was considered to demonstrate statistical significance.

Result

Animal Study

Hg Concentrations in Blood: The time-course changes in Hg concentrations measured in whole blood of the females before pregnancy and after parturition, as well as of the delivered offspring, are depicted in Fig. 1. The Hg concentration of the females increased with the duration of administration, and reached a near plateau after 8 weeks. The Hg concentration of the mothers decreased throughout gestation, and at parturition fell to approximately 50% of that in the mating period. After 20 days of lactation, the Hg concentration of mothers resembled that in the mating period. However, the time-course changes in Hg concentration of the offspring showed a pattern different from that of the mothers. On the day of birth, the concentration in blood was significantly ($p<0.01$ by paired *t*-test) higher, i.e., approximately 2 times that of their mothers on that same day. However, that concentration rapidly decreased throughout their suckling period. All offspring grew up without any physical signs of typical MeHg poisoning, such as ataxia or hind-limb crossing.

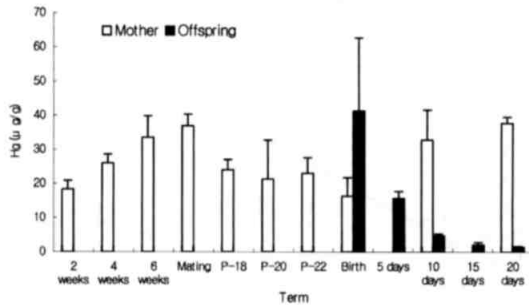

Fig. 1. Time-course changes in Hg concentrations in the whole blood of female rats during 8 weeks before and during pregnancy as well as after parturition and those in their offspring at birth and during suckling. For 8 weeks, female rats were fed a MeHg-containing diet (5 μg/g Hg as MeHg). They were then mated and continuously fed this diet during the gestation and lactation periods. The offspring are fed on mother's milk until weaning on postnatal day 20. Data represent means ± SD for mothers (n = 3-4) and infants (n = 4-6).

Hg Concentrations in the Brain: We also measured the changes in Hg concentration in the brain

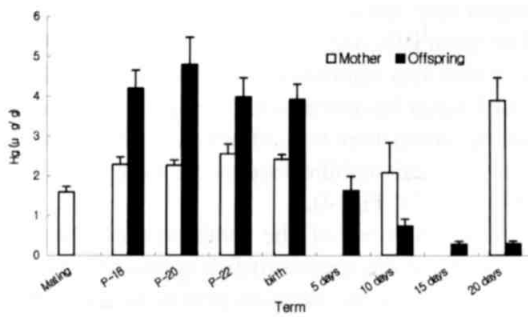

Fig. 2. Time-course changes in Hg concentrations in the brain of maternal rats during late gestation and suckling and those in offspring at during late gestation and during suckling. Data represent means ± SD for mothers (n = 3) and infants (n = 6).

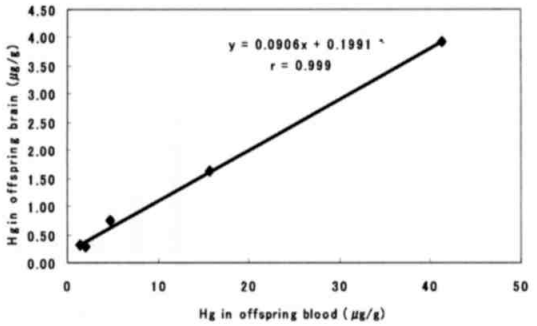

Fig. 3. Correlation between Hg concentrations in blood and brain at birth, days 5, 10, 15 and 20.
A strong correlation was observed in Hg between blood and the brain ($r = 0.999$, $p < 0.01$).

tissue of both mothers and offspring (Fig. 2). The patterns of time-course changes in the brain were similar to those in the blood. The average concentrations in the brain on fetal days E18, E20, E22 and at birth were about 4-4.5 μg/g, which was about 1.5 to 2 times higher than those in the brain of the mothers ($p<0.01$ by Student's *t*-test). Average concentrations of offspring rapidly decreased during the suckling period down to about 1/10 of that at parturition. Correlation between Hg concentrations in blood and the brain at birth, days 5, 10, 15 and 20 is shown in Fig. 3. A strong correlation was observed in Hg concentrations between blood and the brain ($r = 0,999$, $p<0.01$).

Human Study

RBC-Hg in Infants at Birth and 3 Months of Age: At birth, RBC-Hg in umbilical cords were higher than those in mothers in all sixteen cases. The mean RBC-Hg in umbilical cord was 13.0 ng/g, which was significantly higher than in mothers (8.19 ng/g) by paired *t*-test ($p<0.01$; Fig. 3). A strong correlation was observed in RBC-Hg in mothers and umbilical cords at parturition ($r = 0.96$, $p<0.01$, Fig. 4).

Although most of the mothers said that the amount and the species of fish consumed did not change during the lactation period, in all sixteen infants the Hg concentrations decreased throughout this period. The mean RBC-Hg in infants at 3 months of age was 6.87 ng/g, significantly lower than that at birth (13.0 ng/g) by paired *t* test ($p<0.01$; Fig. 5).

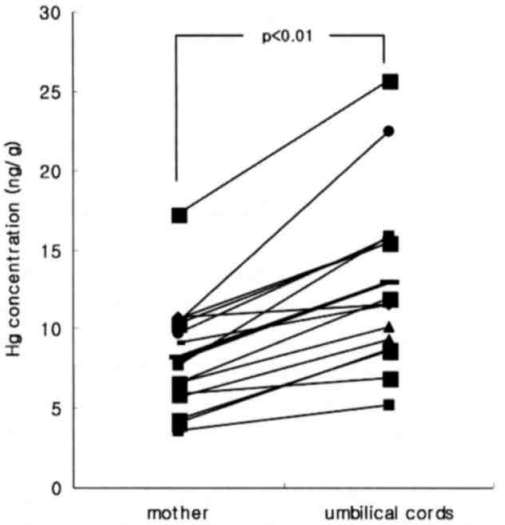

Fig. 4. Comparison of Hg concentrations in maternal and umbilical cord RBC. Fetal RBC-Hg level was significantly higher than that of maternal at birth by paired *t*-test ($p<0.01$). Horizontal lines indicate the means.

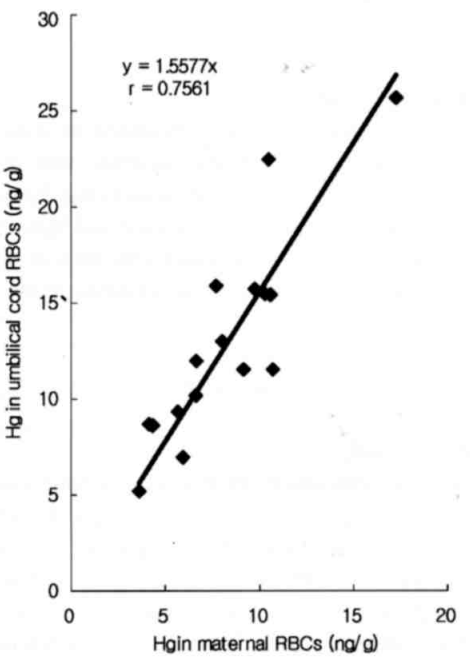

Fig. 5. Correlation between maternal and umbilical cord Hg concentrations in RBC in 16 maternal-fetal pairs. In all 16 cases umbilical cord RBC-Hg levels were higher than maternal levels. A strong correlation was observed in RBCs-Hg between mothers and umbilical cord ($r = 0.76$, $p < 0.01$).

Discussion

Animal Study

This animal study was designed so that fetuses conceived in females that had been exposed to a constant and consecutive dose of MeHg before and throughout gestation were exposed to MeHg transplacentally throughout the entire gestational period, followed by post-partum exposure through contaminated milk. This was considered to simulate the natural course of fetal and infant exposure to MeHg among people who commonly consume much fish and sea mammals, and to reveal the difference in the risk of MeHg to fetus and infants. The concentrations of Hg in the brain of fetus were 1.5 to 2 times higher than those in their mothers throughout late gestation. This is in accordance with the proposal that MeHg is actively transferred to the fetus across the placenta via neutral amino acids carriers (Ashner and Clarkson, 1988; Kajiwara *et al.*, 1996) throughout the late gestation period. The decrease in Hg concentrations in maternal blood during the gestation period partly explains the accelerated MeHg transfer to the fetus according to the demand of amino acids to promote fetal growth. It is known that the developing brain is most vulnerable the toxic effect of MeHg during the third-trimester (Rice and Barone, 2000; Takeuchi, 1982). Our results indicate that the Hg concentrations in offspring brain were higher than that in maternal brain not only at parturition but also throughout the late gestation period when the human brain is most vulnerable. We also demonstrated that Hg accumulations in offspring differ significantly between periods of gestation and suckling. During the 20 days after birth, the offspring concentrations in the blood and brain decreased dramatically as demonstrated in a previous animal experiment (Sakamoto *et al.*, 2002a; Oliveira *et al.*, 2001, Newland *et al.*, 1999; Sundberg *et al.*,1999). This will be explained by limited MeHg transfer from milk (Sundberg *et al.*, 1999; Sundberg *et al.*, 1991; Yoshida *et al.*, 1994) and rapid increase in the organ and body volume. Further, the increase in blood Hg concentrations in maternal blood during suckling can be partly explained by the diminished MeHg transfer to the fetus compared with that during the gestation period. However, our animal study indicated that Hg concentration in blood and brain in offspring increased after weaning when they started to eat MeHg contaminated diet (Sakamoto, 2002a). Therefore, attention should be paid to MeHg exposure through fish and sea mammals as baby food during breast-feeding period and after weaning. The strong correlation in Hg concentrations between blood and the brain also revealed that the Hg concentration in blood reflect the changes in the brain. In human also correlation coefficients for infant blood and the six brain regions were 0.4-0.8 in a population exposed to MeHg in fish (Cernichiari *et al.*, 1995). These results strongly suggest that fetal blood Hg concentration are very good biomarker to now the concentration in the brain which is the primary target organ for MeHg exposure.

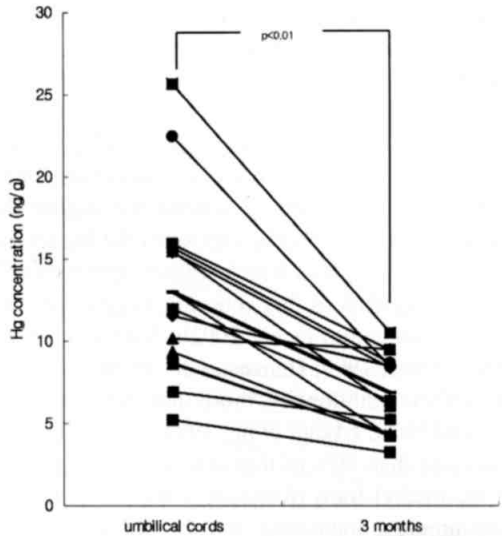

Fig. 6. Changes in Hg concentration in RBC from umbilical cord to those in infants at 3 months of age. The infant RBC-Hg level at 3 months of age was significantly lower than that at birth by paired *t* test ($p < 0.01$). The horizontal lines indicate the means.

Human Study

The present study was designed mainly to determine the changes in MeHg levels in infants after parturition, followed by further MeHg exposure through milk after birth. The primary target organ for MeHg exposure is the brain and blood Hg concentration reflects the concentration in the organ as mentioned in the previous animal study discussion. Not only

blood but also RBC can be used as a biomarker of MeHg exposure (Svensson, 1992; WHO, 1990; Swedish Expert Group, 1971). It is known that the RBC to plasma ratio of Hg concentration is approximately 1:1 in non fish-consuming populations and after exposure to Hg^0 vapor (Svensson *et al.*, 1992; HO, 1990). However, in general the higher the fish consumption (MeHg exposure) the higher the RBC to plasma ratio, which reaches approximately 8-9:1 in populations that consume a higher amount of fish (Sakamoto *et al.*, 2002b; Svensson *et al.*, 1992; WHO, 1990; Hansen *et al.*, 1990; Suzuki *et al.*, 1971). Additionally, more than 80% of Hg in the total blood (Akagi *et al.*, 1998, Kershaw, 1980) and more than 90% of that in RBC is known to be in the methyl form (Kershaw, 1980) in high fish-consumption, indicating that the Hg source was predominantly MeHg from fish. RBC-Hg is one of the best biomarkers to determine MeHg exposure level (Sakamoto *et al.*, 2002b; Oddy, 2001). Therefore, the changes in MeHg level infants during breast-feeding were investigated using the total Hg concentrations in RBCs in our present and previous studies (Sakamoto *et al.*, 2002b; Sakamoto *et al.*, 1993a; Sakamoto *et al.*, 1991) studies. RBC-Hg level in umbilical cords were about 1.6 times higher than that in the mothers, and there was a strong correlation between them at birth. This result was similar to the previous animal study suggesting that MeHg actively transfers to the fetus across the placenta via neutral amino acids carriers (Kajiwara *et al.*, 1996) as mentioned in the animal study. After 3 months of breast-feeding the RBC-Hg in infants dramatically declined to 53% of that at birth as was observed in animal study. During this period, the average body weight of infants quickly increased and became about 1.9 times that at birth. Consequently, the average body volume and the limited Hg transfer from breast milk might have caused the dilution in RBC-Hg levels during this period.

Conclusion

The higher Hg accumulation in fetus than mother was demonstrated in both the animals and humans studies. It is known that the susceptibility of the developing brain in the late gestation period is high (WHO, 1990). Thus, the risk of exposure of the fetus to MeHg must be very high. However, the Hg levels in the blood in infant decreased drastically during breast feeding in both the animals and humans studies. The brain Hg concentration also dramatically decreased during breast feeding. The contribution of breast milk to MeHg transfer to infants seems limited, as was recently suggested by Sandborgh-Englund *et al.* (2001) and Sakamoto *et al.* (2002b) However, from some viewpoints, the rate of MeHg excretion is thought to be low, and the biological half-time of MeHg in lactating women is shorter than in non-lactating women (WHO, 1990). Suckling mice are incapable of excreting MeHg (WHO, 1990). In Iraq, human milk was suspected source of MeHg exposure of poisoned infants (Amin-Zaki *et al.*, 1981). These phenomena may lead to the consideration that infants at breast-feeding also seem to be at high risk for MeHg. However, as were demonstrated by our animal and human studies, once neonates are separated from the active intrauterine amino acid transport system, Hg transfer depends on the milk, in which the Hg concentration is low. Offspring body and their brain grow rapidly after birth. The growth may dilute the Hg concentrations in the body and brain. Grandjean *et al.* (1994) mentioned that human milk seemed to be an important source of MeHg exposure in infants because hair Hg at approximately 12 months of age increased with the length of the nursing period. However, the same authors mentioned the concentration in the child's hair at 1 year was only about 25% of that of the mother at the time of delivery. Also, in MeHg poisoning in Iraq, both the infants' and mothers' clearance half-time was approximately 50 days. However, maternal MeHg can be transferred to infants through breast milk following exposure through the placenta during their intrauterine life. The seeming contradiction that MeHg half-life in infant was about 50 days in the case, even though excretion of MeHg in infants was thought to be much lower than in adults, can be explained by the rapid body and organ growth during the period.

In conclusion, the risk to offspring might be especially high throughout the gestation period but rapidly decreases during suckling under the practical and natural course of MeHg exposure from daily fish consumption. Thus, sufficient attention should

be paid to gestation rather than the breast-feeding period to avoid dangers of MeHg to human infants. Further, if exposure levels are constant and low enough not to cause adverse effects on fetuses during gestation, mothers need not worry about breast-feeding. The benefits of breast-feeding (Oddy, 2001; Kunz *et al.*, 1999) may well outright the possible adverse effects of MeHg in breast milk under these conditions. However, if mothers were exposed to high MeHg levels during the suckling period, due caution is recommended concerning breast-feeding as the possible poisoning was reported in Iraq (Amin-Zaki *et al.*, 1981). In addition, attention should be paid to MeHg exposure through fish and sea mammals as baby food during breast-feeding period and after weaning.

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