

Higher level of multiple contaminations in breast milk of mothers who gave birth to neonates with congenital hypothyroidism

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Introduction

In Japan, mass-screening for congenital hypothyroidism, that is, cretinism has been done since 1979. For this quarter-century, recent positive rate of the mass-screening becomes three times higher than the initial rate, namely, at the beginning the positive rate was about one per 8000 births and recently about one per 2500 births. The reason of this increased positive rate is not known yet. I suppose some chemical compounds which contaminate with Japanese mothers may cause such effect, because we have elucidated perinatal and/or lactational exposures to dioxins, PCBs and pesticides exert undesirable effects on the thyroid hormone system of Japanese infants ^{1, 2, 3, 4, 5}.

In this study, we examined the effects of prenatal exposure to polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and coplanar polychlorinated biphenyls (Co-PCBs), which were so-called dioxins, PCBs and organochlorine pesticides such as hexachlorocyclohexans (HCHs), dichlorodiphenyl-trichloroethane (DDT), dieldrin, heptachlor and chlordane on the induction of congenital hypothyroidism or cretinism. Obviously this is the first study in this field in the world.

Materials and Methods

Positive cases of the mass-screening for congenital hypothyroidism in 2001 to 2004 in Fukuoka visited Fukuoka Children's Hospital, Fukuoka, Japan for the minute examination of cretinism. During these four years, total number of the positive cases was 65 (male: 39, female: 26), in which the organochlorine compounds in their mother's milk were determined in 28 cases (male: 19, female: 9). In the 28 positive neonates, 16 neonates (male: 10, female: 6) were congenital hypothyroidism, 5 neonates (male: 4, female: 1) hyperthyrotropinemia and 7 neonates (male: 5, female: 2) transient hyperthyrotropinemia. Serum concentrations of thyrotropin (TSH), free triiodothyronine (f-T₃) and free thyroxine (f-T₄) in the blood sampled at 5 to 20 days after birth were determined by the electrochemiluminescence immunoassay methods using commercially available kits ⁶ and their concentrations in each group are shown in Table 1, together with the normal group, which means negative cases of the mass-screening for the cretinism. Normal neonates of the mass-screening were born in Shimomura OBGY Clinic, Fukuoka, Japan and their total number was 108 (male: 58, female: 50). In 108 normal neonates, 103 samples of their mother's milk were analyzed for the organochlorine compounds.

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Table 1. Concentrations of TSH, f-T₃ and f-T₄ in the serum of cretinism, hyperthyrotropinemia (high TSH), transient hyperthyrotropinemia (transient) and normal in Japanese neonates

Group	TSH (μ IU/ml)*	f-T ₃ (pg/ml)*	f-T ₄ (ng/dl)*
Cretinism	53.6 \pm 56.7	2.92 \pm 0.94	0.97 \pm 0.34
High TSH	9.98 \pm 3.67	3.11 \pm 0.53	1.20 \pm 0.16
Transient	5.68 \pm 4.48	3.37 \pm 0.87	1.34 \pm 0.13
Normal	8.56 \pm 5.62	3.60 \pm 0.84	2.46 \pm 0.67

*: Mean \pm Standard Deviation

Contamination levels of the organochlorine pesticides and PCBs in the breast milk samples which were collected within 4 weeks after childbirth were quantified by ECD-GC (Hewlett Packard series 6890) using DB-1 fused silica capillary column (30 m length)⁷. Their concentrations of dioxins were also measured by HRGC-HRMS (Agilent 6890 series and JEOL JMS-700D) with a resolving power >3000 for mono-ortho PCBs and >10,000 for non-ortho PCBs and PCDD/DFs⁸. Toxic equivalent quantities (TEQs) were estimated based on human/mammal toxic equivalency factors (TEFs) proposed by the World Health Organization (WHO)⁹. Statistical significance was evaluated by the two-tailed student's T test and less than 10% of *p*-value was considered significant.

Results and Discussion

As indicated in Table 1, serum concentration of TSH was the highest in the cretinism group and those of f-T₃ and f-T₄ the lowest in this group. On the contrary, serum concentration of TSH was the lowest in the transient hyperthyrotropinemia and those of f-T₃ and f-T₄ the highest in the normal group. Contamination levels in the breast milk of PCDDs, PCDFs, Co-PCBs and dioxins in the cretinism group were significantly higher than those in the normal group, as shown in Table 2. Concentrations of PCDFs, Co-PCBs and dioxins in the transient hyperthyrotropinemia were also greater than those in the normal group (Table 2).

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Table 2. Contamination levels of PCDDs, PCDFs, Co-PCBs and Dioxins in the breast milk of Japanese mothers who gave birth to neonates with cretinism, hyperthyrotropinemia (high TSH), transient hyperthyrotropinemia (transient) and normal

Group	Concentration, pg-TEQ/g on whole weight basis*			
	PCDDs	PCDFs	Co-PCBs	Dioxins
Cretinism	0.204 ± 0.173 (0.064)	0.133 ± 0.100 (0.027)	0.248 ± 0.210 (0.036)	0.577 ± 0.457 (0.037)
High TSH	0.194 ± 0.168 (0.302)	0.120 ± 0.103 (0.283)	0.219 ± 0.184 (0.255)	0.541 ± 0.459 (0.269)
Transient	0.135 ± 0.061 (0.251)	0.086 ± 0.025 (0.092)	0.161 ± 0.090 (0.054)	0.382 ± 0.164 (0.099)
Normal	0.105 ± 0.063	0.062 ± 0.033	0.110 ± 0.061	0.277 ± 0.149

*: Mean ± Standard Deviation

Figure in parenthesis indicates *p*-value for the corresponding normal group

In case of PCBs and the organochlorine pesticides, we observed significantly higher contamination levels of these compounds except HCH in the breast milk of the cretinism group than in that of the normal group, as indicated in Table 3. According to the results of this study mentioned above, higher levels of multiple contaminations of dioxins, PCBs and organochlorine pesticides may cause congenital hypothyroidism and have effects on the thyroid hormone system of fetuses and also sucklings, as we have already reported before ^{1, 2, 3, 4, 5}.

This study, however, was done with rather small number of neonate-mother pairs. Therefore, further large-scale investigations are needed to get more conclusive results.

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Table 3. Contamination levels of PCBs, DDT, HCH, chlordanes and HCB in the breast milk of Japanese mothers who gave birth to neonates with cretinism, hyperthyrotropinemia (high TSH), transient hyperthyrotropinemia (transient) and normal

Group	Concentration, ng/g on whole weight basis*				
	PCBs	DDT	HCH	Chlordane	HCB
Cretinism	2.79 ± 2.27 (0.043)	6.91 ± 5.94 (0.049)	2.70 ± 3.88 (0.160)	1.95 ± 1.96 (0.029)	0.34 ± 0.21 (0.001)
High TSH	3.10 ± 3.06 (0.312)	10.7 ± 11.5 (0.242)	2.97 ± 2.65 (0.223)	1.43 ± 1.65 (0.419)	0.35 ± 0.32 (0.284)
Transient	1.62 ± 0.45 (0.609)	5.05 ± 3.14 (0.370)	2.70 ± 3.14 (0.268)	0.80 ± 0.55 (0.880)	0.19 ± 0.07 (0.718)
Normal	1.51 ± 1.27	3.67 ± 3.68	1.25 ± 1.24	0.76 ± 0.68	0.17 ± 0.18

* : Mean ± Standard Deviation

Figure in parenthesis indicates *p*-value for the corresponding normal group

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