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Fetal PCB Syndrome: Clinical Features, Intrauterine Growth Retardation and Possible Alteration in Calcium Metabolism

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Pregnant mothers with Yusho in Fukuoka, Nagasaki and Kochi Prefectures delivered babies with a peculiar clinical manifestation which will be called fetal PCB syndrome (FPS). The birth rate incidences were 3.6% (Fukuoka Prefecture), 4% (Nagasaki Prefecture), 2.9% (Kochi Prefecture) and 3.9% (total). The manifestations consisted of dark brown pigmentation of the skin and the mucous membrane, gingival hyperplasia, exophthalmic edematous eye, dentition at birth, abnormal calcification of the skull as demonstrated by X-ray, rocker bottom heel and high incidence of light for date (low birth weight) babies.

We suggest that there may be a possible alteration in calcium metabolism in these babies, related to the fragile egg shells observed in PCB-contaminated birds and to the female hormone-enhancing effect of PCB.

The high incidence of low birth weight among these newborns and two other similar studies indicated that PCBs supress fetal growth.

Introduction

Yusho (PCB-contaminated oil poisoning) in children can be classified into four categories according to route of PCB-contaminated oil intake, and according to the stage of development of the child at exposure. When the fetus is exposed to PCBs via the placenta of the poisoned mother, we call this fetal PCB syndrome (FPS) or PCB-induced fetopathy (*1*), neonatal Yusho or fetal Yusho.

Yusho in infants fed human milk from PCB-poisoned mothers was described as infantile Yusho. If the children themselves consumed PCB-contaminated oil, they showed what is known as childhood Yusho. There may well be combinations of both FPS and infantile Yusho, and also other combinations.

The purpose of this paper is to review the clinical features, intrauterine growth retardation and the possible alteration in calcium metabolism in bone and dental tissue, based on our study (*1*) of patients admitted to Kurume University Hospital, the studies by Yamaguchi et al., (*2*), Tominaga et al. (*3*) and Hayashi et al. (*4*).

Epidemiology

Since 1968, more than a thousand inhabitants of western Japan have suffered from PCB poisoning due to the ingestion of PCB-contaminated cooking rice oil. Thirty-six babies showing FPS are known; these have also been termed "Coca-Cola" or "Cola Baby" or "black baby" because of the dark brown pigmentation of the skin. These births occurred in Fukuoka, Nagasaki and Kochi-ken, with a birth rate incidence of 3.6% in Fukuoka and 4% in Nagasaki (Table 1). Two of seven mothers consumed PCB-contaminated rice oil through the entire gestational period (Table 2). The oil dose ranged between 0.3 and 2.6 L, with an average of 1.1 L. The pregnancy in which the mother with severe grade IV manifestations who consumed 2.6 L of PCB oil, resulted in a stillbirth (*2*).

The mother (Table 2) without clinical manifestation of poisoning gave birth to an infant with only slight pigmentation of the skin and hypersecretion of conjunctiva. One of two babies from the grade II mothers showed marked pigmentation; in the other it was only slight. All the babies born to grade III mothers showed marked pigmentation. The manifestations in the babies paralleled consumption at PCB-contaminated rice by their mothers.

Table 1. Incidence of fetal PCB syndrome (FPS) (1968-1972).

Prefecture (ken)	No. of FPS cases	No. of deliveries	FPS incidence, %
Fukuoka	15	415	3.6
Nagasaki	18	401	4.4
Kochi	1	35	2.9
Total	34	851	3.9

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Table 2. Epidemiology.

	No. of cases
Gestational age when mother consumed PCB-contaminated oil.[a]	
1st trimester	1
2nd trimester	3
3rd trimester	1
All stages	2
Grade of Yusho in pregnant mothers (N = 12)	
No manifestation	2
Grade 1	2
Grade 2	2
Grade 3	5
Grade 4	1
Mode of delivery (N = 11)[b]	
Normal	9
Forceps	1
Cesarean	1
Sex ratio in live birth newborn (N = 12)	
M	8
F	4

[a]Dose of oil consumed by pregnant mothers = 0.3–2.6 (average (1.1)L.
[b]Gestational ages = 35–42 weeks (average = 39.6 ± 2.1 SD). Two stillborns had 33 and 41 weeks of gestation.

Eleven live births occurred, all but two by normal delivery. There was one forceps birth and one cesarean section. There were two stillbirths. The gestational ages of the neonates were between 35 and 42 weeks, the average being 39.6 weeks. The severity of poisoning in the mother had no correlation with the gestational ages of the neonates.

Three newborns and one 3-month-old baby were admitted to Kurume University Hospital, where clinical observation and laboratory examination including metabolic and endrocrinological investigation and skin and liver biopsies were performed (*10*). These babies were included under the tabulation for Fukuoka-ken in Tables 1 and 3.

Clinical Features

All patients had dark brown skin pigmentation at birth (Table 3). The pigmentation was distributed over the entire skin and mucous membranes. Sites of increased prominence were the axilla, genitalia, the fingers near the nail, hair follicles, the lips, gingiva, palate and corneal limbus and the conjunctiva. Secreta on the conjunctival palpebra were marked. Skin biopsy findings in three patients revealed hyperkeratosis and increased melamin pigment. The pigmentation disappeared within 2 to 5 months of age in all patients.

The face was edematous, and there was exophthalmus in three infants. The frontal and occipital fontanels showed larger and wider openings, and the sagittal suture remained wider than usual in newborns. Spotty calcifications or platelike dense areas were noticed in the parieto-occipital area of the skull on X-ray films on three of three infants examined. Two of three newborns had one or two teeth at birth. Hepatomegaly was noted in one patient in whom liver function tests were normal.

No neurological abnormalities were observed. Neither malformations nor cardiovascular abnormalities were noticed except for slight "rocker-bottom heel."

Table 3. Clinical manifestations of FPS.

Manifestations	Kurume[a]	Fukuoka	Nagasaki	Total (%)
Pigmentation	4/4	11/11	12/12	23/23 (100)
Desquamation	3/3			
LFD baby[b]	3/4 (75%)	3/11 (27%)	1/12 (8.5%)	4/23 (17.4%)
Edematous eyelid	3/3			
Precocious dentition	3/3			
Abnormal calcification of skull	3/3			
Gingival hyperplasia	3/3			
"Rocker-bottom heel"	4/4			

[a]The Kurume patients were included in Fukuoka.
[b]Light for dates (criteria: see text).

Only one baby showed marked anemia. Liver function tests revealed slightly elevated SGOT in two patients, one of whom had normal liver biopsy findings and the other showed swelling of the hepatocytes on histologic studies. Another patient with normal liver function showed slight fibrosis and pigment deposits in the liver.

One baby showed a slight increase in protein concentration in cerebrospinal fluid, whereas the other two had normal findings. The EEG was within normal limits in all three babies.

Serum protein, fraction, electrolyte concentrations, blood glucose, glucose tolerance tests, pH, urinalysis, fasting growth hormone levels, urinary 17-hydroxycosticosteroids, 17 ketosteroids, the Metopiron tests and the Triosorb test were all within normal limits. Bone age was questionably delayed in one infant and normal in the other three babies. Their mothers had consumed 0.6 to 10.6 L of PCB-contaminated rice oil during the entire pregnancy; one mother ingested the contaminated oil for only 4 months.

Three of four newborns with FPS in the Kurume University Hospital series were diagnosed as "light for date" babies (LFD). The diagnostic criterion for LFD was a birthweight for the newborn that is 1.5 SD less than the average appropriate for the stated gestational age. The incidence of LFD was the highest in the Kurume series (75%), and lowest in the Nagasaki prefecture. The total incidence was four cases, 17.4% of 23. No detailed observations, including skull X-ray, were performed in Fukuoka or Nagasaki facilities.

These babies showed growth curves parallel to normal curves, except for one case with "catch-up" growth at 6 months of age. Developmental tests revealed normal quotients in all four babies in our series.

Discussion

New Clinical Entity

The brown pigmentation ("Coca-Cola color") on the skin and the mucous membrane, gingival hyperplasia, early eruption of the teeth, calcification of the skull, and low birth weight (LFD) in our series constitute a new clinical entity in the newborn reflecting PCB poisoning

of the pregnant mother. The same pigmentation was observed in an autopsied stillborn, and PCB was detected by gas chromatography in the adipose tissue and the skin of the fetus (*5*). PCB was also detected in the placenta of one case of our Kurume series. We also confirmed the possibility of transplacental passage of PCBs experimentally in the rat (*6*).

Growth Suppression in Utero

The incidence of LFD was high in the Kurume series but not so high in the Nagasaki cases. Tominaga et al. reported a significant difference in the birth weight between female FPS and female non-FPS infants in Nagaskaki (*3*) (Table 4).

Table 4. Birth weight of the neonates with FPS and growth parameters after 3 years.[a]

Sex	Group[b]	*N*	Birth weight, g	Height/weight at 3 yrs	
				Weight, kg	Height, cm
Male	A	381	3161.6	14.12	94.5
	B	42	3169.6	13.8	94.9
	C	6	3120	13.68	95.3
Female	A	384	3142.8**	13.75	93.4
	B	58	3082.5*	13.33	92
	C	12	2825.5**	13.62	91.6

[a]Data of Tominaga and Hayashi (*3*).
[b]Group A: apparently healthy infants delivered from mothers not ingesting PCB-contaminated rice oil during pregnancy; Group B: children born to mothers who consumed PCB-contaminated rice oil during pregnancy but showing no FPS at birth; Group C: children with FPS.
**Highly significant p value differences ($p < 0.01$).
*Significant differences ($p < 0.05$).

A similar phenomenon was reported by Hayashi et al. (*4*). These authors also have carried out nationwide monitoring of the concentration of PCB or DDT in human milk in Japanese mothers annually since 1972 (*4*). In their survey, only female newborns or infants showed significantly different incidences of low birth weight (LFD), and lower weight and height at later health checks, and these differences correlated with grades of PCB concentration in the mothers' milk (Table 5). These incidences were higher when the mother's milk had a higher concentration of PCBs except for one case (bottom line of Table 5, 105/553 = 19.0%). Male newborns and infants did not show this phenomenon.

Because these female infants showed no differences in rate of weight gain and height increase after birth, the lag in weight and height at followup health checks was attributed to the difference in birth weight and the grade of PCB concentration in the milk.

Further comparative study with the matched conditions revealed the same results as in a nonmatched study for the following factors: gestation of more than 38 weeks; no twin; the first child; mother's age between 20 to 34 years; mother's height > 146 cm; no toxemia; nonsmoker (number of males and females were 77 and 68) (*4*).

If we speculate that the level of PCB concentration indicates the grade of PCB contamination in the mother's body, the above data suggest that maternal PCB contamination had suppressive effects on growth of the female fetus.

Table 5. Growth of the children born to healthy mother by the grade of PCB concentration in human milk of Japanese mother (1972–1981, 10 years).[a]

	PCBs in human milk, ppm fat			PCBs in human milk, ppm of whole milk		
	<0.5	0.6–0.9	⩾ 1.0	< 0.02	0.03–0.4	⩾ 0.05
Low birthweight infants, BW 12500 g)						
Male (*N* = 1756)	2.8%	1.6%	2.1%	2.2%	2.3%	2.6%
	22/772	9/554	9/430	22/1011	11/479	7/266
Female (*N* = 1768)	3.0%	3.6%	5.1%	2.8%*	4.7%	5.3%*
	23/763	20/560	23.451	29/1018	22/472	15/284
LED infants[b]						
Male (*N* = 1751)	3.0%	2.0%	2.6%	2.5%	2.5%	3.0%
	23/769	11/553	11/429	25/1010	12/476	8/265
Female	3.5%**	4.8%	7.1%**	3.6%**	5.1%**	8.8%**
	27/762	27/558	32/448	37/1017	24/468	25/283
Lighter weight[c]						
Male (*N* = 1752)	19.8%	18.7%	18.2%	20.2%	17.8%	17.0%
	152/769	104/555	74/728	204/1011	85/477	45/264
Female (*N* = 1767)	15.0%**	20.4%*	25.6%**	16.5%**	22.0%**	24.5%**
	114/558	114/558	115/450	167/1011	104/472	72/284
Smaller height[c]						
Male (*N* = 1741)	18.8%	21.3%	21.6%	20.0%	21.4%	19.4%
	144/765	117/550	92/426	201/1005	101/473	51/263
Female (*N* = 1757)	23.3%*	19.0%**	29.0%**	21.6%*	24.0%*	28.6%*
	176/755	105/553	130/449	217/1004	113/470	81/283

[a]Data of Hayashi et al. (*24*).
[b]LFD = the neonates with inappropriately lighter birth weight for the gestation period.
[c]Babies with lighter body weight/smaller height (-1.5 SD than average of 1975 statistics in all Japan).
*p10.05.
**p10.01.

Both Tominaga's data on PCB-contaminated oil poisoning in Nagasaki and Hayashi's survey on pollutional PCB contamination of human milk and fetal growth indicate that only the females show significant differences in the incidences of LFD at followup. Hayashi (*4*) speculated an enhancing effect of PCB in suppressing growth, citing the experimental study of Allen (*7*).

The male to female ratio in the three LFD babies of the Kurume series was 2:1. We speculated that the growth-suppressing effect of PCBs may depend on two factors: the level of PCB in fetal tissue and the action of other hormones or enzymes possibly induced by PCB in liver. A temporarily decreased growth rate (both weight and height) in boys with PCB poisoning has been reported (*8*).

Possible Alteration in Calcium Metabolism

The precocious dentition in two of three and abnormal calcification of the skull in all three neonates in the Kurume FPS series suggested a possible alteration in calcium metabolism in bone and teeth or the mechanism triggering their growth or maturation.

A direct relationship between DDT and calcium metabolism in birds has been reported (*9*). Wurster found a significant, widespread decrease between 1946 and 1950 in calcium content of eggshells in the peregrine falcon, golden eagle, sparrow hawk, and *Accipiter nisus*. Widespread introduction of DDT into the environment occurring during this period has been cited as a likely cause for this phenomenon.

Risebrough et al. also reported that PCBs, together with other chlorinated biocides such as DDT, could account in large part for the aberration in calcium metabolism observed in many species of birds since 1945 (*10*). He commented that steroid sex hormones control the deposition of medulary bone which is the chief source of calcium during eggshell formation, and that this steroid hormone may be degraded by hepatic enzymes induced by chlorinated hydrocarbons.

Induction of hepatic enzymes by PCB (Kanechlor-400) has been confirmed pharmacologically and histologically in animals and in human liver (*11–13*). Such induction may lead to degradation of the hormone as speculated by Risebrough. However, PCBs themselves have an estrogenic (*14*) and estradiol-potentiating action (*15*) similar to that of DDT (*14,16,17*). An antiandrogenic effect of PCBs in cockerels has also been reported (*18*). In female Yusho patients, symptoms suggesting female hormonal dysfunction are observed (*19*). Although it is clear that PCB may have both enhancing and depressing effects on female hormones and eggshell formation, no detailed mechanism of action has been determined. The alteration of calcium or mineralization metabolism in bone and teeth may also be connected with such enzyme induction or female hormone-enhancing action of PCBs. Further study should be performed to elucidate the pathophysiology.

Pigmentation and Gingival Hyperplasia

Because PCB has a hepatic enzyme-inducting action which leads to degradation of the corticosteroid hormone, (hypoadrenocorticism), increased secretion of ACTH or MSH should be ruled out for the pathogenesis of dark brown pigmentation in FPS and Yusho in adults. In our series, all three newborns with FPS revealed normal excretion of 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS) in the urine and showed normal function of the hypophyseo-adrenocortical axis by Metopirone test (*4*). Adult Yusho patients showed no evidence of hypoadrenocorticism (*20,21*).

Therefore, the pigmentation that was confirmed as increased melanin by electron microscopy (*22*) could be caused by local events stimulated by PCBs.

The same local mechanism may also cause gingival hyperplasia which resembled that of diphenylhydantoin-induced gingival hyperplasia, the pathogenesis of which is still unknown (*23*).

Conclusions

Peculiar clinical features in neonates whose mothers consumed PCB-contaminated rice oil during pregnancy were reviewed. The term, Fetal PCB Syndrome (FPS) was introduced to describe the clinical entity whose features are dark brown pigmentation of the skin and mucous membrane, gingival hyperplasia, fetal growth suppression, precocious dentition and abnormal calcification of the skull. Suppression of fetal growth by PCBs was observed in female newborns whose mothers consumed PCB-contaminated rice oil during pregnancy; this retardation of growth was similar to that seen in infants ingesting milk from mothers with elevated PCB levels in their milk.

A possible alteration of calcium metabolism in FPS may be related to the action of PCB on female hormone; however, no definite conclusion was obtained. There was no evidence of hypoadrenocorticism which would explain dark pigmentation in FPS and Yusho.

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