Epidemiological aspects of Yusho ; Clinical features and blood levels of pentachlorodibenzofuran in Yusho patients

Tomoaki Imamura[1], Yoshiyuki Kanagawa[1], Shinya Matsumoto[1], Bunichi Tajima[2], Takeshi Uenotsuchi[3], Satoko Shibata[3], Masutaka Furue[3],
[1]Department of Planning Information and Management, University of Tokyo Hospital, Tokyo, 113-8655 Japan; [2]Teradata Division, NCR JAPAN Ltd., Tokyo, 104-0033 Japan; [3]Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Hukuoka, 812-8582 Japan.

Abstract

Kanemi Yusho is a form of food poisoning that broke out in Western Japan, particularly concentrated in the island of Kyushu in 1968, caused by rice bran oil contaminated with polychlorinated biphenyls (PCBs) and various dioxins such as polychlorinated dibenzofurans (PCDFs). We measured the blood levels of dioxins in the annual medical check-up of Yusho patients from 2001 to 2003 and analyzed the relationship between the concentrations of PCDFs/PCBs and the subjective/objective/laboratory findings of patients with Yusho. and compared the present clinical findings with those collected in 1988.

Introduction

Yusho (oil disease) was confirmed to have been caused by PCBs and dioxin-related compounds[1,2)] . More than 1800 people were ultimately diagnosed with Yusho. Blood levels of PeCDF and other dioxin-related compounds in a large number of Yusho patients since 2001.Therefor in this study, we screened the clinical and laboratory findings of patients with Yusho and determined the relationship with blood levels of PeCDF.

1. Materials and Methods

1-1. Subjects and Clinical examination

359 patients were enrolled in this study from 2001 to 2003. 51 patients underwent examination for three consecutive years, 166 for two years, and 142 underwent only one examination. Annual check-up of Yusho patients included 241 items, which included in the analysis of blood levels of dioxin-related compounds.

1-2. Data presentation and Statistical analysis

In order to represent the current state of the patients' condition, we used the mean values of the clinical and laboratory data as being representative for the patients who underwent two or three Yusho examinations from 2001 to 2003. We conducted a three-way ANOVA with logarithms of total PCDF values in an almost normal distribution as dependent variables, gender and age as fixed factors, and the presence of symptom in examination items as an additional various factor. SPSS11.5J software was used for the statistical analysis.

2. Results

2-1. Blood levels of PCB- and dioxin-related compounds obtained from 2001 to 2003 (Table1)

The mean blood levels of the PCB- and dioxin-related compounds measured in the three annual medical checkups were as follows: The dioxin PeCDF was determined to have a TEQ of 88.75 ppb, showing that it was the major toxic compound in Yusho patients. The mean blood levels of PeCDF were markedly higher than those in the normal controls (mean±SD, 15.2±8.9 pg/g lipids, n=52)[3)]

2-2. Relationship between PCDFs Clinical findings (Table2)

Blood levels of PeCDF were significantly correlated with each clinical examination, 6 items in Labolatory examination, 4 items in interview and physical, 10 items in dermatological findings, 1 items in dental examination. Clinical symptoms, such as general fatigue, headache, cough, sputum, numbness, arthralgia and abnormal abdominal ultrasonography were scored ≥1.50.

2-3. Comparison between the present symptoms and those 20 years after onset (1988) (Table3)

General fatigue, headache, numbness in the extremities, and abnormal abdominal ultrasonography were

Table 1. Blood Levels of Dioxins(TEQ level 1.0)

	Efficacy level	Mean value	Standard deviation	Minimum value	Maximum value	TEF	TEQ level
2,3,7,8-TCDD	359	1.66	0.80	0.50	4.99	1	1.66
1,2,3,7,8-PeCDD	359	11.00	6.13	0.99	46.03	1	11.00
1,2,3,6,7,8-HxCDD	359	49.68	40.00	4.88	289.77	0.1	4.97
PeCDF*	359	0.91	0.72	0.50	4.89		
2,3,4,7,8-PeCDF	359	177.50	235.64	2.82	1871.25	0.5	88.75
1,2,3,4,7,8-HxCDF	359	54.75	92.76	1.00	769.89	0.1	5.48
1,2,3,6,7,8-HxCDF	359	21.22	27.55	1.00	210.04	0.1	2.12
3,4,4',5-TCB(81)	359	5.46	2.69	5.00	41.02	0.0001	0.00055
3,3',4,4'-TCB(77)	359	9.69	5.42	5.00	42.05	0.0001	0.00097
3,3',4,4',5-PeCB(126)	359	100.39	70.61	5.00	560.94	0.1	10.04
3,3',4,4',5,5'-HxCB(169)	359	188.69	142.38	12.70	1070.32	0.01	1.89
2,3,4,4',5-PeCB(114)	279	2465.23	2179.28	100.17	18389.77	0.0005	1.23
2,3',4,4',5-PeCB(118)	279	18849.19	14208.08	1918.07	100390.50	0.0001	1.88
2,3,3',4,4',5-HxCB(156)	279	32785.13	37225.65	979.83	287429.76	0.0005	16.39
2,3,3',4,4',5'-HxCB(157)	279	9260.47	10998.22	275.84	92578.68	0.0005	4.63
Total-PCDD	359	902.58	559.58	181.05	6268.57		
Total-PCDF	359	264.26	350.98	12.10	2758.78		
Total-PCDD-PCDF	359	1166.85	673.17	231.90	6345.99		
T-PCDDs-TEQ	359	18.89	10.25	2.73	77.02		
T-PCDFs-TEQ	359	96.81	129.01	1.93	1023.49		
Total - TEQ	359	138.86	147.60	6.81	1183.91		

*PeCDF is an abbreviation of 2,3,4,7,8- pentchlorodibenzofuran

observed in >50% of patients in both the past and present. Approximately 40% of examinees complained of cough and sputum and ~30% complained of abdominal pain and diarrhea. The incidence and severity of most of the dermatological and ophthalmological symptoms decreased from 1988 to 2001–2003.

3. Discussion

Because of the low rates of dioxin excretion from the body [4~6], the mean blood levels of PeCDF (177.50 pg/g lipids) are still very high compared to those of normal controls (*n*=52, 15.2 pg/g lipids). The contaminated rice bran oil has been shown to contain 920 and 5 ppm of PCBs and PCDFs, respectively. The total amounts of PCBs and PCDFs ingested have been estimated to be 633 and 3.4 mg, respectively, on average [1] Among the contaminated PCDFs, PeCDF was found to be a major toxic compound, contributing to 69% of the total TEQ of the contaminated rice bran oil[1]. The estimated blood TEQ levels of dioxins at the onset of Yusho were calculated to be as high as 40 000–60 000 TEQ pg/g lipids[1,2]

Although there was a significant correlation between blood PeCDF levels and urinary glucose, ESR (2-h) TTT and Na, all of the mean values of the urinalysis and blood tests fell within the normal range. These results indicate that laboratory examination data, other than blood PeCDF levels, have little clinical and diagnostic significance for Yusho because >30 years have past since the outbreak..

ANOVA between blood levels of PeCDF and physical examination parameters revealed significantly high correlations with symptoms such as constipation, numbness in the extremities, body weight loss and abnormal abdominal ultrasonography. The chief complaints tended to be more frequent. More than 50% of the examinees complained of general fatigue headache or numbness in the extremities, and cough and sputum were nearly 40%. All of these complaints are clearly chronic. It should be noted that abnormal abdominal ultrasonography (e.g., cyst formation) increased to over 50%.

The dermatological, dental and ophthalmological findings of Yusho patients subsided with time. However, in ANOVA, 10 items were found to be significantly correlated with blood levels of PeCDF, such as a recent tendency to purulent skin eruptions, recent recurrence of cystic lesions, black comedones, acneform eruptions, scar formation and nail deformity. Various dermatological symptoms frequently observed in intoxication by chlorinated compounds have been included in the diagnostic criteria for Yusho. The dermatological symptoms such as acneform eroptions and pigmentation were characteristic for Yosho

Table 2. Three-Way Layout Analysis of Variance conducted with logarithms of total PCDF values as dependent variables

	Efficacy level	Mean value	Standard error of the mean	Standard deviation	Minimum value	Maximum value	P values from three-way layout analysis of variance
Laboratory examination							
Total PCB	353	3.14	0.13	2.45	0.00	25.10	0.000**
Peak 2 (2,2',4,4',5,5'-hexaCB)	329	0.58	0.03	0.45	0.00	2.80	0.000**
Urinalysis(Sugar)	356	1.19	0.04	0.68	1.00	5.00	0.027**
Erythrocyte sedimetation rate (ESR) (2-hour)	335	23.96	0.93	17.05	2.00	111.00	0.020**
Thymol turbidity test(TTT)	330	3.62	0.25	4.50	0.30	31.55	0.039**
Sodium	359	141.25	0.08	1.60	136.00	145.50	0.040**
Interview and physical examination							
Constipation (Frequency)	164	1.35	0.04	0.45	1.00	2.00	0.031**
Numbness	358	1.75	0.03	0.64	1.00	3.00	0.008**
Body weight	359	56.16	0.52	9.89	36.00	90.00	0.038**
Abnormal abdominal ultrasonograph	224	1.60	0.03	0.45	1.00	2.00	0.011**
Dermatological examination							
Recent tendency of purulent skin eruptions	357	1.21	0.02	0.37	1.00	2.00	0.047**
Recent recurrence of cystic lesions	357	1.26	0.02	0.41	1.00	2.00	0.015**
Past history of acneform eruptions	357	1.57	0.02	0.47	1.00	2.00	0.024**
Past history of pigmentation	354	1.45	0.02	0.46	1.00	2.00	0.008**
Black comedones(Trunk)	357	1.29	0.03	0.58	1.00	4.00	0.000**
Black comedones(Other sites)	310	1.11	0.03	0.45	1.00	4.00	0.002**
Acneform eruptions(Genital area)	358	1.18	0.03	0.50	1.00	4.00	0.007**
Acneform eruptions(Buttocks)	356	1.16	0.03	0.51	1.00	5.00	0.044**
Scar formation(Trunk)	358	1.30	0.03	0.64	1.00	4.00	0.007**
Nail deformity	358	1.34	0.03	0.62	1.00	4.00	0.027**
Dental examination							
Mucosal pigmentation of upper gingivae (Diffuse)	294	0.15	0.02	0.33	0.00	1.00	0.045**
Mucosal pigmentation of palate (Spotted)	294	0.00	0.00	0.06	0.00	1.00	0.027**

<Category for "significance probability from three-way layout analysis of variance">
The three-way layout analysis of variance was conducted with logarithms of total PCDF values as dependent variables. Gender and age were always fixed, as was the presence of symptoms in laboratory examinations.
** P value <0.05 without interaction:

patients [7], apparently decreased from 1988 to 2001–2003. In dental findings, PeCDF levels and mucosal pigmentation of the upper gingivae and the palate revealed significant. In ophthalmological findings revealed no significant correlations with PeCDF levels. All of the ophthalmological findings are now mild.
The median half-life of 2,3,4,7,8- PeCDF is 2.9 years in first 15years after onset, becoming 7.7 years in next 15 year stage [8]. However, the blood levels of chlorinated compounds such as PeCDF still remain high in Yusho patients, suggesting that continuous follow-up is indispensable in the future. Blood levels of PeCDF were added to the diagnostic criteria for Yusho in September 2004 [1] . The objective clinical findings have slowly returned to normal over the years since the outbreak of the disease. PeCDF blood level is considered an informative indicator which could provide evidence that Yusho patients have ingested the causative rice oil.

4. References

1. Furue M, Uenotsuchi T, Urabe K, Ishikawa T, Kuwabara M. 2005. Overview of Yusho. J Dermatol Sci Suppl 1:S3-S10.
2. Kuratsune M, Yoshimura H, Hori Y, Okumura m, Matsuda Y. 1996. Yusho - A human disaster caused by PCB and related compounds. Kyushu University Press, Fukuoka.
3. Yamaguchi N, Kaneko S. "A study on evaluation of carcinogenesis in patients with Yusho' and "A study on health evaluation in Yusho." Health and Labour Sciences Research, 2001 and 2002 (integrated study report), 2002 (summarized and allotted study report).
4. Yoshimura T,Yusho in Japan. Ind Health. 2003, 41(3):139-48.

Table3. Prevalence of symptoms of patients with Yusho evaluated in 2001-2003 and 1988

symptoms	2001-2003			<Reference: 1988 data>*		
	Incidence of symptom	Number of examinees with symptoms	Total number of examinees	Incidence of symptom	Number of examinees with symptoms	Total number of examinees
The interview and physical examination						
General fatigue	62.1%	221	356	76.1%	194	255
Headache	52.9%	189	357	67.3%	173	257
Cough	39.2%	140	357	51.0%	131	257
Sputum	42.6%	152	357	52.0%	133	256
Abdominal pain	27.5%	98	357	43.2%	111	257
Diarrhea	31.5%	112	356	42.0%	108	257
Numbness of extremities	53.6%	192	358	61.9%	159	257
Troubles with menstruation	17.5%	20	114	19.3%	16	83
Respiratory sounds	1.4%	5	354	2.7%	7	257
Hepatomegaly	0.6%	2	352	7.8%	20	257
Splenomegaly	0.0%	0	352	0.0%	0	256
Sensing	10.3%	36	350	7.5%	19	253
Abdominal ultrasonograph	50.9%	114	224	33.7%	60	178
The dermatological examination						
Recent tendency of purulent skin eruptions	15.4%	55	357	16.6%	41	247
Past history of acneform eruptions	51.5%	184	357			
Past history of pigmentation	37.9%	134	354			
Black comedones(Face)	6.7%	24	358	12.1%	31	256
Black comedones(Ear)	5.6%	20	358	7.4%	19	256
Black comedones(Trunk)	5.3%	19	357	11.8%	30	254
Black comedones(Other sites)	3.5%	11	310	2.9%	4	139
Acneform eruptions(Face)	5.3%	19	358	4.7%	12	255
Acneform eruptions(Genital area)	3.4%	12	358	4.7%	12	256
Acneform eruptions(Buttocks)	3.1%	11	356	3.5%	9	255
Acneform eruptions(Trunk)	3.4%	12	358	6.3%	16	255
Acneform eruptions(Other sites)	1.0%	3	309	1.5%	2	136
Pigmentation(Face)	2.5%	9	358	2.7%	7	256
Pigmentation(Fingernails)	2.8%	10	358	2.3%	6	256
Pigmentation(Toenails)	3.6%	13	358	6.3%	16	256
Pigmentation(Other sites)	1.0%	3	301	0.0%	0	132
Nail deformity	7.3%	26	358	10.3%	26	253
The ophthalmological examination						
Abnormal discharge from the eyes	16.0%	57	356	15.3%	38	249
Edema of the eyelid	0.8%	3	356			
Conjunctival pigmentation	1.4%	5	356	4.4%	11	248
Cysts of meibomian glands	1.7%	6	356	12.0%	30	249
Cheesy secretions from meibomian glands	1.4%	5	348	4.6%	9	196

* <Reference: 1988 data> is an excerpt from Table 8.1., Chapter 8, "Yusho - A human disaster caused by PCB and related compounds"

5. Imamura T, Kanagawa Y: “A study on correlations between blood serum levels of PCDFs and clinical symptoms in patients with Yusho (78 patients for 2001, 279 patients for 2002).” Health and Labour Sciences Research, 2003 (summarized and allotted study report. In Japanese).
6. Kanagawa Y, Imamuara T. 2005. Relationship of clinical symptoms and laboratory findings with the blood serum levels of PCDFs in patients with Yusho. J Dermatol Sci Suppl 1:S85-S93.
7. Ikeda M. 1996. Comparison of clinical picture between Yusho/Yucheng cases and occupational PCB poisoning cases. Chemosphere. 32(3):559-66.
8. Masuda Y. 2001. Fate of PCDF/PCB congeners and change of clinical symptoms in patients with Yusho PCB poisoning for 30 years. Chemosphere. 43(4-7):925-30