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Current skin symptoms of Yusho patients exposed to high levels of 2,3,4,7,8-pentachlorinated dibenzofuran and polychlorinated biphenyls in 1968

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HIGHLIGHTS

- One-third of Yusho patients still presented with specific skin symptoms in Yusho.
- The blood levels of 2,3,4,7,8-PeCDF and PCBs were still high in Yusho patients.
- The severity of some skin symptoms were correlated with blood dioxins levels.
- The prevalence and severity of black comedones were correlated with age.

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ABSTRACT

Yusho was a mass food poisoning event due to the ingestion of rice oil contaminated with polychlorinated biphenyls (PCBs) and various dioxins and dioxin-like compounds. At its outbreak in 1968, Yusho patients suffered severe skin symptoms. Although the blood concentrations of PCBs and dioxins, especially highly toxic 2,3,4,7,8-pentachlorinated dibenzofuran (2,3,4,7,8-PeCDF) remain high in these patients, extensive analysis has not been performed on their current skin symptoms. We categorized and evaluated the specific skin symptoms in Yusho in 2012 by grading their severity using an arbitrary scoring system, and analyzed their correlations with the blood concentrations of 2,3,4,7,8-PeCDF and PCBs. A total of 352 Yusho patients underwent annual dermatological check-ups, in which five skin symptoms: black comedones, acneiform eruptions, scar formation, pigmentation and nail deformity, were evaluated for their distribution and severity. Approximately one-third of Yusho patients still presented with black comedones, acneiform eruptions and scar formation; the distributions of these symptoms were similar to those at the time of the Yusho outbreak. The mean blood concentrations of 2,3,4,7,8-PeCDF and total PCBs in Yusho patients were still higher than those in controls. The prevalence and severity of black comedones were correlated with age. Severity scores of black comedones and scar formation were positively correlated with 2,3,4,7,8-PeCDF blood level, and those of black comedones, scar formation, and pigmentation were positively correlated with total PCBs blood level. This study suggests that 2,3,4,7,8-PeCDF and PCBs remaining in Yusho patients still play crucial roles in the development of skin symptoms in Yusho.

1. Introduction

A mass food poisoning event, Yusho, which means oil disease in Japanese, occurred in western Japan in 1968. Yusho was

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caused by the ingestion of a commercial brand of rice oil that was contaminated with polychlorinated biphenyls (PCBs) (Kuratsune et al., 1996, 1971). Later, it was revealed that the rice oil contained not only PCBs but also other dioxins and dioxin-like compounds (hereafter simply referred to as dioxins) such as polychlorinated dibenzofurans (PCDFs) that were generated by heat denaturation of PCBs (Masuda, 1994). Since the Yusho incident in 1968, two other mass dioxin poisoning events have occurred. An industrial accident (the Seveso incident) contaminated a residential area surrounding Seveso, Italy, with high levels of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) in 1976 (Caramaschi et al., 1981). In addition, in 1979, mass food poisoning, namely Yucheng, occurred in central Taiwan due to the ingestion of cooking oil contaminated with PCBs and PCDFs (Chen et al., 1981).

The contribution of highly toxic PCDF congeners to the toxic equivalent (TEQ) in the contaminated rice oil in Yusho was 77% (Yao et al., 2002). Among PCDF congeners, 2,3,4,7,8-pentachlorinated dibenzofuran (2,3,4,7,8-PeCDF) was shown to contribute 58% to the total TEQ in the oil (Yao et al., 2002). Later, it was revealed that PCDF congeners contribute approximately 65% of the total TEQ in the blood of Yusho patients (Todaka et al., 2007). Following advances in techniques for measuring dioxins, including PCDF congeners, it became possible in 2001 to measure the concentration of 2,3,4,7,8-PeCDF precisely using a small amount of blood (Iida and Todaka, 2003).

Since the outbreak of Yusho, the Study Group of Yusho (Yusho Group) has been conducting annual medical check-ups on Yusho victims. These check-ups consist of an interview and physical, dermatological, ophthalmological, dental and laboratory examinations. The concentrations of PCBs and dioxins in the blood of Yusho patients have gradually been decreasing over 40 years. However, recent studies showed that the blood level of PCDF congeners in Yusho patients was 10.3 times higher than that of controls, and in particular, the blood level of 2,3,4,7,8-PeCDF was 11.3 times higher than that of controls (Todaka et al., 2007). The concentrations of some PCB congeners in blood collected from Yusho patients in 2004 were also 3.4–3.9 times higher than those of controls (Todaka et al., 2009).

Dioxins are considered to be extremely lipophilic, biologically stable and not readily excreted by the human body (Van den Berg et al., 1994); however, the long-term pharmacokinetics of dioxins in humans are not fully understood. The half-lives of dioxins are considered to vary among individuals. A survey of Seveso (Kerger et al., 2006) demonstrated that the half-lives of dioxins are dependent upon a patient's age and dioxin concentrations. In addition, a recent study of the variation in the half-life of 2,3,4,7,8-PeCDF in the blood of Yusho patients (Matsumoto et al., 2009) showed that there is a group of patients whose dioxins have remained at higher concentrations than previously predicted.

At the time of the Yusho outbreak, characteristic mucocutaneous manifestations, such as black comedones; acneiform eruptions; pigmentation of the nails, oral mucosa, conjunctiva and genitalia; and increased discharge from the eyes, were the major symptoms (Kuratsune et al., 1971). The symptoms of Yusho have gradually been improving over the past 40 years (Furue et al., 2005). Nonetheless, unexpectedly, skin symptoms with various degrees of severity still remain in a certain population of the patients.

In this study, we performed a precise examination of skin symptoms in Yusho patients who underwent annual dermatological check-ups in 2012 and investigated the correlations between the blood levels of 2,3,4,7,8-PeCDF and total PCBs on the one hand and the prevalence and severity of current skin symptoms on the other.

2. Material and methods

2.1. Subjects

A total of 352 Yusho patients (male 185, female 167) who underwent a dermatological check-up in 2012 were enrolled in this study. The mean ages ± standard deviations (SDs) of the male and female patients were 65.2 ± 13.5 and 66.4 ± 13.1, respectively.

2.2. Analysis of 2,3,4,7,8-PeCDF and total PCBs, and dermatological examination

The blood concentrations of 2,3,4,7,8-PeCDF and total PCBs were measured using high-resolution gas chromatography/high-resolution mass spectrometry equipped with a new large-volume injection system (SGE Ltd., Victoria, Australia) at the Fukuoka Institute of Health and Environmental Sciences (Iida and Todaka, 2003).

Whole-body skin examination was performed by expert dermatologists. Black comedones, acneiform eruptions, scar formation, pigmentation and nail deformity, namely skin symptoms characteristic of Yusho, were evaluated carefully using a five-grade scoring system: 0, no lesion; 1, very mild; 2, mild; 3, moderate; and 4, severe. The black comedones were scored in four regions: face, ear lobes, trunk and other sites. Acneiform eruptions were examined in five areas: face, genitalia, hips, trunk and other sites. Scar formation was evaluated on the face, trunk and other sites. Scoring of pigmentation was carried out for the face, fingernails, toenails and other sites. The severity of each skin symptom is defined as the sum of the scores of the different sites.

2.3. Statistical analysis

Statistical analyses were performed using Spearman's rank correlation coefficient, the Mann–Whitney U-test and the Cochran–Armitage test. *P* values < 0.05 were considered to be significant.

3. Results

3.1. The blood levels of 2,3,4,7,8-PeCDF and total PCBs in Yusho patients

Approximately 45% of the patients enrolled in this study were over 70 (Fig. 1a). The mean ± SD of blood 2,3,4,7,8-PeCDF concentration in Yusho patients was 130.8 ± 192.7 (range 2.7–1494.3) pg g^{-1} lipid, which was approximately eight times higher than normal levels: 17 ± 6.6 (range 5.0–37) pg g^{-1} lipid (Todaka et al., 2007). The mean ± SD of blood total PCBs concentration in Yusho patients was 1.9 ± 1.8 (range 0.01–16) ng g^{-1}, which was higher ($p < 0.001$, Mann–Whitney U-test) than that in age- and sex-matched controls ($n = 51$, 1.0 ± 0.8 ng g^{-1} (range 0.08–3.8)). The blood levels of 2,3,4,7,8-PeCDF in female patients (mean ± SD: 196.2 ± 238.5 pg g^{-1} lipid) were significantly higher ($p < 0.0001$, Mann–Whitney U-test) than those in male patients (mean ± SD: 71.7 ± 109.2 pg g^{-1} lipid), whereas the blood levels of total PCBs in females (mean ± SD: 2.0 ± 1.8 ng g^{-1}) were slightly higher ($p = 0.03$, Mann–Whitney U-test) than those in males (mean ± SD: 1.8 ± 1.8 ng g^{-1}). The blood levels of 2,3,4,7,8-PeCDF (Fig. 1b) and those of total PCBs (Fig. 1c) were positively correlated with age.

3.2. Current skin symptoms in Yusho patients

As shown in Table 1, black comedones (32.7%, 115/352), acneiform eruptions (29.3%, 103/352) and scar formation (31.5%,