Environmental Research 166 (2018) 261–268

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Sleep disorders among Yusho patients highly intoxicated with dioxin-related compounds: A 140-case series

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ARTICLE INFO

Keywords:
Dioxin
Yusho
Sleep quality
Insomnia
Restless legs syndrome/Willis–Ekbom disease

ABSTRACT

Purpose: Patients with Yusho, a condition caused by exposure to dioxins and dioxin-like compounds, have diverse mental and physical complaints. However, the relationship between dioxins and sleep disorders has not yet been examined. This cross-sectional study was designed to investigate problems associated with sleep among patients with Yusho.

Methods: A total of 140 participants (52.9% men, average age: 67.1 ± 12.2 years) were examined using questionnaires and medical interviews by an expert on sleep medicine. Demographic and clinical characteristics, including blood concentrations of 2,3,4,7,8-pentachlorodibenzofuran (PeCDF), which is the major cause of Yusho, were obtained from the results of recent surveys conducted by the Yusho Study Group.

Results: Moderate to severe symptoms of insomnia were present in 51.8% of the patients. The median Pittsburgh Sleep Quality Index global score (PSQI GS) was 8 (interquartile range: 5–11). The prevalence of restless legs syndrome/Willis–Ekbom disease (RLS/WED) was 30.7%; 24.3% of patients had severe RLS/WED (distressing symptoms with a frequency ≥ 1day per week). A higher blood concentration of 2,3,4,7,8-PeCDF (≥72.27 pg/g lipid) and severe RLS/WED were associated with higher odds of a PSQI GS ≥8, after adjusting for covariates (odds ratio [95% confidence interval]: 4.84 [1.10–21.25] and 4.15 [1.53–11.28], respectively).

Conclusions: Symptoms of insomnia were frequent, and the prevalence of RLS/WED was high in patients with Yusho. In addition to the presence of RLS/WED, a higher blood concentration of 2,3,4,7,8-PeCDF was associated with lower subjective sleep quality.

1. Introduction

In 1968, an outbreak of Yusho, which means “oil disease” in Japanese, occurred in western Japan. This condition was caused by the ingestion of rice bran oil contaminated with polychlorinated biphenyls (PCBs). It was later found that 2,3,4,7,8-pentachlorodibenzofuran (PeCDF) was the main toxic compound among patients with Yusho. Dioxins, such as 2,3,4,7,8-PeCDF and dioxin-like compounds, are generated by the heat denaturation of PCBs. Dioxins are lipophilic and biologically stable in the body. Even now, 50 years after the outbreak, the levels of dioxins are still high in some patients (Mitoma et al., 2015).

In experimental animals and wildlife, dioxins can be detected in brain samples. After a single administration of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) to rats, TCDD was detected in the brain (Weber et al., 1993). In dead gulls collected along the coast, TCDD and chloroorganic pesticides can be found in the brain (Falkowska et al., 2016). Although the transport of dioxins to the central nervous system has not been documented in humans, it can occur in theory.

Dioxins induce a wide variety of biological responses mediated by the aryl hydrocarbon receptor (AHR), which is one of the basic helix-loop-helix PER-ARNT-SIM transcription factors. After dioxins and AHR

Abbreviations: AHI, apnea-hypopnea index; AHR, aryl hydrocarbon receptor; ARNT, aryl hydrocarbon receptor translocator; BMI, body mass index; CH-RLSq, Cambridge-Hopkins questionnaire; DIS, difficulty initiating sleep; DMS, difficulty maintaining sleep; ESS, Epworth Sleepiness Scale; GS, global score; HVA, homovanillic acid; ISI, Insomnia Severity Index; MCS, mental component summary; ODI, oxygen desaturation index; PCBs, polychlorinated biphenyls; PCS, physical component summary; PeCDF, pentachlorodibenzofuran; PSG, polysomnography; PSQI, Pittsburgh Sleep Quality Index; RBD, rapid eye movement sleep behavior disorder; RBDSQ, RBD Screening Questionnaire; RLS/WED, restless legs syndrome/Willis–Ekbom disease; SCN, suprachiasmatic nucleus; SF8, Short Form-8; SDB, sleep disordered breathing; TCDD, tetrachlorodibenzo-*p*-dioxin; TH, tyrosine hydroxylase; WE, waking up too early

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https://doi.org/10.1016/j.envres.2018.05.033
Received 13 April 2018; Received in revised form 26 May 2018; Accepted 29 May 2018

bind in the cytoplasm, AHR translocates to the nucleus and generates a heterodimer with the aryl hydrocarbon receptor translocator (ARNT). The ligand-AHR-ARNT complex binds to a specific promoter region of genes related to xenobiotic metabolism and induces or suppresses the expression of target genes (Wu and Rastinejad, 2016). AHR and ARNT are expressed in the hypothalamus and in brainstem neurons (Petersen et al., 2000).

Monoaminergic systems are affected by dioxins through the AHR pathway. Expression of tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine synthesis, is induced by the administration of TCDD via AHR activation, causing dopamine levels to be increased in vitro (Akahoshi et al., 2009). After sub-chronic exposure to TCDD, levels of dopamine, norepinephrine, and 5-hydroxy tryptamine are increased in various brain regions of rats (Byers et al., 2006). Moreover, fetal exposure to TCDD upregulates TH expression in mouse midbrain dopaminergic neurons via the AHR signaling pathway (Tanida et al., 2014). Monoaminergic systems are active during wakefulness and inactive during sleep (Scammell et al., 2017). There is concern that chronic dioxin exposure upregulates monoaminergic system activity and disturbs the transition from wakefulness to sleep.

Crosstalk between the AHR pathway and the biological clock system could affect metabolic syndrome through changes in circadian rhythms. AHR activation decreases the amplitude of the expression of circadian clock genes in the suprachiasmatic nucleus (SCN). Conversely, AHR inhibition increases the amplitude of oscillations in the SCN (Jaeger and Tischkau, 2016). Sleep is achieved through a homeostatic process, which rises during wakefulness, and a circadian process interact with a regulatory mechanism for control of sleep (Borbely, 1982). The decrease in oscillation amplitude caused by dioxin exposure could affect sleep/wake regulation.

Patients with Yusho have diverse mental and physical complaints. However, the relationship between dioxins and sleep disorders has not yet been examined. This cross-sectional study was designed to investigate problems associated with sleep, including the prevalence and severity of insomnia, sleep disordered breathing (SDB), rapid eye movement sleep behavior disorder (RBD), and restless legs syndrome/Willis–Ekbom disease (RLS/WED) among patients with Yusho.

2. Materials and methods

2.1. Participants

This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences (approval no. 17062109). A total of 275 officially registered patients with Yusho, residents of Goto city (Nagasaki prefecture, Japan) were asked to participate in this study by mail. A total of 140 patients (74 men and 66 women, average age: 67.1 ± 12.2 years) participated in the study. All patients provided written informed consent.

2.2. Survey and collection methods

The survey was conducted at Goto city. Data were collected between September 2017 and November 2017. Questionnaires were administered during face-to-face interviews by investigators. Following the interviews, an expert on sleep medicine examined the patients. Medications use, including that of hypnotics, was confirmed in the survey. Screening for SDB was performed over two consecutive nights using a pulse oximeter. Demographic and clinical characteristics, including sex, age, body mass index(BMI), habitual drinking, smoking status, and comorbidities, were obtained from the results of a survey of the current health conditions of officially registered Yusho patients, conducted by the Yusho Study Group in 2016 (Ministry of Health, Labour and Welfare, 2017).

Blood concentrations of 2,3,4,7,8-PeCDF are measured every third year in officially registered Yusho patients. The half-lives of 2,3,4,7,8-PeCDF in the blood of patients with Yusho is reported to be unexpectedly long, and a recent study confirmed prolonged half-lives, particularly patients with high blood concentrations (Matsumoto et al., 2017). Therefore, the blood concentration of 2,3,4,7,8-PeCDF was obtained from the results of recent surveys conducted by the Yusho Study Group (Katsuki, 2018).

The concentration of 2,3,4,7,8-PeCDF was measured using a solvent-cut large-volume injection system with high-resolution gas chromatography/high-resolution mass spectrometry (Todaka et al., 2003, 2013). In the diagnostic criteria for Yusho, the following categorization has been made on the basis of the concentration of 2,3,4,7,8-PeCDF in the blood: 1) ≥50 pg/g lipid is an abnormally high concentration; 2) 30–50 pg/g lipid is a moderately elevated concentration, and 3) ≤30 pg/g lipid is a normal concentration (Mitoma et al., 2015).

2.3. Questionnaires

Subjective sleep quality was assessed using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI). The PSQI global score (GS) ranges from 0 to 21, and higher scores indicate worse sleep quality (Buysse et al., 1989). The severity of insomnia was assessed using the Japanese version of the Insomnia Severity Index (ISI). The severity of difficulty initiating sleep (DIS), difficulty maintaining sleep (DMS) and waking up too early (WE) are answered as “none”, “mild”, “moderate”, “severe”, or “very severe”. Responders who had “mild” to “very severe” symptoms were defined as having the presence of DIS, DMS, and/or WE. Responders who had “moderate” to “very severe” symptoms were defined as having the presence of moderate to severe DIS, DMS, and/or WE. The global score on this index ranges from 0 to 28, with high scores indicating greater insomnia severity (Bastien et al., 2001). Daytime sleepiness was assessed using the Japanese version of the Epworth Sleepiness Scale (ESS). The global score on this scale ranges from 0 to 24, with higher scores indicating greater subjective daytime sleepiness (Takegami et al., 2009).

A Japanese version of the RBD Screening Questionnaire (RBDSQ) was used for the screening of RBD (Miyamoto et al., 2009; Stiasny-Kolster et al., 2007). The bed partner's input was encouraged but not required. A Japanese version of the Cambridge-Hopkins questionnaire (CH-RLSq) was used for the screening of RLS/WED (Allen et al., 2009).

Health-related quality of life was evaluated using the Japanese version of the Short Form-8 (SF8). One item is used to measure each of the eight domains of health, including physical functioning, role limitations because of poor physical health (role physical), bodily pain, general health perception, vitality, social functioning, role limitations due to poor emotional health (role emotional) and mental health. Each SF8 single-item scale can be scored on the same norm-based metrics as the SF36; these scales have a mean of 50 and standard deviation of 10 in the Japanese population (Fukuhara et al., 1998). Two summary scores, the physical component summary (PCS) and the mental component summary (MCS), were then calculated.

2.4. Pulse oximeter

SDB was screened using a pulse oximeter (PULSOX-300i, KONICA MINOLTA Japan, Inc., Tokyo, Japan). The pulse oximeter was attached to the first joint of the second or third fingers on the non-dominant hand at bedtime and removed at the time of awakening over two consecutive nights. The data were downloaded to a personal computer using DS-Me (KONICA MINOLTA Japan, Inc.). After the removal of period of poor measurement, the 3% oxygen desaturation index (ODI) was calculated, defined as the number of times per hour in which the oxygen saturation decreased by 3% or more of the baseline. Patients who had a 3% ODI ≥ 15 or used continuous positive airway pressure were defined as having suspected moderate to severe SDB.