表 2　Tenax TA 捕集管の GC/MS 分析条件

使用機器	Agilent 6890N/5973inert
カラム	Inert Cap 1MS　30m*0.25mm*0.25μmdf
温度	50°C（2min）→10°C/min→320°C（5min）
スプリット比	Splitless
測定モード	SCAN
検出器温度	230°C
SCAN パラメータ	m/z 29(Low)~550(High)

表 3　拭き取りガーゼ分析の GC/MS 条件

GC/MS	Simadzu(Japan) GCMS-QP2010Plus
カラム	Inert Cap 1MS　30m×0.25mm, df=0.25μm
温度	50˚C（2min）→10˚C/min→320˚C（15min）
注入温度	280℃
GC 注入量	1μL
スプリット比	splitless
測定モード	SIM(selected ion monitoring) and SCAN
SCAN パラメータ	m/z 29(Low)~550(High)
検出器温度	230˚C

表 4　PVC 床材からの SVOC 放散速度の測定結果[μg/m^2・h]

化合物名	PVC1	PVC2	PVC3	PVC4	PVC5
2E1H	0.62	0.55	0.67	0.38	0.59
D6	—	—	—	—	—
BHT	—	—	—	—	—
DEP	0.23	0.25	0.34	0.13	0.18
C16	0.14	—	—	0.19	—
TBP	—	—	—	—	—
TCEP	—	—	—	—	—
DBA	—	—	—	—	—
DBP	0.42	1.52	0.64	1.34	1.39
TPP	—	—	—	—	—
DOA	—	—	—	—	—
DEHP	12.54	0.95	3.85	9.56	11.13

－：検出限界＜1ng 以下

表 5　試験片表面 DEHP ブリードアウト濃度[μg/試験片]

化合物名	PVC1	PVC2	PVC3	PVC4	PVC5
2E1H	—	—	—	—	—
D6	—	—	—	—	—
BHT	—	—	—	—	—
DEP	—	—	—	—	—
C16	—	—	—	—	—
TBP	—	—	—	—	—
TCEP	—	—	—	—	—
DBA	—	—	—	—	—
DBP	—	—	—	—	—
TPP	—	—	—	—	—
DOA	—	—	—	—	—
DEHP	3157	631	1500	5683	2762

—：検出限界＜1μg 以下

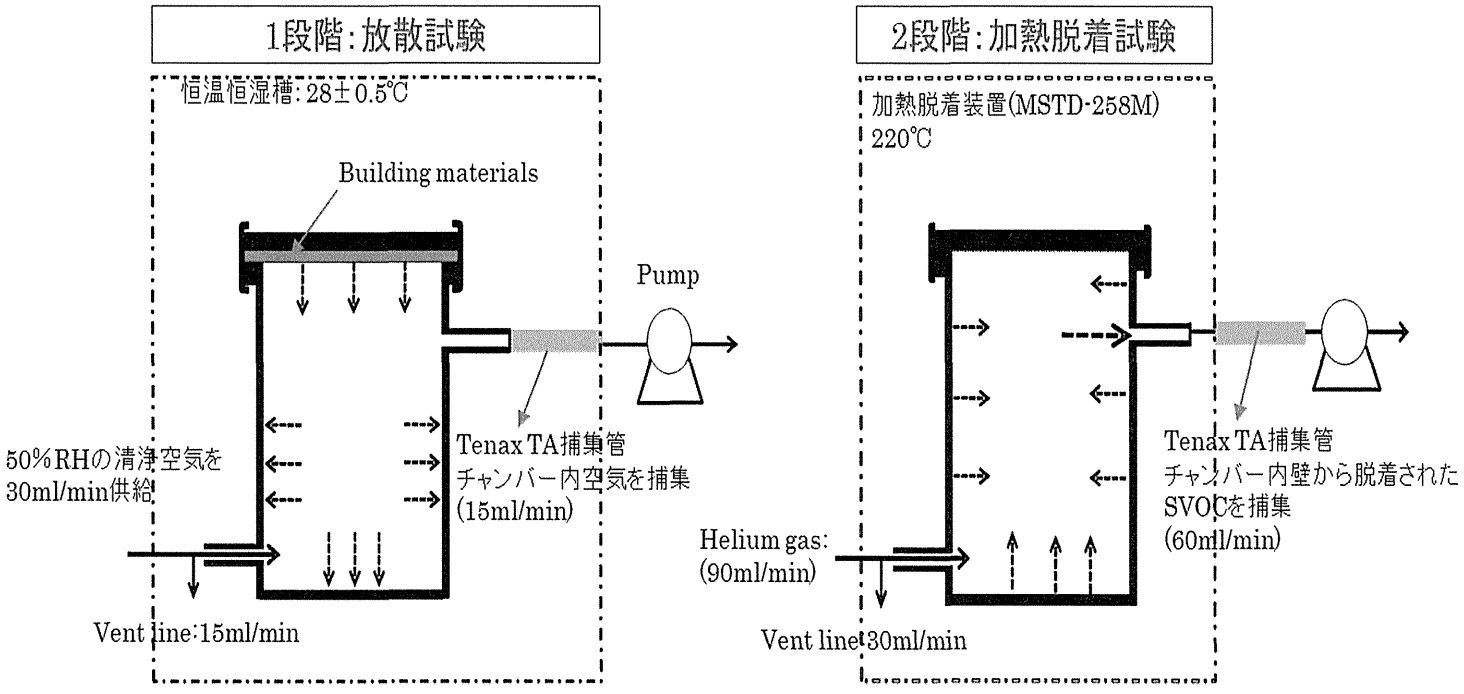
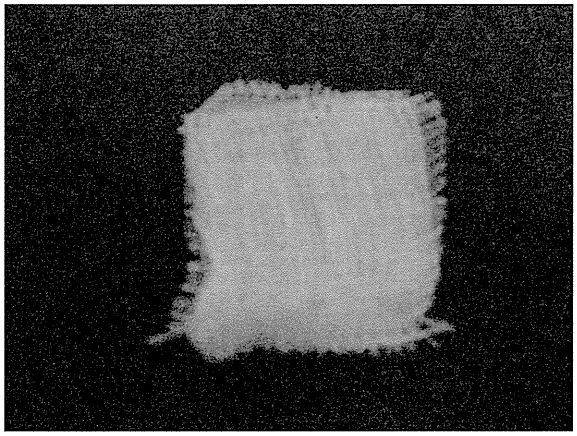
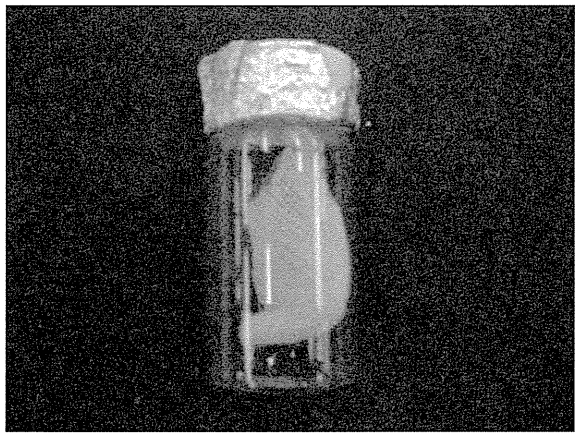


図２　マイクロチャンバーのイメージ



エタノールで洗浄済みの医療用ガーゼ



サンプラをガラス瓶に保管

図３　ガーゼとサンプラ

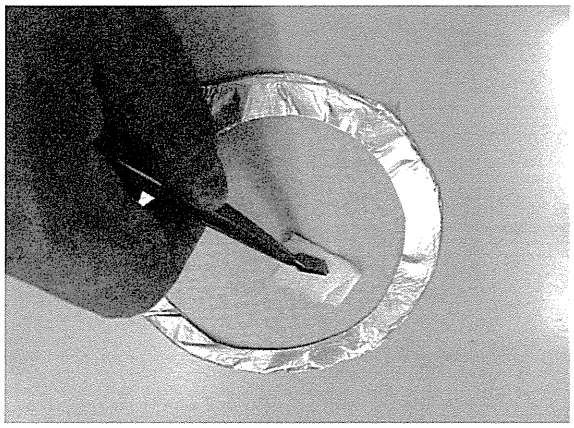


図４　表面ブリードアウト濃度測定様子

シックハウス症候群の
診断基準の検証に関する研究

III.　巻末参考資料

The Diagnosis of Sick House Syndrome: the Contribution of Diagnostic Criteria and Determination of Chemicals in an Indoor Environment

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Objective: The study group for sick house syndrome (SHS) in Japan has proposed the classifications, definition and diagnostic criteria for chemical-associated SHS. We compared the physicians' diagnoses to the diagnoses based on the patients' interview sheets including diagnostic criteria only.
Methods: We examined 287 patients with complaints of SHS-like symptoms. We also checked determinations of chemical substances in the patients' homes.
Results: A total of 76.0% of the patients were diagnosed as having SHS. Physicians diagnosed 87.6% of those patients as having chemical-associated SHS based on SHS classifications, definition and diagnostic criteria. Based on the patients' interview sheets, 50.3% of the patients who were diagnosed as chemical-associated SHS corresponded to the diagnostic criteria. The 51 of those chemical-associated SHS patients had answered that the chemical substance levels in their homes had been checked, and 20 of those patients answered that at least one of the chemical substance levels was above that set in the guideline by the Japanese Ministry of Health, Labour and Welfare.
Conclusions: Physicians should use all of the classifications, definition and diagnostic criteria. Even if the chemical levels in the home are under the guideline levels, the diagnosis of chemical-associated SHS should not be excluded.

Key words: classification, diagnostic criteria, indoor environment, multiple chemical sensitivities, sick house syndrome

INTRODUCTION

In Japan, sick house syndrome (SHS) has been a social problem since the 1990's. SHS is a distinctively Japanese concept that generally indicates various health disturbances induced by indoor environmental pollution. It is originally derived from sick building syndrome (SBS) [1, 2]. SBS is characterized by nonspecific complaints, such as mucous membrane irritation, skin symptoms, headache, and dizziness, due to a problem with the office building an individual works in. All except skin symptoms usually improve within a few hours after the individual leaves a suspected problem building. Therefore, the environment in the office building is considered to be the cause of the disease [2]. While, SHS is caused by the patients' house instead of an office building. The pathogenesis of SHS has not been clearly elucidated. In addition to the mechanism related to indoor chemical substances, intoxication and chemical intolerance, allergies and/or psychological factors have been suggested as the mechanism of SHS [3, 4].

The study group on the health effect of the indoor environment proposed the definition of SHS in a broad sense (bSHS) which is the general term of health disturbances induced by the environment in homes [5]. We have also proposed further classification types of bSHS [6, 7]. Those classifications are: type 1 (symptoms of chemical intoxication), type 2 (symptoms developed possibly due to chemical exposure), type 3 (symptoms developed not because of chemical exposure but because of psychological or mental factors), and type 4 (symptoms developed due to allergies or other diseases).

Because SHS includes a broad scope of sicknesses, chemical-associated SHS should be distinguished from other types of SHS as SHS in a narrow sense (nSHS). The study group aided by the Japanese Ministry of Health Labour and Welfare proposed a definition and diagnostic criteria of nSHS [8]. The definition of nSHS is a syndrome that has various non-specific symptoms including mucous membrane irritation, skin complaints, headache, and general fatigue, which are all closely related to chemical substances. Intoxication cases, that show specific symptoms, from a high dose of chemical substances and/or allergies, are excluded

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Table 1 Classification and diagnostic criteria for SHS.

Type	Classification criteria	Example
1	Symptoms of chemical intoxication	Intoxication by agricultural chemicals
2	Symptoms developed possibly due to chemical exposure (nSHS) Definition of nSHS A syndrome which has various non-specific symptoms including mucous membrane irritation, skin complaints, headache and general fatigue which are related to chemical substances. Intoxication and allergy are excluded from nSHS. Diagnostic criteria of nSHS 1. The cause of the onset of a disease relates to a move, a new house/building, reconstruction of house/building, and/or use of new or different daily toiletry necessities. 2. Symptoms appear within the particular room and/or the particular house/building.* 3. When a patient leaves the house/building, symptoms improve or disappear. 4. When indoor environmental pollution is detected, it is critical evidence.	A new house, reconstruction of house/building, and/or use of new or different daily toiletry necessities.
3	Symptoms developed not because of chemical exposure but rather because of psychological or mental factors.	Psychological or mental factors
4	Symptoms developed due to allergies or other diseases.	Asthma and dermatitis

*Buildings include working places and schools.

from nSHS. The diagnostic criteria of nSHS were the following.

1. The cause of the onset of a disease relates to a move, a new house or building, the reconstruction of a house or building, and/or the use of new or different daily toiletry necessities.
2. Symptoms appear within a particular room and/or a particular house/building.
3. When a patient leaves the house/building, symptoms improve or disappear.
4. When indoor environmental pollution is detected, it is critical evidence.

When patients met all of the criteria 1-3, they were diagnosed as nSHS.

However, an epidemiological survey has not been performed to establish the diagnostic criteria as the gold standard for the diagnosis of SHS. There were no established diagnostic criteria. Also there has been no gold standard for the diagnosis of SHS.

We examined diagnosed cases of SHS in 7 medical institutions in Japan for patients' symptoms, their diagnosis of SHS, and environmental pollutants in their homes. If the use of the classifications, the definition and the diagnosis criteria was effective for the diagnosis of patients of SHS, physicians would be able to use them for the diagnosis of SHS. For the diagnosis of type 2 (chemical-associated SHS), the diagnostic criteria were specifically used as references. Miyajima *et al.* proposed to use both the classification and the diagnostic criteria together to select patients suffering from indoor pollution as subjects for the present study [7] (Table 1).

For the examining the effectiveness of using all of the classification, the definition and the diagnosis criteria, it was needed to compare the diagnosis using all of the classification, the definition and the diagnostic criteria, to the diagnosis criteria only.

We also examined whether or not the level determinations of the chemical substances in the patients' homes contributed to their diagnosis of type 2.

SUBJECTS AND METHODS

Subjects

The subjects in the present study were a total of 287 patients (65 males and 222 females) who presented with the chief complaint of various SHS-like symptoms at a clinical environmental medical department (6 hospitals and 1 clinic) from April 2001 through October 2010. The mean ages were 40.2 (range, 8-70) and 46.1 (range, 8-81) years old for men and women, respectively.

Methods

This study was a questionnaire survey for which the questionnaires were composed of sheets to be filled out by a doctor or doctors and self-interview sheets for the patients. When patients could not fill out the interview sheets themselves, their physicians filled out the sheets for them. The sections to be completed by the physicians included: laboratory data, results of other examinations, and the diagnosis. The physicians made the diagnoses based on the clinical records from the patients' first visit. When patients were diagnosed as suffering from bSHS, physicians classified them into types based on the SHS classifications, the definition and the diagnosis criteria [7]. If a patient could be classified as either of two types, the physician classified the patient as a main type and a subtype; when three types were possible, the classification would be a main type and two subtypes. The questionnaires for patients included questions regarding main symptoms, diagnostic criteria of nSHS, chemical intolerance based on the Japanese version of the Quick Environmental Exposure Sensitivity Inventory (QEESI) [9-11]. The questionnaires also included the results of the chemical substance levels found in the patients' homes in cases

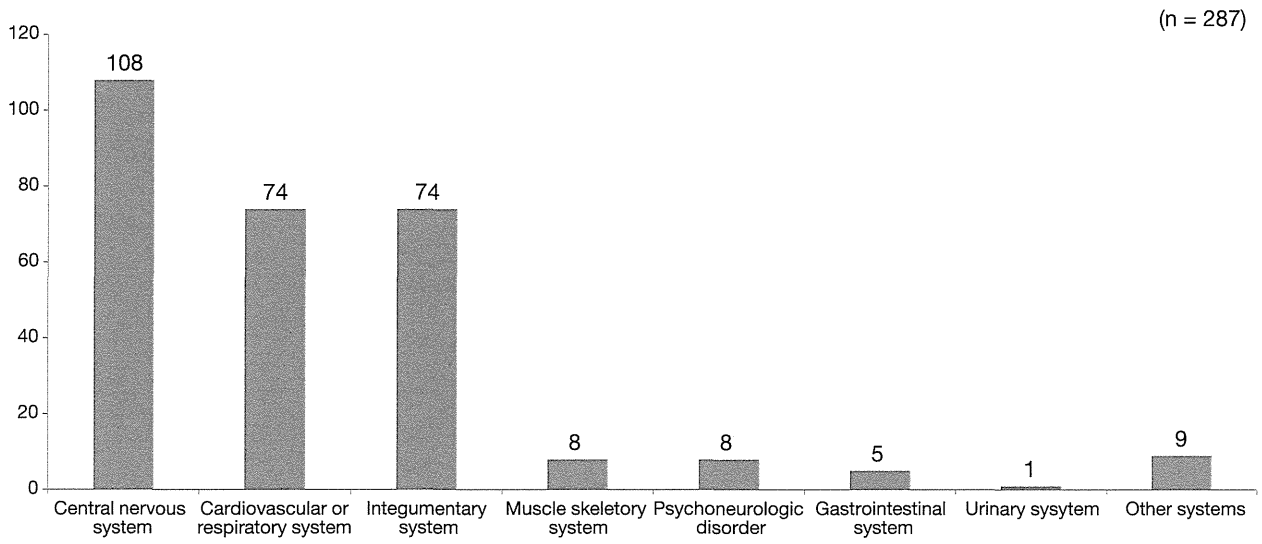

Fig. 1 Main complaints of patients from the questionnaire from their doctors.

for which the data were available. The chemical substances included: formaldehyde, toluene, xylene, ethylbenzene, styrene, paradichlorobenzene, acetaldehyde, and tetradecane. The results were checked to determine whether or not at least one of the chemical substances' levels, which were listed by the Japanese Ministry of Health, Labour and Welfare, was above the level in the guideline. Regarding informed consent, the doctors explained the study to the patients and only the data of the patients who agreed to participate in the study were used.

We recruited the patients who agreed to the determination of the levels of chemical substances in the air of their homes that were related to the patient's symptoms. We determined the levels of chemical substances in the air of two rooms of a patient's house: the room where the patient's symptoms were exacerbated most by a chemical or chemicals and another room where their symptoms improved. We determined the levels of the following eight chemical substances by the passive sampling method: formaldehyde, toluene, xylene, ethylbenzene, styrene, paradichlorobenzene, acetaldehyde, and tetradecane.

Statistical analysis

The number of patients who had complaints for each system was itemized. The numbers and the percentages of the patients who were diagnosed as bSHS by their doctors are also given. In addition, each of the bSHS patients was classified as one of the SHS types. We independently checked whether or not the patients met the diagnostic criteria of nSHS 1-3. Cross-sectional analysis was performed to check whether or not the patients who had rooms in which at least one of the levels of chemical substances was above the guideline were related to the SHS classification types.

This study was approved by the Ethics Committee at the Kitasato Institute Hospital and Kitasato University School of Medicine.

RESULTS

Questionnaires for doctors

The numbers of patients who had complaints for related to a particular body system or organ were: 108 for the central nervous system, 74 for a cardiovascular or respiratory organ, 74 for the skin or a mucous membrane, 8 for a muscle or bone, 8 for psychoneurologic disorders, 5 for a gastrointestinal organ, 1 for a urinary organ, and 9 for other organs (Fig. 1). The numbers of patients and their symptoms were: 63 with headache, 23 with cough, 17 with difficulty breathing, and 16 with itchy eyes.

The numbers and the percentages of the patients who were diagnosed as having bSHS are shown in Fig. 2. Among 287 subjects, 218 (76.0%) patients were diagnosed as suffering from bSHS. Fifty-five patients were diagnosed with diseases other than bSHS. Among those 55 patients, 18 patients were diagnosed as having MCS (multiple chemical sensitivities) or CS (chemical sensitivities), and 5 patients were diagnosed as having psychosomatic diseases.

The numbers of main types and subtypes based on the classification of bSHS are shown in Table 2. Among 218 patients who were diagnosed as suffering from bSHS symptoms, 150 (68.8%) patients were classified as type 2 (main type only, without a subtype), and 41(18.8%) patients were classified as type 2 (main type, and subtypes).

Correspondence to the diagnostic criteria of nSHS based on the interview sheets for patients or the physicians' classifications

Based on the answers by patients to questions about the diagnostic criteria of nSHS, 117 (40.8%) patients corresponded to the diagnostic criteria for nSHS while 170 (59.2%) did not. Based on the physicians' diagnosis (by using all of the classification, the definition and the diagnostic criteria), the numbers and percentages of patients who corresponded to the diagnostic criteria of nSHS are shown in Table 3. The data were divided into type 2 and other types (types 1, 3, and 4). Remarkably, 50.3% of the patients who were classified as type 2 corresponded to the nSHS diagnostic criteria, and 49.7% of patients didn't corresponded to the criteria.

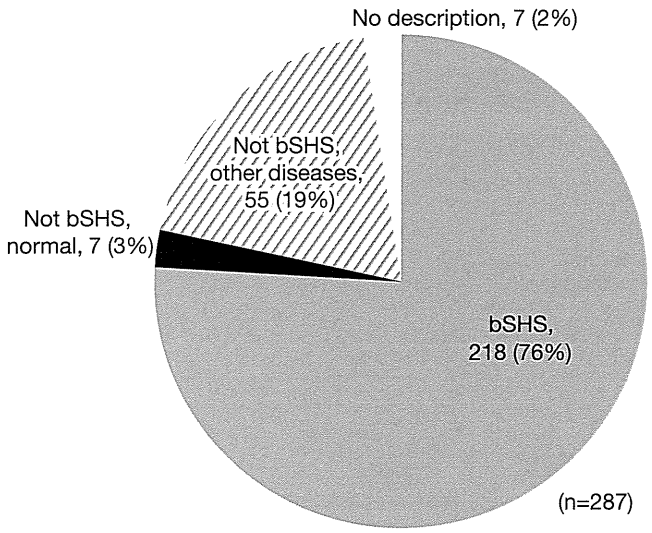

Fig. 2 Patients diagnosed with bSHS.

Table 2 Main types and subtypes of bSHS patients.

Classification type	*n*
Type 1	1
Type 2	150
Type 2 & subtype 1	7
Type 2 & subtype 3	23
Type 2 & subtype 4	8
Type 2 & subtypes 3 & 4	2
Type 2 & subtype no description	1
Type 3	7
Type 3 & subtype 2	4
Type 3 & subtype 4	1
Type 4	11
Type 4 & subtype 2	3
Total	218

Table 3 Types of bSHS and nSHS.

Type	nSHS	(%)	not-nSHS	(%)	Total
Type 2	96	(50.3)	95	(49.7)	191
Other types	21	(21.9)	75	(78.1)	96
Total	117	(40.8)	170	(59.2)	287

Table 4 Classification types and chemical substance levels in patients' homes based on interview sheets.

Level	Classification						
	Type 2	Type 2 & subtype 1	Type 2 & subtype 3	Type 2 & subtype 4	Type 3	Type 4	Total
Above guidline	17 (81.0%)	1 (4.8%)	2 (9.5%)	0 (0.0%)	0 (0.0%)	1 (4.8%)	21 (100.0%)
Below guidline	26 (74.3%)	0 (0.0%)	4 (11.4%)	1 (2.9%)	4 (11.4%)	0 (0.0%)	35 (100.0%)
Total	43	1	6	1	4	1	56

Relationships between classifications of patients and levels of chemical substances in their homes based on the interview sheets

According to the interview sheets, 71 patients answered that there were levels of chemical substances in their homes that were related to their symptoms. Twenty-four of those 71 patients (33.8%) answered that the level of at least one of chemical substances listed by the Ministry of Health, Labour and Welfare was above the guideline level. Thirty-six patients (50.7%) answered that there was none above the levels in the guideline. For 11 patients (15.5%) there were no descriptions about the levels of chemical substances.

Fifty-six of those 71 patients (78.8%) were diagnosed as suffering from bSHS. The relations between the levels of chemical substances and the types of SHS are shown in Table 4. Among 56 patients who were diagnosed as suffering from bSHS, 21 patients answered that the level of at least one of the chemical substances was above that in the guideline. In addition, 20 of those 21 patients (95.2%) were classified as type 2 and 1 patient was classified as type 4. While 31 of 35 bSHS patients (88.6%), who answered that none was above the guideline level, were classified as type 2, and only 4 patients (11.4%) were classified as type 3. Among 51 type 2 patients who checked chemical substance levels, 20 patients (39.2%) answered that at least one of the chemical substance levels was above that in the guideline. I.e., regarding the diagnosis of type 2, the sensitivity of determination of chemical substances levels was 39.2%. The specificity was 80.0% due to the fact that 4 of 5 patients of types 3 or 4 answered that there were no chemical substances in their homes that were above the guideline levels.

The chemical substances that showed levels in the patients' homes above the guideline levels based on the interview sheets are shown in Table 5. There were 13 homes for formaldehyde and 5 for toluene that were reported to be above the guideline levels.

Relation between the levels of chemical substances in the air of the patients' homes based on the determination and diagnosis of SHS

The results of the determination of the chemical levels are shown in Table 6. We recruited 10 patients who agreed that the levels of the chemical substances in their homes were related to their symptoms. Among those 10 patients, 4 patients lived where at least one chemical substance was above the level in the guideline. Three patients lived where the level of paradichlorobenzene

Table 5 Chemical substances with levels above the guideline.

Chemical substance	*n*
Formaldehyde	13
Toluene	5
Xylene	3
Paradichlorobenzene, acetaldehyde	2
Styrene, mepronil, fenitrothion, TVOC*	1
Total	24

*TVOC, total volatile organic compounds

Table 6 Chemical levels in 10 SHS patients' homes.

Patient No.	Place (symptom score)	Temperature (°C)	Humidity (%)	Formaldehyde	Toluene	Xylene	Styrene	Ethylbenzene	Paradichloro-benzene	Acetaldehyde	Tetradecane	Classification type
1	Bedroom (3)	30	72	30	11	11	UD	UD	6.9	10	UD	2 & subtype 3 + 4
	Living room (8)	30	69	33	14	14	UD	UD	7.2	11	UD	
2	Living room (5)	23	70	41	15	6.4	UD	UD	24	49	UD	2 & subtype 3
	Child's room (8)	27	71	39	27	8.2	UD	UD	72	46	UD	
3	Daughter's room (8)	19	70	19	9.7	7.6	UD	UD	82	16	UD	2 & subtype 3
	Bedroom (10)	24	63	6.7	6.7	4.8	UD	UD	420	9.1	UD	
4	Living/kitchen	14	UK	8.9	32	7.1	UD	UD	410	8.2	UD	4
	Bedroom	15	UK	8.3	30	13	UD	UD	430	6.5	UD	
5	Living room (0)	21	64	12	21	14	UD	UD	11	15	UD	2
	Toilet (8)	21	70	8.2	22	17	UD	7.2	8.3	14	UD	
6	Living room	23	64	8.7	13	66	<2.2	9.8	498	<4.8	<3.3	2
	Kitchen	23	70	31	16	25	<2.2	<3.8	38	9.6	<3.3	
7	European-style room	21	67	26	3.8	<8.7	<2.2	<3.8	<2.4	13	<3.3	2
	Bedroom	22	62	19	4.1	<8.7	<2.2	<3.8	<2.4	7.2	<3.3	
8	Living room (1st floor)	22	47	16	5.8	44	<2.2	44	<2.4	16	<3.3	2
	Bedroom (2nd floor)	19	50	16	5.7	43	<2.2	32	<2.4	15	59	
9	European-style room (2nd floor)	23	64	57	3.3	<8.7	<2.2	<3.8	<2.4	14	<3.3	2
	Japanese-style room (2nd floor)	23	70	97	<2.6	<8.7	<2.2	<3.8	12	7.7	<3.3	
10	Living room	29	62	37	12	<8.7	<2.2	<3.8	<2.4	26	<3.3	2
	Bedroom	29	64	39	16	<8.7	<2.2	<3.8	<2.4	25	<3.3	
Total		-	Guidline level (μg/m³)	100	260	870	220	3,800	240	48	330	10

UK, Unknown; UD, Undetectable

was above the level in the guideline, and 1 patient lived where acetaldehyde was above the guideline level. And among those 4 patients, 2 patients were classified as type 2 & subtype 3, 1 patient was classified as type 2, and 1 patient was classified as type 4.

Among 6 patients at whose homes there were no chemical substances above the guideline levels, 5 patients were classified as type 2, and 1 patient was classified as type 2 & subtype 3 + 4.

DISCUSSION

The results of this study, we help clarify the current situation regarding the diagnosis of SHS and the chemical environments of patients who visited medical institutions dealing with environmental medicine in Japan.

The major symptoms that many patients complained of were: headache, cough, dyspnea, and itchy eyes. In previous studies, toluene, which is considered one of the major causes of SHS, induced symptoms in the nervous system, e.g., stress and anxiety, and mucous membrane irritation [12]. Formaldehyde, which is also considered as a major cause of SHS [13, 14], also induced mucous membrane irritation. Therefore, some of the symptoms among those patients who had complained might likely have been caused by the chemical substances in their homes.

Totally, 76.0% of the patients were diagnosed as suffering from bSHS. Among the bSHS patients, 87.6% were classified as type 2. The results suggested that many of the patients who visited a specific department complaining of SHS-like symptoms could be diagnosed as suffering from bSHS, and most of those could be classified as type 2. On the other hand, about 20% who complained of SHS-like symptoms and visited a specific department of SHS in hospital were diagnosed as suffering from diseases other than bSHS. Most of those were diagnosed as having MCS/CS or psychosomatic diseases. When physicians diagnose patients who complain of SHS-like symptoms, these other diseases should be ruled out.

Only 50.3% of the patients who were diagnosed as nSHS (type 2) by their physicians by using all of the classification, the definition and the diagnostic criteria corresponded to the diagnostic criteria of nSHS based on the patients' interview sheets. That is, when the gold standard is physician's diagnosis, the accuracy of the diagnostic criteria was about 50%. For the classification of patients as type 2, diagnostic criteria alone are not sufficient. The diagnostic criteria mainly focus on the symptoms and the patients' living situations and homes; however, they do not include items for exclusion. On the other hand, the classification of bSHS and the definition of nSHS include exclusion items. Therefore, for the diagnosis of nSHS (type 2), the diagnostic criteria and definition of nSHS, and the classifications of bSHS should be used. In clinical practice, physicians could diagnose nSHS patients using the diagnostic criteria after exclusion of other diseases by using the definition of nSHS, the classifications of bSHS, and the results of clinical examinations.

From the levels of chemical substances in the patients' homes based on the interview sheets, the sensitivity of determination of chemical substances levels for the diagnosis of type 2 was 39.2% and specificity was 80.0%. The records of the detection of chemical substances based on the interview are helpful to diagnose nSHS; however, even if the chemical levels were under the guideline levels in the records, the diagnosis of nSHS (type 2) should not be excluded. When we are considering a diagnosis other than type 2, if the chemical levels are under the guideline levels, then that will be compelling evidence to make the diagnosis. The main chemical substances that had levels in the patients' homes above the guideline levels were formaldehyde, toluene, and xylene. Among the patients who answered that at least one of the chemical substances levels was above that in the guideline, 95.2% of the patients were classified as type 2. For type 2 patients, it is important to reduce the chemical substances in their homes.

From the results of the chemical level determinations in the homes of 10 patients, 4 of them lived where at least the level of one chemical substance was above the guideline level. The chemical substances detected as being above the guideline levels were paradichlorobenzene and acetaldehyde. Because paradichlorobenzene was detected, it is important for the patients who suffer from chemical intolerance to be careful about daily toiletry necessities that come into contact with the skin, such as insect repellent and deodorant, in addition to being careful about building materials [4].

The detection of chemicals at levels above the guideline is one of the determining factors to help diagnose nSHS (type 2). However, in the present study, even if all the variable chemical levels were below those in the guideline, many patients were diagnosed as suffering from nSHS (type 2). We recommend that, whenever possible, in the differential diagnosis, and when making a working diagnosis, the physician refers to the determined levels of chemical substances in the patient's home.

As conclusion, for clinicians to make a diagnosis of nSHS, it is helpful to use all of the nSHS diagnostic criteria, the classification and the definition that includes the exclusions. The determined levels of chemical substances in a patient's home should be used as one of the references to diagnose a patient as suffering from nSHS (type 2).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Article

In-situ Real-Time Monitoring of Volatile Organic Compound Exposure and Heart Rate Variability for Patients with Multiple Chemical Sensitivity

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Abstract: *In-situ* real-time monitoring of volatile organic compound (VOC) exposure and heart rate variability (HRV) were conducted for eight multiple chemical sensitivity (MCS) patients using a VOC monitor, a Holter monitor, and a time-activity questionnaire for 24 h to identify the relationship between VOC exposure, biological effects, and subjective symptoms in actual life. The results revealed no significantly different parameters for averaged values such as VOC concentration, HF (high frequency), and LF (low frequency) to HF ratio compared with previous data from healthy subjects (*Int. J. Environ. Res. Public Health* **2010**, *7*, 4127–4138). Significant negative correlations for four subjects were observed between HF and amounts of VOC change. These results suggest that some patients show inhibition of parasympathetic activities along with VOC exposure as observed in healthy subjects. Comparing the parameters during subjective symptoms and normal condition, VOC concentration and/or VOC change were high except for one subject. HF values were low for five subjects during subjective symptoms. Examining the time-series data for VOC exposure and HF of each subject showed that the subjective symptoms, VOC exposure, and HF seemed well related in some symptoms. Based on these characteristics, prevention measures of symptoms for each subject may be proposed.

Keywords: real-time monitoring; MCS; VOC; HRV

1. Introduction

Multiple chemical sensitivity (MCS) has been defined as an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects [1]. Medical researchers and clinicians from the United States and Canada signed the 1999 Consensus on MCS and established the following criteria: (1) The symptoms are reproducible with (repeated chemical) exposure; (2) The condition is chronic; (3) Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome; (4) The symptoms improve or resolve when the incitants are removed; (5) Responses occur to multiple chemically unrelated substances; (6) Symptoms involve multiple organ systems [2].

As defined above, chemical exposure has been assumed to trigger the symptoms, although the underlying mechanism of MCS remains disputed. Therefore, it is inevitable to investigate the relationship between chemical exposure and symptoms for understanding the pathogenesis, making a diagnosis, and proposing a measure of cure and prevention of symptoms. Provocation challenges have been conducted to clarify whether the patients actually show different responses to low levels of exposure [3]. These tests are conducted in controlled environments. However, in actual life where various chemicals exist, it is assumed that "masking" (acclimatization, apposition, and addiction) may hide the exposure-symptom relationships [4]. As a result, exposure-symptom relationships in actual lives may be different from those in controlled environments. It is therefore essential to understand the actual conditions of MCS measurements of chemical exposure and symptoms in actual life. Few studies have been done measuring chemical exposure of patients in actual lives and evaluating the relationship to the

symptoms. Shinohara *et al.* [5] measured the exposures of 15 MCS patients to both carbonyl compounds and volatile organic compounds (VOCs) that may induce hypersensitive reaction in actual lives. The results demonstrated that the chemicals responsible for hypersensitive reactions varied from patient to patient. Moreover, the concentration during symptoms was far below the WHO indoor guidelines. Saito *et al.* [6] used Ecological Momentary Assessment to monitor everyday symptoms in addition to the environmental chemical exposure measurement. The results showed that some causative chemicals were detected in 11 of 14 MCS patients and 11 physical symptoms and four mood subscales were significantly aggravated when they experienced hypersensitivity symptoms. In those studies, chemical compounds were collected by adsorbents and the composition and concentration were analyzed using gas chromatography-mass spectrometry (GCMS) and high-performance liquid chromatography (HPLC). These integration analysis tests are general methods to measure the concentration of volatile organic compound (VOC) components and the result obtained by this method is the average concentration during a certain period (e.g., from 30 min to 1 week).

To elucidate the responsible exposure for each symptom, it is necessary to detect the fluctuation of personal exposure because personal exposure fluctuates according to personal activities and locations in a short period. However, it is difficult to obtain the personal exposure fluctuation from the data of average concentration. On the other hand, measurement methods with higher time resolution such as real-time monitoring using portable VOC monitors to measure total VOC concentrations [7–9] provide time-series data of personal exposure concentrations, but do not elucidate the VOC components. Therefore, it is assumed that using these monitors the fluctuation of personal exposure can be detected and the information about the context or simultaneity between exposure and symptoms of MCS patients can be obtained.

To investigate the relationship between the fluctuation of VOC exposure and its biological effects, it is necessary to know the change in biological parameters in a relatively short time. Since MCS patients usually report various autonomic nerve symptoms, it is desirable to know the temporal changes in autonomic nerve function in actual life. Heart rate variability (HRV) measured by Holter monitor has been used to evaluate the biological effects caused by environmental factors [10–17].

In our previous study, VOC exposure concentrations and HRV using VOC and Holter monitors were measured for seven healthy subjects [18]. In this study, we applied this method to MCS patients and identified characteristics of the relationship between VOC exposure, biological effects, and subjective symptoms in actual lives. In this paper, first, VOC exposure and HRV parameters of MCS patients were compared to controls. Moreover, the correlations between VOC exposure and HRV parameters were considered. Further, the parameters during subjective symptom and normal condition were compared. Finally, time-series data for each subject were observed in detail.

2. Experimental Section

2.1. Study Design

This study was designed to simultaneously monitor personal VOC concentrations and HRV for eight MCS patients under usual daily life conditions. The measurements were conducted from 2006 to 2007. The subjects were requested to wear the Holter monitor, carry the VOC monitor, and record the time-activity logs during monitoring.

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Research Ethical Committee of the Kitasato Institute Hospital of No.13 D-180-10.

2.2. Subjects

The subjects were eight MCS patients including three adult males and five adult females, and the ages ranged from 31 to 62 years (44 ± 11 years). These patients consulted doctors in the Division of Environmental Medical Center, Kitasato Institute Hospital. Various examinations for diagnosis, including neuro-ophthalmologic examination, medical examination by interview, and questionnaire survey were performed in a clean room. The questionnaire included the reason for visiting, subjective symptoms, questions about life environment, and the Quick Environment Exposure Sensitivity Inventory (QEESI) in Japanese [19]. The patients were diagnosed with MCS by medical specialists from the comprehensive results of these examinations.

Because the responsible chemical compounds are expected to be different for each patient, it is difficult to lump MCS patients together. Therefore, MCS patients were limited to those advanced from Sick Building Syndrome whose responsible compounds were considered to be VOCs.

2.3. VOC Monitoring

VOC exposure concentrations were measured for 24 h by a portable real-time VOC monitor with photo ionization detector (PID) (ppbRAE plus; RAE Systems, San Jose, CA, USA). Detailed information on VOC monitoring has been described in a previous study [18]. Before each measurement, calibrations were conducted using 10 or 100 ppm isobutylene gas. Temperature and relative humidity (RH) were measured by a thermo-hygrometer (HOBO; Onset Computer Corporation, Jackson, MS, USA) carried with the VOC monitor.

For the analysis, VOC concentration averaged over each 5-min interval and the changes in VOC concentration amount in 5-min interval (ΔVOC), calculated by subtracting the minimum value from the maximum value of each interval, were used. Additionally, the differential changes of 5-min averaged VOC concentration from the previous 5-min averaged VOC concentration were calculated and divided into positive values (d + VOC) and negative values (d − VOC). Temperature and RH, averaged over each 5-min interval, were also used for the analysis.

2.4. HRV Analysis

The continuous electrocardiogram (ECG) data were recorded for 24 h by the Holter monitor (FM-150 or FM-180; Fukuda Denshi, Tokyo, Japan). Detailed information on HRV analysis has been described in a previous study [18]. To avoid eliciting a response to the electrode seals, they were exposed to air before use and dispelled their smell as much as possible.

For the analysis, high frequency (HF) and low frequency (LF) power were averaged over 5-min intervals, HF power was used as an indicator of parasympathetic activity, and the power ratio of 5-min averaged LF to 5-min averaged HF (LF/HF) was used as an indicator of sympathetic activity [20,21].

2.5. Time-Activity Pattern

The time-activity patterns were recorded by the subjects (Figure 1). The subjects were requested to select their locations and activities in each 5-min interval from the following alternatives: four kinds of locations including home, office, other indoor, and outdoor; and six kinds of personal activities including sitting, standing, walking, exercising, eating, and sleeping. In addition, when a symptom was induced, subjects were instructed to indicate the symptom level on a 0–10 scale (0 = not at all a problem, 5 = moderate symptoms, and 10 = disabling symptoms) and select the type from the symptom severity items in QEESI [22,23] including musculoskeletal, airway/mucous membranes, heart/chest-related, gastrointestinal, cognitive, affective, neuromuscular, head-related, skin, and genitourinary. Responsible exposure chemicals or events could be written in the remarks column.

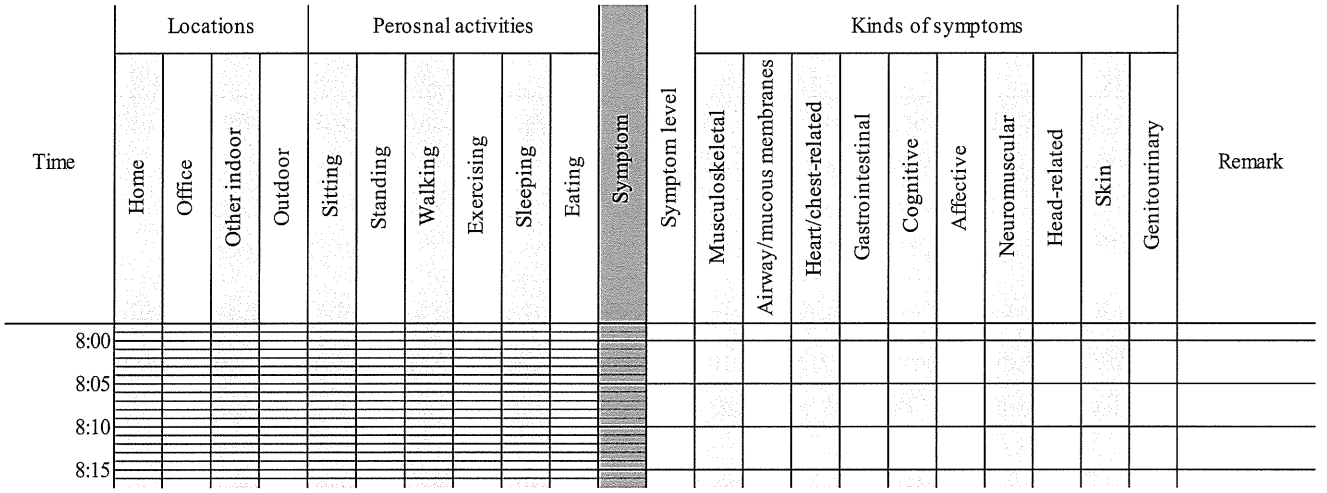

Figure 1. An example of a time-activity log sheet.

To ignore the confounding factors, we excluded the data of the time spent for these activities (*i.e.*, exercising, eating, and sleeping) and the duration of the effect (*i.e.*, 15 min after exercising and 1 h after eating) from the analyses in the same manner as the previous study [18].

2.6 Statistical Analysis

VOC exposure concentration and HRV parameters of MCS patients were compared to controls using Wilcoxon non-parametric test. To assess the relationships between VOC exposures and HRV parameters Spearman rank correlation coefficients were calculated. Time ratios of respective symptoms were analyzed using principal component analysis to figure out the characteristics of subjective symptoms. The parameters during subjective symptom and normal condition were compared using Wilcoxon non-parametric test. All analysis were conducted using IBM SPSS Statistics Version 22 (IBM).

3. Results

3.1. Statistical Summary

Table 1 shows a summary of VOC exposure concentrations and HRV parameters observed for all subjects who participated in this study. The results indicate that exposure concentrations differed for

each patient. Table 1 also shows control (healthy subject). Only the data from a previous study [18] was used. No significant difference was observed between patients and healthy subject for all the parameters (Wilcoxon non-parametric test).

Table 1. Summary of VOC exposure concentrations and HRV parameters for patients and controls.

Parameters	Patients		Controls [c]		p [d]
	n [a]	Mean ± SD [b]	n	Mean ± SD	
VOC exposure concentration ($\mu g \cdot m^{-3}$)					
Total	8	306 ± 148	7	176 ± 130	0.12
Home	8	262 ± 204	7	299 ± 267	1.00
HRV parameters					
$Log_{10}HF$ ($m \cdot sec^2$)	8	1.5 ± 0.2	7	1.7 ± 0.4	0.34
LF/HF	8	3.8 ± 1.9	7	3.8 ± 2.2 [e]	1.00

[a] Sample size; [b] Standard deviation; [c] Data from a previous study [18]; [d] Wilcoxon non-parametric test; [e] LF/HF was calculated using LF and HF averaged over 5-min intervals.

3.2. Bivariate Analysis

Spearman rank correlation coefficients were calculated to assess the relationships between VOC exposures and HRV parameters measured within the same 5-min intervals. Table 2 shows a summary of the correlations for all subjects. The sex and age of these subjects are also listed in Table 2.

Table 2. Correlations between VOC exposure and HRV parameters.

Parameters	Subject								− [d]	+ [e]
	A	B	C	D	E	F	G	H		
Sex (M: male, F: female)	M	F	F	F	M	M	F	F		
Age (years)	39	62	33	46	31	49	35	54		
VOC *vs.* HF	−0.35 ** [a]	0.19 *	−0.03	−0.00	−0.34 **	−0.04	0.06	−0.13	6 (2)	2 (1)
ΔVOC *vs.* HF	−0.38 **	0.01	0.11	−0.32 **	0.07	−0.03	−0.24 *	−0.30 **	5 (4)	3 (0)
d+VOC *vs.* HF	−0.46 **	−0.17	0.13	−0.37 *	0.02	0.04	−0.38 *	−0.45 **	5 (4)	3 (0)
d−VOC *vs.* HF	0.31 * [b]	−0.08	0.09	0.45 **	0.30 **	0.39 **	0.15	0.34 **	1 (0)	7 (5)
VOC *vs.* LF/HF	0.06	−0.22 *	0.01	−0.16	0.26 **	−0.04	−0.06	0.01	4 (1)	4 (1)
ΔVOC *vs.* LF/HF	0.08	0.11	0.02	0.28 **	−0.09	−0.08	0.29 **	0.04	2 (0)	6 (2)
d+VOC *vs.* LF/HF	0.04	0.10	0.27	0.45 **	0.04	−0.18	0.27	0.12	1 (0)	7 (1)
d−VOC *vs.* LF/HF	0.13	−0.21	−0.13	−0.33 *	−0.27 **	−0.30 *	−0.21	−0.08	7 (3)	1 (0)
Temp *vs.* HF	−0.01	0.38 **	−0.07	0.13	- [c]	0.15	0.21 *	−0.40 **	3 (1)	4 (2)
RH *vs.* HF	0.10	−0.61 **	0.15	0.18	-	−0.21 *	0.16	0.38 **	2 (2)	5 (1)
Temp *vs.* LF/HF	0.20 *	−0.12	−0.02	−0.03	-	−0.04	−0.12	0.09	5 (0)	2 (1)
RH *vs.* LF/HF	−0.08	−0.15	−0.14	−0.22 *	-	0.18	−0.20 *	−0.10	6 (2)	1 (0)

[a] ** Spearman rank correlation, $p < 0.01$; [b] * Spearman rank correlation, $p < 0.05$; [c] Data not obtained; [d] − Numbers of the subjects showing negative correlation (significant); [e] + Numbers of the subjects showing positive correlation (significant).