Symptom Profile of Multiple Chemical Sensitivity in Actual Life

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Objective: This study was conducted to confirm the definition of multiple chemical sensitivity (MCS) in actual life: that multiple symptoms are provoked in multiple organs by exposure to, and ameliorated by avoidance of, multiple chemicals at low levels. We used the Ecological Momentary Assessment to monitor everyday symptoms and the active sampling and passive sampling methods to measure environmental chemical exposure. **Methods:** Eighteen patients with MCS, diagnosed according to the 1999 consensus criteria, and 12 healthy controls participated in this study. Fourteen patients and 12 controls underwent 1-week measurement of physical and psychologic symptoms and of the levels of exposure to various chemicals. Linear mixed models were used to test the hypotheses regarding the symptom profile of MCS patients. **Results:** Some causative chemicals were detected in 11 of 14 MCS patients. Two other patients did not report any hypersensitivity episodes, whereas passive sampling showed far less exposure to chemicals than control subjects. Another subject reported episodic symptoms but was excluded from the following analyses because no possible chemical was detected. Eleven of the 17 physical symptoms and all four mood subscales examined were significantly aggravated in the interview based on "patient-initiated symptom prompts." On the other hand, there were no differences in physical symptoms or mood subscales between MCS patients and control subjects in the interview based on "random prompts." **Conclusions:** MCS patients do not have either somatic or psychologic symptoms under chemical-free conditions, and symptoms may be provoked only when exposed to chemicals. **Key words:** multiple chemical sensitivity, ecologic momentary assessment, linear mixed model, active sampling and passive sampling methods.

AS = active sampling; **AS–PS method** = active sampling and passive sampling methods; $\mathbf{C_{AS}}$ = the concentration of exposure estimated by the AS method; **CFS** = chronic fatigue syndrome; $\mathbf{C_{PS}}$ = the concentration of exposure estimated by the PS method; **CS** = chemical sensitivity; **DAMS** = Depression and Anxiety Mood Scale; **DNPH** = 2,4-dinitrophenyl-hydrazine; **ED** = electronic diary; **EESI** = Environmental Exposure and Sensitivity Inventory; **EMA** = Ecological Momentary Assessment; **FM** = fibromyalgia; **M.I.N.I.** = Mini International Neuropsychiatric Interview; **MCS** = multiple chemical sensitivity; **PS** = passive sampling; **RSD** = relative standard deviation; $\mathbf{RSD_{AS}}$ = RSD of repeatability test in the AS method; $\mathbf{RSD_{PS}}$ = RSD of repeatability test in the PS method; **VOCs** = volatile organic compounds.

INTRODUCTION

Multiple chemical sensitivity (MCS) was defined by Cullen in 1987 as an acquired disorder that develops after some identifiable environmental exposure. This condition was 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 to cause harmful effects in the general population (1).

The most recent and now widely used case definition of this disorder is a consensus published in 1999: 1) the symptoms are reproducible with repeated chemical exposure, 2) the condition is chronic, 3) low levels of exposure (ie, 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, and 6) symptoms involve multiple organ systems (2).

The clinical characteristics of MCS patients are usually evaluated using questionnaires such as the Environmental Exposure and Sensitivity Inventory (EESI) (3) or clinical interviews that rely on the subjects' retrospective self-reports. However, humans do not have infinite recall capacity and events may fade from memory over time. There are several cognitive processes involved in recall that introduce significant bias into the information recalled (4,5). In MCS patients, the definitions of this syndrome that multiple symptoms are provoked in multiple organs by exposure to, and ameliorated by avoidance of, multiple chemicals at low levels have not been confirmed in actual life. In addition, we found that MCS patients did not complain of psychologic symptoms as often as somatic symptoms in a clean room (6), although problems with mood are included among the symptoms in the EESI and MCS patients were reported to have higher rates of current psychiatric disorders (7,8). This finding suggests that there is a discrepancy between the symptoms experienced in actual life and those reported retrospectively under conditions with no chemical exposure. Therefore, it should be clarified when, where, and to what extent they experience psychologic as well as somatic symptoms compatible with the definition of this syndrome. Although paper-and-pencil diaries are commonly used to record symptoms in natural settings, they have serious problems with regard to actual compliance (9). Recently, the computerized Ecological Momentary Assessment (EMA) has been developed to capture phenomena at the moment they occur in natural settings, thus maximizing ecologic validity avoiding retrospective recall and compliance problems (4).

Provocation challenges were used to investigate whether

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the patients actually show differential responses to low concentrations of chemical agents compared with room air (10–12). In this method, we can investigate only a few of various chemical agents that could produce MCS symptoms in everyday life. Therefore, this method does not always guarantee that the chemicals identified are the cause of MCS symptoms in a natural setting. To resolve these problems, Shinohara et al. (13) developed a sampling methodology using both active sampling (AS) and passive sampling (PS) methods (the AS–PS method) to identify dozens of carbonyl compounds and volatile organic compounds (VOCs) in the surrounding air that induce hypersensitivity symptoms and to determine their concentrations. MCS patients were asked to carry both active and passive samplers for 1 week. When the hypersensitivity symptoms appeared, subjects turned on the pump connected to the active sampler until the symptoms disappeared. Concentrations obtained by the AS method represent exposure levels for the period during which the patient had hypersensitivity symptoms. On the other hand, the concentrations obtained by the PS method represent the patient's personal exposure levels for the entire periods of monitoring. The compounds of which the concentrations measured by the AS method were higher than those determined by the PS method were assumed to be those responsible for the hypersensitivity symptoms.

The present study was performed to confirm in actual life the definitions of this syndrome in which multiple symptoms occur coincident with exposure to multiple chemicals at low levels and abate in their absence. This was performed as follows: 1) determination of the responsiveness of MCS patients to various chemicals using the AS–PS method, 2) clarification of the symptom profiles of MCS patients in actual life using the EMA, and 3) confirmation of the correspondence of chemical exposure and symptom manifestations in actual life by simultaneously recording multiple chemical exposure and symptoms. Then the following two hypotheses on symptom profiles of MCS patients with exposure to multiple chemicals were tested: 1) There are significant differences in not only physical symptoms, but also psychologic symptoms between when MCS patients have episodic symptoms and when they do not; and 2) there are no significant differences in any items of physical or psychologic symptoms between patients with no episodic symptoms and control subjects. These methods can confirm that exposure to chemicals triggers symptoms. However, it does not necessarily follow that they are the actual cause of the symptoms because Pavlovian conditioning to a specific environment where some chemicals are present could produce similar symptoms without the biologic effects of the chemical agents (14). Furthermore, the present strategy cannot exclude the possibility that some patients may intentionally expose themselves to chemical agents to confirm the association they believe to be present or that others may withhold reports of symptoms occurring in the absence of an obvious chemical source, which can bias the results of the study. Therefore, although the results of this study may not be a sufficient condition for confirming the definition of MCS, they must be a necessary condition for it, which has not been proved previously.

METHODS

Subjects

Eighteen patients with MCS and 12 healthy controls participated in this study (Table 1). MCS was diagnosed according to the 1999 consensus criteria (2) at the Environmental Control Unit of the Kitasato Institute Hospital between November 2001 and March 2002 (n = 18). Four patients were excluded because one was in poor compliance with the EMA, one caught a common cold during the study, one showed deterioration of depression during the study, and one could not stand the smell of the nylon strap of a small watch-type computer used for the EMA. Eleven patients had identifiable onset such as moving into a new house or office, whereas three patients did not; these cases were designated according to Fiedler et al. (7) as MCS and chemical sensitivity (CS), respectively (Table 2). Healthy controls were recruited through a magazine advertisement for the larger MCS research project, including a clinical interview, questionnaire surveys, and autonomic function tests, in addition to the present EMA study, on the following conditions: 1) Controls were healthy individuals aged 20 to 70 years; 2) they had either moved to a new house or renovated their home during the past 3 years; 3) they were not taking medicine prescribed by medical facilities; and 4) none had been diagnosed as having MCS or Sick Building Syndrome. Thirty-two subjects participated in the project and all of them had heard of MCS or Sick Building Syndrome before the study. One female subject was excluded because she was diagnosed as having MCS based on the 1999

TABLE 1. Demographic Data of MCS Patients and Controls Who Underwent the 1-Week Measurement of Subjective Symptoms and Chemical Exposure

		MCS Patients (n = 14 [13]*)	Controls (n = 12)
Gender	Male	7 [6]	2
	Female	7	10
Education	≥16 yrs	6 [5]	6
	≤12–16 yrs	4	4
	12 yrs	4	3
Occupation	(+)	9 [8]	8
	(−)	5	4
Marriage	(+)	10 [9]	9
	(−)	4	3
Age	Mean ± SD	38.2 ± 7.6 [37.8 ± 7.6]	36.2 ± 6.5
	Range	23 to 53 [23 to 47]	26 to 48

*Figures in parentheses represent the results of 13 MCS patients included in the analyses of symptom profile.
MCS = multiple chemical sensitivity; SD = standard deviation.

TABLE 2. Profiles of the MCS Patients, Including Identifiable Onset, Psychiatric Comorbidity, and Participation in 1-Week Measurement

Patient	Identifiable Onset	Psychiatric Comorbidity	Participation
A1	(−)	Panic disorder with agoraphobia	(−)
A2	Moving into a new house	Agoraphobia	(+)
A3	Use of chemicals in the office	(−)	(+)
A4	Use of chemicals in the office	(−)	(+)
A5	Moving into a new house	Agoraphobia	(+)
A6	Use of chemicals in the office	Agoraphobia	(+)
A7	(−)	Agoraphobia	(+)
A8	(−)	Social anxiety disorder, Agoraphobia	(+)
A9	Use of chemicals in the office	Major depression, Agoraphobia	(+)
A10	(−)	(−)	(+)
A11	Moving into a new office	Agoraphobia	(+)
A12	Moving into a new office	Major depression, Obsessive–compulsive disorder	(−)
A13	Moving into a new office	Panic disorder (lifetime) with agoraphobia	(+)
A14	Moving into a new house	Agoraphobia	(+)
A15	Moving into a new office	Agoraphobia	(+)
A16	Moving into a new house	Agoraphobia	(+)
A17	Use of chemicals in the office	Agoraphobia	(−)
A18	Moving into a new house	Agoraphobia	(−)

MCS = multiple chemical sensitivity.

consensus criteria at the initial interview. Because the subjects in the EMA study must operate small electronic devices accurately, an exclusion criterion of age <20 or >55 years was set for all subjects. Twelve control subjects participated in this study after receiving a detailed explanation of the entire protocol. Although the demographic variables, including gender, education, occupation, marriage, and age, were not significantly different between the two groups, the number of female subjects was somewhat larger in the control group (Table 1), and the effect of gender was controlled for in the statistical analysis of symptom profiles. We thus controlled for exposure to relevant chemicals in the indoor environment and knowledge of the disorder in addition to these demographic variables between the MCS and healthy subjects. This study was approved by the Human Ethical Committee of the Kitasato Institute Hospital, and all participants gave their written informed consent to participate.

Procedures

The Mini International Neuropsychiatric Interview (M.I.N.I.) (15) was used to assess the comorbidity of psychiatric disorders. After the interview, participants were instructed to keep an electronic diary (ED) with individualized training for its use. The ED is a small watch-type computer (Ruputer, 52 g; Seiko Instruments Inc., Tokyo, Japan) using software specially developed for this study. Questions were presented in simple Japanese language on two lines of an eight-character LCD screen. Participants used a "navigation joystick" to scroll through a lengthening and shortening bar scale with 21 steps to record the severity of each symptom at that moment.

Each participant was requested to wear the ED 24 hours per day during the 1-week study period. MCS patients were instructed to respond to the ED once in the morning and once in the afternoon prompted by beeps at random intervals (*random prompts*) and to answer the same ED questions when they experienced hypersensitivity symptoms that were sufficiently annoying to record (*patient-initiated symptom prompts*). We allowed the possibility that the criteria to respond to the ED might vary across the patients because of the subjective nature of their symptoms. On the other hand, controls were instructed to answer the ED four to five times per day in response to beeps at random intervals (*random prompts*). Because none of the control subjects had as strong episodic symptoms as were diagnosed with MCS, they were not instructed to respond to the ED based on their subjective symptoms. In addition, all of the participants were asked to respond to the ED interview when they woke up at the start of each day and when they went to bed at the end of each day. The former ED interview only inquired about the quality of sleep. The random beeps were stopped during sleep.

The ED asked subjects about location, activities, physical symptoms (17 items designed to evaluate representative symptoms of MCS after the EESI, including fatigue, concentration problems, forgetfulness, sore throat, headache, muscle weakness, joint pain, muscular pain, nausea, breathlessness, abdominal pain, feverishness, eye irritation/problems, skin itching/problems, dizziness/vertigo, stuffy or runny nose, palpitations) and mood states (nine items in the Depression and Anxiety Mood Scale [DAMS]) (16). The DAMS was composed of nine adjectives representing mood states and was developed to measure anxious and depressive mood as separately as possible. The scale included three factors: anxious mood, positive mood, and negative mood, the last two of which were combined to represent the fourth subscale, total depressive mood.

MCS patients were requested to carry an air sampling pump (AirCheck2000; SKC Ltd., Dorset, UK. 14.2 × 7.6 × 5.8 cm, 624 g) with two cartridges for carbonyl compounds and VOCs, respectively, for the AS method and two passive samplers for carbonyl compounds and VOCs, respectively, without an air sampling pump for the PS method for 1 week. Controls were asked to carry only two passive samplers for the PS method for 1 week because none had as strong episodic symptoms as were diagnosed with MCS. For the sampling of carbonyl compounds (formaldehyde, acetaldehyde, and acetone), a 2,4-dinitrophenyl-hydrazine (DNPH) cartridge (XPoSure Aldehyde Sampler; Waters Ltd., Milford, MA) was used for both AS and PS methods, whereas for the sampling of VOCs (chloroform, 2,4-dimethylpentane, 1,2-dichloroethane, 2,2,4-trimethylpentane, 1,2-dichloropropane, heptane, trichloroethylene, chlorodibromomethane, octane, tetrachloroethylene, 1,3,5-trimethylbenzene, 1,2,4-trimethylbenzene, 1,2,3-trimethylbenzene, butanol, ethyl acetate, 1,1,1-trichloroethane, benzene, toluene, butyl acetate, ethenylbenzene, m/p-xylene, styrene, o-xylene, p-dichlorobenzene, α-pinene, decane, undecane, nonanal, 1,2,4,5- tetramethylbenzene, dodecane, tridecane, tetradecane, pentadecane, and hexadecane), a charcoal tube (standard type [8015–054]; Shibata Scientific Technology Ltd., Tokyo, Japan) was used for the AS method and a passive gas tube (8015–066; Shibata Scientific Technology Ltd.) was used for the PS method. The patients were asked to turn on the pump at the moment hypersensitivity symptoms appeared together with answering the ED questions and to switch it off when the symptoms disappeared.

Gas Sampling Data Analysis

Shinohara et al. (13) conservatively defined a compound as likely to be causative of MCS when the following condition is satisfied:

$$C_{AS} \times (100 - RSD_{AS}) > C_{PS} \times (100 + RSD_{PS})$$

where C_{AS} is the concentration of exposure estimated by the AS method (ppb), RSD_{AS} is the relative SD (RSD; the SD divided by the mean multiplied by 100) of repeatability test in the AS method (%), C_{PS} is the concentration of exposure estimated by the PS method (ppb), and RSD_{PS} is the RSD of repeatability test in the PS method (%). RSD_{AS} and RSD_{PS} of each chemical substance were obtained as follows. The concentrations of exposure were measured by five active and five passive samplers in each of several different places for 8 hours and for 1 week, respectively, the RSD of five measurements was calculated for each chemical in each place, and the largest RSD was designated as the RSD of the measured substance. The RSD is usually used as the degree of measurement accuracy, and differences fulfilling these mentioned criteria can be regarded as significant.

Statistical Analysis

The following two hypotheses on symptom profiles of MCS patients were tested by linear mixed models using the SAS MIXED procedure (17): 1) There are significant differences in the scores of not only physical symptoms, but also mood states between the interview based on patient-initiated symptom prompts and that based on random prompts in the MCS patient group; and 2) there are no significant differences in any items of physical symptoms or mood states between the patient and control groups in the interview based on random prompts. The linear mixed model for the former hypothesis included a random effect for subjects and a fixed effect for the event of experiencing symptoms. The model for the latter hypothesis included a random effect for subjects and a fixed effect for the groups. A power analysis for linear mixed models (18) was performed to ensure that nonsignificant results in the latter hypothesis testing were not the result of low statistical power. The detectable effect size was 0.29 if type I error was 0.05, type II error was 0.20, and the number of subjects was 25 with 20 samples each. Cohen (19) reported previously that effect sizes of 0.20 and 0.50 are small and medium, respectively. Therefore, the analyses performed in the present study should have sufficient power to detect at least a medium-sized effect. To control for the effect of gender, sex was included as a covariate in both models as mentioned in the Subjects section. Because a large number of comparisons (17 physical symptoms and four mood states) were included in each hypothesis testing, Bonferroni corrections were applied resulting in a significant p value of $<.0023$ (.05 divided by 21).

In addition, to compare the exposure levels to multiple chemicals during the entire periods of monitoring between the patient and control groups, the passive sampling data were assessed by Wilcoxon's rank sum test. Because the medians of 19 of 30 chemical compounds measured by passive sampling were below the levels of detection in both groups, the remaining 11 compounds were analyzed.

RESULTS

Psychiatric Comorbidity

Seventy-nine percent (11 of 14) of MCS patients and none of controls were compatible with one or two Axis I psychiatric diagnoses. Agoraphobia without history of panic disorder was diagnosed in 71% (10 of 14) of MCS patients. Lifetime panic disorder with agoraphobia, social anxiety disorder, and major depressive disorder were diagnosed in one patient each (Table 2).

Chemical Exposure

The possible causative chemicals for each patient are listed in Table 3. Some causative chemicals were detected in 79% (11 of 14) of MCS patients. One subject (A13) reported episodic symptoms but no possible chemical was detected. This suggested that a diagnosis of MCS might not be correct for this subject although the possibility could not be ruled out that he responded to some other chemicals than were measured by the AS–PS methods. Therefore, he was excluded from subsequent analyses of symptom profiles (Table 1). Two other patients did not report any hypersensitivity episodes, and passive sampling showed far lower levels of exposure to chemicals than control subjects (see subsequently), suggesting that they avoided chemicals because they feared the symptoms of hypersensitivity. The exposure levels to multiple chemicals during the entire periods of monitoring for each group are shown in Table 4. The medians of nine of 11 chemicals were lower in the patient group than in the control group, and the differences were significant for four chemicals, including possible causative agents for many MCS patients according to Table 3 such as formaldehyde, acetaldehyde, and toluene. The exposure levels of these four chemicals of the two patients mentioned were less than or equal to the medians of the patient group except for the toluene exposure level of patient A4 (33.0 $\mu g/m^3$).

Symptom Profile

The 13 MCS patients responded to 226 beeps and the 11 MCS patients reported 128 episodes of hypersensitivity. The 12 controls responded to 410 beeps.

Analysis within the MCS group in the first hypothesis: The differences in each item score of 17 physical symptoms (Table 5) and four mood measures (Table 6) were analyzed between the interviews based on patient-initiated symptom prompts and those based on random prompts. The results indicated that the scores of 11 physical symptoms other than skin itching/problems, abdominal pain, feverishness, joint pain, fatigue, and muscle weakness were significantly higher; three negative mood subscales were significantly higher; and one positive mood subscale was significantly lower in the interviews based on patient-initiated symptom prompts. The effect of gender was significant in none of the 21 measures.

Analysis between the patient and control groups in the second hypothesis: Analyses of the 17 physical symptoms (Table 7) and four mood measures (Table 8) revealed no differences between 13 MCS patients and control subjects in the interview based on random prompts. The effect of gender was significant in none of the 21 measures.

DISCUSSION

To our knowledge, this is the first study to clarify the symptom profiles of MCS patients with exposure to multiple chemicals in actual life using the EMA. We also demonstrated the responsiveness of MCS patients to various chemicals using the AS–PS method. In the MCS patients, 11 of the 17 physical symptoms examined and all of four mood subscales were significantly aggravated in the interview based on patient-initiated symptom prompts. On the other hand, there were no differences in physical symptoms or mood subscales between MCS patients and control subjects in the interview based on random prompts. The definition of this syndrome, ie, multiple symptoms are provoked in multiple organs by exposure to, and ameliorated by avoidance of, multiple chemicals at low levels, was thus supported by this study.

TABLE 3. Possible Causative Chemicals* for Hypersensitivity Symptoms

Patient	Chemicals	Exposure Concentration	
		Symptom Prompts	Random Prompts
A2	Formaldehyde	15.5 ppb	6.7 ppb
	Acetaldehyde	13.5 ppb	4.0 ppb
	Acetone	35.1 ppb	22.0 ppb
	Propionaldehyde	2.1 ppb	1.0 ppb
	Tridecane	48.3 $\mu g/m^3$	11.9 $\mu g/m^3$
A3	None	—	—
A4	None	—	—
A5	Formaldehyde	31.1 ppb	17.5 ppb
	Toluene	11.3 $\mu g/m^3$	9.1 $\mu g/m^3$
	m/p-Xylene	13.8 $\mu g/m^3$	8.9 $\mu g/m^3$
	α-Pinene	248.4 $\mu g/m^3$	129.1 $\mu g/m^3$
	Limonene	16.5 $\mu g/m^3$	7.4 $\mu g/m^3$
A6	Formaldehyde	13.8 ppb	5.4 ppb
	Acetaldehyde	6.4 ppb	tr (<5.4 ppb)
	Toluene	26.0 $\mu g/m^3$	6.9 $\mu g/m^3$
	m/p-Xylene	22.3 $\mu g/m^3$	15.4 $\mu g/m^3$
	Undecane	24.2 $\mu g/m^3$	9.8 $\mu g/m^3$
	Tridecane	41.6 $\mu g/m^3$	12.6 $\mu g/m^3$
A7	Formaldehyde	24.0 ppb	16.5 ppb
	Acetaldehyde	12.1 ppb	9.0 ppb
	Acetone	13.6 ppb	8.9 ppb
A8	Formaldehyde	25.8 ppb	20.1 ppb
	Acetaldehyde	9.1 ppb	6.7 ppb
	Propionaldehyde	4.0 ppb	2.5 ppb
	Toluene	27.5 $\mu g/m^3$	22.9 $\mu g/m^3$
A9	Formaldehyde	14.5 ppb	8.0 ppb
	Acetaldehyde	8.3 ppb	5.5 ppb
	Acetone	12.9 ppb	10.9 ppb
	Propionaldehyde	1.6 ppb	1.1 ppb
	Toluene	769.5 $\mu g/m^3$	108.9 $\mu g/m^3$
	Butyl Acetate	459.6 $\mu g/m^3$	26.6 $\mu g/m^3$
	Ethylbenzene	130.1 $\mu g/m^3$	8.2 $\mu g/m^3$
	m/p-Xylene	207.6 $\mu g/m^3$	17.5 $\mu g/m^3$
	1,2,4-Trimethylbenzene	14.3 $\mu g/m^3$	8.9 $\mu g/m^3$
A10	Formaldehyde	20.2 ppb	9.7 ppb
	Acetaldehyde	10.4 ppb	5.0 ppb
	Toluene	28.6 $\mu g/m^3$	20.7 $\mu g/m^3$
A11	Formaldehyde	71.8 ppb	18.9 ppb
A13	None	—	—
A14	Formaldehyde	33.9 ppb	30.3 ppb
	Acetaldehyde	5.8 ppb	3.5 ppb
	Propionaldehyde	1.6 ppb	0.8 ppb
	Toluene	48.6 $\mu g/m^3$	27.5 $\mu g/m^3$
A15	Butanol	55.5 $\mu g/m^3$	33.4 $\mu g/m^3$
	Methyl Isobutyl Ketone	4.2 $\mu g/m^3$	ND (<1.4 $\mu g/m^3$)
	Limonene	5.7 $\mu g/m^3$	ND (<2.2 $\mu g/m^3$)
A16	Formaldehyde	71.3 ppb	50.6 ppb
	Butanol	15.7 $\mu g/m^3$	11.0 $\mu g/m^3$

*Chemicals fulfilling the following criteria were listed: $C_{AS} \times (100 - RSD_{AS}) > C_{PS} \times (100 + RSD_{PS})$, where C_{AS} is the concentration of exposure estimated by the AS method (ppb), RSD_{AS} is the relative SD (RSD; the SD divided by the mean multiplied by 100) of repeatability test in the AS method (%), C_{PS} is the concentration of exposure estimated by the PS method (ppb), and RSD_{PS} is the RSD of repeatability test in the PS method (%).
tr = trace; ND = not detected.

Like in previous studies (6,7,20–23), MCS patients had significantly higher rates of current psychiatric disorders than normal controls. However, most were agoraphobia without history of panic disorder that can hardly be distinguished from phobias regarding the places where relevant chemicals might be present. We not only identified the causative chemical compounds for inducing hypersensitivity symptoms, but also found no differences between MCS patients without hypersensitivity symptoms and control subjects, suggesting that there are important differences between MCS and depression, somatoform disorders, chronic fatigue syndrome (CFS), and fibromyalgia (FM). However, because the considerable over-

TABLE 4. Differences in Exposure Levels to Multiple Chemicals* Measured by Passive Sampling Between MCS Patients and Controls

	MCS Patients		Controls		
	No.	Median	No.	Median	*p* Value (Z)
Formaldehyde†	13	16.50 ppb	12	28.10 ppb	.0276 (2.20)
Acetaldehyde†	13	7.20 ppb	12	12.70 ppb	.0240 (2.26)
Acetone	13	20.10 ppb	12	17.85 ppb	.4625 (0.73)
Propionaldehyde	13	1.30 ppb	12	1.95 ppb	.5268 (0.63)
Benzene	13	0.00 $\mu g/m^3$	11	1.30 $\mu g/m^3$	.1026 (1.63)
Toluene†	13	19.30 $\mu g/m^3$	11	35.90 $\mu g/m^3$	.0275 (2.20)
Ethylbenzene	13	3.40 $\mu g/m^3$	11	11.00 $\mu g/m^3$	.1150 (1.58)
m/p-Xylene	13	17.50 $\mu g/m^3$	11	13.80 $\mu g/m^3$	.6844 (-0.41)
1,2,4-Trimethylbenzene	13	5.20 $\mu g/m^3$	11	10.00 $\mu g/m^3$	1.0000 (0.00)
p-Dichlorobenzene†	13	0.00 $\mu g/m^3$	11	94.60 $\mu g/m^3$	.0016 (3.16)
Limonene	13	0.00 $\mu g/m^3$	11	21.00 $\mu g/m^3$	.1296 (1.52)

*Only those chemicals whose medians of at least one group were above the levels of detection were included.
†Significant difference ($p < .05$).
MCS = multiple chemical sensitivity.

TABLE 5. Differences in 17 Physical Symptoms Between the Interview Based on Patient-Initiated Symptom Prompts and That Based on Random Prompts Within the MCS Group

	Symptom Prompts (n = 128)		Random Prompts (n = 226)		
	Estimate	SEM	Estimate	SEM	*p* Value (*df*, t)
Fatigue	31.11	1.68	25.96	7.11	.0106 (11,3.07)
Concentration problems*	30.07	1.88	20.56	7.22	.0004 (11,5.07)
Forgetfulness*	24.02	1.33	17.98	9.02	.0009 (11,4.53)
Sore throat*	32.58	1.81	21.01	9.12	<.0001 (11,6.39)
Headache*	25.94	1.92	11.77	6.40	<.0001 (11,7.38)
Muscle weakness	9.71	1.32	5.44	8.04	.0079 (11,3.24)
Joint pain	9.22	1.26	6.07	6.99	.0291 (11,2.51)
Muscular pain*	12.03	1.38	6.34	6.91	.0017 (11,4.11)
Nausea*	9.20	1.35	1.37	5.67	.0001 (11,5.80)
Breathlessness*	8.94	1.42	1.91	5.14	.0004 (11,4.96)
Abdominal pain	2.03	0.98	0.91	5.19	.2743 (11,1.15)
Feverishness	6.69	1.46	3.40	5.84	.0451 (11,2.26)
Eye irritation*	36.39	1.97	24.86	7.72	.0001 (11,5.85)
Skin itching/problems	20.73	1.66	19.50	8.15	.4747 (11,0.74)
Dizziness/vertigo*	13.47	1.42	4.19	6.24	<.0001 (11,6.53)
Stuff and runny noses*	26.03	1.48	18.96	7.25	.0006 (11,4.77)
Palpitation*	11.06	1.44	2.79	4.99	.0001 (11,5.76)

*Significant difference ($p < .0023$) after Bonferroni correction.
MCS = multiple chemical sensitivity; SEM = standard error of mean.

lap among unexplained illness syndromes such as MCS, CFS, and FM, have led some to suggest that all may be variants of a single functional disorder (7,24–26), the present method should be used to investigate whether the different symptom profiles are indeed seen in patients with CFS and FM without comorbid MCS.

In this study, 12 patients reported hypersensitivity episodes, whereas no causative chemical was detected by the AS–PS method in one of them (A13). This subject had a history of panic disorder and might have continued to experience limited symptom attacks even during the study period. In this respect, it is noteworthy that his mean scores of not only muscle weakness and muscular pain, but also abdominal pain were higher than those of 13 MCS patients reported in the interview based on random prompts. Although the item score of abdominal pain was not significantly higher even before Bonferroni correction in 11 MCS patients in the interview based on random prompts, the diagnostic criteria for panic attack include abdominal distress and high comorbidity rates of panic disorder and irritable bowel syndrome have been reported (27). When MCS is diagnosed according to the 1999 consensus criteria, the subjects who have similar episodic symptoms for reasons other than chemical exposure cannot always be excluded, and the AS–PS method is very useful in such cases.

On the other hand, two MCS patients did not report any

TABLE 6. Differences in Four Mood Measures Between the Interview Based on Patient-Initiated Symptom Prompts and That Based on Random Prompts Within the MCS Group

	Symptom Prompts (n = 128)		Random Prompts (n = 226)		
	Estimate	SEM	Estimate	SEM	p Value (df, t)
Anxious mood*	64.84	4.30	47.72	28.50	.0022 (11, 3.98)
Positive mood*	41.90	3.82	59.69	20.41	.0007 (11, −4.65)
Negative mood*	44.53	3.64	20.86	21.14	<.0001 (11, 6.50)
Depressive mood*	302.56	5.87	261.14	27.01	<.0001 (11, 7.06)

*Significant difference (p <.0023) after Bonferroni correction.
MCS = multiple chemical sensitivity; SEM = standard error of mean.

TABLE 7. Differences in 17 Physical Symptoms Between MCS Patients and Controls in the Interview Based on Random Prompts

	MCS Patients (n = 226)		Controls (n = 410)		
	Estimate	SEM	Estimate	SEM	p Value (df, t)
Fatigue	29.38	9.11	33.29	6.42	.6723 (22,−0.43)
Concentration problems	22.27	7.06	22.22	4.96	.9951 (22,0.01)
Forgetfulness	22.26	8.78	22.81	6.19	.9510 (22,−0.06)
Sore throat	19.62	8.19	14.67	5.77	.5519 (22,0.60)
Headache	12.42	5.78	9.63	4.06	.6347 (22,0.48)
Muscle weakness	6.46	6.70	9.38	4.73	.6671 (22,−0.44)
Joint pain	7.83	6.98	10.43	4.92	.7128 (22,−0.37)
Muscular pain	9.23	8.50	15.30	6.00	.4826 (22,−0.71)
Nausea	2.03	4.43	2.23	3.12	.9638 (22,−0.05)
Breathlessness	3.93	4.54	5.99	3.18	.6553 (22,−0.45)
Abdominal pain	1.49	4.24	4.23	2.98	.5249 (22,−0.65)
Feverishness	5.53	5.30	7.13	3.70	.7663 (22,−0.30)
Eye irritation	25.21	9.56	24.17	6.74	.9140 (22,0.11)
Skin itching/problems	21.96	8.82	25.09	6.18	.7261 (22,−0.35)
Dizziness/vertigo	3.80	4.98	6.12	3.51	.6467 (22,−0.46)
Stuff and runny noses	20.81	10.02	36.78	7.05	.1252 (22,−1.59)
Palpitation	4.01	3.98	5.03	2.79	.8019 (22,−0.25)

MCS = multiple chemical sensitivity; SEM = standard error of mean.

TABLE 8. Differences in Four Mood Measures Between MCS Patients and Controls in the Interview Based on Random Prompts

	MCS Patients (n = 226)		Controls (n = 410)		
	Estimate	SEM	Estimate	SEM	p Value (df, t)
Anxious mood	54.88	26.38	75.77	18.58	.4369 (22,−0.79)
Positive mood	58.95	24.68	97.35	17.42	.1340 (22,−1.56)
Negative mood	25.44	20.63	45.53	14.53	.3408 (22,−0.97)
Depressive mood	266.42	32.42	248.28	22.86	.5815 (22,0.56)

MCS = multiple chemical sensitivity; SEM = standard error of mean.

hypersensitivity episodes during the week of the study period. This was probably because these two patients avoided causative chemicals during the study period, considering their far lower levels of exposure to possible causative chemicals for many MCS patients such as formaldehyde, acetaldehyde, or toluene, as indicated by the AS–PS method. However, they may have similar symptoms when exposed to these chemicals because they were indeed diagnosed as having MCS. Therefore, in addition to those patients 1) who have acute symptoms that are reproduced with chemical exposure, there are some patients 2) who do not have acute symptoms because they avoid the causative chemicals. In the former cases, we can make full use of the AS–PS and EMA methodology, because the score of symptoms will be significantly aggravated under the symptomatic condition, and the causative chemicals will be detected. However, the latter cases are difficult to assess by the AS–PS method, although their chronic symptoms can still be detected by the EMA method. In a previous 9-year follow-up study of patients with MCS, 83% of the patients continued to avoid places or situations in which they might

encounter chemical fumes or odors, and more than half of the patients continued to report chronic symptoms, including headache, dermatologic complaints, gastrointestinal complaints, and pain (28). Patients A3 and A4 may have chronic symptoms of this kind. Indeed, the mean scores of abdominal pain, skin itching/problems, palpitation, and forgetfulness of A3 were higher than those of control subjects, and the mean score of positive mood was lower and those of negative mood, and the total depressive mood of A4 was higher than those of control subjects, although the small sample size prevented statistical analyses of these observations. In the future, it will be necessary to devise a methodology to investigate the pathophysiology of the latter cases, eg, the inclusion of an experimental exposure session during the study period.

The present EMA method is useful for MCS patients with acute symptoms, but the problem remains that it is only a double-blind provocation challenge test that can reliably exclude the pathology of a Pavlovian conditioning paradigm. If a patient has felt sick repeatedly as a result of some causes other than chemicals in a specific environment where some chemicals are present, some components or context of the environment may become conditioning stimuli to cause similar symptoms. In this case, although some specific chemical agents will also be detected in the AS–PS method, the symptoms will not be induced in the double-blind provocation challenge test because this response is not caused by chemicals. However, the double-blind provocation challenge test also has some problems. As mentioned in the Introduction, we can investigate only a few of various chemical agents that could produce MCS symptoms in everyday life. The process may be rather invasive for MCS patients who often fear undergoing it. In addition, it is very costly because it requires a specific provocation chamber in a clean room. Nevertheless, we plan to evaluate the consistency of the AS–PS method with the double-blind provocation challenge test in as many cases as possible to establish the accuracy of estimation by this method. In addition, Devriese et al. (14) reported that odorous substances with negative affectivity could become conditioning stimuli that are also generalized to new substances. Therefore, it is necessary to check the perception of odors when a provocation challenge test is performed and to consider the presence of odors of detectable levels of various chemicals when examination of possible candidates for hypersensitivity symptoms is performed by the AS–PS method.

In conclusion, MCS patients do not have either somatic or psychologic symptoms under chemical-free conditions, and symptoms may be provoked only when exposed to chemicals.

REFERENCES

1. Cullen MR. The worker with multiple chemical sensitivities: an overview. Occup Med 1987;2:655–61.
2. Multiple chemical sensitivity: a 1999 consensus. Arch Environ Health 1999;54:147–9.
3. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. Toxicol Ind Health 1999; 15:370–85.
4. Stone AA, Shiffman S. Ecological momentary assessment (EMA) in a behavioral medicine Ann Behav Med 1994;16:199–202.
5. Stone AA, Broderick JE, Shiffman SS, Schwartz JE. Understanding recall of weekly pain from a momentary assessment perspective: absolute agreement, between- and within-person consistency, and judged change in weekly pain. Pain 2004;107:61–9.
6. Tsujiuchi Y, Kumano H, Yoshiuchi K, Tsujiuchi T, Nakao M, Kuboki T, Okano T. A study on multiple chemical sensitivities from psychosomatic perspectives. Jpn J Psychosom Med 2002;42:205–16.
7. Fiedler N, Kipen HM, DeLuca J, Kelly-McNeil K, Natelson B. A controlled comparison of multiple chemical sensitivities and chronic fatigue syndrome. Psychosom Med 1996;58:38–49.
8. Black DW, Okiishi C, Gabel J, Schlosser S. Psychiatric illness in the first-degree relatives of persons reporting multiple chemical sensitivities. Toxicol Ind Health 1999;15:410–4.
9. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient non-compliance with paper diaries. BMJ 2002;324:1193–4.
10. Staudenmayer H, Selner JC, Buhr MP. Double-blind provocation chamber challenges in 20 patients presenting with 'multiple chemical sensitivity.' Regul Toxicol Pharmacol 1993;18:44–53.
11. Leznoff A. Provocative challenges in patients with multiple chemical sensitivity. J Allergy Clin Immunol 1997;99:438–42.
12. Hummel T, Roscher S, Jaumann MP, Kobal G. Intranasal chemoreception in patients with multiple chemical sensitivities: a double-blind investigation. Regul Toxicol Pharmacol 1996;24:S79–86.
13. Shinohara N, Mizukoshi A, Yanagisawa Y. Identification of responsible volatile chemicals that induce hypersensitive reactions to multiple chemical sensitivity patients. J Expo Anal Environ Epidemiol 2004;14:84–91.
14. Devriese S, Winters W, Stegen K, Van Diest I, Veulemans H, Nemery B, Eelen P, Van de Woestijne K, Van den Bergh O. Generalization of acquired somatic symptoms in response to odors: a pavlovian perspective on multiple chemical sensitivity. Psychosom Med 2000;62:751–9.
15. Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini-International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(suppl 20):22–33; quiz 34–57.
16. Fukui I. The depression and anxiety scale (DAMS): scale development and validation. Jpn J Behav Ther 1997;23:83–93.
17. Little RC, Milliken GA, Stroup WW, Wolfinger RD. SAS System for Mixed Models. Cary, NC: SAS Institute; 1996.
18. Shijders TAB, Bosker RJ. Standard errors and sample sizes for two-level research. J Educ Stat 1993;18:237–59.
19. Cohen J. Statistical Power Analysis for the Behavioral Sciences, 2nd ed. Hillsdale, NJ: Lawrence Erlbaum; 1988.
20. Davidoff AL, Fogarty L, Keyl PM. Psychiatric inferences from data on psychologic/psychiatric symptoms in multiple chemical sensitivities syndrome. Arch Environ Health 2000;55:165–75.
21. Simon GE, Daniell W, Stockbridge H, Claypoole K, Rosenstock L. Immunologic, psychological, and neuropsychological factors in multiple chemical sensitivity. A controlled study. Ann Intern Med 1993;119: 97–103.
22. Osterberg K, Karlson B, Orbaek P. Personality, mental distress, and risk perception in subjects with multiple chemical sensitivity and toxic encephalopathy. Scand J Psychol 2002;43:169–75.
23. Tonori H, Aizawa Y, Ojima M, Miyata M, Ishikawa S, Sakabe K. Anxiety and depressive states in multiple chemical sensitivity. Tohoku J Exp Med 2001;193:115–26.
24. Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 1994;154:2049–53.
25. Jason LA, Taylor RR, Kennedy CL. Chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities in a community-based sample of persons with chronic fatigue syndrome-like symptoms. Psychosom Med 2000;62:655–63.
26. Ciccone DS, Natelson BH. Comorbid illness in women with chronic fatigue syndrome: a test of the single syndrome hypothesis. Psychosom Med 2003;65:268–75.
27. Kumano H, Kaiya H, Yoshiuchi K, Yamanaka G, Sasaki T, Kuboki T. Comorbidity of irritable bowel syndrome, panic disorder and agoraphobia in a Japanese representative sample. Am J Gastroenterol 2004;99:370–6.
28. Black DW, Okiishi C, Schlosser S. A nine-year follow-up of people diagnosed with multiple chemical sensitivities. Psychosomatics 2000;41: 253–61.