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Int. J. Hyg. Environ. Health ■ (■■■■) ■■■–■■■

**International Journal
of Hygiene and
Environmental Health**www.elsevier.de/ijheh

Clinical characteristics of physician-diagnosed patients with multiple chemical sensitivity in Japan

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Received 2 March 2007; received in revised form 31 July 2007; accepted 11 September 2007

Abstract

Multiple chemical sensitivity (MCS), a syndrome in which multiple symptoms occur with low-level chemical exposure, has not been clarified in detail. The aim of our study was to clarify the clinical characteristics of physician-diagnosed MCS patients in Japan. We analyzed patient characteristics based on the medical records of 106 patients diagnosed with MCS according to the 1999 Consensus and the Japanese diagnostic criteria for MCS. We evaluated subjective symptoms using the Quick Environment Exposure Sensitivity Inventory (QEESI[®]) and compared the QEESI[®] scores with those of four MCS patient groups in the US reported by Miller and Prihoda [Miller, C.S., Prihoda, T.J., 1999b. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients, and persons with multiple chemical sensitivity. *Toxicol Ind Health* 15, 386-397].

Female patients accounted for 74.0%. Most male patients were in their 30s, whereas female ages ranged widely from 10 to 65 years. Among estimated onset factors, those seen in males tended to be workplace related, while female patients showed a variety of factors. Co-morbid allergic disease was present in 84.0% of patients. A significant difference in the QEESI[®] score between male and female patients was found in only one item out of 10 in symptom severity and life impact. However, all 10 items in chemical intolerance were significantly higher in females than in males. The mean QEESI[®] score in the patient group in our study was lower than those in any of the four self-reported patient groups in the US.

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Keywords: Multiple chemical sensitivity (MCS); Onset factors; Allergy; Quick Environment Exposure Sensitivity Inventory (QEESI[®])

Introduction

Multiple chemical sensitivity (MCS) patients have symptoms associated with low-level exposure to a variety of substances. Patients suffering from MCS have been reported in many countries, including the US

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(Ashford and Miller, 1996; Caress and Steinemann, 2003, 2004; Kreutzer et al., 1999; Meggs et al., 1996), Japan (Hojo et al., 2003, 2005), Canada (McKeown-Eyssen et al., 2000) and Germany (Hausteiner et al., 2005).

At present, there are at least seven case definitions for MCS, including those of Randolph (1965), Cullen (1987), Nethercott et al. (1993) and the 1999 Consensus in the US (MCS Consensus Conference, 1999). The most comprehensive and well-known case definition is the 1999 Consensus (Lacour et al., 2005).

In addition, international unified diagnostic criteria have not been established. Thus, there is little information allowing international comparison of the clinical characteristics of MCS patients among countries.

In Japan, Kitasato University had the first outpatient department specializing in patients with MCS in 1991. In 1998, we opened the Environmental Medical Center of Kitasato Institute Hospital specializing in MCS. This center is equipped with a clean room in which levels of contaminant chemicals are 1/10–1/50 of usual ambient concentrations. Patients with MCS referred from other institutes and hospitals have come to this center from all over Japan. Japanese MCS diagnostic criteria (Table 1) were devised under the auspices of the Ministry of

Health, Labour and Welfare in 1997 (Ishikawa et al., 1998), and were then applied at this center. However, based on the 1999 Consensus, patients diagnosed by the Japanese criteria were reassessed for an international comparison between Japanese patients and those from other countries, and patients who satisfied both criteria were designated as having MCS. Furthermore, subjective symptoms were evaluated according to the Quick Environment Exposure Sensitivity Inventory (QEESI[®]) developed by Miller and Prihoda (1999a) in the US, which is a questionnaire recommended in the 1999 Consensus. Hojo et al. (2003) surveyed the reliability and validity of the QEESI[®] (Japanese version) in the general population as well as in patients with suspected MCS (self-reported MCS). We concluded that 30 questions in three subscales (symptom severity, chemical intolerance and life impact) of the QEESI[®] showed high reliability and validity, allowing comparative studies between patients in Japan and those in the US.

The purpose of this study was to clarify the characteristics of physician-diagnosed MCS patients in Japan. Thus, based on the medical records of 106 patients diagnosed with MCS according to both the 1999 Consensus and the Japanese diagnostic criteria for MCS, we analyzed demographic characteristics (sex and age), estimated onset factors and co-morbid allergic diseases. In addition, subjective symptoms were evaluated using the QEESI[®], and we compared the QEESI[®] scores with those of four MCS patient groups in the US reported by Miller and Prihoda (1999b).

Materials and methods

Subjects

The subjects were 106 patients seen at the outpatient department of the Environmental Medical Center of Kitasato Institute Hospital during the 3-year period from 2001 to 2004, who met the 1999 Consensus and the Japanese diagnostic criteria for MCS (Table 1). In our subjects, the diagnosis was made separately by three physicians, all of whom were specialists in environmental medicine, and the final diagnosis was agreed upon by all three.

Ethical considerations

This study was approved by the Human Ethics Committee of the Environmental Medical Center of Kitasato Institute Hospital, and all participants gave written informed consent to participate. No individual names were listed in the database.

Table 1. Japanese MCS diagnostic criteria

Major symptoms	(1) Persisting or repetitive headache, (2) myalgia or uncomfortable muscular sensation, (3) persistent malaise or fatigue, (4) arthralgia
Minor symptoms	(1) Sore throat, (2) mild fever, (3) abdominal pain, repetition of diarrhea, constipation, glare, blurred vision, temporary appearance of dark spots or dry eye, (4) loss of concentration, reduction in thinking ability or loss of memory, forgetfulness or amnesia, (5) dysesthesia or olfactory disorder/dysgeusia, (6) excitement, depression, mental instability or insomnia, (7) skin inflammation or itching, (8) hypermenorrhea or menstrual disorder, (9) autonomic dysfunction
Objective examinations	(1) Abnormal smooth pursuit eye movement, (2) abnormal contrast sensitivity function, (3) abnormal pupil reaction to light, (4) positive reaction to chemical loading, (5) improvement of symptoms by elimination of causative chemical(s)

MCS patients are applicable to one of the following criteria:

1. Positive for two major items + four minor items.
2. Positive for one major item + six minor items + two items of objective examinations.

The Japanese diagnostic criteria were devised by Ishikawa et al. (1998) sponsored by the Ministry of Health, Labour and Welfare of Japan in 1997.

Inquiry by physicians and inquiry sheet used

A detailed environmental inquiry is very important for the diagnosis of this disease. We asked the subjects detailed questions regarding their occupation, birth place, lifestyle habits, hobbies, drinking of coffee and tea, alcohol consumption, smoking, passive smoking, use of flavoring agents or deodorants, environmental factors around the home, presence or absence of new construction or renovation, and the number of years since building, and history of moving. These data allowed us to suggest relationships between the course of symptom onset and possible exposures to harmful chemicals. The inquiry also included history of allergic diseases. In addition, at the first examination, the patient completed the QEESI[®] (Japanese version). However, a nurse helped patients for whom it was difficult to complete the questionnaire due to the severity of their condition.

Quick Environment Exposure Sensitivity Inventory (QEESI[®])

The QEESI[®] consists of a total of 50 questions with five subscales (Miller and Prihoda, 1999a). We performed the present study using three subscales (Q1, Q3 and Q5 shown in Table 2) suitable for international comparison (Hojo et al., 2003). In this study, the mean scores of 30 items in these three subscales were calculated separately for male and female patients, and we investigated each item for sex-related differences. We also compared the scores with those of four patient groups in the US (MSC-event, MCS-non-event, Implant and Gulf War Veterans) using the QEESI[®] (Miller and Prihoda, 1999b).

Analyses of statistical data

We performed all statistical analyses using SPSS (Ver. 13) for Windows. We compared the scores of the 30 QEESI[®] items between male and female patients employing one-way analysis of variance.

Results

Characteristics of patients

The number of females was markedly higher than that of males. Among these patients, 29 (27.4%) were referred for suspected MCS by other hospitals, while the remaining patients consulted the center directly.

Mean ages were 36.2 ± 9.9 years for males and 42.9 ± 13.8 years for females. The age distribution differed between male and female patients (Fig. 1).

Estimated onset factors

We estimated the main onset factors after final evaluation by the physicians, based on the results of inquiry and clinical examinations, summarized in Table 3.

We were able to investigate these factors in 95 of 106 patients (89.6%). Factors that could be estimated included a single factor is 73 (76.8%) and multiple factors is 22 (23.2%). Among males, exposure to chemicals in workplace (using chemical substances, new construction or renovation in workplace) accounted for 77.2% of cases. Occupations in which the patients were exposed to chemicals included printing businesses using toluene, work at gas stations, researchers and technicians using chemical agents, painters, barbers and others. On the other hand, estimated onset factors were more varied among the females.

Co-morbid allergic diseases

Patients with allergic disease of any type accounted for 84.0% of cases (89/106 patients). These allergies included pollinosis 53 (50.0%), house dust allergy 43 (40.6%), drug allergy 34 (32.1%), fungus allergy 19 (17.9%), food allergy 9 (8.5%), allergic rhinitis 8 (7.5%), atopic dermatitis 5 (4.7%), eczema 5 (4.7%), urticaria 5 (4.7%), bronchial asthma 4 (3.8%) and anaphylaxis 1 (0.9%).

QEESI[®] subscale scores

Table 2 shows the mean QEESI[®] scores (30 items of three subscales) for male and female patients.

Chemical intolerance

Hyperosmia is a major characteristic of MCS patients (Bell et al., 1992; Caccappolo et al., 2000; Greene and Kipen, 2002). Q1 Chemical intolerance is a scale used to evaluate hyperosmia in the QEESI[®]. The mean scores in total subjects, from highest to lowest, in the total patient population were: insecticide $\geq$ paint or paint thinner > cleaning products > fragrances > nail polish or hair spray > tobacco smoke. All of these scores exceeded 5.0. The mean levels of the other four items were more than 4.0. The standard deviation was very large, and individual differences were thus large. The scores of all 10 items of this subscale were significantly higher in females than in males.

Symptom severity

High scores were found in the following categories: airway/mucous membrane > cognitive > neuromuscular > head-related. Only the scores for cognitive symptom showed a significant difference between the sexes

Table 2. The mean scores of 30 items of three subscales in QEESI©

	Male patients (n = 25)	Female patients (n = 81)	Total patients (n = 106)	Significant difference
Q1 Chemical intolerance				
q1_1 Diesel or gasoline exhaust	3.0 (2.5)	4.8 (2.6)	4.4 (2.6)	**
q1_2 Tobacco smoke	3.6 (3.2)	5.5 (2.7)	5.1 (3.0)	**
q1_3 Insecticide	4.4 (3.7)	6.4 (3.0)	5.9 (3.3)	**
q1_4 Gasoline	3.0 (2.7)	5.2 (2.6)	4.6 (2.8)	***
q1_5 Paint or paint thinner	4.5 (3.5)	6.3 (3.0)	5.9 (3.2)	**
q1_6 Cleaning products	4.3 (3.4)	5.7 (2.8)	5.3 (3.0)	*
q1_7 Fragrances	4.2 (3.4)	5.4 (2.9)	5.1 (3.1)	*
q1_8 Tar or asphalt	2.6 (3.2)	4.8 (3.0)	4.3 (3.2)	**
q1_9 Nail polish or hairspray	3.8 (2.9)	5.5 (2.9)	5.1 (3.0)	**
q1_10 New furnishings	3.6 (3.3)	5.2 (2.9)	4.8 (3.1)	*
Total	37.0 (24.7)	54.8 (22.9)	50.5 (24.3)	**
Q3 Symptom severity				
q3_1 Musculoskeletal	4.5 (3.3)	4.0 (3.5)	4.1 (3.5)	NS
q3_2 Airway/mucous membranes	5.7 (3.0)	6.0 (2.9)	5.9 (2.9)	NS
q3_3 Heart/chest-related	4.1 (3.1)	3.9 (3.3)	3.9 (3.2)	NS
q3_4 Gastrointestinal	4.2 (3.3)	4.8 (3.3)	4.7 (3.3)	NS
q3_5 Cognitive	6.6 (2.0)	5.0 (3.3)	5.4 (3.1)	*
q3_6 Affective	4.8 (2.9)	4.7 (3.3)	4.7 (3.2)	NS
q3_7 Neuromuscular	5.0 (3.5)	5.2 (3.5)	5.1 (3.4)	NS
q3_8 Head-related	4.3 (3.2)	5.2 (3.3)	5.0 (3.3)	NS
q3_9 Skin	3.4 (3.0)	4.0 (3.2)	3.9 (3.1)	NS
q3_10 Genitourinary	2.5 (2.7)	3.5 (3.2)	3.3 (3.1)	NS
Total	45.1 (4.0)	46.3 (2.6)	46.0 (2.2)	NS
Q5 Life impact				
q5_1 Diet	0.8 (1.0)	2.1 (2.8)	1.8 (2.5)	
q5_2 Ability to work or attend school	6.4 (2.9)	4.9 (3.5)	5.3 (3.4)	NS
q5_3 Choice of home furnishings	4.0 (3.6)	5.2 (3.8)	4.9 (3.8)	NS
q5_4 Choice of clothing	2.4 (3.2)	3.2 (3.3)	3.0 (3.3)	NS
q5_5 Ability to drive or travel	3.2 (3.4)	4.4 (3.4)	4.1 (3.4)	NS
q5_6 Choice of personal care products	4.9 (3.8)	4.8 (3.7)	4.8 (3.7)	NS
q5_7 Ability to be around others and enjoy social activities	3.3 (3.1)	4.3 (3.8)	4.1 (3.6)	NS
q5_8 Choice of hobbies or recreation	2.8 (3.2)	3.7 (3.5)	3.5 (3.4)	NS
q5_9 Relationships with spouse and family	2.1 (3.1)	2.3 (2.8)	2.2 (2.8)	NS
q5_10 Ability to perform household chores	3.1 (3.0)	3.4 (3.4)	3.3 (3.3)	NS
Total	33.0 (20.7)	38.3 (24.4)	37.0 (23.6)	NS

We compared the scores of 30 QEESI© items between male and female patients by one-way analysis of variance. Individual items were scored from 0 to 10 (0: not at all, 5: moderately, 10: severely). Mean ($\pm$ standard deviation). NS: not significant.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

($p < 0.05$), with no sex-related differences in the other scores.

Life impact

The high mean levels in the entire patient population were in the order: ability to work or attend school > choice of home furnishing > choice of personal care products > ability to drive or travel > ability to be around others and enjoy social activities. Conversely, the lowest mean level was for dietary

disorder. A significant difference between males and females was found only for dietary disorder ($p < 0.05$) (Table 2).

Comparison of QEESI© scores between Japanese and American patients

A comparison of the mean scores of three QEESI© subscales between MCS patients in Japan (black solid line) and four patient groups in the US reported by

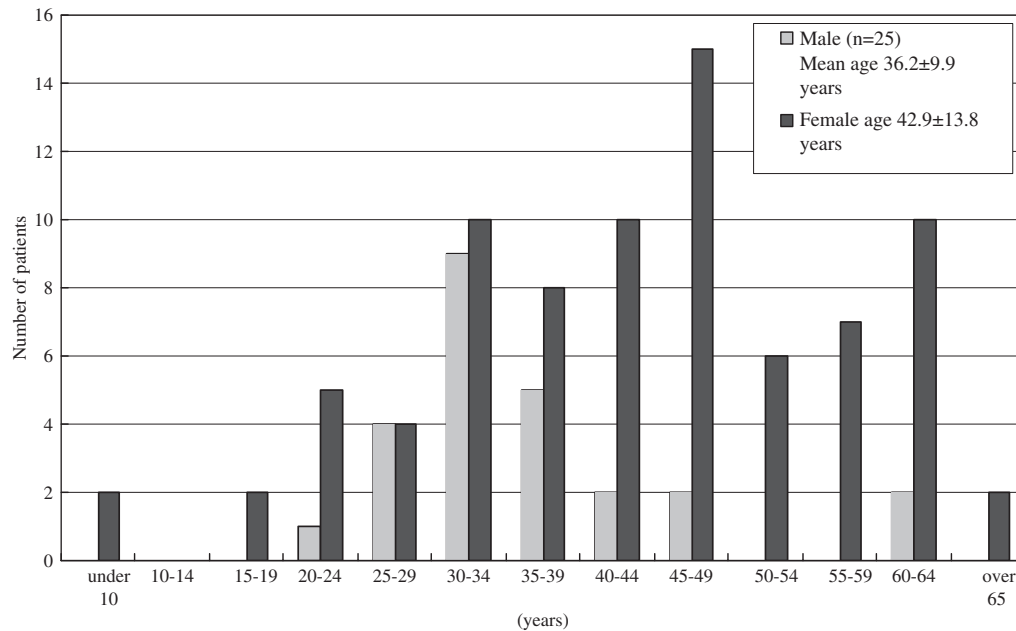


Fig. 1. Age distribution of male and female patients diagnosed with MCS at the Environmental Medical Center of Kitasato Institute Hospital.

Table 3. Estimated onset factors

	Male patients		Female patients		Total patients	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Exposure to indoor air contaminants by new construction or renovation	10	(45.5)	50	(68.5)	60	(63.2)
In home	7	(31.8)	41	(56.2)	48	(50.5)
In workplace or school	3	(13.6)	9	(12.3)	12	(12.6)
Exposure to pesticide or agricultural chemicals	3	(13.6)	23	(31.5)	26	(27.4)
Using chemical substances in workplace or school	14	(63.6)	11	(15.1)	25	(26.3)
Exposure to toxic substance by neighborhood	0	(0.0)	3	(4.1)	3	(3.2)
Dental treatment	0	(0.0)	2	(2.7)	2	(2.1)
Exposure to chemicals in home	0	(0.0)	2	(2.7)	2	(2.1)
Acute organophosphorus in toxication	0	(0.0)	1	(1.4)	1	(1.1)

Multiple answers possible. *n* = 106.

Miller and Prihoda (1999b) is presented in Fig. 2 as radar charts.

Changes in symptoms before and after onset

All patients had higher scores in all 10 QEESI symptom severity items after (current score) than before (past score) onset. Fig. 3 shows symptom severity changes before and after onset. Large score differences were seen in the order: cognitive > airway/mucous membranes > head-related > neuromuscular. There were many patients in whom symptoms affecting the mucosa, respiratory organs and nervous system increased after

onset. However, the standard deviation was very large, indicating marked differences among individuals.

Discussion

We demonstrated the clinical characteristics of physician-diagnosed MCS patients in Japan. As shown in Table 3, the most common estimated onset factors for MCS included exposure to indoor air contaminants caused by new construction or renovation of a home or office (63.2%), followed by exposure to pesticides or agricultural chemicals (27.4%), and exposure to chemicals at work or engaged in hobbies (26.3%), in

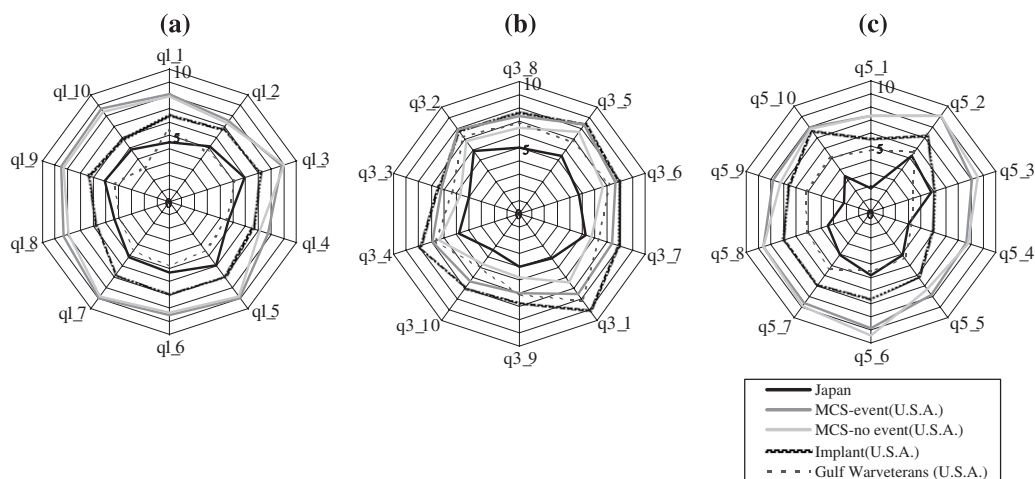


Fig. 2. Mean scores for three QEESI[®] subscales in one Japanese and four American patient groups. (a) Q1 chemical intolerance, (b) Q3 symptom severity and (c) Q5 life impact. We used the mean scores of the four American MCS patient groups reported by Miller and Prihoda (1999b). See Table 2 for the details of questionnaire.

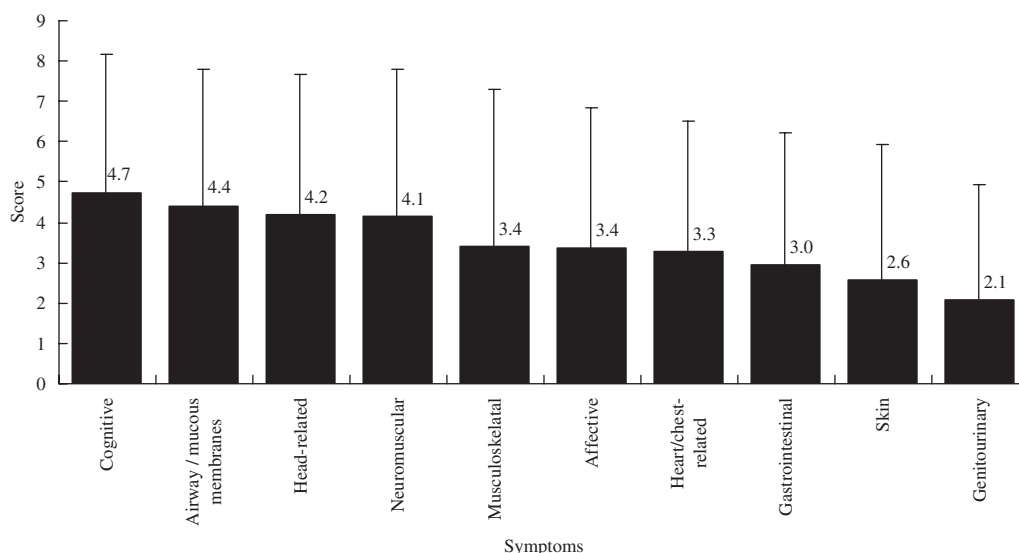


Fig. 3. Changes in symptoms before and after onset. The numerals indicate the mean values of changes in each symptom severity score before and after onset [(current score)–(past score)] in one patient. Vertical lines show standard deviations.

descending order. On the other hand, Miller and Prihoda (1999b) reported that the initiating events in self-reported MCS patients in the US included exposure to various solvents and cleaners (54%), indoor air contaminants (45%), agricultural chemicals (24%) and drugs (6%). The observation that the most common estimated onset factors for MCS in Japan were exposure to indoor air contaminants may be due to the frequent new construction or renovation of Japanese houses. It is noteworthy that most Japanese homes are constructed of wood. The second most common estimated onset factor in Japan, pesticides or agricultural chemicals, accounting for approximately one-fourth of cases in the present study, is also common in other countries including the US and Germany (Caress and Steinemann,

2003; Miller Prihoda, 1999b; Hausteiner et al., 2005). Hence, pesticides and agricultural chemicals may be emphasized as being among the main onset factors of MCS.

Many researchers have reported that the number of middle-aged female MCS patients is high in the US and Europe (Bell et al., 1992; Caress and Steinemann, 2003; Fiedler and Kipen, 1997; Hausteiner et al., 2005; Miller and Mitzel, 1995). Similarly, females accounted for 74.0% of cases in the present study, suggesting that the trend in Japan is similar to those in other countries. However, a sex difference in the age distribution was noted among Japanese MCS patients. The peak age in males was 30–34 years, whereas females showed a wide age distribution with three peaks, 30–34, 45–49 and

60–64 years (Fig. 1). Comparing estimated onset factors between male and female patients, revealed exposure to chemicals in the workplace to be markedly higher in males, while a variety of estimated onset factors were noted in females (Table 3).

MCS and allergy are reportedly closely related (Ashford and Miller, 1996; Meggs, 1999). In Japan, the prevalences of allergies, such as pollinosis, house dust allergy and drug allergy in MCS patients were significantly higher (84% in the present study) than those in the general population (about 30%, Hasegawa, 2003).

In this study, we compared the subjective symptoms of patients evaluated by QEESI[®] scores to those of MSC patient groups in the US (Miller and Prihoda, 1999b). As shown in Fig. 2, some differences in the life impact subscale were noted in the radar chart patterns as well as QEESI[®] scores, suggesting that life impacts may vary greatly depending on lifestyle and nationality. On the other hand, symptom severity and chemical intolerance observed in the radar chart pattern were similar between Japan and the US. MCS patients in both countries exhibited several chemical intolerances and developed multiple organ dysfunction. However, the mean QEESI[®] score in the patient group in our study was lower than those in any of the four self-reported patient groups in the US. Such differences between Japan and the US may not be attributable to differences between self-reported and physician-diagnosed patients, because there were no differences in QEESI[®] scores between self-reported patients described by Hojo et al. (2003) and those who participated in this study. Miller and Mitzel (1995) reported that pesticide-exposed MCS patients showed significantly greater severity of symptoms such as neuromuscular, affective, airway, gastrointestinal and cardiac symptoms than did MCS patients exposed to remodeling of a building. Thus, the differences in QEESI[®] scores between the US and Japan may be due to differences in the onset factors mentioned above.

Further international comparison of MCS symptoms should be conducted in the future, using the same questionnaires for patients who are diagnosed as having MCS according to common diagnostic criteria. Our results confirmed the usefulness of QEESI[®], which was also recommended in the 1999 Consensus. This questionnaire employed a 10-point evaluation instead of a binary choice system such as yes or no, making it possible to compare the degree of subjective symptoms and it may also be appropriate for inter-institutional and international comparison. In Japan, the QEESI[®] has already been used in MCS diagnostic facilities other than the Environmental Medical Center of Kitasato Institute Hospital. Determining the cut-off point of QEESI[®] to differentiate between physician-diagnosed MCS patients and healthy subjects is now in progress.

Acknowledgments

This study was supported in part by a Grants-in-Aid for Scientific Research (Hojo; C19510074), JSPS, Japan and a Grant-in-Aid for Scientific Research subsidized by the Ministry of Health, Labour and Welfare of Japan (Aizawa; H18-010).

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