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Comparison of environmental intolerances and symptoms between patients with multiple chemical sensitivity, subjects with self-reported electromagnetic hypersensitivity, patients with bronchial asthma, and the general population

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Abstract

Background Environmental hypersensitivity/intolerance is considered closely related to allergic diseases. To understand these conditions, the environmental intolerances and symptoms of patients with multiple chemical sensitivity (MCS), subjects with self-reported electromagnetic hypersensitivity (EHS), patients with bronchial asthma (BA), and the general population were compared using universal questionnaires.

Methods A survey was conducted from 2012 to 2015. The subjects were categorized in four groups: 111 patients with physician-diagnosed MCS, 119 subjects with self-reported EHS, patients with 98 physician-diagnosed BA, and 619 controls from general population. The Quick Environmental Exposure and Sensitivity Inventory and EHS questionnaire were used. The differences between the questionnaire scores among the four groups were tested using logistic regression analyses adjusted for age and gender as covariates.

Results The MCS and EHS groups had significantly high scores of intolerances to multiple environmental factors, life impact, and multiple symptoms than the BA and control groups. Although the differences between most of these scores of the MCS and EHS groups were not significant, the electromagnetic hypersensitivity reaction was significantly higher in the EHS group than in the MCS group. In addition, the scores for intolerances to chemicals and other compounds, life impact, and several symptoms of the BA group were significantly higher than those of the control group.

Conclusions This study clarified the similarities and differences of the environmental intolerances and symptoms between the four groups.

Keywords Environmental intolerance, Chemical intolerance, Multiple chemical sensitivity, Electromagnetic hypersensitivity, Bronchial asthma, Quick environmental exposure and sensitivity inventory

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Background

In recent years, the development of agricultural chemicals, insecticides, and herbicides has made agriculture more efficient, and the invention and spread of personal computers, smartphones, wireless local area networks, and so on have dramatically facilitated the acquisition and transmission of information, making our lives more convenient, rich, and comfortable. However, environmental factors that can affect people's health have also diversified, and various health disorders have become apparent in highly sensitive groups. One of these health disorders is known as "environmental hypersensitivity" or "environmental intolerance," and its acute increase is beginning to be reported worldwide. Environmental hypersensitivity/intolerance is a general term for health disorders that present with various clinical symptoms in response to external environmental stimuli in daily life. It is often characterized by hypersensitivity (photosensitivity, sound hypersensitivity, odor hypersensitivity, barometric sensitivity, chemical sensitivity, hypersensitivity to electromagnetic fields [EMFs], etc.), autonomic symptoms, immune allergic symptoms, chronic pain, chronic fatigue, memory/affective disorders, and so on. Typical examples include multiple chemical sensitivity (MCS), electromagnetic hypersensitivity (EHS), and sick building syndrome (SBS). Many epidemiological reports have demonstrated that environmental hypersensitivity is closely related to allergic diseases. Among these reports, many epidemiological studies have reported the association between MCS and bronchial asthma (BA) [1, 2].

Cullen [3] defined MCS 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." The prevalence of MCS in different countries has been reported to range from 0.3% to 33.0% [2, 4–10]. Steinemann [11] reported that the prevalence rates of physician-diagnosed and self-reported MCS were 12.8% and 25.9%, respectively, in the United States in 2016, which had doubled and tripled, respectively, from 10 years before.

On the other hand, EHS is a general term for health disorders that are considered to induce various symptoms that mainly affect the autonomic nervous system due to exposure to weak EMFs from electromagnetic wave sources around us (e.g., personal computers, home electrical appliances, lighting, mobile phones, and mobile phone base stations). The prevalence rates of EHS in different countries have been reported to range from 0.7% to 13.3% [12, 13].

The common points between MCS and EHS are that the symptoms are nonspecific complaints of multiple organs centered on the autonomic nervous system. However, elucidation of the causal relationship between chemical substance or EMF exposure and the symptoms has remained challenging; a valid objective test method does not yet exist, and no universal diagnostic criteria have been established. A recent report by a French research group [13] that investigated 2000 EHS and/or MCS self-reported cases indicated that EHS and MCS clinically show a similar symptomatic picture, and both are likely to be chronic neurodegenerative diseases of the brain. Therefore, they also stated that by using a combination of the currently available clinical tests, an objective test and diagnostic criteria for both diseases could be established.

Questionnaires to assess environmental intolerances have been commonly used in many countries worldwide. For example, for chemical intolerances, the Quick Environmental Exposure and Sensitivity Inventory (QEESI), developed by Miller and Prihoda [14, 15] in the United States, has been translated into various languages [16–19] and is used in 16 countries [20]. For the evaluation of EHS, some questionnaires have been developed and used in multiple countries, such as that developed by Eltiti et al. [21] in the United Kingdom to evaluate the health effects of EMFs.

In Japan, Ishikawa and Miyata [18] created a Japanese version of the QEESI. Hojo et al. [19] confirmed its reliability and validity, set the original Japanese criteria for screening of MCS specific to the Japanese population, and conducted various epidemiological surveys for MCS and SBS in Japan [22–24]. Through these surveys it was revealed that many patients with MCS and SBS reported hypersensitivity reactions to various weak EMFs around them and that they could not improve their symptoms using measures against chemical substances. Therefore, Hojo et al. [25] created a Japanese translation of Eltiti's questionnaire, which was then modified to suit the Japanese lifestyle; after confirming its reliability and validity, the EHS screening criteria for Japanese was set. Since then, various epidemiological surveys using the QEESI and EHS questionnaires have been conducted [25–27].

In this study, to understand the actual condition of environmental hypersensitivity/intolerance, we conducted a survey among patients with physician-diagnosed MCS, subjects with self-reported EHS, patients with physician-diagnosed BA, and individuals from the general population by using the combined QEESI and

EHS questionnaires and compared their environmental intolerances and symptoms.

Methods

Study design and participants

This survey was conducted from 2012 to 2015 [25–27]. The subjects aged 13 to 79 were divided into the following four groups: patients with MCS, subjects with self-reported EHS, patients with BA, and controls (general population). One hundred eleven patients had MCS diagnosed by four medical specialists at four medical institutions (Soyokaze Allergic Clinic, National Hospital Organization (NHO) Morioka National Hospital, NHO Sagamihara National Hospital, and NHO Kochi National Hospital). The criteria used for diagnosing MCS satisfied both the US 1999 consensus [28] and Japanese diagnostic criteria [29] in exclusion of known diseases (e.g., mental disorder, lifestyle diseases, chronic fatigue syndrome, fibromyalgia). The attending physician distributed the questionnaires by hand to patients who provided informed consent and collected them after the patients had completed them. The patients were randomly selected during the survey period.

The subjects with self-reported EHS were recruited through two EHS self-help groups in Japan (Life-Environmental Network and Kansai Association on Electromagnetic Wave and Environment). We mailed the questionnaires to 165 subjects with EHS, of whom 128 responded (recovery rate 77.6%). The data from 119 questionnaires (72.1%) were valid.

Patients with BA were those who were diagnosed as having BA by allergy specialists at the National Hospital Organization Sagamihara National Hospital on the basis of Global Initiative for Asthma (GINA) guidelines [30]. We asked 100 patients to participate in the study and received informed consent from all (recovery rate 100%); of the patients, 98 (98%) had valid responses.

The control subjects were members of the general population residing in the 35 prefectures of Japan. Survey requests were made through the communication networks of various organizations to which the co-researchers belonged (academic societies, study groups, universities, vocational schools, architects' associations, regional neighborhood associations, and environmental non-profit organizations). We sent a questionnaire and reply envelope to those who provided research cooperation and asked them to mail the questionnaire to the data administrator after completing it anonymously. The questionnaire was distributed to 2007 subjects, of whom 1327 returned the questionnaire (recovery rate, 66.1%). The data were valid in 1313 of the returned questionnaires. Of the subjects, 689 had information on whether they had a medical history or was under treatment for

SBS, MCS, EHS, or BA. After excluding those diagnosed as having SBS, MCS, EHS, or BA, 619 subjects were included as controls.

Questionnaires

Demographics

Section I of the EHS questionnaire asks the subject about their demographic characteristics, including gender, age, employment, working hours per day, and education.

QEESI: assessment of chemical intolerances

The QEESI consists of five subscales as follows [14, 15]: Q1 Chemical intolerances, mainly assesses the hypersensitivity reaction (intolerance) to chemicals inhaled into the respiratory tract; Q2 Other intolerances, assesses the hypersensitivity reaction to chemicals that people are exposed to via routes other than the respiratory tract; Q3 Symptom severity, assesses the severity of various symptoms; Q4 Masking index, asks participants about the presence or absence of chemical substances that they may be taking in regularly; Q5 Life impact, assesses the level of disruption in daily life activities. Each subscale contains 10 items, making a total of 50 items. For Q1, Q2, Q3, and Q5, the subjects were asked to select the degree of the item from 0 (not at all) to 10 (quite severe or frequent). In the Q4 Masking index, the subjects were asked to select “yes (1)” or “no (0),” depending on whether they were exposed to (intake or use) the item. The new criteria for screening patients with MCS by using QEESI in Japan are to satisfy all cutoff values as follows: Q1 total ≥ 30 points, Q3 total ≥ 13 points, and Q5 total ≥ 17 points [26].

EHS questionnaire: assessing electromagnetic intolerances

The EHS questionnaire includes the following sections: I Demographics; II-1 Symptoms (57 items, classified into eight principle components (c1–c8); II-2 EMF-producing objects (nine items, q58–q66) presumed to be the cause of symptoms; II-3 Reaction to EMFs (q67–q71); III General health (d1 Well-being, d2 Good health, d3.1 Sleep [fatigue recovery by sleep], d3.2 Sleeping hours per day, d3.3 Sleep disorder, and d4 Chronic illness); and IV Total health index-depression (THI-D) [31, 32] (10 items, d5.1–d5.10, added only in the Japanese version). The cutoff value of the depressive state is ≥ 22 points [31, 32]. The subjects were then asked to select the degree of the item from 0 (not at all) to 4 (quite frequent) for q1–q66, q70, and q71, and “yes (1)” or “no (0)” for q69 and d4. q68 is the detailed description of the EMF sources and symptoms. For III General health, the subjects were asked to select the degree of the item for d1, d2, and d3.1 from 0 (not at all) to 4 (quite good) and for d3.3 from 0 (not at all) to 4 (quite frequent). For IV THI-D, the subjects

were asked to select the degree of fatigue for the item as follows: “no (1),” “neither (2),” and “yes (3).” The screening criteria for EHS set by Hojo et al. [25] are to satisfy all of the following three cutoff values: II-1 Symptoms total ≥ 47 points, q67 ≥ 1 point, and descriptions of two or more items for q68.

Statistical analyses

For the statistical analysis, IBM SPSS Statistics version 23.0 for Microsoft Windows (IBM, Armonk, NY, USA) was used. For gender and age, the odds ratios of two groups (MCS vs. EHS, MCS vs. BA, MCS vs. controls, EHS vs. BA, EHS vs. controls, and BA vs. controls) were calculated using a logistic regression analysis. For the scores of other items in QEESI and EHS questionnaire, adjusted odds ratios of the two groups were calculated using logistic regression analysis with gender and age as covariates. Significant differences were evaluated using a Wald test. The p-value was adjusted using the Dunn-Bonferroni test, that is, multiplied by 6, which was the trial number of all combinations of comparison between the four groups. The significance level was set at 0.05. The analysis was performed without using missing values including “unknown” and subscales including them.

Ethical considerations.

This study was approved by the research ethics committees of Morioka National Hospital (No. 24-01), the Environmental Center of Oita University (No. 304), Sagami National Hospital (No. 6), Shokei Gakuin University (No. 2020-2), and Kindai University Faculty of Medicine (No. R02-185). Informed consent for the survey was obtained from all the subjects in accordance with the Declaration of Helsinki.

Results

Comparison of demographics

Table 1 shows a summary of the demographics of the four groups. The proportion of the classification by age groups, 95% confidence intervals (CIs) of odds ratio (ORs) or adjusted odds ratios (AORs), and the p-values were shown in Additional file 1: Table S1. The proportion of females was not significantly different among the four groups in the range from 69.4% to 81.1%. The median age was in the range from 43 to 54 years in the four groups. The age of the EHS group was significantly higher than that of the MCS and control groups ($p < 0.001$ and $p < 0.0001$, respectively). Moreover, the age of the BA group was significantly higher than that of the control group ($p < 0.0001$). The proportion of subjects who were unemployed was significantly higher in the MCS and EHS groups than in the control group ($p < 0.0001$),

whereas the proportion of full-time workers was significantly lower in the EHS group than in the control group ($p < 0.001$), and the working hours per day were significantly less in the MCS and EHS groups than in the control group ($p < 0.05$ and $p < 0.001$, respectively).

Comparison of QEESI scores

Table 2 shows the comparison of total scores in each subscale of the QEESI between the four groups. The scores of all 50 items, 95% CIs of AORs, and p-values were shown in Additional file 1: Table S2. The frequency distributions of the total scores and radar chart for the median values of the scores in each subscale are shown in Figs. 1, 2, respectively.

Q1 Chemical intolerances

The total score in Q1 was significantly higher for the MCS and EHS groups than for the BA and control groups ($p < 0.0001$; Fig. 1a and Table 2). The difference in total score between the MCS and EHS groups was not significant. Meanwhile, the total scores of the BA group were significantly higher than those of the control group ($p < 0.01$).

For each item in Q1, the MCS and EHS groups scored significantly higher than the BA and control groups in nine items ($p < 0.001$) except for q1.2 tobacco smoke (Fig. 2a and Additional file 1: Table S2). The difference in the score in each item between the MCS and EHS groups was also not significant. Between the BA and control groups, the scores in five items, namely q1.2 Tobacco smoke, q1.3 Insecticides, q1.5 Paint or paint thinner, q1.6 Cleaning products, and q1.10 New furnishings, were significantly higher for the patients with BA than those for the controls ($p < 0.001$, $p < 0.01$, $p < 0.001$, $p < 0.05$, and $p < 0.05$, respectively).

Q2 Other intolerances

The total score in Q2 was significantly higher for the MCS and EHS groups than for the BA and control groups ($p < 0.01$; Fig. 1b and Table 2). The difference in total score between the MCS and EHS groups was not significant; however, the total score of the BA group was significantly higher than that of the control group ($p < 0.0001$).

The MCS and EHS groups scored significantly higher than the BA and control groups in six items in Q2 ($p < 0.05$) except for q2.3 Food cravings or feeling ill if a meal is missed, q2.6 Feeling ill if caffeine intake is stopped or decreased, q2.7 Alcohol in small amounts, and q2.10 Classical allergic reactions (Fig. 2b and Additional file 1: Table S2). The differences in the scores in all 10 items between the MCS and EHS groups were not significant. No significant differences in the scores were observed between the BA and control groups,

Table 1 Demographics of the four groups

	OR or AOR ^a				Order ^b and difference ^c						
	MCS	EHS	BA	Controls							
Gender, % (n)											
Female	81.1 (90)	80.7 (96)	69.4 (68)	72.2 (447)	1.0	1.9	1.6	1.8	1.6	0.87	M, E, C, B
Male	18.9 (21)	19.3 (23)	30.6 (30)	27.8 (172)							
Age											
Median (IQR) (years)	46 (19)	54 (16)	49.5 (24.25)	43 (33)	0.96***	0.97	1.0	1.0	1.0****	1.0****	E, B, M, C
Minimum–Maximum (years)	13–79	14–77	17–78	12–79							
Employment, % (n)											
Unemployed	29.4 (30)	29.3 (34)	16.7 (15)	6.4 (38)	1.0	1.1	1.2****	1.1	1.1****	1.1	M, E, B, C
Student	4.9 (5)	2.6 (3)	1.1 (1)	24.1 (143)	0.35	2.3	0.14**	8.4	0.27	0.047*	C, E, M, B
Homeworker	25.5 (26)	31.0 (36)	28.9 (26)	10.6 (63)	0.99	0.87	1.5*	0.93	1.5*	1.7**	B, E, M > C
Part-time worker	6.9 (7)	14.7 (17)	11.1 (10)	14.8 (88)	0.70	0.82	0.71	1.1	0.92	0.84	C, E, B, M
Full-time worker	33.3 (34)	22.4 (26)	42.2 (38)	44.0 (261)	1.2	0.91	0.88	0.82	0.78***	0.98	C, B, M, E
Working hours per day, Median (IQR) (h)	8 (7)	6 (5)	8 (4.5)	8 (4)	1.03	0.93	0.91*	0.89	0.87***	1.0	B, C > M, E
Education, % (n)											
Primary school	64 (5)	2.5 (3)	6.3 (6)	2.0 (12)	1.7	1.1	3.2	0.51	1.3	3.0	M, B, E, C
High school	34.6 (27)	22.9 (27)	38.9 (37)	42.8 (253)	1.4	0.97	0.90	0.64*	0.7*	1.0	B, C, M, E
College/university	56.4 (44)	67.8 (80)	53.7 (51)	50.8 (300)	0.85	0.98	1.0	1.2	1.2	0.99	E, M, B, C ^d
Graduate	2.6 (2)	6.8 (8)	1.1 (1)	4.4 (26)	0.78	1.4	0.87	1.7	1.1	0.68	E, C, M, B

MCS and M Multiple chemical sensitivity, EHS and E Electromagnetic hypersensitivity, BA and B Bronchial asthma, C Controls, OR Odds ratio, AOR Adjusted odds ratio, IQR Interquartile range

^a In case of A vs. B, OR or AOR of the score of A against the score of B. For gender and age OR was calculated. For employment and education AOR was calculated using age and gender as covariates

^b Order based on the OR or AOR

^c In case of A > B, the score of A was significantly higher than that of B (p < 0.05)

^d Order based on the proportion

* p < 0.05,

** p < 0.01,

*** p < 0.001

**** p < 0.0001

Table 2 Comparison of the scores of subscales and other items between the four groups

	AOR ^a				Order ^b and difference ^c						
	MCS	EHS	BA	Controls	MCS vs. EHS	MCS vs. BA	MCS vs. controls	EHS vs. BA	EHS vs. controls	BA vs. controls	
Items of QEESI											
Total of Q1 Chemical intolerances, median (IQR)	68 (33)	64 (48.5)	31 (37)	18 (32)	1.0	1.1 ^{****}	1.1 ^{****}	1.0 ^{****}	1.1 ^{****}	1.0 ^{**}	M, E > B > C
Total of Q2 Other intolerances, median (IQR)	25 (25)	21 (27.25)	10 (18.25)	6 (12)	1.0	1.1 ^{****}	1.1 ^{****}	1.0 ^{**}	1.1 ^{****}	1.1 ^{****}	M, E > B > C
Total of Q3 Symptom severity, median (IQR)	52.5 (34.25)	42 (37.25)	13 (14.75)	10 (17)	1.0	1.1 ^{****}	1.1 ^{****}	1.1 ^{****}	1.1 ^{****}	1.0	M, E > B, C
Total of Q4 Masking index, median (IQR)	3 (3)	2 (2)	5 (1)	4 (2)	1.5 ^{***}	0.65 ^{****}	0.78 ^{***}	0.40 ^{****}	0.48 ^{****}	1.2 [*]	B > C > M > E
Total of Q5 Life impact, median (IQR)	49 (36.5)	40 (56.25)	5 (12)	2 (8)	1.0	1.1 ^{****}	1.1 ^{****}	1.1 ^{****}	1.1 ^{****}	1.0 [*]	M, E > B > C
Items of EHS questionnaire											
Total of II-1 Symptoms, median (IQR)	94.5 (69.75)	69 (63)	37 (33.5)	30 (29.25)	1.0	1.0 ^{****}	1.0 ^{****}	1.0 ^{****}	1.0 ^{****}	1.0 [*]	M, E > B > C
Total of II-2 EMF-producing objects, median (IQR)	5 (21)	19 (21)	0 (3.5)	1 (4)	0.93 ^{**}	1.1 ^{**}	1.1 ^{****}	1.2 ^{****}	1.2 ^{****}	1.0	E > M > B, C
II-3 Reaction to EMFs											
q67 Sensitive to EMFs, median (IQR)	2 (4)	3.5 (3)	0 (1)	0 (0)	0.66 ^{****}	2.3 ^{****}	3.0 ^{****}	4.4 ^{****}	5.0 ^{****}	1.2	E > M > B, C
q68 Detailed description, % (n) ^d	58.9 (53)	89.1 (106)	20.6 (20)	9.4 (58)	0.17 ^{****}	5.2 ^{****}	13 ^{****}	33 ^{****}	71 ^{****}	2.4 [*]	E > M > B > C
q69 Experience a severe electric shock, % (n) ^e	57.0 (61)	67.5 (79)	38.5 (37)	49.4 (298)	0.58	1.9	1.3	3.6 ^{***}	2.2 ^{**}	0.66	E, M, C, B
q70 Frequency of static electricity, median (IQR)	1 (2)	2 (2)	1 (1)	1 (1)	0.80	1.5 [*]	1.2	2.0 ^{****}	1.4 ^{***}	0.74 [*]	E, M, C > B
q71 Frequency of negative health around EMFs, median (IQR)	1 (3)	3 (3)	0 (0)	0 (0)	0.61 ^{****}	2.7 ^{****}	3.5 ^{****}	4.9 ^{****}	5.6 ^{****}	1.3	E > M > B, C
III General health											
d1 Well-being, median (IQR)	2 (1)	2 (2)	2 (1)	2 (1)	0.59 ^{**}	0.24 ^{****}	0.31 ^{****}	0.66 [*]	0.66 ^{**}	1.0	B, C > E > M
d2 Good health, median (IQR)	1 (1)	1 (1)	2 (1)	2 (0)	0.60 [*]	0.22 ^{****}	0.20 ^{****}	0.47 ^{****}	0.37 ^{****}	0.75	C, B > E > M
d3.1 Sleep, median (IQR)	1 (2)	2 (1)	2 (1)	2 (1)	0.63 [*]	0.37 ^{****}	0.38 ^{****}	0.68 ^{****}	0.63 ^{****}	0.90	C, B, E > M
d3.2 Sleeping hours per day, median (IQR)	7 (2)	7 (2)	6 (2)	6 (1)	1.1	1.8 ^{***}	1.6 ^{****}	1.5 ^{**}	1.3 [*]	0.76	M, E > C, B

Table 2 (continued)

	MCS	EHS	BA	Controls	AOR ^a	MCS vs. EHS				Order ^b and difference ^c	
						MCS vs. EHS	MCS vs. BA	MCS vs. controls	EHS vs. BA		EHS vs. controls
d3.3 Sleeping disorder, median (IQR)	2 (2)	2 (2)	1 (1)	1 (2)	1.1	1.6**	2.0****	1.5**	1.8****	1.2	M, E > B, C
d4 Chronic illness, % (n) ^e	63.6 (70)	59.6 (68)	87.4 (83)	44.4 (272)	1.2	0.22****	2.2**	0.17****	1.8*	8.2****	B > M, E > C
Total of IVTHI-D, median (IQR)	22 (9)	21 (9)	16 (7)	15.5 (8)	1.0	1.2****	1.2****	1.1***	1.1****	1.0	M, E > B, C

MCS and M Multiple chemical sensitivity, EHS and E Electromagnetic hypersensitivity, BA and B Bronchial asthma, C Controls, AOR Adjusted odds ratio, QEESt Quick Environmental Exposure and Sensitivity Inventory, IQR Interquartile range, EMF Electromagnetic field, THI-D Total health index-depression

^a In case of A vs. B, AOR of the score of A against the score of B. AOR was calculated using age and gender as covariates

^b Order based on the AOR

^c In case of A > B, the score of A was significantly higher than that of B (p < 0.05)

^d Proportion and number of the subjects who described two or more items

^e Proportion and number of the subjects who selected "yes (1)"

* p < 0.05

** p < 0.01

*** p < 0.001

**** p < 0.0001

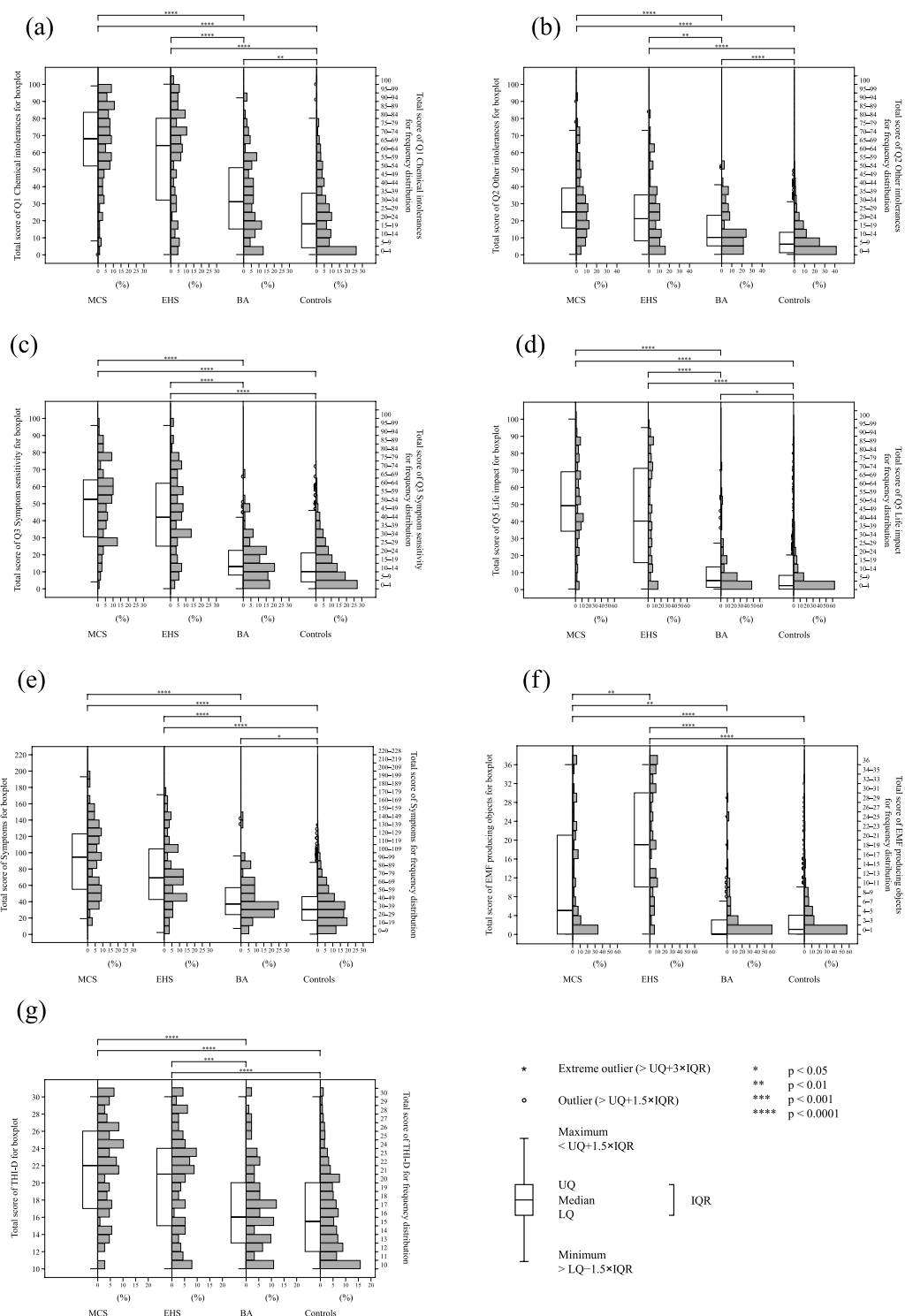


Fig. 1 Comparison of the total scores of subscales among the four groups. Box plot and frequency distribution of the total scores of **a** Q1 Chemical intolerances, **b** Q2 Other intolerances, **c** Q3 Symptom severity, **d** Q5 Life impact, **e** I-1 Symptoms, **f** I-2 EMF-producing objects, and **g** IV THI-D. MCS Multiple chemical sensitivity, EHS Electromagnetic hypersensitivity, BA Bronchial asthma, EMF Electromagnetic field, THI-D Total health index-depression, UQ Upper quartile, IQR Interquartile range, LQ Lower quartile

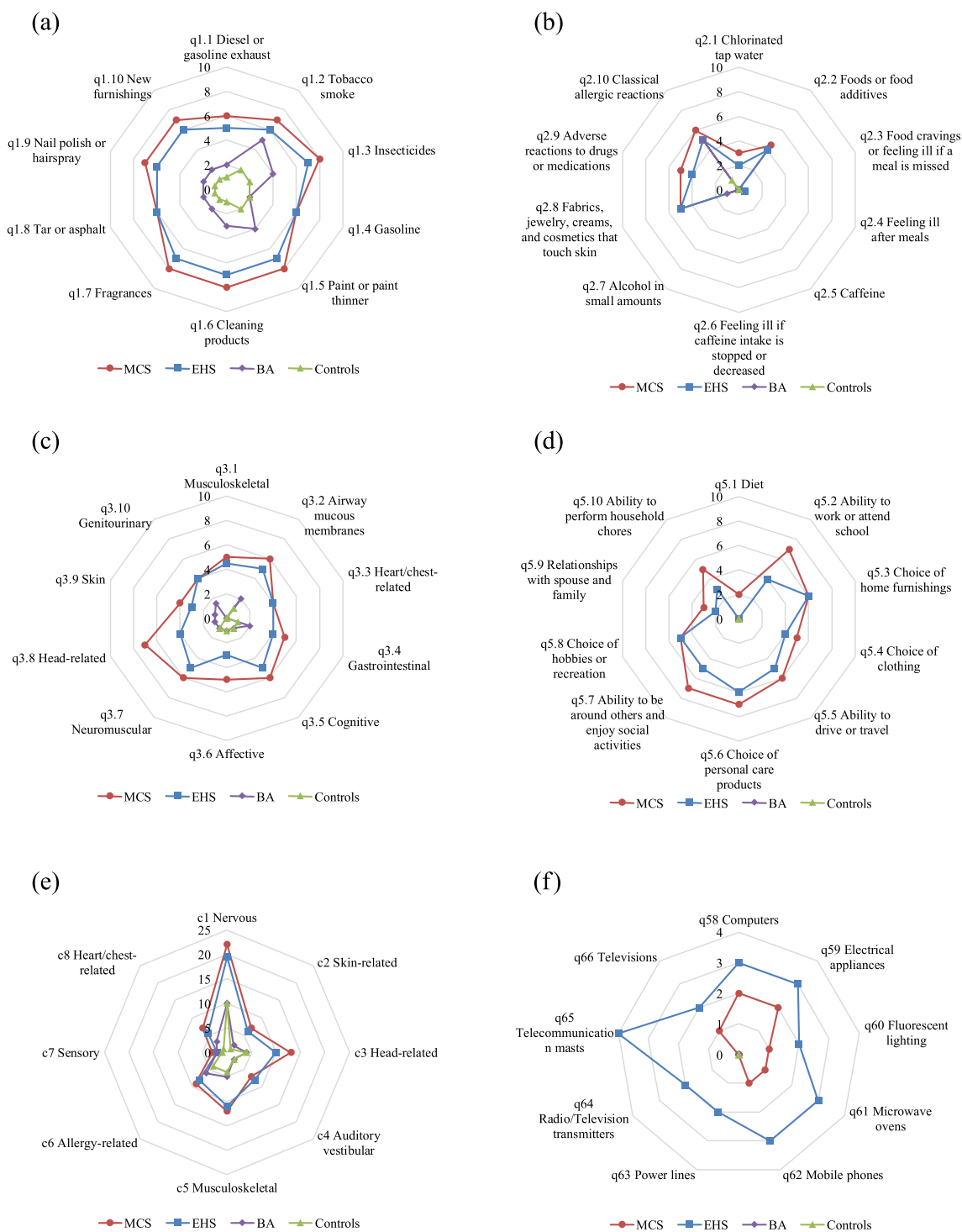


Fig. 2 Comparison of the scores in each item of subscales among the four groups. Radar chart for the median values of the scores in each item of **a** Q1 Chemical intolerances, **b** Q2 Other intolerances, **c** Q3 Symptom severity, **d** Q5 Life impact, **e** II-1 Symptoms, and **f** II-2 EMF-producing objects. MCS Multiple chemical sensitivity, EHS Electromagnetic hypersensitivity, BA Bronchial asthma, EMF Electromagnetic field

except for q2.7 Alcohol in small amounts; q2.8 Fabrics, jewelry, creams, and cosmetics that touch skin; q2.9 Adverse reactions to drugs or medications; and q2.10 Classical allergic reactions, for which the scores were significantly higher for the patients with BA than for the controls ($p < 0.001$, $p < 0.05$, $p < 0.01$, and $p < 0.0001$, respectively).

Q3 Symptom severity

The total score for Q3 was significantly higher for the MCS and EHS groups than for the BA and control groups ($p < 0.0001$; Fig. 1c and Table 2). The differences in the total scores between the MCS and EHS groups and between the BA and control groups were not significant.

For each item in Q3, the MCS and EHS groups showed significantly higher scores than the BA and control groups in all 10 items ($p < 0.001$; Fig. 2c and Additional file 1: Table S2). Meanwhile, the difference in score between the MCS and EHS groups was not significant. In addition, the differences in scores between the BA and control groups were significant for q3.2 Airway mucous membranes ($p < 0.001$) and q3.9 Skin ($p < 0.05$), which were found to be higher in the BA group.

Q4 Masking index

Significant differences were observed among four groups for the total score in Q4 Masking index; the total score of the EHS group was significantly lowest ($p < 0.001$), followed by those of the MCS, control, and BA groups with significance ($p < 0.05$; Table 2). Regarding the proportion of exposure to each item, no significant difference was observed between the two groups for q4.1 Tobacco and q4.7 Secondhand smoke. For the intake of alcohol (q4.2) and caffeine (q4.3), the MCS and EHS groups had significantly lower proportions than the controls ($p < 0.01$; Additional file 1: Table S2). For the use of scented personal care products (q4.4) and fabric softener (q4.9), the proportions of the EHS and MCS groups were significantly lower than those of the control and BA groups ($p < 0.0001$). For q4.9 Fabric softener, the proportion of the EHS group was significantly lower than that of the MCS group ($p < 0.01$). The proportion of insecticides use (q4.5) was significantly lowest in the EHS group ($p < 0.01$). Regarding q4.6 Chemical or smoke exposure at work, the proportion of MCS group was significantly highest ($p < 0.001$) and the proportions of the MCS and EHS groups were higher than those of the BA and control groups ($p < 0.05$). The proportion of gas or propane stove use (q4.8) was significantly highest in the control group ($p < 0.05$). The proportion of drugs use (q4.10) was

significantly highest in the BA group ($p < 0.0001$), followed by that of the MCS group, indicating a significantly higher proportion than those of the EHS and control groups ($p < 0.05$ and $p < 0.0001$, respectively).

Q5 Life impact

The total score for Q5 was significantly higher in MCS and EHS groups than in the BA and control groups ($p < 0.0001$; Fig. 1d and Table 2). The total scores between the MCS and EHS groups were not significantly different. Meanwhile, the total score of the BA group was significantly higher than that of the control group ($p < 0.05$).

The MCS and EHS groups showed significantly higher scores than the BA and control groups in all items ($p < 0.001$; Fig. 2d and Additional file 1: Table S2). Furthermore, no significant difference in the scores for all items was found between the MCS and EHS groups. The BA group had significantly higher scores than the control group for q5.5 Ability to drive or travel, q5.6 Choice of personal care products, and q5.7 Ability to be around others and enjoy social activities ($p < 0.01$, $p < 0.01$, and $p < 0.05$, respectively), but no significant difference was found between the two groups for the other seven items.

Comparison of the EHS questionnaire

Table 2 shows the comparison of items in the EHS questionnaire between the four groups. The scores of all items, 95% CIs of AORs, and p-values were shown in Additional file 1: Table S3. The frequency distributions of the total scores and radar chart for the median values of the scores in each subscale are shown in Figs. 1, 2, respectively.

II-1 Symptoms

The total score in II-1 Symptoms was significantly higher in the MCS and EHS groups than in the BA and control groups ($p < 0.0001$; Fig. 1e and Table 2). Moreover, no significant difference in total score was determined between the MCS and EHS group. Meanwhile, the total scores of the BA group was significantly higher than that of the control group ($p < 0.05$).

In terms of the scores of the eight principal components of II-1 Symptoms [25], all six items except for c6 Allergy-related and c7 Sensory showed significantly higher scores in the MCS and EHS groups than in the BA and control groups ($p < 0.0001$; Fig. 2e and Additional file 1: Table S3). The scores of c6 Allergy-related and c7 Sensory were found to be significantly lowest in the controls ($p < 0.0001$). The difference between the MCS and EHS groups was not significant. In the BA group, the

scores in four items (c2 Skin-related, c6 Allergy-related, c7 Sensory, and c8 Heart/chest-related) were significantly higher than those in the control group ($p < 0.01$, $p < 0.0001$, $p < 0.0001$, and $p < 0.01$, respectively), but no significant differences in the scores in the other four items were found.

II-2 EMF-producing objects

The total score for the II-2 EMF-producing objects was significantly higher in the EHS and MCS groups than in the BA and control groups ($p < 0.01$; Fig. 1f and Table 2). No significant difference in total score was found between the BA and control groups. Meanwhile, the total scores of II-2 EMF-producing objects had a significant difference between MCS and EHS groups, which indicates that the EHS group had higher total scores than the MCS group ($p < 0.01$).

For each item, the scores in all the items were significantly higher in the EHS and MCS groups than in the BA and control groups ($p < 0.01$) except for q64 Radio/Television transmitters (Fig. 2f and Additional file 1: Table S3). For q64 Radio/Television transmitters, the score of the EHS group was significantly highest ($p < 0.001$) and the score of the MCS group was higher than in that of the control group ($p < 0.0001$). The scores for q58 Computers, q61 Microwave ovens, q62 Mobile phones, q64 Radio/Television transmitters, and q65 Telecommunication masts were significantly higher for the EHS group than for the MCS group ($p < 0.05$, $p < 0.01$, $p < 0.001$, $p < 0.001$, and $p < 0.0001$, respectively). Meanwhile, between the BA and control groups, no significant difference was observed.

II-3 Reaction to EMFs

Of the scores for II-3 Reaction to EMFs, the q67 Sensitivity to EMFs, q68 Detailed description, and q71 Frequency of negative health around EMFs were all significantly higher in the EHS group than in the other three groups ($p < 0.001$; Table 2). The MCS group also showed significantly higher scores than the BA and control groups ($p < 0.001$). For q68 Detailed description, the proportion of BA group was significantly higher than that of the control group ($p < 0.05$).

No significant difference in electrostatic response (the proportion of q69 Experience a severe electric shock and q70 Frequency of static electricity) was found between the EHS and MCS groups. For these items, the scores of the EHS groups were significantly higher than those of the control and BA groups ($p < 0.01$). The scores of the BA group were significantly lower than those of the other three groups for q70 Frequency of static electricity ($p < 0.05$).

III General health and IV THI-D

The MCS group had the lowest scores for d1 Well-being and d2 Good health, followed by the EHS group, and these differences were statistically significant ($p < 0.05$; Table 2). The differences between the BA and control groups were not significant. For d3.1 Sleep (fatigue recovery by sleep), the MCS group had the significantly lowest score ($p < 0.05$), and the EHS group had a significantly lower score than the control group ($p < 0.001$). The daily sleeping time (d3.2) was significantly longer for the MCS and EHS groups than for the control and BA groups ($p < 0.05$). Regarding the score for d3.3 Sleep disorder, the differences between the MCS and EHS groups and between the BA and control groups were not significant, and the scores of the MCS and EHS groups were significantly higher than those of the BA and control groups ($p < 0.01$).

The total scores of the MCS and EHS groups were significantly higher than those of the BA and control groups ($p < 0.001$; Fig. 1g and Table 2). Moreover, no significant difference in total score was found between MCS and EHS groups and between the BA and control groups. The exceedance proportions of the cutoff value of depressive state (≥ 22 points) [31, 32] were 53.3%, 44.2%, 19.8%, and 15.1% for the MCS, EHS, BA, and control groups, respectively.

Exceedance proportions of the screening criteria for environmental hypersensitivity/intolerance

Table 3 shows the exceedance proportions of the screening criteria for MCS by QEESI [27] and EHS by the EHS questionnaire [25] in the four groups. The CIs of AORs and p-values were shown in Additional file 1: Table S4. As a result, 43.8% of the MCS group exceeded the criteria for EHS and 61.3% of the EHS group exceeded the criteria for MCS. Of the MCS and EHS groups, 45.8% and 47.3% exceeded the criteria for both MCS and EHS, respectively. The criteria for MCS, EHS, either MCS or EHS, and both MCS and EHS were exceeded by 18.8%, 13.0%, 29.5%, and 1.6% of the BA group and 6.1%, 3.8%, 9.6%, and 0.9% of the control group, respectively.

Discussion

In recent years, a rapid increase in the numbers of people with asthma, MCS, and EHS has been reported worldwide. The close relationships between these three diseases have been discussed, and the similarities between their environmental intolerances and symptoms have been recognized; however, reports are scarce. Therefore, by combining common questionnaires (QEESI and EHS questionnaire), we conducted a survey among subjects with MCS, EHS, and BA, and the general population to

Table 3 Comparison of exceedance proportions of the screening criteria for environmental hypersensitivity/intolerance between the four groups

	Controls			AOR ^a				Order ^b and difference ^c			
	MCS	EHS	BA	MCS vs. EHS	MCS vs. BA	MCS vs. controls	EHS vs. BA		EHS vs. controls	BA vs. controls	
Exceeding screening criteria of MCS, % (n)	85.9 (73)	61.3 (46)	18.8 (15)	6.1 (32)	3.7 [*]	29 ^{****}	95 ^{****}	8.5 ^{****}	32 ^{****}	4.2 ^{***}	M > E > B > C
Exceeding screening criteria of EHS, % (n)	43.8 (28)	69.0 (58)	13.0 (9)	3.8 (20)	0.34 [*]	5.1 ^{**}	19 ^{****}	14 ^{****}	52 ^{****}	3.6 [*]	E > M > B > C
Exceeding screening criteria of MCS or EHS, % (n)	83.3 (40)	76.4 (42)	29.5 (18)	9.6 (43)	1.5	12 ^{****}	46 ^{****}	11 ^{****}	30 ^{****}	4.0 ^{***}	M, E > B > C
Exceeding screening criteria of MCS and EHS, % (n)	45.8 (22)	47.3 (26)	1.6 (1)	0.9 (4)	0.88	55 ^{***}	1.0 × 10 ² ^{****}	60 ^{***}	1.2 × 10 ² ^{****}	1.9	E, M > B, C

AOR Adjusted odds ratio, MCS and M Multiple chemical sensitivity, EHS and E Electromagnetic hypersensitivity, BA and B Bronchial asthma C Controls

^a In case of A vs. B, AOR of the score of A against the score of B. AOR was calculated using age and gender as covariates

^b Order based on the AOR

^c In case of A > B, the score of A was significantly higher than that of B (p < 0.05)

* p < 0.05

** p < 0.01

*** p < 0.001

**** p < 0.0001

clarify their similarities and differences. As a result of the mutual comparison, new findings were obtained.

Demographics

As shown in Table 1, more than 80% of the participants with MCS or EHS were female. This finding is consistent with the findings from European and American studies [1, 9, 13, 33, 34]; thus, female gender was reconfirmed to be an important characteristic of MCS and EHS. Changes in the physical condition of females due to endocrine fluctuations, female hormones involved in the growth of the hippocampal neural network, and the higher sensitivity of the hypothalamic–pituitary–adrenal system associated with the hippocampal circuit in females have been posited to be the factors that make females more susceptible to MCS and EHS [27, 35]. However, the mechanisms of these associations have not been fully elucidated. Understanding the cause(s) of the higher prevalence rates of MCS and EHS among females may reveal the etiology of these diseases.

The proportion of unemployed subjects was significantly higher among the MCS and EHS groups, and the proportion of full-time workers was significantly lower in the EHS group than in the control group. Previous studies reported that when patients with MCS or EHS become severely ill, they become unable to undertake normal daily activities and find it difficult to work full-time owing to their poor physical condition [13]. Therefore, the above-mentioned results suggest that there are patients who are severely ill with MCS/EHS.

Comparison between four groups

Scales related to environmental intolerances includes intolerances to inhalant chemicals and other compounds (Q1 and Q2, respectively), intolerances to biological allergens (q2.10 Classical allergic reactions), life impact (Q5), and EMF intolerances (II-2 EMF-producing objects and II-3 Reaction to EMFs). For Q1, Q2, and Q5, which are suggested to assess intolerances to chemicals and other compounds directly or indirectly, no significant differences in the total scores and scores in most of items between MCS and EHS groups were observed, and most of the scores were significantly higher than those of the BA and control groups. In addition, the total scores in Q1, Q2, and Q5, and the scores in several items for the patients with BA were significantly higher than those for the controls, which suggests that the patients with MCS and the subjects with EHS were more intolerant to various chemicals and other compounds than the patients with BA and controls, and that the patients with BA were more intolerant to several chemicals and other compounds than the controls. Meanwhile, for II-2 and II-3, which are suggested to assess intolerance to EMF sources

and reaction to EMFs, respectively, the total scores and scores in most items of II-2 EMF-producing objects, q67 Sensitive to EMFs, q68 Detailed description, and q71 Frequency of health change around EMFs were significantly highest in the EHS group among four groups, and the scores of the MCS group were significantly higher than those of the BA and control groups. Moreover, no significant difference was observed in these scores between the BA and control groups except for q68 Detailed description. These results suggested that EMF intolerances are the specific characteristics of EHS but are also found in patients with MCS as compared with the general population.

Scales related to symptoms include multiple symptoms (Q3 and II-1), health condition (d2 Good health), sleep-related factors (d3.1 Sleep, d3.2 Sleeping hours per day, and d3.3 Sleep disorder), and mental symptoms (q3.6 Affective, d1 Well-being, and IV THI-D). The total scores and scores in most items in the MCS and EHS groups were significantly higher than those in the BA and control groups (for d1 and d2, the tendency was adverse), which suggests that the onset of MCS and EHS can increase various symptoms, including mental symptoms. In terms of sleep, the d3.1 Sleep scores of the MCS and EHS groups were significantly lower than those of the controls, although the sleep hours were significantly longer than those of the controls, which suggests poor sleep quality in the patients with MCS and subjects with EHS. Overall, these results imply more severe symptoms in the patients with MCS and subjects with EHS than in the patients with BA and controls.

Regarding Q4 Masking index, which shows ongoing chemical exposure, the tendency was different from the other items. The total score of the EHS group was significantly lowest, and the total scores of the MCS groups were significantly lower than those of the control and BA groups ($p < 0.001$). Previous studies reported that subjects with MCS and EHS often avoid chemical exposures that worsen their symptoms (e.g., smoking, secondhand smoke, drinking alcohol, insecticide/insect repellent use, and softener use) [26]. Thus, the above-mentioned findings may reflect the results of avoiding chemical exposure, and these were presumed to be the cause of the symptom worsening in the subjects with EHS and patients with MCS. For the use of drugs (q4.10), the proportion of BA group was significantly highest, followed that of the MCS group with significance, which may imply that the patients with BA and those with MCS use drugs for treatment purposes.

In summary of the results, it was suggested that the patients with MCS and subjects with EHS were more intolerant to multiple environmental factors such as chemicals, other compounds, and EMF sources, and had

more severe symptoms and less chemical exposures than the patients with BA and the controls.

Comparison between the MCS and EHS groups

On the basis of the above-mentioned tendencies of the difference between the four groups, we focused on the differences between the patients with MCS and the subject with EHS, and between the patients with BA and the controls. Between the MCS and EHS groups, we found that the scores in most of the items for chemical and other intolerances, biological allergen intolerances, and life impact were not significantly different. However, EMF intolerances were significantly higher in the EHS group than in the MCS group, which suggests that EMF intolerances are specific subjective symptoms of subjects with EHS. This tendency observed in this study was similar to the previous study [36]. Among the EMF sources that the subjects with EHS presumed as being related to their own symptom triggers, q65 Telecommunication masts had the highest median score (4; Fig. 2f). Meanwhile, among the EMF sources presumed by the patients with MCS as being related to their own symptom triggers, q58 Computers (2) and q59 Electrical appliances (2) were identified as having a higher median score, which were clearly different from the EMF source presumed by the subjects with EHS. This result suggests that many cases of EHS included in this study consider the relationship between the symptoms and EMFs from telecommunication masts.

In terms of symptoms, no significant difference was observed between the MCS and EHS groups for most items. This tendency may suggest the similarities of symptoms between MCS and EHS. The similarities of the symptoms and environmental hypersensitivity between MCS and EHS were reported in a previous study from Europe [13]. The tendency observed in this study was consistent with this study. Meanwhile, health condition and a few mental symptoms tended to be worse in the MCS group than in the EHS group, with a significantly lower score for d1 Well-being and a significantly higher score for d5.1 Feel blue in the MCS group, in addition to good health (significantly lower score for d2) and sleep (significantly lower score for d3.1). This tendency may be because the patients with MCS were outpatients undergoing treatment.

Comparison between the BA and control groups

In terms of environmental intolerances, the scores of the BA group in several items (mainly chemical related), namely q1.2 Tobacco smoke; q1.3 Insecticides; q1.5 Paint or paint thinner; q1.6 Cleaning products; q1.10 New furnishings; q2.7 Alcohol in small amounts; q2.8 Fabrics, jewelry, creams, and cosmetics that touch skin;

q2.9 Adverse reactions to drugs or medications; q2.10 Classical allergic reactions; q5.5 Ability to drive or travel; q5.6 Choice of personal care products; q5.7 Ability to be around others and enjoy social activities; and q68 Detailed description, were significantly higher than those of the controls. These environmental factors may trigger or worsen the symptoms of patients with BA. The score for q70 Frequency of static electricity was significantly lower in the BA group. This tendency may be due to avoidance of the materials that induce symptoms contributing to the reduction of the frequency of static electricity.

Regarding symptoms, the scores in several items were significantly higher in the patients with BA than in the controls, namely q3.2 Airway mucous membranes, q3.9 Skin, c2 Skin-related, c6 Allergy-related, c7 Sensory, and c8 Heart/chest-related. These symptoms might reflect the symptoms of BA or other allergies. In addition, these symptoms may include environmental intolerances other than allergic reaction. To elucidate the relationship between environmental factors and the symptoms of patients with BA, further study would be necessary, such as classification of patients with BA according to questionnaire results and comparison using demographic and clinical characteristics (age, gender, onset age of BA, immunoglobulin E (IgE) antibody, eosinophil count, severity, atopic type, non-atopic type, etc.).

Exceedance proportions of the screening criteria for environmental hypersensitivity/intolerance

Exceeding the screening criteria is considered to represent environmental intolerances abstractly. Using the QEESI and EHS questionnaire simultaneously, information on the proportion of suggestive environmental intolerances for either or both MCS and EHS was obtained. Similarly to the above-mentioned tendency, both the MCS and EHS groups had higher exceeding proportions of the screening criteria for MCS and EHS, which suggests that MCS and EHS were complicated by each other (complication proportion: 45.8% in the patients with MCS and 47.3% in the subjects with EHS). Overlap in prevalence between various types of environmental intolerance has been reported [37]. Belpomme and Irigaray [13] reported that 30% of EHS cases were associated with MCS in France. The proportion of 47.3% was higher than that in the previous study, and the difference was attributed to the difference between the countries and/or organizations. In addition, the BA group had higher exceeding proportion for MCS and EHS (18.8% and 13.0%, respectively) than the controls (6.1% and 3.8%, respectively), which suggests that the patients with BA included subjects with environmental intolerances much more than the general population. This suggests that

29.5% of patients with BA may have MCS or EHS. Moreover, 9.6% of the controls may have either MCS or EHS, and 0.9% of the controls may have both MCS and EHS. These proportions were considered to be an approximate scale in the patients with BA and general population who described environmental intolerances. Therefore, preventive measures would be necessary for MCS/EHS. However, whether the underlying etiology is common between MCS and EHS has not been fully elucidated. Thus, we should clarify the common etiology of environmental sensitivities/intolerances and consider preventive measures, including health care and environmental improvement, on the basis of the evidence of common and specific etiologies of each environmental sensitivity/intolerance.

Limitations of the study and future challenges

This study had limitations. First, because the 1,313 control subjects in this study were not randomly sampled, selection bias may have occurred. Second, some of the subjects with EHS or MCS wrote, as additional comments, about the difficulty of undergoing medical examinations or treatments owing to hypersensitivity to the EMFs from medical devices (e.g., MRI and radiography) in addition to the nine EMF sources listed in the EHS questionnaire. Therefore, EMF sources in medical fields should also be taken into consideration. Furthermore, with the rapid development of information technology equipment, the electromagnetic environment surrounding us may have changed drastically; thus, consideration of the effects from these new EMF sources would be necessary. Finally, in the EHS questionnaire, information regarding the frequency or level of electromagnetic exposure was not covered; thus, the relationship between electromagnetic exposure and hypersensitivity was not analyzed. In addition, regarding electromagnetic exposure, many researchers have suggested the presence of a placebo effect [38, 39]. Therefore, in the future, the relationships between EHS, electromagnetic exposure, and psychological effects must also be considered.

Conclusions

This study compared the environmental intolerances of the MCS, EHS, and BA groups, and the general population using the QEESI and EHS questionnaire. In summary of the results, it was suggested that the patients with MCS and subjects with EHS were more intolerant to multiple environmental factors such as chemicals, other compounds, and EMF sources and had more severe symptoms and less chemical exposures than the patients with BA and general population. Only the scores related to electromagnetic hypersensitivity were

significantly higher in the EHS group than in the MCS group. Meanwhile, the patients with MCS may have some worse symptoms and more chemical exposure than the subjects with EHS. In addition, the patients with BA were suggested to be more intolerant to several chemicals and other compounds than the general population. Considering the increase in environmental hypersensitivity/intolerance worldwide, elucidation of the etiology of these conditions is urgent, and further clarification is thus necessary for the actual situation of patients with environmental hypersensitivity/intolerance using questionnaires that include items on multiple environmental factors.

Abbreviations

BA	Bronchial asthma
EHS	Electromagnetic hypersensitivity
MCS	Multiple chemical sensitivity
QEESI	Quick Environmental Exposure and Sensitivity Inventory
SBS	Sick building syndrome
AOR	Adjusted odds ratio
IQR	Interquartile range
OR	Odds ratio
EMF	Electromagnetic field
THI-D	Total health index-depression

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12302-023-00735-2>.

Additional file 1: Table S1. Demographics, 95% confidence intervals of odds ratios or adjusted odds ratios, and p-values for comparison between the four groups. Table S2. Scores in the Quick Environmental Exposure and Sensitivity Inventory, adjusted odds ratios with 95% confidence intervals, and p-values for comparison between the four groups. Table S3. Scores in the electromagnetic hypersensitivity questionnaire, adjusted odds ratios with 95% confidence intervals, and p-values for comparison between the four groups. Table S4. Exceedance proportion of the screening criteria for environmental hypersensitivity/intolerance, adjusted odds ratios with 95% confidence intervals, and p-values for comparison between the four groups.

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Author contributions

Conceptualization, AM, SH and KA; methodology, AM, SH and KA; formal analysis, AM, SH and KA; investigation, SH, MM, MM, HO, NT and CO; resources, SH, MM, MM, HO, NT and CO; data curation, AM and SH; writing—original draft preparation, AM and SH; writing—review and editing, AM, SH, KA, MM, MM, HO, KS, NT, CO and JO; visualization, AM and SH; supervision, SH; project administration, SH All authors read and approved the final manuscript.

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Availability of data and materials

All datasets used and/or analyzed during the current study are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the research ethics committee of Morioka National Hospital (No. 24-01), the Environmental Center of Oita University (No. 304), Sagamihara National Hospital (No. 6), Shokei Gakuin University (No. 2020-2), and Kindai University Faculty of Medicine (No. R02-185). Informed consent for the survey was obtained from all the subjects in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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