ORIGINAL ARTICLE

Exploring the contributing factors to multiple chemical sensitivity in patients with migraine

Keisuke Suzuki[1] | **Madoka Okamura[1]** | **Yasuo Haruyama[2]** | **Shiho Suzuki[1]** | **Tomohiko Shiina[1]** | **Gen Kobashi[3]** | **Koichi Hirata[1]**

[1]Department of Neurology, Dokkyo Medical University, Tochigi, Japan

[2]Integrated Research Faculty for Advanced Medical Science, Dokkyo Medical University School of Medicine, Tochigi, Japan

[3]Department of Public Health, Dokkyo Medical University School of Medicine, Tochigi, Japan

Correspondence
Keisuke Suzuki, Department of Neurology, Dokkyo Medical University, 880 Kitakobayashi, Mibu, Shimotsuga, Tochigi 321-0293, Japan.
Email: keisuke@dokkyomed.ac.jp

Abstract

Objective: Multiple chemical sensitivity (MCS) is a form of chemical intolerance in which various systemic symptoms are triggered by exposure to a variety of chemical substances. Although migraine has been associated with central sensitivity syndrome, the relationship between MCS and migraine has not been studied. We assessed the frequency of MCS and its related factors in patients with migraine.

Methods: We performed a cross-sectional study that included 95 patients (14 M/81 F; age, 45.4 ± 12.4 years) out of 100 consecutive patients with migraine from our outpatient headache clinic. MCS was defined as having a combination of Q1 ≥ 30, Q3 ≥ 13, and Q5 ≥ 17 on the quick environment exposure sensitivity inventory (QEESI; Japanese version). Central sensitization inventory-A scores >40 were considered an indication of central sensitization. Headache-related disability and psychological distress were evaluated with the Migraine Disability Assessment score (MIDAS) and Kessler Psychological Distress Scale (K6), respectively.

Results: MCS was identified in 20% of patients with migraine; however, none had previously been diagnosed with MCS. The MCS-positive group had higher rates of photophobia, osmophobia, visual aura, sensory aura, and central sensitization and higher MIDAS and K6 scores than the MCS-negative group. A logistic regression analysis showed that osmophobia, sensory aura, and central sensitization were significant contributors to MCS.

Conclusion: We showed that MCS was observed in 20% of patients with migraine, and our study results may indicate a possible association of MCS with central sensitization and hypersensitivity-related symptoms in patients with migraine.

K E Y W O R D S
headache-related disability, hypersensitivity, migraine, multiple chemical sensitivity, stress

1 | INTRODUCTION

Multiple chemical sensitivity (MCS), known as chemical intolerance or toxicant-induced loss of tolerance, is a medical condition in which various systemic symptoms, such as persistent headache, fatigue, and muscle pain related to low concentration, slight fever, and abnormal sensations, are triggered by exposure to many chemical substances with high reproducibility.[1-3] A web-based survey including 7245 adults in Japan showed that 7.5% of adults suffered from chemical intolerance.[4] MCS has been reported to overlap with fibromyalgia, which is a disease that has been related to central sensitivity syndrome (CSS) and involves hypersensitivity of the central nervous system.[1] Other diseases that have been suggested to have an association with CSS include restless legs syndrome, migraine, irritable bowel syndrome, depression, and chronic fatigue syndrome.[5]

We recently reported that symptoms related to CSS were significantly associated with pain severity, pain interference with daily activities, and depressive symptoms in 551 patients with various neurological, psychological, and pain disorders in a multicenter setting.[6] In patients with migraine, the presence of CSS, as assessed by the central sensitization inventory (CSI),[5,7] was shown to be associated with comorbid restless legs syndrome and pain-related interference.[8] The CSI is a widely used, reliable, validated questionnaire-based assessment for central sensitization.[9] Patients with migraine present with a variety of sensory sensitivities, including sensitivity to smell, light, and sound, and central sensitization is suggested to be involved in the chronicity of headache. In addition, considering that migraine has been associated with CSS, it is possible that the prevalence of MCS in patients with migraine may be high compared with healthy individuals and that MCS can be closely related to some clinical factors in patients with migraine. However, to our knowledge, no study has examined the relationship between MCS and migraine. The purpose of this study was to evaluate MCS in patients with migraine using a validated questionnaire and to identify the factors relevant to MCS.

2 | MATERIALS AND METHODS

We performed a cross-sectional study in a single-center setting. Migraine was diagnosed by headache specialists based on the International Classification of Headache Disorders, 3rd edition.[10] This study included 95 patients (14 M/81 F; age, 45.4 ± 12.4 years) out of 100 consecutive patients with migraine (16 M/84 F; age, 44.9 ± 12.4 years) from our single-center outpatient headache clinic; five patients were excluded due to incomplete data on MCS. In Japan, unlike in Europe and America, there is no formal system of medical referral, and a referral is recommended but not necessary. Patients living around our university hospital can choose whether they go to local clinics or our outpatient clinic.

The patients completed a questionnaire on habits including smoking, caffeine intake and alcohol consumption. The presence of various auras (visual, sensory, speech, and motor auras), accompanying symptoms, and hypersensitivity to light (photophobia), noise (phonophobia), and smell (osmophobia) was obtained from the patients' clinical records. For the MCS assessment, we used the quick environment exposure sensitivity inventory (QEESI; Japanese version),[11] which consisted of the following items: Q1, chemical intolerances; Q2, other intolerances; Q3, symptom severity; Q4, masking index; and Q5, life impacts. The QEESI has been validated in many languages and is widely used.[12] MCS was defined as having combinations of Q1 ≥ 30, Q3 ≥ 13 and Q5 ≥ 17, based on the latest cutoff values.[13] The Migraine Disability Assessment (MIDAS)[14] has been used to assess disability in daily life related to the incidence of headaches. Migraine days in the last 3 months and migraine severity were obtained from MIDAS A and B, respectively. The Kessler Psychological Distress Scale (K6) was used to assess psychological distress.[15] Central sensitization-related symptoms were assessed by the Japanese version of the CSI-A, which includes 25 items on somatic symptoms related to central sensitization (score, 0–100; 100 = worst).[7] CSI-A scores >40 were considered to be an indication of central sensitization. The CSI-B addresses 10 specific diseases that are self-reported as previously diagnosed and related to central sensitization, including restless legs syndrome, chronic fatigue syndrome, fibromyalgia, temporomandibular joint disorder, migraine or tension headaches, irritable bowel syndrome, MCS, neck injury, anxiety or panic attacks, and depression.

2.1 | Statistical analysis

Chi-square tests or Fisher's exact tests for categorical variables and Student's t-tests or Mann–Whitney U tests for continuous variables were used to compare MCS-positive and MCS-negative groups, where appropriate. Univariate logistic regression analyses related each factor with the MCS status of patients with migraine. Logistic regression analyses using likelihood ratio forward selection and age- and sex-adjusted methods were performed to determine contributing factors to MCS in patients with migraine.

A two-tailed p value <0.05 was considered statistically significant. IBM SPSS Statistics software version 26.0 (IBM SPSS, Inc., Tokyo, Japan) was used for statistical analysis.

3 | RESULTS

MCS was observed in 19 of 95 patients with migraine (20.0%). Self-reported central sensitization-related diseases from the CSI-B were as follows: restless legs syndrome, $n = 4$ (4.2%); chronic fatigue syndrome, $n = 2$ (2.1%); fibromyalgia, $n = 5$ (5.3%); temporomandibular joint disorder, $n = 10$ (10.5%); migraine or tension headaches, $n = 95$ (100%); irritable bowel syndrome, $n = 5$ (5.3%); MCS, $n = 0$ (0.0%); neck injury, $n = 7$ (7.4%); anxiety or panic attacks, $n = 13$ (13.7%); and depression, $n = 11$ (11.7%). Among these self-reported central sensitization-related diseases, anxiety or panic attacks (31.6% vs. 9.9%, $P = .017$) and depression (31.6% vs. 6.9%, $P = .003$) were found to be more prevalent in the MCS-positive group compared with the MCS-negative group. Frequencies of other diseases did not differ between the groups. In Table 1, there were no differences in the rates of smoking, caffeine intake, and alcohol intake between the MCS-negative and MCS-positive groups. The MCS-positive group had higher rates of photophobia, osmophobia, visual aura, sensory aura, and central sensitization and higher MIDAS and K6 scores than the MCS-negative group (Table 2). Migraine days in the last 3 months and migraine severity did not differ between the groups. In univariate logistic regression analysis, osmophobia, visual aura, sensory aura, MIDAS total scores, central sensitization, and K6 scores were related to MCS status (Table 3). Logistic regression analyses using likelihood ratio forward

selection and age- and sex-adjusted methods showed that the presence of osmophobia, sensory aura and central sensitization were significant contributors to MCS in patients with migraine (Table 4).

4 | DISCUSSION

This is the first study to investigate MCS in patients with migraine. We found that MCS was identified in 20% of patients with migraine by using the QEESI, and the MCS prevalence in our cohort was higher than that in the general population (7.5%).[4] Of note, none of these patients had previously received a diagnosis of MCS as assessed by the CSI-B, suggesting that the detection of MCS with the QEESI was much superior to the self-reported diagnosis by the CSI-B, and MCS may be underestimated in patients with migraine. We used the latest cutoff values for the QEESI (Japanese version) for MCS that yielded 82.0% sensitivity and 94.4% specificity.[13] The updated cutoff changes were mainly due to increased opportunities for exposure to various chemicals related to our social lifestyle changes.

We found MCS and central sensitization in patients with migraine. Central sensitization is a condition that results from alterations in the somatosensory system involving a shift from high- to low-threshold pain hypersensitivity. Both migraine and MCS have been speculated to be diseases related to central sensitization.[5] During central sensitization, increased activity in the primary somatosensory area was shown to be correlated with the intensity of pain, and the pons and thalamus are thought to have a specific role in the maintenance of central sensitization.[16] In our study, although headache-related disability, as evaluated by MIDAS total scores, was more severe in patients with MCS than in those without MCS, the MIDAS total score was not a determinant for MCS in the logistic regression analysis.

The MCS-positive group included more alcohol drinkers and smokers than the MCS-negative group, and an increase in the sample size may lead to a significant difference. We performed a logistic regression analysis of MCS in patients with migraine, adjusting for alcohol and smoking; however, alcohol and smoking were not relevant factors for MCS in our study. Although MCS individuals tend to avoid chemical exposure, the association of MCS with alcohol consumption and smoking has been shown to vary among studies.[17,18]

Our study showed that the K6 score was higher in the MCS-positive group compared with the MCS-negative group, thus suggesting that stress has a role in MCS in patients with migraines, although the K6 score did not remain as a significant contributor to MCS in the logistic regression analysis. Chronic stress is known to be a

TABLE 1 Differences in lifestyle habits in patients with migraine with and without MCS

	MCS negative (n=76)	MCS positive (n=19)	P value[a]
N (M/F)	11/65	3/16	1.000
Age (years)	44.9±13.1	47.5±9.3	0.415[b]
Smoking, n (%)			0.158
Never	68(89.5)	14(73.7)	
Past	6(7.9)	3(15.8)	
Current	2(2.6)	2(10.5)	
Caffeine, n (%)	71(93.4)	15(78.9)	0.075
Alcohol intake, n (%)			0.772
Never	41(53.9)	10(52.6)	
<1 day/week	26(34.2)	5(26.3)	
1–2 days/week	5(6.6)	2(10.5)	
3–5 days/week	3(3.9)	1(5.3)	
6–7 days/week	1(1.3)	1(5.3)	

Abbreviation: MCS=multiple chemical sensitivity.

[a]Using Fisher's exact test.

[b]Using Student's t-test.

	MCS negative (n = 76)	MCS positive (n = 19)	P value[a]
Accompanying symptoms, n (%)			
Nausea	46(60.5)	15(78.9)	.134
Photophobia	56(73.7)	19(100.0)	**.010**[b]
Phonophobia	52(68.4)	17(89.5)	.066
Osmophobia	38(50.0)	16(84.2)	**.007**
Allodynia	13(17.1)	5(26.3)	.346[b]
Aura, n (%)			
Visual aura	29(38.2)	13(68.4)	**.018**
Sensory aura	13(17.1)	9(47.4)	**.012**[b]
Language aura[c]	6(8.1)	3(15.8)	.382[b]
Migraine onset age (years)[c]	19.3 ± 8.7	16.8 ± 5.9	.262
MIDAS total score	9.4 ± 13.9	17.3 ± 9.3	**<.001**[b]
Migraine days in the last 3 months[c]	22.5 ± 22.4	28.9 ± 20.2	.059[b]
Migraine severity[c]	5.7 ± 2.6	9.8 ± 17.1	.208[b]
Central sensitization, n (%)	13(16.9)	11(57.9)	**<.001**[b]
K6 score	4.3 ± 4.7	8.8 ± 6.1	**.002**[b]

TABLE 2 Clinical characteristics of patients with migraine with and without MCS

Abbreviations: K6, Kessler Psychological Distress Scale; MCS, multiple chemical sensitivity; MIDAS, Migraine Disability Assessment.

[a]Using chi-square test or Student's t-test.

[b]Using Fisher's exact test or Mann–Whitney U test.

[c]Statistics excluded missing values for language aura (n = 2), migraine onset age (n = 5), migraine days (n = 2), and migraine severity (n = 6).

Statistically significant values (P < .05) are shown in bold.

major trigger for migraines due to a hyperalgesic state related to central sensitization or through the activation of N-methyl-d-aspartate receptors or opioid receptors.[19] Limbic systems are brain regions that participate in the processing of fear, stress reactivity, learning, and memory. Stress-related symptoms that accompany the headache are linked to limbic processes, and repetitive psychosocial stress may make the limbic system more susceptible, thus triggering migraine attacks.[20] In fact, the MCS-positive group was found to be related to more severe headache-related disability and higher stress compared with the MCS-negative group in our study.

In our cohort, MCS was associated with several important features of migraine involving hypersensitivity, such as photophobia, osmophobia, and visual and sensory aura statuses. Cortical hyperexcitability may increase the probability of the development of cortical spreading depression, which has been implicated in migraine auras,[21] whereas the increased excitability of trigeminal neurons may facilitate peripheral and central sensitization.[22] In migraineurs, altered functional connectivity between brainstem pain-modulating circuits and the limbic cortex, including the amygdala, which facilitates pain perception through the sensory cortex and plays a role in fear conditioning and

stress responsiveness, has been described.[23] Patients with MCS showed significantly higher metabolism in the bilateral olfactory cortices than healthy controls during the resting state.[24]

As MCS is commonly triggered by olfactory stimulation, involvement of olfactory systems in the pathophysiology of MCS has been suggested.[25] Chemically sensitive individuals are more likely to react to suprathreshold olfactory stimulation than healthy subjects.[26] Individuals with electromagnetic hypersensitivity have been reported to have greater odor and noise intolerance than healthy controls.[27] Nonmigraine individuals with MCS reported greater perceived odor intensities and more unpleasantness following exposure to odorants than controls.[28] In contrast, it has been reported that several odors, such as perfume, rose, and Japanese cypress, were more offensive to patients with migraine than to healthy controls.[29]

The limitations of the study included the small sample size, the inability to evaluate the association between MCS and headache onset and the lack of healthy controls. The background of this study differs from that of general population studies; although referral is not mandatory, there may be a selection bias in that some patients have intractable headache because of the specialized outpatient

TABLE 3 Factors related to MCS in patients with migraine

	Crude odds ratio	95% CI	P value[a]
Sex, female vs. male	0.903	0.225–3.619	.885
Age, years	1.018	0.976–1.061	.411
Smoking			
Never	Ref		
Past	2.429	0.542–10.890	.246
Current	4.857	0.630–37.453	.129
Caffeine, yes vs. no	0.264	0.063–1.101	.068
Alcohol intake			
Never	Ref.		
<1 day/week	0.788	0.242–2.568	.693
1–2 days/week	1.640	0.277–9.721	.586
3–5 days/week	1.367	0.128–14.567	.796
6–7 days/week	4.100	0.236–71.357	.333
Accompanying symptoms, yes vs. no			
Nausea	2.446	0.740–8.079	.142
Photophobia	n/s		
Phonophobia	3.923	0.839–18.353	.083
Osmophobia	**5.333**	**1.435–19.817**	**.012**
Allodynia	1.731	0.530–5.649	.363
Aura, yes vs. no			
Visual aura	**3.511**	**1.202–10.261**	**.022**
Sensory aura	**4.632**	**1.480–12.85**	**.008**
Language aura[b]	2.125	0.479–9.420	.321
Migraine onset age[b] (years)	0.961	0.896–1.030	.261
MIDAS total score	**1.037**	**1.001–1.075**	**.042**
Migraine days in the last 3 months[b]	1.012	0.991–1.034	.262
Migraine severity[b]	1.067	0.945–1.204	.294
Central sensitization, yes vs. no	**6.663**	**2.243–19.799**	**<.001**
K6, score	**1.158**	**1.054–1.273**	**.002**

Abbreviations: K6, Kessler Psychological Distress Scale; MCS, multiple chemical sensitivity; MIDAS, Migraine Disability Assessment.

[a]Using univariate logistic regression analysis.

[b]Statistics excluded missing values for language aura ($n = 2$), migraine onset age ($n = 5$), migraine days ($n = 2$), and migraine severity ($n = 6$).

Statistically significant values ($P < .05$) are shown in bold.

clinic at the University hospital. In our study, the patients' work or professional statuses may have influenced their

TABLE 4 Factors related to MCS in patients with migraine ($n = 87$)

	Odds ratio	95% CI	P value
Forward selection			
Osmophobia	4.511	1.028–19.791	.046
Sensory aura	5.946	1.617–21.869	.007
Central sensitization	6.116	1.755–21.308	<.001
Age- and sex-adjusted			
Osmophobia	5.038	1.147–24.57	.033
Sensory aura	5.609	1.504–20.918	.010
Central sensitization	7.152	0.917–26.681	.003

Note: Logistic regression analysis was performed with a likelihood ratio forward selection model and an age- and sex-adjusted method.

Independent variables used in the likelihood ratio forward selection model included age, sex, caffeine, smoking, alcohol, nausea, photophobia, phonophobia, osmophobia, allodynia, visual aura, sensory aura, language aura, MIDAS total score, MIDAS A, MIDAS B, and CSI and K6 scores

stress, but this was not investigated. Indoor air problems and other environmental issues were also not assessed. Moreover, the diagnosis of MCS was not made by using face-to-face interviews but by using questionnaires. However, the validity of the questionnaire (QEESI) used in this study has been well verified.[13] Further prospective studies with larger sample sizes will clarify the detailed associations between MCS and migraine and treated course of MCS. In conclusion, our study showed that MCS was observed in 20% of patients with migraine, and the results indicated significant associations of MCS with central sensitization and hypersensitivity-related symptoms in patients with migraine.

DISCLOSURE

This study was approved by the institutional review boards of Dokkyo Medical University (approval number, 2020–016). *Informed consent*: all of the participants provided written informed consent to participate in this study. *Registry and Registration No. of the Study/trial*: N/A. *Animal Studies*: N/A. *Conflict of Interest*: the authors declared that they have no conflicts of interest.

AUTHORS CONTRIBUTIONS

KS, MO, YH, GK, and KH contributed to the study design. MO, SS, TS, and KH collected the data. KS drafted the manuscript. KS and YH analyzed the data. KH supervised the study. All the authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The relevant data are within the paper, but the data sets from this study are available from the corresponding author upon reasonable request.

ORCID

Keisuke Suzuki https://orcid.org/0000-0003-0320-8993

REFERENCES

1. Aaron LA, Buchwald D. Chronic diffuse musculoskeletal pain, fibromyalgia and co-morbid unexplained clinical conditions. *Best Pract Res Clin Rheumatol*. 2003;17(4):563-574. doi:10.1016/s1521-6942(03)00033-0

2. Miller CS. Toxicant-induced loss of tolerance–an emerging theory of disease? *Environ Health Perspect*. 1997;105(Suppl 2):445-453. doi:10.1289/ehp.97105s2445

3. Nethercott JR, Davidoff LL, Curbow B, Abbey H. Multiple chemical sensitivities syndrome: toward a working case definition. *Arch Environ Health*. 1993;48(1):19-26. doi:10.1080/00039896.1993.9938389

4. Azuma K, Uchiyama I, Katoh T, Ogata H, Arashidani K, Kunugita N. Prevalence and characteristics of chemical intolerance: a Japanese population-based study. *Arch Environ Occup Health*. 2015;70(6):341-353. doi:10.1080/19338244.2014.926855

5. Mayer TG, Neblett R, Cohen H, et al. The development and psychometric validation of the central sensitization inventory. *Pain Pract*. 2012;12(4):276-285. doi:10.1111/j.1533-2500.2011.00493.x

6. Suzuki K, Haruyama Y, Kobashi G, et al. Central sensitization in neurological, psychiatric, and pain disorders: a multicenter case-controlled study. *Pain Res Manag*. 2021;2021:6656917. doi:10.1155/2021/6656917

7. Tanaka K, Nishigami T, Mibu A, et al. Validation of the Japanese version of the Central Sensitization Inventory in patients with musculoskeletal disorders. *PLoS One*. 2017;12(12):e0188719. doi:10.1371/journal.pone.0188719

8. Suzuki K, Suzuki S, Haruyama Y, et al. Central sensitization in migraine is related to restless legs syndrome. *J Neurol*. 2020;268(4):1395-1401. doi:10.1007/s00415-020-10295-7

9. Scerbo T, Colasurdo J, Dunn S, Unger J, Nijs J, Cook C. Measurement properties of the central sensitization inventory: a systematic review. *Pain Pract*. 2018;18(4):544-554. doi:10.1111/papr.12636

10. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders. 3rd edition, Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202

11. Hojo S, Kumano H, Yoshino H, Kakuta K, Ishikawa S. Application of quick environment exposure sensitivity inventory (QEESI) for Japanese population: study of reliability and validity of the questionnaire. *Toxicol Ind Health*. 2003;19(2–6):41-49. doi:10.1191/0748233703th180oa

12. 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(3–4):370-385. doi:10.1177/074823379901500311

13. Hojo S, Mizukoshi A, Azuma K, Okumura J, Mizuki M, Miyata M. New criteria for multiple chemical sensitivity based on the Quick Environmental Exposure and Sensitivity Inventory developed in response to rapid changes in ongoing chemical exposures among Japanese. *PLoS One*. 2019;14(4):e0215144. doi:10.1371/journal.pone.0215144

14. Stewart WF, Lipton RB, Whyte J, et al. An international study to assess reliability of the Migraine Disability Assessment (MIDAS) score. *Neurology*. 1999;53(5):988-994. doi:10.1212/wnl.53.5.988

15. Furukawa TA, Kawakami N, Saitoh M, et al. The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. *Int J Methods Psychiatr Res*. 2008;17(3):152-158. doi:10.1002/mpr.257

16. Lee MC, Zambreanu L, Menon DK, Tracey I. Identifying brain activity specifically related to the maintenance and perceptual consequence of central sensitization in humans. *J Neurosci*. 2008;28(45):11642-11649. doi:10.1523/JNEUROSCI.2638-08.2008

17. Dantoft TM, Nordin S, Andersson L, Petersen MW, Skovbjerg S, Jorgensen T. Multiple chemical sensitivity described in the Danish general population: Cohort characteristics and the importance of screening for functional somatic syndrome comorbidity-The DanFunD study. *PLoS One*. 2021;16(2):e0246461. doi:10.1371/journal.pone.0246461

18. Heinonen-Guzejev M, Koskenvuo M, Mussalo-Rauhamaa H, Vuorinen HS, Kaprio J, Heikkilä K. Noise sensitivity and multiple chemical sensitivity scales: properties in a population based epidemiological study. Article. *Noise and Health*. 2012;14(60):215-223. doi:10.4103/1463-1741.102956

19. Sauro KM, Becker WJ. The stress and migraine interaction. *Headache*. 2009;49(9):1378-1386. doi:10.1111/j.1526-4610.2009.01486.x

20. Stankewitz A, Keidel L, Rehm M, et al. Migraine attacks as a result of hypothalamic loss of control. *Neuroimage Clin*. 2021;32:102784. doi:10.1016/j.nicl.2021.102784

21. Hadjikhani N, Sanchez del Rio M, Wu O, et al. Mechanisms of migraine aura revealed by functional MRI in human visual cortex. *Proc Natl Acad Sci USA*. 2001;98(8):4687-4692. doi:10.1073/pnas.071582498

22. Srikiatkhachorn A, le Grand SM, Supornsilpchai W, Storer RJ. Pathophysiology of medication overuse headache–an update. *Headache*. 2014;54(1):204-210. doi:10.1111/head.12224

23. Maizels M, Aurora S, Heinricher M. Beyond neurovascular: migraine as a dysfunctional neurolimbic pain network. *Headache*. 2012;52(10):1553-1565. doi:10.1111/j.1526-4610.2012.02209.x

24. Alessandrini M, Micarelli A, Chiaravalloti A, et al. Involvement of subcortical brain structures during olfactory stimulation in multiple chemical sensitivity. *Brain Topogr*. 2016;29(2):243-252. doi:10.1007/s10548-015-0453-3

25. Viziano A, Micarelli A, Pasquantonio G, Della-Morte D, Alessandrini M. Perspectives on multisensory perception disruption in idiopathic environmental intolerance: a systematic review. *Int Arch Occup Environ Health*. 2018;91(8):923-935. doi:10.1007/s00420-018-1346-z

26. Das-Munshi J, Rubin GJ, Wessely S. Multiple chemical sensitivities: a systematic review of provocation studies. *J Allergy Clin Immunol*. 2006;118(6):1257-1264. doi:10.1016/j.jaci.2006.07.046

27. Nordin S, Neely G, Olsson D, Sandstrom M. Odor and noise intolerance in persons with self-reported electromagnetic hypersensitivity. *Int J Environ Res Public Health*. 2014;11(9):8794-8805. doi:10.3390/ijerph110908794

28. Andersson L, Claeson AS, Dantoft TM, Skovbjerg S, Lind N, Nordin S. Chemosensory perception, symptoms and autonomic responses during chemical exposure in multiple chemical sensitivity. *Int Arch Occup Environ Health*. 2016;89(1):79-88. doi:10.1007/s00420-015-1053-y

29. Saisu A, Tatsumoto M, Hoshiyama E, Aiba S, Hirata K. Evaluation of olfaction in patients with migraine using an odour stick identification test. *Cephalalgia*. 2011;31(9):1023-1028. doi:10.1177/0333102411410612