Review

Chemical Sensitivity-The Frontier of Diagnosis and Treatment

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Abstract

The history of chemical sensitivity (CS) concept is quite old; it was established in the 1950s as part of the environmental illness. Following this, in the beginning of 1980s various respiratory symptoms with induced inhalation, such as perfume inhalation, were identified through many reported cohort studies. Thereafter, CS was relabeled as multiple chemical sensitivity (MCS). This was introduced in Japan in the 1990s, but standardized diagnostic criteria or diagnostic guidelines were not yet established at the time. However, despite the presence of CS symptoms in patients, the actual pathogenesis has not yet been developed, and the management of this condition will differ significantly depending on the medical institution. As a biggest season for that, we would like to report on the considerable difficulty in establishing the causal relationship between exposures to small amounts of chemical substances in the environment compared to large amounts. Therefore, establishing and standardizing highly specified objective diagnostic parameters is required. In this paper, we propose a scientific approach to the management of CS, by introducing the latest developments in diagnosis and treatment and provide insight into requirements for future study.

《**Key words**》 chemical sensitivity, olfactory stimulation, olfactory response, psychological-somatic symptoms, methods of objective examination

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Ⅰ Introduction

Chemical sensitivity (CS) is considered to be a syndrome causing a variety of indefinite complaints due to contact with a very small amount of chemicals in the surrounding environment.

The definition by Cullen MR[1] from Chicago University is general and concludes as follows: "Group of clinical syndromes which are observed after re-contact with the chemical substances of a fairly small amount and the same quality as chemical substances being in contact with the patient over a long period or caused poisoning symptoms in the past." In other words, a patient develops hypersensitivity to the chemicals such that exposure to very small amounts in future may cause a reaction.

The main symptoms include the following: 1) mucous membrane irritation such as airway hyper-reactivity; 2) headache, and dizziness, such as a somatoform autonomic dysfunction and nausea; 3) neuropsychiatric symptoms and 4) worsening of existing allergies. Although there are a wide variety of organs being influenced differently, olfactory hypersensitivity is observed in the majority of cases.

In addition, similarities to chronic fatigue syndrome and fibromyalgia have been reported; some scholars have even described it as the condition of the Gulf War syndrome[2]. Many uncertainties regarding the relationship between a very small amount of chemical substance revelation and various malaises, but the psychosomatic stress caused by the syndrome may significantly affect the psychosomatic relation and the course-outcome of this disease. It is important to evaluate appropriately the influence of different stress factors on the patient's daily life[3]. The diagnosed cases were studied in detail from the standpoint of psychosomatic medicine; regarding the onset, the possibility that psychosocial stress may also influence the symptoms along with chemical substances was suggested, but the personality characteristics or stress coping-style were not taken into account. It was assumed that those who developed the disease did not have specific tendencies. However, after a variety of mainly physical symptoms were observed, it was found that, in many cases, the disease co-exists with mental illness. That is to say that there is a close relation between the body and the psychological condition[3]. In this paper, we summarize the latest trends on unknown medical aspects of this disease, and we organized them to assist in developing measures for the future.

Ⅱ Pathophysiology

In Japan, a recent large-scale epidemiological study reported[4] that about 7.5% of the population has CS. Meggs WJ from the University of South Carolina reported that 35% of the population is diagnosed with allergies, and 14% of these allergic patients have CS in the United States[5], with similar statistics in Japan. Regarding the pathophysiology, there are still many unknowns, and the rate of bronchial asthma, allergic rhinitis, and atopic dermatitis co-existing with any of the allergic diseases such as urticaria is very high at about 60-80%, which is much higher than the rate of 30% for typical allergic diseases in Japan[6]. Consequently, the pathophysiologically relevant responses of the immune system to the allergic reactions were suggested as follows[7]: 1) the critical form, 2) skin, mucous membrane symptoms, and 3) the effect of cause avoidance of substances. These are the same for the CS disease and allergy. In other words, immune sensitivity is strongly associated with individual susceptibility at the disease onset. Additionally, this disease is characterized by olfactory hypersensitivity symptoms[8, 9], the limbic system relation and characteristic dysfunctions as expressed by patients[10]. Thus, it is easy to imagine that CS depends to some extent on the genetic or biochemical individual differences in chemical metabolism. Based on this information, Matsuzaka et al studied the genetic background and 7 enzymes to understand the difference in detoxification enzymes of people who were exposed to environmental chemicals and had not contracted the disease, but they found

none[11]. However, a recent study investigated patatin-like phospholipase (PNPLAs) genes which may influence the evaluation of sensitivity. The neuropathy target esterase (NTE) enzyme belonging to the PNPLA6 gene family code is present in the nervous system (in the brain) and the immune system (in lymphocytes); it is involved in choline production and related to the delayed impact of organophosphates. In tracing exposure to environmental chemicals, there is a difference in enzyme activity between the group of people who developed the symptoms and those who did not, and a tendency was found that the enzyme activity of Peripheral Blood Mononuclear Cells (PBMCs) was high in people in the highly sensitive group[12]. Moreover, regarding finding a genetic polymorphism associated with NTE enzyme activity, the result of the correlation analysis between NTE enzyme activity and NTE genetic polymorphism in preparative lymphocytes from peripheral blood indicated that the population with the genotype A/A in the genetic polymorphism (rs480208) which exists in intron21 of the NTE gene had significantly lower NTE enzyme activity12). Regarding the pathogenesis, the molecular biological approach is expected to be developed in the future.

Ⅲ Clinical symptoms

Agricultural chemicals, exhaust gas, building materials, products and furniture made with building materials, volatile organic compounds of daily necessities, combustion gas or heating, daily necessities (styling agents, perfumes, and softener), and others are included among substances that cause symptoms. Any contact with even an extremely small amount of the substances listed above, which are tolerated by healthy people, may cause symptoms for people who have CS. Reactive symptoms include olfactory hypersensitivity, including irritation of the eyes, nose, and throat, erythema, itching of the skin, easy fatigue, headaches, poor concentration, dizziness, nausea, and others; there are also a variety of non-specific symptoms along with autonomic symptoms[13]. In severe cases, those with CS may also exhibit strong neuropsychiatric symptoms. Standardized diagnostic criteria and diagnostic guidelines have yet to be established, but using the "Chemical Sensitivity: Agreement of 1999" is convenient[14]. After ruling out other organic diseases which could explain varying symptoms, the following six items are left:

(1) The symptoms are reproducible with (repeated chemical) exposure.
(2) The condition is chronic.
(3) Low levels of exposure (lower than previously or commonly tolerated) result in manifestations of the syndrome.
(4) The symptoms improve or resolve when the irritants are removed.
(5) Responses occur to multiple chemically unrelated substances.
(6) Symptoms involve multiple organ systems.

The paper to which Miller refers[15] as the Quick Environmental Exposure Sensitivity Inventory (QEESI) is used for auxiliary diagnosis. Scoring includes subjective symptoms (100 points), intolerance scores against chemicals (100 points), and a masking score (10-point scale); forty points and 4 points, respectively, are the cut-off values. This is suitable for obtaining information about the resistance against symptoms and chemical appeal of patients, and is useful for the initial diagnosis as well as to understand the conditions elapsed.

Ⅳ Clinical examination

Although auxiliary diagnosis for CS already exists, objective examination leading to definitive diagnosis of the disease is not yet present. However, based on the fact that many patients complain of unpleasant symptoms due to "olfactory hypersensitivity", evaluation methods of the olfactory pathway and limbic system in the brain have attracted recent attention. Azuma et al[16] compared the variation of cerebral blood flow rate during odorous substance reaction in patients with CS using common olfactory test kits and near-infrared spectroscopy (NIRS)

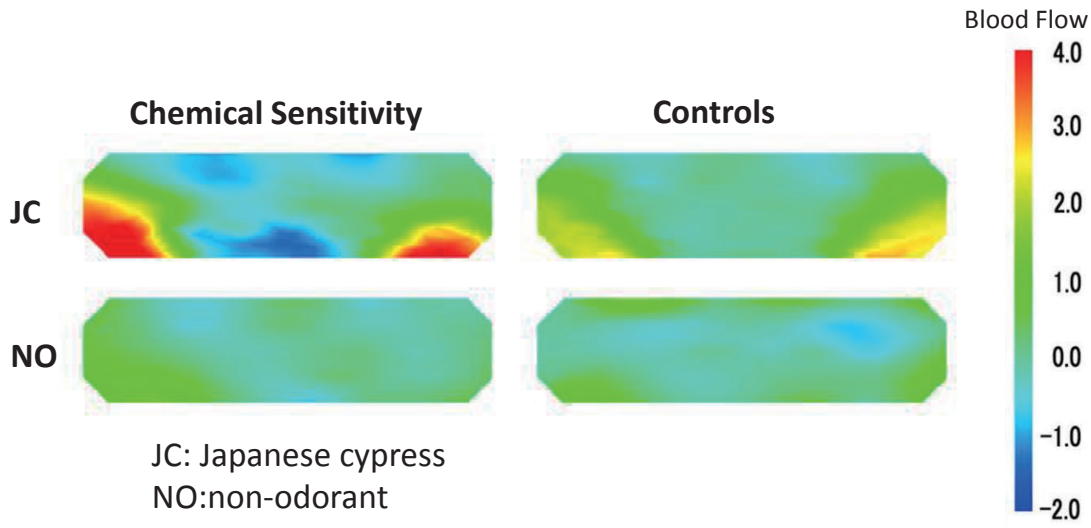

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Figure 1

(Figure 1). In patients with CS, the site of brain blood flow at the time of recovery is when odorous substance is loaded, load at the time of the prefrontal cortex (PFC), recovery at the time of the orbitofrontal cortex (OFC); it has been proven that this part has been strongly activated in patients with CS compared to healthy individuals. Additionally, according to Chiaravalloti et al[17], the glucose consumption in the cerebral cortex of each part during olfactory stimulation, has revealed different patterns in patients with CS and healthy individuals.

Ⅴ Course, treatment and prognosis

There are many examples of poor prognosis in CS. In particular, regarding occupational exposure, if a history of poisoning symptoms in response to the high concentration of chemical exposure is present then the prognosis is poor; a long period of time from the first visit to the avoidance of chemical exposure results in a poor prognosis. As noted above, since there are many unknown aspects of the pathophysiology, specialized treatments for this disease have not been established. At the moment, the most effective remedy is to avoid the causative agent that is believed to induce symptoms. Since there is a high co-existence rate of allergic disease with CS, it is also necessary to enhance the QOL to fully control the allergic symptoms. In addition, since the co-existence rate of mental illness with CS is as high as 80%, a psychosomatic and psychiatric approach is also effective[3].

Ⅶ Future prospects

CS usually presents as a reaction to a small amount of chemicals which would not induce any toxicological effects. It is generally a disease exhibiting the various symptoms, as defined

above. In addition to the diversity of developmental factors, and the onset of symptoms and severity, a method for diagnosing the disease is still being established. Since it is the "small amount effect" of chemicals, because of the so-called concept of addiction, it is difficult to describe the conditions (dose-response relationship); additionally, individual differences are considerable at the same time and certain tendencies for the patient are difficult to understand. In this paper, the disease was generally described in the following question-answer form, which is the subject theme of pros and cons: 1) Can CS be considered as a chemical hypersensitivity, a mental illness, or otherwise? 2) Do the chemical exposure and appearance of symptoms match? 3) Can the allergic mechanisms incidentally be explained? 4) Do differences exist in gene analysis? We focused on these questions and others.

According to recent research, 1) in groups of patients and healthy people, there is a possibility that differences from the brain physiology point of view may appear, so, for the future, it is very important to deepen the knowledge of the psychosomatic approach if possible, and, 2) when this disease is treated from the immunological aspects, the relationship between some immune responses, mainly pathophysiologically allergic reactions, are strongly suggested to be clarified; 3) individual differences cause chemical sensitivity; it can be mentioned that genetic factors (genomic information) are deeply involved, so, in the future, focused basic research is required with respect to these points, as it would allow for the promotion of interdisciplinary clinical research.

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Reference

1) 1) Cullen MR. The worker with multiple chemical sensitivities: an overview. OccupMed:State Art Rev 2: 655-662, 1987
2) Reid S, Hotopf M, et al. Multiple chemical sensitivity and chronic fatigue syndrome in British Gulf war veterans. Am J Epidemiol 153: 604-609, 2001
3) Saito M, Kumano H, et al. Symptom profile of multiple chemical sensitivity in actual life. Psychosomatic Med 67: 318-325, 2005
4) Azuma K, Uchiyama I, et al. Prevalence and characteristics of chemical intolerance: a Japanese population-based study. Arch Environ Occup Health 70: 341-353, 2015
5) Meggs WJ: Mechanism of allergy and chemical sensitivity. Toxicol Indust Health 15: 331-338, 1999
6) Hojo S, Ishikawa S, et al. Subjective and objective characteristics of patients with multiple chemical sensitivity in Japan.-sex, age, onset factors, allergy, subjective symptoms, and objective symptoms-. Jpn J Clin Ecol 16: 104-116, 2007 (written in Japanese)
7) Graveling RA, Pilkington A, et al. A review of multiple chemical sensitivity. Occup Environ Med 56: 73-75, 1999
8) Ojima M, Tonori H, et al. Odor perception in patients with multiple chemical sensitivity. Tohoku J Exp Med 198: 163-173, 2002
9) Hillert L, Musabasic V, et al. Odor processing in multiple chemical sensitivity. Hum Brain Mapping 28: 172-182, 2007
10) Gilbert ME. Does the kindling model of epilepsy contribute to our understsnding of multiple chemical sensitivity?. Ann New York Acad Sci 933: 68-91, 2001
11) Matsuzaka Y, Kikuti YY, et al. Association study between sick building syndrome and polymorphisms of seven human detoxification genes in the Japanese. Environmental Toxicol Pharmacol 29: 190-194, 2010
12) Matsuzaka Y, Ohkubo T, et al. Association of sick building syndrome with neuropathy target

esterase (NTE) activity in Japanese., Environmen. Toxicol. 29: 1217-1226, 2014
13) Hojo S, Ishikawa S, et al. Clinical characteristics of physician-diagnosed patients with multiple chemical sensitivity in Japan. Int J Hyg Environ Health 211: 682-689, 2008
14) Multiple chemical sensitivity: a 1999 consensus. Arch Environ Health 54: 147-149, 1999
15) Miller CS, Prihoda TJ. The environmental exposure sensitivity inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. Toxicol Ind Health 15: 370-385, 1999
16) Azuma K, Uchiyama I, et al. Assessment of cerebral blood flow in patients with multiple chemical sensitivity using near-infrared spectroscopy--recovery after olfactory stimulation: a case-control study. Environ Health Prev Med 20: 185-194, 2015
17) Chiaravalloti A, Pagani M, et al. Cortical activity during olfactory stimulation in multiple chemical sensitivity: a 18F-FDG PET/CT study. Eur J Nucl Med Mol Imaging 42: 733-740, 2015

要約

化学物質過敏症の疾患概念の歴史はかなり古く、1950年代では、環境病（Environmental illness）の一つとして、概念的に捉えられていた。その後、1980年代に入り、化学物質曝露により主として呼吸器症状を呈した後，　香水などの吸入に誘発されて多彩な症状を呈する一群の症例が数多く報告され、化学物質過敏症、あるいは多種化学物質過敏症（Multiple Chemical Sensitivity, MCS）と命名された。本邦においても、1990年代に紹介されたが、未だ標準化された診断基準・診断ガイドラインの作成・確立までには至っていない。しかしながら，化学物質過敏症状を訴える患者が存在することは明らかであるにも関わらず，その病態解明が未だ進展していないために，取り扱う臨床家・医療機関によって患者への対応は大きく異なっているのが実状である。 その最大の理由として，環境中の大量ではなく，極めて微量な化学物質との因果関係の証明が非常に困難であることがあげられる。そのため特異度の高い客観的な診断パラメータの抽出とその標準化が不可欠となっている。そこで本稿では、化学物質過敏症に対する脳科学的アプローチはじめとして、本症に関する診断と治療の最新動向を紹介し、今後のあるべき方策について提案した。

《キーワード》化学物質過敏症、嗅覚刺激、嗅覚応答、心身相関、客観的検査法