

Clinical aspects of allergic disease

Provocative challenges in patients with multiple chemical sensitivity

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Whether multiple chemical sensitivity (MCS) is an organic disease initiated by environmental exposure or a psychologic disorder is a subject of controversy. The identification of pathophysiologic or psychophysiologic mechanisms occurring in patients with MCS after provocative challenges should be illuminating. Fifteen patients with MCS were challenged with their trigger substances and observed clinically. Prechallenge and postchallenge pulmonary function tests and P_{CO_2} , P_{O_2} , and oxygen saturation were measured. All of the patients whose symptoms were reproduced by the challenge (11 of 15) showed clinical evidence of acute hyperventilation with a rapid fall in P_{CO_2} and no change or a rise in oxygen saturation. The symptoms and signs were consistent with an anxiety reaction with hyperventilation. Pulmonary function was unchanged; and recovery was rapid, aided in two cases by rebreathing into a paper bag. The most logical conclusion is that in these patients the MCS disorder is a manifestation of an anxiety syndrome triggered by their perception of an environmental insult, with at least some of their symptoms induced by hyperventilation. (*J Allergy Clin Immunol* 1997;99:438-42.)

Key words: Multiple chemical sensitivity, hyperventilation, anxiety reaction, psychosomatic

Patients who respond to a chemically diverse variety of olfactory and other common environmental stimuli with characteristic symptoms that are associated with normal results of physical examination and laboratory tests are often described as having "multiple chemical sensitivity" (MCS),¹ also called environmental sensitivity and other appellations. Although the problem may develop slowly over many years, many patients identify a specific occupational or environmental exposure (e.g., to volatile solvents) as the initial trigger of the problem.² Eventually, they experience an increasing number of symptoms caused by an ever-expanding array of low-concentration common stimuli, which inhibit their social and occupational function.

There is vigorous debate about the pathophysiology of MCS. Some claim that patients with MCS react directly to their trigger stimuli because of some unidentified physiologic abnormality induced by previous chemical

Abbreviations used

DBPC:	Double-blind, placebo-controlled
MCS:	Multiple chemical sensitivity
SaO ₂ :	Oxygen saturation

exposure.³ As a result, they require "special" testing and therapeutic methods,³ which are considered to be unproven by most orthodox organizations.^{4,5} Others claim MCS is a psychologic syndrome and cite psychometric or psychoanalytic testing evidence.⁶⁻⁸ In the latter, a completely different management approach would be necessary.⁹ Objective reproducible physiologic data (in contradistinction to unorthodox tests or psychometric testing) would be very useful in resolving this controversy.

The most frequent symptom complex experienced by patients with MCS comprises lightheadedness, impaired mentation, poor coordination, paresthesia, breathlessness without wheezing, headache, tremor, sweating, and abdominal discomfort.^{1,2} These same symptoms are those reported by patients with multiple, atypical non-IgE-mediated food sensitivities.^{10,11} When these patients with MCS underwent double-blind, placebo-controlled (DBPC) food challenge, they reacted similarly to the challenge food and to the placebo, proving that the putative sensitivities were subjective only,^{10,11} and probably psychosomatic.^{11,12}

In contradistinction to the above, it is difficult to determine whether patients with MCS have "real" sensitivity by using DBPC challenges. Nevertheless, two DBPC studies were reported. In one study¹³ the authors claim the data support the conclusion that patients with MCS responded to blinded chemicals more than placebo, but in fact, 99.4% of the authors' chemical challenges produced no reaction, which contradicts their conclusion. Staudenmayer et al.¹⁴ performed DBPC challenges in 20 selected patients with MCS and showed that they reacted similarly to self-identified chemicals and to unoffensive, disguised placebo. Such a study cannot be performed in the many patients with MCS who claim to be sensitive to all scents or who attest (with support from their alternative physicians) that their sensitivities change frequently.

It has been postulated but not proven that the most common symptom complex in MCS is due to anxiety-induced chronic or acute hyperventilation,¹¹ which produces very similar symptoms.^{11,15,16} To test this hypoth-

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esis we proposed to challenge some patients with MCS with some of their self-identified triggers in an open experiment to determine whether the challenge would induce clinically observed hyperventilation and documentable diagnostic changes in blood gases.

METHODS

Patients claiming to have MCS were referred by Workers' Compensation Board, by disability insurance carriers, or by their physicians for consultation concerning the possible allergic basis of their symptoms. The experimental protocol was approved by the Hospital Ethics Committee. Twenty-five patients were seen; and they fulfilled Cullen's criteria for the disorder,¹ with the exception of the requirement for an identified initial inciting exposure, which is not considered a necessary criterion by most authorities. Nineteen of the 25 patients described a symptom complex suggestive of hyperventilation syndrome, with breathlessness in the presence of normal pulmonary function, lightheadedness, impaired mentation, depersonalization, incoordination, and paresthesia. In addition, some had headache, trembling, sweating, and abdominal distress. (The other six had a different pattern of symptoms, most typically hoarseness and "throat closing.")

Fifteen of these 19 patients consented to the challenge procedure. All had previously been examined and had normal laboratory test results for complete blood count, erythrocyte sedimentation rate, blood glucose, serum creatinine, alkaline phosphatase, aspartate aminotransferase, sodium, potassium, chloride, CO₂, and urinalysis, as well as normal pulmonary function test results and chest x-rays.

The patients were asked to list some of the products that they had perceived to cause the most immediate and dramatic symptoms. From this list, we selected one or two common domestic products for the challenge test. They were advised that we would do pulmonary function tests and arterial blood gas measurements (patients 1 and 2) or end-tidal PCO₂ and oximeter measurements (subsequent patients) before and after the challenges. End tidal PCO₂ measurements were made by using an Ohmeda CO₂ monitor (model 5200), and transcutaneous oxygen saturation (SaO₂) determination was done by using an Ohmeda Bi, OX 370 pulse oximeter. Each instrument was standardized against arterial blood controls. The challenge was not started until a steady-state PCO₂ had been established (except in cases 1 and 2).

The challenge procedure varied with the substance being tested. For example, when scented hair spray was used (French Formula, Nestelmar), it was directed 45 cm above the patient's head for 20 seconds. Patient 3's challenge involved leafing through the *Yellow Pages* of a 6-month-old telephone directory. The challenges were conducted in a 7 × 7 m closed room. Exposure was planned for a maximum of 15 minutes or less, but in all subjects who reacted exposure was terminated before 15 minutes. The author remained with the patient throughout the exposure and examined the patient before and after exposure.

CASE REPORTS

Patient 9

A 46-year-old nurse attributed the cause of her symptoms to daily exposure to nebulized albuterol solution in the emergency department. Over a year, she experienced cough, dyspnea, "brain fog," nausea, and retching caused by an expanding array of domestic and other smells but claimed that the residual presence of even minute quantities of albuterol, such as those

present on the uniform of someone who had been in a room where albuterol had been used, could induce symptoms. We attempted a single-blind experiment comparing her response to albuterol with her response to normal saline solution. In the initial challenge normal saline solution was nebulized vertically into the air, 1 m from the patient and 12 cm higher than the patient's head. Within 2 minutes she was breathing rapidly, retching, coughing, and sweating. She was taken to an adjacent room where she improved in 5 minutes. Postchallenge flow-volume curves were unchanged from prechallenge values. Reliable end-tidal PCO₂ measurements could not be obtained because of her distress.

Patient 10

A 54-year-old nurse attributed the onset of her symptoms of breathlessness, hoarseness, mental confusion, lightheadedness, weakness, and headaches to sterilizing surgical instruments with glutaraldehyde. Despite avoidance of this exposure, she gradually experienced more intense (but similar) symptoms caused by any smell. She identified three "attacks" prompting emergency department visits, which were caused by cigarette smoke, perfume, and hamburger smell, respectively. Physical examination on each occasion revealed breathlessness with no other abnormality. She remained in her home and avoided social intercourse. On the day of the challenge, results of physical examination and prechallenge flow-volume curves were normal. End tidal PCO₂ was 37 mm Hg, and SaO₂ was 98%. Her daughter was then asked to sit 2 m from the patient and smoke a cigarette. The patient began to hyperventilate. By the time that two thirds of the cigarette was consumed, the PCO₂ had fallen to 23 mm Hg, and SaO₂ had risen to 102. The patient stated that she felt as she had during her previous "attacks." The cigarette was extinguished. The patient could not rise from the chair. Results of chest examination were normal except for tachypnea. She was given a 1 L paper bag in which to breathe and recovered in 5 minutes, despite the persistence of cigarette smoke in the room. Repeat flow-volume curve was unchanged from prechallenge values.

RESULTS

Fifteen patients underwent open challenge with products they deemed to cause distressing symptoms. Patient 2 had diabetes that was under good control, and postchallenge blood sugar was normal. No other patients had evidence of preexisting metabolic, renal, or pulmonary disease. In patients 1 and 2 immediate prechallenge data are not available because they were first seen with distressing symptoms after accidental exposure. Both claimed to have been well before this exposure. Patient 1 had driven past a road that had been paved with asphalt 5 minutes before entering the hospital, and patient 2 experienced symptoms after entering the pulmonary function laboratory on perceiving the faint smell of sterilizing solution (she was not a medical professional and had not been sensitized to glutaraldehyde). The patients' age and sex, the challenge substances, the prechallenge and postchallenge symptoms and signs, and the time to develop symptoms are detailed in Table I. In each case results of the patient's physical examination were normal before challenge, except in patients 1 and 2 for whom a prechallenge examination could not be done. In 11 of the 15 cases, the challenge reproduced the

TABLE I. Patient characteristics and challenge results

Patient No.	Sex	Age (yr)	Challenge substance	Symptoms before	Major symptoms after	Duration of challenge (min)
1	M	35	Asphalt fumes*	Normal	Triad† & panic	3
2	F	49	Disinfectant smell*	Anxiety	Triad & palpitations	2
3	M	53	Telephone directory	Anxiety	Triad & panic	4
4	F	29	Nail polish remover	Normal	Triad & panic	5
5	F	37	Hair spray	Normal	Triad & crying	5
6	F	44	Disinfectant	Normal	Triad & weakness	5
7	F	49	Flour (tactile)	Normal	Triad & panic	2
8	M	53	New carpet	Normal	Triad & nausea	10
9	F	46	Nebulized saline solution	Normal	Triad & retching	2
10	F	54	Cigarette smoke	Hoarseness	Triad & weakness	6
11	F	49	Perfume	Anxiety	Triad & weakness	6
12	F	41	Perfume	Normal	Normal	15
13	M	51	Bath tub sealant	Normal	Normal	15
14	M	33	Aliphatic hydrocarbon solvent	Normal	Normal	15
15	F	60	Perfume	Normal	Normal	15

*Challenge occurred unintentionally before testing was done.

†Triad: Breathlessness without wheezing, light headedness, confusion with incoordination.

TABLE II. Blood and alveolar gas analysis

Patient No.	Pco ₂ before challenge	Pco ₂ before challenge	Sao ₂ before challenge	Po ₂ or Sao ₂ after challenge
1†	—	18*	—	104*
2†	—	20*	—	92*
3	22	13	98	99
4	38	22	—	—
5	39	32	98	100
6	37	29	97	104
7	30	20	94	98
8	37	27	96	98
9‡	37	—	97	—
10	35	21	97	99
11	29	20	98	99
12	35	35	99	99
13	32	30	100	100
14	37	37	98	98
15	35	33	98	98

*Arterial Pco₂ and Po₂ (other values by end-tidal Pco₂ and oximeter Sao₂).

†No prechallenge data: triggers experienced just before experiment.

‡Patient too distressed after placebo challenge. Experiment aborted.

symptoms described by the patient as being characteristic of his or her disease. After the challenge, each of these patients was observed to be breathing rapidly and deeply. Some showed tachycardia, pallor, tremors, and sweating but did not reveal evidence of upper or lower airway or pulmonary disease. Patients 1 and 2 had repeat blood tests (as noted in Methods) because of extreme symptoms. The results of these tests were normal.

Blood and alveolar gas analysis is noted in Table II. Patients 3, 7, and 11 had low prechallenge Pco₂. In 10 of 11 responding patients (with the exception of patient 9), the measured Pco₂ was lower (by 18% to 42%), and Sao₂ was higher or unchanged after challenge compared with prechallenge values. In no case was there any change in the flow-volume curve. All patients recovered

with no medication in 5 to 90 minutes and were able to return home. Rapid recovery was aided by breathing into a paper bag in the two cases in which it was used (cases 10 and 11).

In four patients (patients 12 to 15), the challenge produced no symptoms, and these patients showed no clinical abnormalities and no objective evidence of hyperventilation. Pco₂ and Sao₂ values were unchanged.

DISCUSSION

The patients described here are typical of many who have been labeled with the diagnosis of MCS and fulfill Cullen's criteria for this disorder, except for his requirement of an initial identified trigger.¹ In the 11 patients who responded to the challenge, their typical symptoms

were reproduced and were characteristic of symptoms described in MCS.¹ In these cases the challenge induced hyperventilation, which was observed clinically and confirmed by the demonstration of a rapid fall in the P_{CO_2} in blood or end-tidal gas and either no change or a rise in P_{O_2} or SaO_2 . Because these same symptoms and signs are those classically demonstrated to be a consequence of hyperventilation,^{15, 16} it is reasonable to conclude that hyperventilation is, at least in part, one of the mechanisms by which this group of patients develop their symptomatology. Indeed, the most common symptom of MCS, impaired mentation, often described as "brain fog," is to be expected in acute hypocarbia, which causes restriction of cerebral flow and decreased brain perfusion.¹⁷

As expected, there was a considerable variation among the patients' prechallenge P_{CO_2} values. Patients 3, 7, and 11 were clinically hyperventilating before the challenge, and may well be chronic hyperventilators,¹⁵ because they complained of constant lightheadedness and breathlessness. There was also variation in the extent of the fall in P_{CO_2} , but the rapidity of the decline on which symptoms are, in part, dependent was typical of the entire set of responding patients.

Could the rapid fall in P_{CO_2} have been due to some mechanism other than hyperventilation? Only one patient (patient 2 with diabetes) had preexisting metabolic disease, and her blood sugar was normal after challenge. None had performed strenuous anaerobic physical exercise. It would be very unlikely for other unknown metabolic disease, other than exposure to exogenous toxins (none of which had been identified here), to induce such a rapid onset of symptoms accompanied by such an abrupt fall in the P_{CO_2} with spontaneous rapid recovery in 11 patients who have nothing in common other than MCS.

The four patients for whom the challenge did not reproduce their characteristic symptoms did not hyperventilate, despite the fact that the challenge consisted of self-identified triggers in exposures more intense and longer than those described by the patients as causing symptoms.

Why do those patients who responded to the challenge hyperventilate? One might postulate a direct action on the central nervous system through an olfactory pathway. Such an effect could not relate to an idiosyncratic reaction to a particular chemical structure because the same reaction is reported by the patients in response to organic chemicals of very different structures, as well as inorganic molecules such as $HOCl$ or NH_4 . Indeed, the fact that individuals such as patients 2 and 3 react to unscented foods such as sugar and tap water, as well as to electromagnetic fields, and that others such as patient 7 react to tactile stimuli (in addition to odors) makes a direct neurophysiologic mechanism very unlikely. The concept that some unusual immune reaction is involved has been discarded.^{11, 18}

Other described causes of hyperventilation such as

acute physical trauma, pain, excessively bright lights or other massive stimuli, vigorous physical exercise, or metabolic abnormality (see above) were not present in these patients.

The logical explanation is that these patients respond to their putative environmental insults (whether scented, tactile, or electromagnetic) by experiencing an acute anxiety reaction.¹⁹ Some individuals, like patient 10, who avoid social interaction while sequestered in their "safe" homes, behave remarkably like agoraphobics²⁰; whereas others show features typical of triggered panic attacks.¹⁹ Hyperventilation manifested clinically by breathlessness without wheezing (classically the statement "I can't get enough air in my chest") is a component of anxiety and panic reactions,^{16, 19, 20} and the physiologic effects of hyperventilation induce some of the somatic symptoms described. Other physiologic responses to acute anxiety result in increased production of adrenal medullary and cortical hormones, which add to the somatic sensations and induce pallor, sweating, and tremulousness. We did not study our patients for these hormone changes. Finally, the rapidity with which symptoms develop on exposure and resolve when exposure ceases is most consistent with an acute anxiety reaction.

In the one patient, patient 9, in whom we were able to do a blinded challenge because her perceived environmental insult (albuterol) is odorless, dramatic symptoms were experienced after exposure to saline solution nebulized into the air 1 m from the patient. Her retching necessitated aborting the experiment before reliable end-tidal P_{CO_2} measurements could be made. There was no change in pulmonary function. This demonstration with rapid recovery is highly suggestive of an acute anxiety reaction.

The rapid decrease in symptoms in patients 10 and 11 on rebreathing their own CO_2 from the paper bag, despite the persistence of the trigger odors, indicates that the symptoms were not due to a toxic effect of the scent. An acute anxiety reaction accompanied by hyperventilation is a much more logical explanation.

It should be noted that patients who chronically hyperventilate for reasons of anxiety do not achieve adequate renal compensation by excretion of bicarbonate because they do not hyperventilate during sleep.¹⁵ Thus they experience the physiologic and somatic consequences of uncompensated hypocarbia.

We are not suggesting that anxiety-induced hyperventilation is the only psychophysiologic mechanism in MCS. Only 19 of our 25 patients had symptoms suggestive of hyperventilation. In others, trigger stimuli may induce globus hystericus (acute hoarseness and a feeling that the throat is swollen) or vasovagal or other psychosomatic reactions, as illustrated by the placebo-induced symptoms in patient 9. With well-designed challenge experiments it should be possible to demonstrate these other mechanisms. The study by Staudenmayer et al.¹⁴ provided strong evidence for a psychosomatic cause of MCS in the selected patients who were eligible for a DBPC challenge. Most of our patients claimed sensitiv-

ity to all odors or refused to commit themselves as to which scents they could consistently tolerate, which precluded a DBPC study. Thus our data does not rigorously prove an emotional cause for MCS. Nevertheless, the objective physiologic measurements are meaningful support for a mechanism that explains the generation of psychosomatic symptoms in many cases of MCS.

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