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Review Article

Multiple Chemical Sensitivity and Idiopathic Environmental Intolerance (Part Two)

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Abstract

Multiple chemical sensitivity/idiopathic environmental intolerance (MCS/IEI) is a commonly used diagnostic term for a group of symptoms without apparent organic basis. The symptoms are characteristic of dysfunction in multiple organ systems. They wax and wane fluctuate according to exposure to low levels of chemical agents in the patient's environment, and sometimes begin after a distinct environmental change or injury such an industrial accident or chemical introduced after remodeling. Although traditional medical organizations have not agreed on a definition for this syndrome, it is being increasingly recognized and makes up an increasing percentage of the caseload at occupational/environmental medical clinics.

Part two of this review article discusses diagnosis, clinical examination, long-term follow up of MCS/IEI, and the role of physicians, research on odor and treatment, diseases with similar symptoms, and further research regarding MCS/IEI patients.

Key words: multiple chemical sensitivity, idiopathic environmental intolerance, chemical intolerance, diagnosis, treatment

Introduction

Multiple chemical sensitivity/idiopathic environmental intolerance (MCS/IEI) has been postulated to be a disease unique to modern industrial society in which certain people are suggested to acquire high sensitivity to numerous chemically unrelated environmental substances. The patient experiences wide-ranging symptoms, but evidence of pathology or physiologic dysfunction in such patients has been lacking in studies to date. Due to the subjective nature of the illness, an objective case definition is problematic. Allergic, immunotoxic, neurotoxic, cytotoxic, psychologic, sociologic, and iatrogenic theories have been postulated for both etiology and production of symptoms, but there is an absence of scientific evidence to establish any of these mechanisms as definitive. This article reviews the literature on diagnosis, clinical examinations, treatment, and long-term follow up of MCS/IEI, and demonstrates the relation of MCS/IEI with the diseases having similar symptoms, such as psychiatric diseases, sick-building syndrome, chronic fatigue syndrome (CFS), fibromyalgia (FM), allergic diseases, and Persian Gulf War (PGW) syndrome.

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Abbreviations: CFS, Chronic fatigue syndrome; FM, Fibromyalgia; IEI, Idiopathic environmental intolerance; PGW, Persian Gulf War; MCS, Multiple chemical sensitivity; PTSD, Posttraumatic stress disorder.

Diagnosis of MCS/IEI

There are some difficulties in making a widely accepted diagnosis of MCS/IEI because MCS/IEI patients report that so many inhaled and ingested chemical stimuli elicit symptoms, and also because elicited symptoms vary markedly among individuals (1–3). Diagnosis of multiple chemical sensitivity relies heavily on subjective symptoms and typically not on objective clinical or laboratory findings (4, 5). Since there is no widely accepted definition, the controversy and confusion regarding the etiology of MCS/IEI translate into poor medical diagnosis and treatment for patients. In an earlier study reported by Gibson et al. (6), people with MCS/IEI reported seeing a mean of 8.2 physicians each, waiting 7.5 years for a diagnosis, spending a considerable amount of money on their health, receiving misdiagnoses, and suffering iatrogenic harm.

As defined by Cullen (7), MCS/IEI is "…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, and which cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with the symptoms (Table 1)". Some investigators (8, 9) have elected to enroll patients in their studies based upon Cullen's criteria for MCS/IEI. However, this definition excludes 'definable' clinical conditions, such as asthma, which was suggested to overlap with MCS/IEI, and asthma may also be exposure-induced and is commonly reported by patients with MCS/IEI. Kreutzer et al. (10) also suggested an association

Table 1 Definition criteria derived from Cullen (1987)

1	Initial symptoms occur following an idenitifiable environmental exposure(s) such as pesticide poisoning, respiratory tract irritation, or solvent intoxication.
2	Symptoms involve more than one organ system and almost always include the central nervous system.
3	Symptoms recur and abate in response to predictable stimuli, particularly perceived environmental exposure.
4	Symptoms occur in response to low-level exposure to multiple agents of varying structural classes.
5	The doses of these agents are at least two ordors of magnitude lower than the established thresholds for acute health effects.
6	Tests of physiologic function are unable to explain the symptoms.
7	The pattern of symptoms cannot be explained by any other organic disorder.

Table 2 1999 Consensus on multiple chemical sensitivity (1999)

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

between asthma and perceived chemical sensitivity.

As of 1993, five case definitions had been proposed (7, 11–14). The sixth definition, the 1999 consensus on multiple chemical sensitivity (Table 2), was recently published (15). This definition has been widely used in many studies papers for selecting MCS/IEI patients since its publication. McKeown-Eyssen, et al. (16) observed that good reproducibility regarding self-report of symptoms was shown in this case definition.

The role of physicians for MCS/IEI patients

Spark et al. (17) warned that the usual approach for diagnosing MCS/IEI requires time and resource-intensive evaluation by a physician trained in occupational and environmental medicine. Problems regarding the diagnosis by physicians were reported by Kreutzer et al. (10). Of the 253 people who reported doctor-diagnosed MCS/IEI, 109 people (43.5 percent) did not also report unusual chemical sensitivity. In addition, they found, among traditional physicians, the lowest rate of 5% (95% CI=3, 9) in otolaryngology clinics, an intermediate rate of 13% (95% CI=9, 17) in the allergy practice, and the highest rate of 27% (95% CI=20, 35) among occupational medical clinics. The rates found in at investigation may also have been inflated because the participating study physicians had greater than average interest in MCS/IEI syndrome and, therefore, may have attracted a relatively larger proportion of such patients. Kreutzer et al. (10) also suggested that clinical ecologists are more likely than traditional physicians to ask questions about chemical sensitivities because such sensitivities are central to their interest.

The evaluating and the treating physician must be wary of excessive ordering in addition to misinterpretation of diagnostic tests because these may reinforce a detrimental pattern of illness behavior (18). As with other types of unexplained symptoms, the primary physician should function as a gatekeeper and should order diagnostic tests primarily to identify the presence of other environmental or non-environmental illnesses in the differential.

Clinical examinations

The difficulty in adequately defining the group of patients with MCS/IEI-like symptoms has been attributed to the use of varied nomenclature, the heterogeneity of substances and symptoms reported, the lack of objective findings upon physical examination, and the lack of consistent abnormal diagnostic testing, including provocation testing (8, 19, 20). Thus, the diagnosis rests largely on self-reported symptoms.

Though most previous studies have tried to clarify the mechanisms, prevalence, or definition of MCS/IEI by conducting numerous kinds of questionnaires, several existing questionnaires focus only on one domain, such as the number of odorous chemical exposures that elicit symptoms or the frequency with which specific chemical odors cause illness (21, 22), and they do not attempt to include other facets of the illness. Other questionnaires propose idiosyncratic criteria (23). Others are long and are intended for hypothesis testing and, therefore, are not appropriate for screening (3). A recent formulation (10) proposes 15 questions, with a branching structure for the screening of "MCS/IEI sufferers in a medical setting," and it is defined in terms of 3 criteria: 〈1〉 physician-diagnosis of MCS/IEI, 〈2〉 self-assessed unusual sensitivity to chemicals, and 〈3〉 health problems which restrict the patient's daily activities. Hu et al. (24) also developed a parsimonious set of factors to screen for MCS/IEI that would allow greater applicability of such a screening instrument in population studies that have multiple objectives and that must employ a number of other questionnaires.

Other than questionnaires, some abnormal findings of MCS/IEI patients have been reported. Abnormal MRI (25), nasal abnormalities (26), damaged detoxification pathways (27), and pesticides in blood (13) have been found in some studies.

With regard to electric encephalography, Bell et al. (28) found that middle-aged women with chemical intolerance and associated lifestyle changes sensitize resting frontal alpha activity in the EEG in comparison with depressed and normal controls from one session to the next. Furthermore, chemical exposure can elicit acute changes

in the human EEG. Chronically solvent-exposed workers reportedly exhibit increased alpha and delta EEG activity immediately after a typical workday of relatively high level exposure (29). Locatelli et al. (30) also reported that panic disorder patients with symptoms of limbic dysfunction show an acute increase in EEG delta activity during odor exposure not seen in panic patients without limbic symptomatology or normal controls.

As for single photon emission computed tomography (SPECT), preliminary studies suggest that there may be significant but not clinically visible changes in brain SPECT images in individuals with MCS/IEI compared with controls (31). Callender et al. (32) also reported the effectiveness of brain metabolic SPECT scans in following the objective chronic central nervous system effects subsequent to acute insecticide exposure. Workers with long term mixed solvent exposure and neuropsychiatric symptoms have positron emission tomography (PET) evidence of increased brain dopamine synthesis (33). In contrast, neurologists and nuclear radiologists have cautioned against inappropriate use of brain imaging methods applied by Callender et al. (34).

Research on odor related to MCS/IEI symptoms

Some investigators have focused on an odor test as one of the most characteristic indices to diagnose MCS/IEI. Doty et al. (35) examined odor detection thresholds for two substances, irritant and non-irritant odorants, in MCS/IEI subjects and healthy controls. In two studies investigating the olfactory system in MCS/IEI patients, it was determined that MCS/IEI subjects do not detect odors at lower thresholds, although they may respond more markedly once odors are detected (35–36). The relation of this finding to other observations of nasal pathology and increased nasal resistance has remained unexplored, and pathologic findings require confirmation with controlled studies (26, 35, 37, 38). However, an MCS/IEI group exhibited higher nasal resistance and respiration rate both before and after testing.

In another study, MCS/IEI subjects did not demonstrate lower olfactory threshold sensitivities to irritant odors known as trigeminal irritation that elicits sensations by means of a common chemical sense served by cranial nerve V, and non-irritating chemicals, as the major component in rose oil, a common constituent of fragrances, or an enhanced ability to identify odors accurately. Furthermore, they were differentiated from other groups, such as chronic fatigue syndrome and fibromyalgia, in their symptomatic and esthetic ratings of non-irritating odors, but not irritants (39).

Previous studies (40) suggested that concerning symptoms which MCS/IEI patients exhibit, cognitive factors are involved which probably modulate odor perception, irritation and health symptoms in individuals who exhibit extreme sensitivity and do not adapt. Somatic symptoms may be acquired in response to odors (38).

As for the gender differences regarding odor perception, females as a group have lower detection thresholds than males (41). Women also score better on tests of odor identification (42–44) and long-term odor recognition (45). There are also differences between men and women with respect to ratings of odor intensity (46). Findings of gender differences in response to olfaction-related demand characteristics may have relevance to MCS/IEI. Female-biased gender differences are reported consistently in populations identified as suffering from MCS/IEI (47). These conditions are believed by some to be associated with odor exposure (3, 48, 49).

An increase in sensory detection acuity (particularly olfaction) in females was found to be most acute during the follicular phase of the menstrual cycle when estrogen levels are highest, and least acute during the luteal phase when estrogen levels are relatively low (50). Furthermore, studies have shown that hypogonadal women often have poor olfactory acuity which is significantly improved following estrogen administration (51, 52). Other possible reasons for the gender differences, such as differences in early learning, verbal ability, anatomy/physiology of nasal airways, and olfactory/neural pathways have also been suggested (43).

Although a sine qua non in pharmacological research, a placebo control has rarely, if ever, been used in studies of human olfactory response.

Research on the treatment of MCS/IEI patients

Basically, therapies for MCS/IEI syndrome have included restricted diets and avoidance of environmental triggers. Short-term removal from exposure to the environmental chemical of concern may have diagnostic value; this short-term removal may also have palliative value while interventions that are more suitable for long-term case management are arranged. People with MCS/IEI are generally advised to avoid places or situations in which they might encounter chemical fumes or odors (53, 54). This may prompt patients to move to locations they believe are less polluted, to quit work if they believe it contributes to their disorder, or to reduce their social interactions. In addition to avoidance, other treatments reported included special diets, vitamins and other supplements (e.g., antioxidants, essential fatty acids, garlic), primrose oil, the use of charcoal (or cotton) filter masks, special enemas/douches, oxygen per nasal cannula, and the use of neutralizing injections/sublingual drops. Clinical ecologists and alternative practitioners may recommend herbs and minerals to treat their patients by improving their tolerance of the environment (55). Some clinical ecologists postulated that MCS/IEI sufferers have deficits of essential cofactors or enzymes necessary for chemical detoxification; they prescribe dietary supplements, oxygen, antioxidants, or vitamins to repair such unproven deficiencies (7, 13, 53). Clearly allergic symptoms may respond to desensitization, bronchodilators, and other allergy medications; however, medication is rarely used as treatment by alternative practitioners. None of these types of treatment were prescribed on the basis of careful, controlled clinical trials. Odors and exposure to volatile organic compounds in the workplace and home, which are perceived as irritating or noxious by the symptomatic person, should be reduced and controlled as much as possible. Unfortunately, no therapy has been subjected to controlled clinical trials to confirm short- or long-term efficacy with these patients.

Some specialized hospital wings are constructed of less polluting construction materials and have a highly filtered air system. Organically grown food, bottled water, and specialized procedures are employed to minimize indoor air pollutants. This creates a safe environment for the stabilization, investigation, and treatment of chemically sensitive patients (56). A comprehensive treatment program was developed (57) that included avoiding chemical triggers, eating a rotational diet of organically grown foods, administration of immunotherapy antigens to reduce the extent and severity of allergies and sensitivities, environmental cleanup at home (using less toxic materials), and specific nutritional support to enhance detoxification ability to supply antioxidant

nutrients. Some outcome studies (58–60) have shown evidence of the efficacy of such comprehensive treatment programs for polysymptomatic patients who report chemical sensitivity. Maberly et al. (58) found positive results in the treatment of asthma in the controlled atmosphere and surroundings of the Environmental Control Unit, clearly demonstrating the adverse effects of certain food and chemicals on the peak flow rate. They also found successful and significant reduction of symptoms and medication use after treatment involving dietary modification and subcutaneous immunotherapy antigens to alleviate complex allergy and sensitivities (59).

Maberly et al. (60) also cited evidence of beneficial outcomes in polysymptomatic patients using a comprehensive environmental medical approach. These authors' experience parallels the improvement in symptoms reported by chemically sensitive and polysymptomatic patients treated at the Nova Scotia Environmental Medicine Clinic, in Halifax, Canada, a government-sponsored project. In an uncontrolled study of 85 patients reporting chemical sensitivity symptoms, scores were followed by the Nova Scotia Department of Health over 10 months of treatment. In addition to assessing the level of patient satisfaction with the services provided, symptom changes were carefully evaluated using pre- and post-treatment questionnaires. There were significant improvements in the scores for a number of symptoms using comprehensive environmental medical treatment; these included scores for mental confusion, fatigue, headache, and anxiety.

The limitations of such unblinded and uncontrolled global outcome measurements are obvious. Nevertheless, such information provides a starting point from which to pose more definitive questions. This pilot clinic has now been superseded by the Nova Scotia Environmental Health Clinic, a medical school-based research and treatment program that is also funded by the government of Nova Scotia. It is hoped that more answers will be forthcoming from well-designed clinical trials currently planned and underway.

Cognitive behavioral therapy for medically unexplained symptoms, not specifically including MSC, has been shown to be effective in two randomized trials, with a return-to-work rate of up to 70% in one study (61, 62). Guglielmi et al. (63) identified three MCS/IEI patients who met criteria for simple phobia and who were, at least initially, successfully treated by an intensive desensitization program consisting of biofeedback-assisted relaxation training, *in vivo* exposure to offending chemicals, and cognitive restructuring procedures.

Kipen et al. (64) reported that it has often not been found helpful to directly confront or debate whether chemicals could or could not cause the patients symptoms. Rather, as for any organic illness with a behavioral component (e.g., heart disease), they focus on coping strategies that will improve the quality of life and prevent disability. Specifically, they work collaboratively with the patients to develop prudent avoidance of those substances that cause the most symptoms, and practical guidance (e.g., ventilation, work breaks) to minimize exposure when the patients need to work or function. Although radical avoidance is inimical to enhancement of function at work, the ability to use judicious avoidance for control of regular and severe symptoms may foster a therapeutic relationship. Balancing the benefits of any avoidance measures with the potential risks of a spiraling pattern of progressively severe environmental restrictions and loss of employment is the ultimate challenge of the MCS/IEI patient who is still employed. Kipen and Fiedler (64) also work with patients to identify symptoms associated with fear or anxiety about exposure. The authors then used relaxation methods with or without biofeedback to address the anxiety responses. Overall, treatment was behavioral in nature, making use of both cognitive behavioral and physical relaxation techniques. Once litigation or a worker compensation claim has arisen, the prognosis for behavioral approaches to treatment is less optimistic. An approach to thinking through litigation issues according to the magnitude of the initiating stimulus has been previously outlined (65).

Practitioners who have a more psychologic view of MCS/IEI have tried to apply pharmacologic and behavioral techniques (65–67). Andine et al. (68) reported that a 53-year old man with depression suffered from MCS/IEI, and received the selective serotonin re-uptake inhibitor (SSRI) citalopram for treatment of depression. The treatment was successful and, in parallel to the remission of the depressive symptoms, all MCS/IEI symptoms vanished. They concluded that a subgroup of MCS/IEI patients may have atypical depression, that they should be psychiatrically evaluated, and that antidepressive pharmacological treatment may be considered in cases of MCS/IEI. One study (64) reported that, if psychiatric medication is used, it must be given at very low doses and then titrated up to give these patients time to adjust to potential side effects, which are anecdotally reported to be more problematic in these individuals and others with medically unexplained physical symptoms (63).

Long-term follow up of MCS/IEI patients

Although longitudinal findings are limited, a recent follow up of 18 subjects with MCS/IEI showed that 89% of MCS/IEI patients had improved since a baseline assessment 9 years earlier, five (28%) subjects had claimed remission, and only 2 patients (11%) were still impaired socially and psychiatrically; none had died (69). A 2-year follow up of 50 subjects with MCS/IEI showed that 96% were unchanged or worse at follow up (19). A 1.4-year follow up of 35 people seen in an occupational health clinic found that 46% reported improvement, although the subjects at that time had a mean of 7.4 more symptoms than they had at their initial evaluation (70). Thus, follow-up studies show that people with MCS/IEI frequently suffer symptoms for many years but may show gradual improvement over time. The condition has not been demonstrated to affect mortality.

Gupta and Horne (71) suggested that MCS/IEI patients who at the outset thought that their treatment should comprise complete avoidance of chemicals, regular monitoring and the use of alternative rather than conventional medicine were significantly less likely to achieve a favorable consultation outcome. Patients' chemical sensitivities treatment preferences were related to the more general beliefs on health, food and the harmful nature of chemicals and were not related to the chemical exposure variables.

Diseases with similar symptoms to MCS/IEI

Psychiatric disorders

One previous study (72) suggested that the incidence of significant psychiatric disease as a major causative factor in MCS/IEI is very low, probably less than 2% or 3%. Some studies also have ascribed vasospastic phenomena and dysautonomia in chemical sensitive patients to psychiatric diagnosis (23, 73), but the validity of these conclusions have been seriously questioned in a

recent critical review (74). These authors reviewed 10 studies considered to support a psychogenic origin for MCS/IEI. Some of their primary conclusions were that reporting multisystem complaints in the absence of physical findings is not sufficient evidence to purpose psychogenic origins, especially when MCS/IEI has not been subjected to rigorous scientific studies. More recent controlled studies suggest that chemically sensitive individuals have unique characteristics. They differ from depressive and/or normal subjects in measures such as resting electroencephalographic alpha patterns (75), polysomnographic sleep (76), performance on visual (77) and verbal memory (78) and divided-attention tests (79), and cardiovascular measures (80) as well as personal and family medical (cardiovascular disease, diabetes) and substance-abuse history findings (3, 81).

Levin and Byers (82) suggested that MCS/IEI has a psychological overlay that can distract health providers from the organic origins of the disease. For example, Morrow et al. (83) showed personality disturbance in solvent-exposed workers, and Dager et al. (84) discussed panic disorder as a result of exposure to organic solvents. Heuser et al. (25) noted that patients with systemic lupus erythematosus often exhibit psychiatric symptoms. They further suggested, on the basis of their findings of abnormal neurological functioning in a high percentage of MCS/IEI patients, that psychiatric symptoms exhibited in MCS/IEI may be neurologically based. In an attempt to separate physiological from psychological indicators, Bell et al. (81) examined self-reported illness from odors in a nonclinical population and found that it was predicted by physiological illnesses in close family members. Miller (85) made a cogent theoretical argument for the construal of chemicals as broad-based causal factors in illness, bolstering care with historical examples of medical findings that were ignored due to their failure to coincide with the then-current medical paradigms.

Many physicians have written against the practice of assuming a psychological origin for MCS/IEI (54, 57, 82); Ziem (54) reported that several of her patients were made worse by advice not to worry about chemical exposure. Research also suggests an excess of symptoms of psychologic distress consistent with anxiety and depression in many but not all MCS/IEI patients (66, 73, 86). Tonori et al. (87) observed that significantly higher mean values of subjective anxiety and a depressive state were obtained in 18 MCS/IEI patients than in 18 controls for the follow-up patients, while no significant difference was obtained between MCS/IEI and controls of 30 new patients for each group. In addition, because of the high prevalence of MCS/IEI among people who were separated or divorced, and low-income, the symptoms experienced after exposure to triggered substances may not fit a purely psychogenic theory (88).

Psychiatric evaluation may be necessary for some patients diagnosed with MCS/IEI, given the high prevalence of coexisting psychiatric disorders in these patients. Unfortunately, many patients given a diagnosis of MCS/IEI resist the idea that psychologic factors may play any etiologic role in their distress, however, this should not necessarily be interpreted that the patient has primary psychiatric disorders in our society, but such disorders probably play a major role in the tendency to somatize. The adamant rejection of psychologic factors in symptom formation and expression by MCS/IEI patients is a challenge for physicians, who must establish a workable strategy for approaching this issue that is both sensitive to the patient's feelings and effective in exploring possible emotional contributors to the syndrome (18). For psychiatric evaluation to be most useful, it is necessary to ensure that the clinician is familiar with the subtle nature of the toxicologic controversities in MCS/IEI.

For those who are interested in assessing the contribution of psychological status to illness, longitudinal studies preceding symptoms of illness in high-risk populations are likely to be the most valuable strategy. A second, potentially useful, less-costly technique is the use of a case-control strategy that examines pre-existing objective evidence of psychopathology/mental health predating exposure and early symptoms of illness (e.g., psychiatric treatment histories, divorce rates, school failure, frequent absenteeism, and job assessment).

Sick building syndrome

In the field of occupational health, non-specific symptoms have been recorded in relation to a variety of long-term hazards. For example, during the 1970's the term "sick building syndrome" was created to describe a range of symptoms frequently reported by office workers. The main symptoms comprised headache and fatigue, concentration difficulties, mood disturbance, gastrointestinal problems and eye, skin, and upper airway irritation (89). Similar symptoms were identified in a large scale investigation of the health of civil servants employed in London office buildings (90). For example, most findings suggest that women report more symptoms than men (91, 92). These symptoms and the predominance of women are similar to those of MCS/IEI. Some authors thought sick building syndrome as a common risk factor for MCS/IEI in other studies (3, 93).

Chronic fatigue syndrome, fibromyalgia and allergic diseases

Subjective intolerance to low levels of environmental chemicals is a symptom of patients with polysystematic chronic conditions such as chronic fatigue syndrome (CFS) (94), fibromyalgia (FM) (94), and Persian Gulf War (PGW) syndrome (95, 96). Many studies have reported MCS/IEI symptoms as overlapping extensively with other illnesses, including somatoform disorders, CFS, FM, panic disorder and post-traumatic stress disorder (PTSD) (19, 23, 73, 84, 97, 98).

Despite self-reports of MCS/IEI patients that suggest heightened sensitivity and attribution of illness to chemical exposure, no objective tests have been developed to diagnose MCS/IEI or to differentiate MCS/IEI from other illnesses with similar features. For example, some asthmatic patients report respiratory symptoms in response to odors (65, 99, 100). In another study, both MCS/IEI patients and asthmatics reported higher levels of sensitivity to environmental exposure than a control group (22). They resemble MCS/IEI patients in their experience of environmentally induced symptoms, in their tendency to avoid certain environmental stimuli, and their female predominance (101). In a sample of 33 PGW veterans with CFS, 42% had concurrent MCS/IEI, and 6% had concurrent FM (102). In addition, Buchwald and Garrity (94) found that 30% of participants with MCS/IEI met criteria for CFS. Donnay and Ziem (103) studied a sample of 100 patients with MCS/IEI and found that 88% met criteria for CFS and 49% met criteria for FM.

Several disorders that appear to overlap with MCS/IEI are associated with altered functioning of the hypothalamic-pituitary-adrenal axis, including FM, CFS, PTSD, depression, and chemical intolerance, a hallmark feature of MCS/IEI (70, 104). Clauw and Chrousos (105) hypothesized that FM and CFS are a result of

dysregulation of the hypothalamic-pituitary-adrenal axis. Similar results were reported in FM and CFS as well as in patients with PTSD (106, 107). These findings may offer some support for dysregulation of the hypothalamic-pituitary-adrenal axis in MCS/IEI. Furthermore, Buchwald and Garrity (94) compared clinical findings for patients who met criteria for MCS/IEI, FM, or CFS (30 patients per group) and found that patients in these groups had strikingly similar health problems, and that the diagnoses patients received depended more upon their chief complaints and the types of physicians they saw than on the illness process itself.

Persian Gulf War syndrome

Between August, 1990 and June, 1991, approximately 697,000 USA and 53,462 UK military personnel were deployed to the Persian Gulf to serve in Operations Desert Shield and Desert Storm. Soon after the end of the Persian Gulf War (PGW), deployment during Operation Desert Storm led to medical complaints from many veterans collectively referred to as the "PGW Syndrome (108, 109)." These varied symptoms range from relatively minor complaints (e.g., skin rash and headache) to more profound problems, including cognitive dysfunction, chronic fatigue, bronchitis, asthma, FM, depression, PTSD, alcohol abuse, anxiety, and sexual discomfort (110, 111). Although the validity of the PGW syndrome is still being debated, it is clear that PGW veterans report more physical and psychologically based symptoms than do controls (108), and this syndrome is found in American as well as British Gulf War veterans (112).

An aberrant response to organic chemicals through airborne or other routes of exposure is one potential explanation for the symptoms reported by PGW veterans (113, 114). According to this hypothesis, exposure to oil and gas fumes or other chemical agents may be partly responsible for their complaints, which may represent a form of MCS/IEI. Many complaints of MCS/IEI are similar to those reported by PGW veterans.

MCS/IEI and CFS have been investigated by questionnaire surveys in previous studies of PGW veterans (111, 115, 116). Black et al. (117) observed that the prevalence of self-reported MCS/IEI symptoms of PGW veterans was significantly higher than that of non-PGW military personnel. In an epidemiologic study (118), 3.2 percent of PGW veterans believed or had been told that they had CFS, with 0.8 percent reporting MCS/IEI. The Iowan Persian Gulf Study Group (111) found that from 1 percent (regular military) to 2.9 percent (reservist) of PGW veterans reported symptoms of chronic fatigue as opposed to 0.2–1.1 percent in non-PGW veterans. Five percent of PGW veterans (2 percent in non-PGW veterans) reported symptoms of chemical sensitivity in the study by Fukuda et al. (115). They also interviewed a sample of the PGW veterans and, using the Centers for Disease Control and Prevention (CDC) criteria for CFS (119), estimated the prevalence at 5 percent. Kipen et al. (116) studied 1,161 members of the Veterans Affairs' Gulf Registry who responded to a questionnaire survey. Sixteen percent of the veterans reported symptoms of CFS, as defined by the CDC, and 13 percent reported symptoms of MCS/IEI.

Summary and problems in studying MCS/IEI

The results of many previous studies are limited by because subjects were selected without referral to normal controls and specific criteria for a definition of MCS/IEI. MCS/IEI was diagnosed after subjects completed the questionnaires and case reviews to determine adverse responses to environmental chemicals in the absence of other medical conditions that could explain these symptoms. In addition to the lack of a single case definition, several methodologic problems limit the interpretation of published MCS/IEI research (120). These problems include over-reliance on surveys and self-reported symptoms, selection bias, lack of blinding, and inconsistent quality assurance of laboratory determinations. Many proposed outcome measures also require validation. Definitive research on controlled challenge procedures using appropriate controls is necessary before these procedures can be recommended as tools for diagnosis (13, 121, 122).

As for the design of research on MCS/IEI, there appears to be several problems. Participants typically are recruited from a variety of clinical settings. Results from studies conducted in referral practices may not be generalizable to persons in the general community or patients in primary care settings (5). A number of cross-sectional studies are introduced for evaluating MCS/IEI, but only few longitudinal studies have been used. Thus, the statistical relations that have emerged should be viewed with caution and verified through longitudinal research. There is a need for additional research on MCS/IEI. In addition to double-blinded placebo-controlled testing of specific outcome measures of subjects under rigidly controlled conditions, there is a need to determine the actual prevalence and incidence of MCS/IEI in various populations in addition to changes over time (123).

In the area of psychiatry, patients acceptance of and compliance with psychiatric intervention is often poor (63, 124), and recruitment into formal intervention studies has been difficult (125). The Berlin workshop on MCS/IEI convened by the World Health Organization (WHO) recommended that high priority be given to challenge and distinguish psychogenic from toxicogenic or other responses, and that such studies are research prerequisites that must precede further mechanistic studies (126).

Further study

The Council on Scientific Affairs of the American Medical Association, the American College of Physicians, the American College of Occupational and Environmental Medicine, and other professional groups have all issued position papers that are openly skeptical of MCS/IEI as a distinct medical entity (127–129). They call for more scientific research into the tenets of clinical ecology and MCS/IEI in order to subject the numerous theories concerning these disorders to peer reviews of evidence-based, controlled investigation. Research is made more difficult because of the lack of objective findings; some patients claim that their chemical sensitivities may shift from one chemical agent to another without warning. This olfactory difficulty invoked by MCS/IEI sufferers makes the design of double-blind studies problematic.

American College of Occupational and Environmental Medicine (129) declared the following research agenda: limited research dollars and similarities between the nonspecific syndromes of CFS, FM, and MCS/IEI point to a need for a corporative research agenda. No assumptions should be made, however, that these conditions represent the same phenomenon. Research into societal factors that influence the prevalence and natural course of MCS/IEI should be high on this agenda.

As with research on any medical condition, consensus must be reached on a clear case definition that establishes diagnostic

criteria and specifies which individuals may be included in a study. Pending consensus on the case definition, researchers must describe the definition they have used in sufficient detail to be reproducible by other investigators seeking to confirm the published findings. Pathologic mechanisms leading to the development of this condition should be investigated. Of primary interest is further study of the influence concerning the central nervous system and the olfaction system on an organism's response to low-level chemical exposure.

Perhaps most importantly, research must focus on the efficacy and side effects of treatment modalities. Long-term outcomes of those treated by various modalities and those untreated must be examined.

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