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MINI REVIEW

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Multiple chemical sensitivities

Is there a scientific basis?

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The term multiple chemical sensitivity (MCS) describes a syndrome which is treated quite skeptically by the majority of scientists. Various editorials and comments have dealt with the subject [3, 8, 10, 15, 16, 24, 31]. The term MCS is attributed to Cullen [7]. A similar syndrome was postulated by Randolph and others, who developed the concept of clinical ecology [22]. Reports of comparable conditions were published already around the turn of the century. The synonyms are manifold and irrational [3, 10]: Twentieth century disease, total allergy syndrome, environmental illness, chemical AIDS, allergic toxemia, cerebral allergy, to name just a few.

MCS has been characterized as an acquired disease. According to the concept of clinical ecology various humans are unable to cope with the stress of today's exogenous influences. These exogenous influences are supposedly food, chemicals, and microorganisms, in particular *Candida albicans* [3]. Electromagnetic fields have also been accused of causing this syndrome [6]. Just as manifold as the terminology are the diagnostic criteria.

In a cross-sectional survey Nethercott evaluated the diagnostic criteria used most by physicians who are familiar with the syndrome [21]. Five major criteria were found:

1. The symptoms are reproducible on exposure.
2. The condition is chronic.
3. Particularly low concentrations of causative agents produce symptoms.
4. Avoidance of exposure leads to improvement or complete recovery of the symptoms.
5. The reactions appear subsequent to multiple exposure to chemically unrelated substances.

The complaints can basically be classified into three groups: (1) central nervous complaints, (2) irritative complaints, and (3) gastrointestinal complaints.

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Headaches, general weakness, loss of concentration, memory disturbances, eye irritations, cough, sore throat, diarrhea, and other unspecific complaints were described as the most symptoms. Ultimately though, any possible exogenous effect could cause any possible symptom in these sensitized individuals. This universalness of symptoms [13] impairs a clear definition of the clinical picture. According to the initial concept of clinical ecology, it is neither possible nor necessary to prove the symptoms by objective measurements (Cullen [7]: "No single widely available test of organ system function can explain symptoms.").

Opponents of the MCS theory explain all symptoms by classic phenomena of conditioning and psychological processes [10, 12, 27]. Attempts to compensate for the various kinds of environmental and occupational stress could intensify these symptoms. Examples of the various approaches to MCS with regards to clinical ecology can be found in Levin and Byers [18], with regards to orthodox medicine in the position paper of the American College of Physicians [1].

This syndrome is found typically in middle-aged, often well-educated women. Diagnostic procedures usually include immunological testing and toxicological analysis but reveal in nearly all cases only normal values. Typically, the patients reject the psychological, the physician the somatic etiology. Frequent change of doctor and renewed medical testing is the rule. Ultimately, many such patients turn to alternative medicine, whose representatives consider themselves competent in the diagnosis and treatment of this condition. Precise data regarding incidence and prevalence are missing.

Therapy consists basically of avoiding that presumed to be responsible for the condition, which can be evaluated by special provocation testing and treated by so-called neutralization procedures. Additionally, special diets, antioxidants, megadoses of vitamins, antimycotic drugs, enemas, sweating cures etc. are recommended.

It is remarkable that orthodox medicine has not succeeded in defeating the theory of MCS with widespread impact nor has clinical ecology been able to confirm its

theories on a scientific basis. The latter could be achieved basically via three different approaches: toxicology; immunology; and neurology, psychology, and psychiatry.

The toxicological approach

The concept of clinical ecology implies an extremely increased sensitivity of the individual against various chemical substances. As a rule of thumb, exposures below 1% of the allowed threshold values are said to release syptoms [7].

According to toxicological principles, a toxic effect of a single substance would have to be of the same quality as the effect on individuals with normal sensitivity, only at a lower dosage. Therefore, plausible effects characteristic for the respective agent could be expected.

Controlled scientific studies have failed to prove that chemical exposure in doses generally tolerated have reproducible effects: The analytic discourse of the formaldehyde problem is a good example in this context. As it has been calculated by Waddell [35] the total amount of formaldehyde utilized daily by an adult male in intermediary metabolism is about 58000 mg and therefore much larger than the quantity inhaled with polluted air. (For example, breathing ambient air at 0.2 ppm leads to a systemic formaldehyde exposure of 5 mg!) A systemic pathogenetic effect of formaldehyde is therefore rather unlikely. Further examples for a scientic-based answer to the question of the low-dosage effect of a single substance are the surveys of the possible toxicity of aspartame. By means of a placebo-controlles, double-blind survey of the FDA, as described in [34], it was possible to exclude a toxic effect of aspartame with regards to its use as a sweetener.

Even after multiple exposure it was impossible to successfully confirm a toxic cause. According to Cullen's definition of MCS, every aspect of the relationship between exogenous influences and symptoms has become generalized [7]. Ultralow dosages of multiple agents provoke multiple symptoms. However, the effects cannot be classified due to the lack of defined stress factors and symptoms, and so it is impossible to establish a dose-response relationship.

From the toxicological point of view, toxic effects have to be both measurable and reproducible but, according to the original definition of MCS, the diagnosis of MCS does not necessarily include measurements by objective methods. It should also be expected that low-level exposure will show effects after a latency period. Sudden occurrence of symptoms at the beginning of exposure strongly argues against a toxic cause of MCS. Sudden occurrence suggests more an irritative cause.

In the course of double-blind provocation testing, it was impossible to demonstrate a reproducible effect [29]; however, compared to the large number of patients with suspected MCS, the number of individuals subjected to the provocation testing was relatively small. Therefore, it could not be completely excluded that some individuals are located at the end of the Gaussian curve who have a significantly increased irritability.

One of the studies which revealed pathologic effects was that of Meggs et al. [20]. In fiberoptic examinations of the rhinolarynx, they demonstrated pathological findings in 10 patients with suspected MCS. This survey, though, is methodologically problematic since not all individuals were examined allergologically and 5 of 7 subjects examined were sensitized against inhalational allergens. Therefore it seems unlikely to conclude that enhanced irritability is the cause of these abnormalities.

According to present knowledge MCS cannot be explained by classic toxicology, and it must be said that toxicology does not have yet a convincing concept for evaluating a health risk by multiple chemical exposure. In addition, data on the effects of long-term, low-level exposures are relatively rare. This problem has been addressed with respect to MCS by Ziem and Davidoff [8].

The immunological approach

None of the theories which hold immunological or allergic phenomena responsible for the development of MCS could be proved [30, 32, 34]. The initial theory that chemical substances from the environment acting as haptenes produce immunoglobulin G (IgG)-antibodies and generate an inflammation by complement activation and mediator release could not be confirmed [23], nor was it possible to prove a change of the helper/suppressor cell ratio. It was also impossible to demonstrate reproducible pathological effects of free oxygen radicals in so-called MCS patients. Compared to controls, patients with suspected MCS had lower interleukin-1 levels [27], but the authors reported methodological problems as a possible explanation. The inconsistency of the immunological findings in MCS patients is obvious here. In a controlled survey, 41 individuals with so-called MCS were examined regarding their immune system and the presence of autoantibodies. There were no significant differences between patients and controls [27]. Thrasher et al. [33] found activation of the immune system after long-term inhalation of formaldehyde but they were not able to show a clear dose-response relationship.

Although a possible influence of various chemicals on immunological mechanisms has been suggested the results of experimental studies, there is still no definite evidence that a syndrome such as MCS does exist and that it is immunological mediated [19].

Provocation testing, if blinded, was unable to allow any conclusions in favor of MCS either. Staudenmayer et al. described a clinical algorithm devised to distinguish such hypersensitivity from psychological phenomena; however, reproducible hypersensitivity could not be recorded in double-blind inhalative provocation testing of 20 so-called MCS patients [29]. The authors stated explicitly that not necessarily all individuals who were hyperreactive to low-level chemical influences demonstrated psychopathological symptoms.

In a double-blind survey based on supposed food hypersensitivity it was impossible to evaluate significant

distinctions between reactions to placebo and provocation substances. A randomized, double-blind study of nystatin therapy in postulated *Candida* hypersensitivity syndrome failed to show any effect [14].

In conclusion, according to data published so far, the probability of an immunotoxic or allergic cause for MCS is very low.

The neurological, neurophysiological and psychiatric approach

Psychiatric symptoms are very common with MCS patients [3, 17, 28]. According to Schottenfeld [25] amplification of somatic symptoms may play a part in the genesis of so-called MCS. Besides evident correlation between preexisting psychological disturbances and somatic symptoms, Brodsky also shows the medicosociological dynamic of MCS [5], whereby dissatisfaction with and nonacceptance of psychological explanations suggest that the defect is internal rather than external to such patients.

The authors of a control study who examined immunological, psychological, and neuropsychological causes for MCS believe that preexisting psychological disturbances are relevant to the development of MCS [27].

A team of psychiatrists who examined an endemic outbreak in a plastic factory together with occupational medicine, immunology, and allergy specialists gathered similar results [28]. Even though no objective reason was found, 50–75 of more than 400 exposed workers became acutely ill after the introduction of a new chemical substance; 37 filed compensation claims. After assessment of the severity of generalized chemical sensitivity by means of a four-item survey 13 of these 37 workers were diagnosed as having environmental disease; 1 subject did not complete the study. The remaining 23 patients were classified as controls. Patients with suspected environmental illness could not be significantly distinguished from the controls regarding the present rating of depression, anxiety, and panic but remarkably more symptoms of preexisting disturbances such as depression, panic, somatoform disorders, and hypochondria were found.

A case control study of 26 individuals with suspected MCS revealed that significantly more depression, anxiety disorders, and somatoform disorders were found in the so-called MCS group [4]. In a smaller group of only 11 patients with so-called MCS Fiedler et al. found no indication of premorbid psychological defects, but rather central nervous symptoms such as cacosmia and memory disturbances [9]. Although any of the psychological or psychiatric studies state that depression, anxiety, and somatoform disorders prevail with MCS patients, none of the studies succeeded in finally proving that this is the cause of MCS and not a results of it. Because of the lack of longitudinal studies, a definite classification of these psychological disturbances is impossible [12].

Hypersensitivity to odors is also a suspected cause for MCS. Exacerbation of bronchial asthma triggered by odors has been described repeatedly [2]. The precise pathophysiology of this phenomena cannot be determined. Odors are also suspected to trigger neurological symptoms [26]. In survey of 643 students, 15% classified themselves as sick due to environmentally caused odors [7]. The authors discussed the "kindling" phenomenon, which describes an increase in neuronal sensitivity after repeated, intermittent low-level irritations. Pesticides as well as other chemicals are supposed to trigger this. These conditioning phenomena, which are not completely understood, suggest a close relationship between psychological and physical components mediated by biochemical processes. According to presently available data, it has not been proven that conditioning is the only cause for MCS [8].

Conclusion

None of the original theories of clinical ecology can explain MCS scientifically. There is no doubt, however, that a remarkable number of persons have unspecific complaints related to low-level occupational or environmental chemical stress. This fact demands that academic medicine deal with the problem, however, using objective and quality-controlled methods. Unqualified statements of physicians who claim to be experts only encourage these vulnerable patients to fixate on inadequate explanations of the causes of their symptoms. Tendentious media reports increase this danger [11]. The term MCS should therefore only be accepted as a working diagnosis if, for the individual case, methodically incontestable provocation testing succeeds in proving the hypersensitivity and if this proof is reproducible. In this case the hypersensitivity has to be tested with regard to its toxic, irritative, or neurophysiological causes. Following a step-by-step procedure, a comprehensive and detailed case history should be taken first in which the supposed exposure factors are identified. An extensive medical diagnostic examination should exclude any other disease. The next step consists of blinded provocation testing. If the proof is reproducible, environmental and biological monitoring should be implemented to evaluate the probability of intoxications or irritations due to individually increased sensitivities.

If the somatic cause cannot be determined by the methods stated, the symptom complex would most probably have to be classified as a psychopathological phenomenon. In this case, it has to be proved whether the psychological symptom is an epiphenomenon of a prior-existing somatic disease, keeping in mind that somatic causes are excluded by presently available methods only!

The toilsome and time-consuming work with these stigmatized, polysymptomatic patients should not, however, tempt the physician to declare the patient psychologically abnormal before a somatic cause is excluded. Only an open, comprehensive, and, above all, unbiased analysis of the symptoms will help to maintain patient confidence in orthodox medicine. This confidence is particularly essential if any possible psychological cause is to be dis-

cussed. If confidence cannot be maintained, patients will search for other – alternative – ways to receive the expected medical attention.

If a hypersensitivity is determined, exposure must be avoided. Even in the case of psychogenic symptoms, a temporary cessation of exposure can be helpful. The complete isolation of the patients and other irrational diagnostic and therapeutic procedures described in connection with MCS should be strictly avoided. Universal symptoms demand universal medical strategies, but ones which are grounded in scientific knowledge.

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