Research article

Clin Ter 2020; 171 (2):e?-?. doi: 10.7417/CT.2020.????

A Proposal for Clinical Biomarkers in Multiple Chemical Sensitivity

M. Vadalà[1,2], C. Laurino[1,2], V. Corazzari[2], B. Palmieri [1,2]

[1] *Department of General Surgery and Surgical Specialties, University of Modena and Reggio Emilia, Medical School, Surgical Clinic, Italy* [2] *Second Opinion Medical Network, Modena, Italy*

Abstract

Multiple chemical sensitivity (MCS) is increasingly widespread disease, characterized by non-specific and recurring symptoms from various organs associated with exposure to common chemicals, even if inhaled at low concentrations, usually harmless for normal people.

MCS is not yet well recognized from common point of view and for this reason affected patients risk marginalization and their symptoms are often trivialized. It is actually a devastating chronic disease that affects not only the patients in the daily routine but partly conditions their survival.

Despite more than 50 years of research, the action mechanisms of MCS is still undefined. In this study we examine the theories about the etiopathogenesis of multiple chemical sensitivity that include genetic susceptibility factors, immunological factors, neurological factors and psychiatric factors. Since no specific diagnostic markers are currently available for the MCS, the diagnosis can only be supposed on the basis symptomatic criteria and patient's medical history. However new biochemical markers and diagnostic imaging techniques have emerged, useful to postulate at least the clinical-diagnostic hypothesis of MCS and in this paper we discuss a list of biomarkers studied for the diagnosis of MCS, based on the available scientific literature.

At last but not least, we propose four-levels MCS tests that could help the clinician in the diagnosis of the pathology both through the use of quantifiable serological parameters, both through diagnostic tools, genetic testing and through clinical observation of symptoms.
Clin Ter 2020; 171 (2):e?-?. doi: 10.7417/CT.2020.????

Key words: *MCS, clinical biomarkers, level tests, diagnosis, SNPs, genetic testing*

Definition and symptoms of multiple chemical sensitivity

Multiple chemical sensitivities (MCS) is a pathological condition, with a major prevalence in female gender (90%) at about 52 years old as mean age (1), characterized by systemic discomfort, irritation and inflammation of sensory organs, respiratory symptoms, hypersensitivity of skin and epithelial lining of the gut, throat and lungs, agitation, and learning and memory loss (2). Specifically the symptoms include fatigue, fevers, respiratory impairment and discomfort, food allergies, gastrointestinal distress, skin irritation, dry throat, cough, eye irritation, nasal burning, acutely unpleasant smells, rash, nervousness, and loss of memory and learning deficit (3, 4). In addition, the affected patients may experience panic, anxiety and transformation of personality (2). MCS is considered a chronic acquired disorder which symptomatology depends to the exposure to many chemically-unrelated compounds at doses far below those established as having harmful effects in the general population (5). At the beginning of the '50, the allergist Theron G. Randolph (6) was the first to note that some patients became sick after exposures to a wide range of substances, either job-related, either, broadly speaking, environmental, in concentrations below those considered toxic for most individuals, speculating a possible sensitization to these substances.

However, the lack of objective scientific support has contributed to the confusion and discrepancies surrounding the real significance of symptoms and the pathogenic mechanisms of the disease (7).

Theories about the etiopathogenesis of multiple chemical sensitivity

The latest studies confirm the hypothesis that MCS is based on a multifactorial model hierarchically contributed to by genetic factors (phase I and phase II classes scores), environmental (chemical compound exposures), and anamnestic characteristics (presence of previous surgery events) of the patients. The genetic risk related to phase I and II enzymes involved in xenobiotic detoxification, olfactory, and neurodegenerative diseases play a necessary along the pathophysiological route of the disease. This tends to confirm previous hypotheses suggesting the inherited and acquired dysfunction of the chemical defensive system as a molecular basis for MCS complaints (8-10).

The same pathways involved in the metabolism of xenobiotics have been previously linked both to impairment in the olfactory system and involvement in neurodegenerative as well as psychiatric diseases (11). Oxidative stress has proven to impair cognitive behavior including olfactory learning and memory, especially in those conditions where detoxification pathways may not properly counterbalance the generation of damage (12,13). Clinical ecologists and

Correspondence: Dr. Vadalà Maria, Department of General Surgery and Surgical Specialties, University of Modena and Reggio Emilia, Italy
E-mail: mary.vadala@gmail.com

ISSN 1972-6007

specialists in environmental medicine recognize that immunological, neurological, and physiological symptoms of MCS have psychological components (2, 3, 14). However, behavioural treatment of MCS is exhausting for patients, and may cause iatrogenic illness. Factors who lead to MCS may be genetic, infectious, or neurological (2). The trigger may be a neurological reflex mechanism, a stimulus to emotional memory, or a conditioned response to olfactory stimuli.

Genetic susceptibility factors

The polymorphism in genes encoding both metabolizing enzymes and the receptors and transcriptional factors regulating their expression, may account for the existing interindividual variations in xenobiotics metabolizing activity, and it has been suggested as a possible mechanism underlying MCS (9). On the other hand, individual peculiarity of adaptive response to chemical stressors at the epigenetic level through the direct interaction of these substances and their metabolites with biologically important molecules and cellular membranes may also play an important role in the disease pathogenesis. In theory, the pharmacogenetic model could explain some of the interindividual differences in response to directly acting toxic chemicals as well. Polymorphisms and (or) acquired differences in enzyme function might be a likely basis for differential responses to metals, solvents, and cholinesterase-inhibiting pesticides, but consistent correlations between human enzyme concentrations and host differences in toxicity remain to be demonstrated (15).

Immunological factors

Dysregulation of the immune system has frequently been proposed as a pathophysiological mechanism likely to play a role in the etiology (9, 16) and common MCS symptom-triggering compounds, such as formaldehyde, hydrocarbons and organochlorines, have been shown to suppress immune system functioning in humans (17). However, immunological testing has failed to reveal any consistent pattern of reactivity or abnormalities indicative of common immunological deficiency in MCS (18,19). One study by De Luca et al. (2010) reported increased levels of six immune-modulating cytokines in MCS individuals compared with healthy controls and abnormal serum levels of several biomarkers related to redox balance and metabolic functioning, which could suggest an impaired chemical defensive system and dysfunctional immune regulation (9). In fact, some cytokines act as messengers between the immune system and the central nervous system with the potential to induce various neuropsychological manifestations (20). Furthermore, inflammatory cytokines have been found in the nasal passages and lungs of individuals exposed to some toxicants, which might explain various respiratory and other common symptoms in others sensitivity-related illness (SRI) (21).

There is also suspicion that adipokines (22) — cytokines released from adipose tissue (23) — may be involved in hypersensitivity reactions. Adipose tissue is an active endocrine organ that discharges several bioactive mediators that influence homeostasis and inflammation (24) and serves as an active participant in regulating certain physiological processes. Adipose tissue is also a main storage site for lipophilic toxicants and holds much of the toxicant burden within the body. As release of adipokines can be involved in the process of inflammation as well as being implicated in disease development, it is hypothesized that contaminated adipose tissue may be involved in impaired tolerance and hypersensitivity (25).

Hyperactivity of the immune system to environmental stimuli could explain both the diversity of symptoms in MCS and the very low levels of chemical exposures with which those symptoms have been associated. This hypothesis has been investigated in case series and controlled studies (26) but many of these studies have been controversial and/or difficult to interpret, for at least two reasons. First, the reliability of many of the immunological methods and tests used has not been demonstrated by standard epidemiological and laboratory criteria. While markers used for the diagnosis or management of known immunological diseases such as human immunodeficiency virus infection are now routinely validated and quality controlled, this is not true for many of the immunological markers studied for MCS (26), particularly those related to lymphocyte phenotype and function. Second, diagnostic criteria and epidemiological case definitions of MCS have been inconsistent across studies, and many studies did not consider the possibility that some of the controls could have had MCS; this could be important given that up to 16% of those surveyed in recent population studies indicated that they had some degree of hypersensitivity to environmental chemicals (27,28).

Neurological factors

Brain dysfunction has been proposed as a risk factor to develop MCS. Single photon emission computed tomography (SPECT) investigations evidenced alterations in the areas involved in odour processing suggesting a neurologic pathogenesis of this disorder (5). From the physiologic viewpoint, the pathway that joins the olfactory region to the orbito-frontal cortex through the thalamus is considered to be a control area of olfactory stimuli (5). It would therefore be feasible for reduced neuronal activity of this pathway, like that found in MCS patients to be able to alter the perception of the odour stimulus. Furthermore, the olfactory region is also connected to the limbic system, a highly sensitizable area, which is responsible for vegetative responses and some emotions related to smell (5). This pathway, if altered, could give rise to symptoms that confuse the observer such as those presented in MCS patients after odour stimulus. Neurologic transmission is a selective process in which excitatory and inhibitory signals control the final information transmitted. Inhibitory signals help to stabilize nervous system function and prevent excessive intensity and spread of neurologic circuits. Thus, reduced activity of inhibitory neurologic mechanisms can produce much greater excitability and facilitation of nervi stimuli, even in apparently unrelated areas (5). This proposed mechanism may also be coherent with a sensitization process (29).

Psychiatric factors

Another explanation could be that MCS is caused by mental illness and that MCS symptoms are somatization of other psychopathology (30). It may be that individuals with major depressive disorder and/or generalized anxiety disorder have increased sensitization to stimuli in general (31), or also that they use external stimuli to explain their mental health-related symptoms. This theory also suggests that MCS is not the only medically unexplainable condition to feature psychological components. In fact, individuals with chronic fatigue syndrome, heart palpitations, and fibromyalgia frequently exhibit symptoms of anxiety, as well as mood disorders (32). It may be that these medically unexplainable conditions, along with MCS, are different manifestations of underlying psychological distress. Another possible explanation for the findings is that MCS precedes the onset of mental illness (33). One such study showed that individuals with baseline chemical intolerance had the onset and the exacerbation of anxiety and negative affect occurred over a 5 year period (34). Evidence has also shown that these mental health outcomes can influence the maintenance of chemical intolerance (35). If genetic, metabolic, and other physiological factors negatively influence how individuals react to chemicals in their environment. The individuals may find their symptoms of MCS distressing enough to induce psychopathology, which in turn, may negatively influence chemical intolerance symptomatology.

Biomarkers in multiple chemical sensitivity

It would be ideal to have a single characteristic of MCS that could be objectively measured as an indicator of the pathogenic process associated with this condition. The ideal biomarker for MCS would help link specific levels of certain environmental exposures to toxicants and subsequent disease outcomes.

Basic tools in this phase are questionnaires (QEESI, UTHS, IESI, etc.), to be used before verifying that recognized diagnostic criteria are met. Tests may then be scheduled based on each individual's history, the objective findings and/or any suspicion of associated pathologies, so as to exclude any other disorders (36).

Some useful first-stage laboratory tests have been proposed by Martini et al. (36). In addition to laboratory tests, it may be useful to do an instrumental test such as global spirometry, which is fairly frequently used in occupational medicine. Then, we discuss a list of biomarkers studied for the diagnosis of MCS, based on the available scientific literature: the critical and relevant aspects in order to identify this highly disabling pathology and to be discriminated against by other diseases that are difficult to interpret. We summarize in Table 1 some 4-levels tests that could help the clinician in the diagnosis of the pathology both through the use of quantifiable serological parameters, both through diagnostic tools, genetic testing and through clinical observation of symptoms.

Provocative Challenge

Provocative challenge, in which individuals with alleged hypersensitivity are exposed to incriminated chemicals in a blinded fashion, is the standard in the field of human immunotoxicology. Ashford and Miller (1989) found agreement on this point in their interviews of allergists and clinical ecologists. However, provocative challenge is a research tool only, and it must be refined. One problem involves odor masking for testing individuals who might suffer from cacosmia (a disorder of the sense of smell) (37). It is difficult to determine whether patients with MCS have "real" sensitivity by using double blind, placebo-controlled provocative (DBPC) challenges. Nevertheless, two DBPC studies were reported. In one study (38) the authors concluded that patients with MCS responded to blinded chemicals more than placebo, but the 99.4% of the authors' chemical challenges produced no reaction, which contradicts their conclusion. Staudenmayer et al. (39) 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. Then, it has been postulated but not proven that the most common symptom complex in MCS is due to anxiety induced chronic or acute hyperventilation, which produces very similar symptoms (40,41).

Skin Tests

Skin testing with automobile exhaust, formaldehyde, and synthetic alcohol, for example, has been used as a diagnostic test for chemical hypersensitivity. For skin tests to be accepted, several large, independent studies of patients must demonstrate that persons with verified MCS have positive skin tests, and that an equal number of individuals without MCS has negative skin tests to these substances. Until these studies are done, skin tests must be considered experimental and a research tool (37).

Antibodies To Formaldehyde-Human Serum Albumin Adducts

One group has advocated using the presence in serum of Formaldehyde-Human Serum Albumin Adducts (f-HAS) antibodies as a biologic marker for MCS. For these tests to be accepted, it must be demonstrated in several large series of patients by independent investigators that persons with verified chemical susceptibilities have positive tests and that an equal number of individuals without unique problems associated with chemical exposure have negative titers to these antibodies. Until these studies are done, these tests must be considered experimental and a research tool (37).

T-cell Helper-to-Suppressor Ratios

Ratios of CD4 to CD8 cells, measured by fluorescence-activated cell sorters or other instruments, have been proposed as biologic markers of chemical sensitivity. Rea et al. (1982) suggest that this ratio is elevated for patients with

some, but not all, diagnoses. Because there is considerable overlap between normal and affected subjects, this test is not used in the clinical evaluation of individual patients. Levin and Byers (1987), on the other hand, claim a decrease in this ratio; Terr (1986) finds no abnormality of the ratio. However, the exposure in the workplaces may not be equivalent. The CD4:CD8 ratio cannot be recommended as a biologic marker for chemical sensitivity, although it could have some use in comparing groups of patients in clinical research settings (37).

Immunologic markers

Immunological biomarker should indicate impaired tolerance and immune dysregulation. In MCS reactions, there have been various reports of atypical laboratory findings, (42) but thus far, there is no single marker or pathologic finding that is pathognomonic for MCS. Ongoing study, nonetheless, continues to explore immunogenic markers associated with MCS responses. In searching for a consistent indicator, it has been noted that some patients will have cytokine changes, antibody responses, assorted autoimmune markers, (43) as well as general inflammatory marker changes (42). In addition, to high values for IgE, patients with atopic disease demonstrate elevations in selected neurotropins upon exposure to antigens such as automobile exhaust (44). IgA responses may be found in some sensitivity reactions (45) and IgG antibodies have been found to be useful markers with some types of food intolerance (46) and the associated inflammation (47). Research is also demonstrating that antigen-specific serum IgE, IgG, IgG4, and IgA response levels may vary significantly between each specific antigen tested in patients with MCS (48).

A recent study demonstrated that some chemical triggers evoke changes in IgE and Th2 cytokines while others elicit a Th1 cytokine response with no elevation of serum IgE (49).

Some mold exposures can induce immune dysregulation (50) through IgE changes as well as other non-IgE immune mechanisms (51). These findings further the hypothesis that diverse triggers elicit different immunological responses — that might in turn account for various clinical manifestations. There are limitations, however, with using serologic immune indicators as markers of sensitivity. Serologic markers may be inconsistent as cytokine levels measured in peripheral blood on a single occasion, for example, can change rapidly and only represent a brief or transient snapshot of cytokine activity (52). Although such testing may benefit some individuals, some food antigens elicit cytokine release, which may not be detected on antibody based testing.

Neurologic markers

Patients with MCS may display changes in markers of brain function. Recent study has demonstrated alteration in positron emission tomography (PET) scans, (53) SPECT (54) as well as electroencephalography (EEG) studies (55). Objective clinical signs are also being investigated including signs of autonomic nervous system dysfunction — such as distortions of heart rate variability and pupillary response. SPECT investigation may be useful to identify dysfunctions in some areas of the brain confirming the neurological hypothesis for MCS. Specifically this test might be relevant after exposure to a chemical challenge revealing a potential hypoperfusion in brain areas involved in the elaboration of olfactory stimuli (37). Near-infrared spectroscopy (NIRS) activation study on olfactory stimulation in patients with MCS have also been used to assess brain dysfunctions in the olfactory areas (56). This technique is suitable for detecting oxygenation changes in higher cortical regions and results of challenge tests by exposure to odorous chemicals indicated a neuro-cognitive impairment in patients with MCS (confirmed also with SPECT investigations). Brain dysfunction was found particularly in odor-processing areas, thereby suggesting a neurogenic origin of MCS (56).

Genetic polymorphisms

Altered redox and cytokine patterns suggest inhibition of expression/activity of metabolizing and antioxidant enzymes in MCS. Metabolic parameters indicating accelerated lipid oxidation, increased nitric oxide production and glutathione depletion in combination with increased plasma inflammatory cytokines should be considered in biological definition and diagnosis of MCS (9). Significant case-control distributed differences were observed in different genes that have been summarized in Table 1.

Future researches

Many interesting explanations for MCS and chemical-induced toxicity in general have been advanced. The theories of MCS as explained in this paper, are currently undergoing formulation and refinement. Moreover, the absence of stronger evidence in MCS diagnosis protocols, based on specific measures of exposure to chemicals and their biological and physiological effects, could lead to an erroneous estimation of the impact of MCS on the population health status. This is a major problem especially in the field of prevention, particularly for groups at greater risk. We should at least draw up validated and harmonized guidelines for this type of essays, which involves serious ethical issues, and have an appropriate number of repeatable tests just like it does for the toxicological evaluation of chemical substance.

From the statistical and epidemiological point of view, it would be appropriate to detect temporary or permanent unfitness to chemical risk, or even the reasons for sudden changes in position that could occur in different working environments. Executing appropriate and consistent environmental controls for chemical risk is an important factor to prevent both accidents and occupational diseases in workplaces with exposures above the limits and to prevent workers to stay in contaminated places (57).

The analysis of the patient at anamnestic and etiological level is of great importance. In particular, it should be inquired about the differences in timing and mode of manifestation between endogenous psychiatric syndromes and those caused by chemicals in order not to err on the diagnosis, as symptoms can overlap. In this regard, more information gathering would be useful so as to perform longitudinal epidemiological studies.

Table 1. Proposed four-levels Multiple Chemical Sensitivity (MCS) tests for the diagnosis and the identification of the disease. The first level includes basal test (e.g. QUEESI questionnaire, serological laboratory tests, main organs functioning, brain instrumental diagnostics, neurological, psychological and psychiatric clinical examination). The second level concernes antioxidant power and oxidative stress status assessment. The third level checks autoimmune and allergic profile and systemic inflammation. Finally, the fourth level consists in genetic predisposition to develop MCS by Single Nucleotide Polymorphisms (SNPs examination).

First level tests
- Provocative challenge test; - QUEESI questionnaire; - Laboratory tests [blood count, serum proteins, glycemia, vitamins levels, kidney, lipid, thyroid and liver parameters, immunoglobulins (IgG, IgM, IgA, IgE), specific IgE, coagulative parameters, Virus antibodies (HbsAg, anti-HCV antibodies, anti-HAV antibodies), CPK, Gluten antibodies (anti-endomysium antibodies, anti-transglutaminase antibodies, anti-gliadin antibodies), lymphocytes characterization, inflammatory parameters (CRP, VES), screening for viruses, chemical and biological urine analysis]; - Respiratory function and spirometry; - Electrocardiogram (ECG), Echocardiogram, Abdomen echography, Magnetic Resonance Imaging (MRI), Positron emission tomography (PET), Single photon emission computed tomography (SPECT), electroencephalography (EEG); - Psychological, psychiatric and neurological clinical examination; - Minerals quantifications in hair, stool and urine;
Second level tests
- Antioxidants levels (total antioxidant capacity of blood plasma, catalase, superoxide dismutase, glutathione transferase, peroxidase, reduced and oxidized glutathione, reduced and oxidized Q coenzyme, vitamins A, C, E, leucocytes and erythrocytes membrane fatty acids); - Reactive oxygen species (blood ROS, nitrites and nitrates, MDA, 4-HNE, ATP production of erythrocytes and platelets);
Third level tests
- Autoantibodies (ANA, ENA, anti-ds-DNA, AMA, ASMA) - Cytokines, chemokines and growth factors quantification by immunoenzymatic microarray and multiplex fluorescence techniques; - Allergic and challenge tests (breath test, LTT test, basophiles activation test, titanium test, nagalase test); - Environmental tests (heavy metals, chemicals, pesticides and toxic substances in domestic dust);
Fourth level tests
- Single nucleotide polymorphisms (SNPs) for individual genetic susceptibility about genes involved in detoxifying and antioxidant enzymes (CYP2C9, GSTT1, CYP2C19, GSTP1, I105V and A114V, CYP2D6, CAT, NAT2, UGT, PON1, NOS2, GSTM1, NOS3, MHTFR, AHR, Mn SOD C(-28)T and T175C, SOD3 C760G); - Personalized Single nucleotide polymorphisms (SNPs) screening: FCRL3_3/FCRL3_5/FCRL3_6/ FCRL3_8 (Fc Receptor-Like 3), COMT (Catecol-O-metiltransferasi), RGS4 (Regulator of G protein signaling 4), CD28, LPP (Lipoma-preferred partner), ETS1 (ETS proto-oncogene 1), MPZ (Myelin protein zero), GBP1 (Guanylate-binding protein 1), NR3C1 (Nuclear Receptor Subfamily 3 Group C Member 1), CTLA-4 (cytotoxic T lymphocyte-associated antigen-4), GABRB3 (GABA-A β receptor gene), TAAR1 (trace amine-associated receptor 1), PARP-1 Poly (ADP-ribose) polymerase-1, GRIA4, (AMPA-sensitive, glutamate receptor subunit 4), PMP22 (Peripheral myelin protein 22), CASP1 (Caspase 1), TPH2 (Tryptophan hydroxylase 2), VDR (vitamin D receptor), HTR2A, (5-Hydroxytryptamine Receptor 2°), DLEU1 (Deleted In Lymphocytic Leukemia 1), CREBBP (CREB-binding protein), SLC6A4 (Solute Carrier Family 6 Member 4), UBTF (Upstream Binding Transcription Factor, RNA Polymerase I), MBP (myelin basic protein), TUBB6 (tubulin beta-6 chain), LOC100506457, LPIN3 (Lipin 3), IFNGR2 (Interferon Gamma Receptor 2), CD80, CD86, CCR2 (C-C Motif Chemokine Receptor 2), IL12A (interleukin-12 subunit alpha), IL7RA (IL7 receptor), TIM-3 (T-cell immunoglobulin mucin-3), miR-146° (MicroRNA 146a), PIK3R1 (phospahtidylinositol 3-kinase regulatory subunit alpha), TNF (Tumor Necrosis Factor), VLA4 (Integrin alpha-4 subunit), CNR1 (Cannabinoid receptor), C282Y, NKC57, MRPS6 (Mitochondrial Ribosomal Protein S6), GSTP1 (Glutathione S-Transferase Pi 1), SOD2 (Superoxide Dismutase 2), CAT (Catalase), 8-OGG1 (8-Oxoguanine glycosylase), PON1 (Paraoxonase 1), eNOS (Nitric Oxide Synthase), CYP2C19 (Cytochrome P450 Family 2 Subfamily C Member 19), CYP2D6 (Cytochrome P450 Family 2 Subfamily D Member 6), UGT1A1 (UDP Glucuronosyltransferase Family 1 Member A1), CYP3A4 (Cytochrome P450 Family 3 Subfamily A Member 4), CYP3A5 (Cytochrome P450 Family 3 Subfamily A Member 5), CYP2C9 (Cytochrome P450 Family 2 Subfamily C Member 9), MTHFR (MetilenTetraHydroFolate reductase), GSTM1 (Glutatione S-transferase mu, M1), PAI 1 (Plasminogen activator inhibitor-1), GSTT1 (Glutathione S-transferase theta, T1), OPRM1 (opioid receptor mu subunit gene), MC1R (melanocortin 1 receptor), MDR1 (Multi Drug Reactivity 1), ALDH2*2 (Aldehyde Dehydrogenase 2 Family (Mitochondrial)), ALDOB 149 (Aldolase, Fructose-Bisphosphate B), ALDOB 174 (Aldolase, Fructose-Bisphosphate B), ALDB 334 (Aldolase, Fructose-Bisphosphate B), SI 117 (Sucrase-Isomaltase), SI 340 (Sucrase-Isomaltase), SI 620 (Sucrase-Isomaltase), SI 1098 (Sucrase-Isomaltase), G6PD (Glucose-6 -Phosphate Dehydrogenase), HFE (Hemochromatosis), HLA-DQ2 (Major Histocompatibility Complex, Class II, DQ), FLG (Filaggrin)

Conclusions

MCS is a pathology that is still little known and needs of studies to detect the early phase and to intervene promptly to prevent its aggravation of symptoms. Identifying those subjects mostly at risk of developing the symptoms is one of the objectives we set ourselves, as well as the correlation between positivity and genetic factors, clinical symptoms, laboratory and instrumental examinations in order to identify effective and customizable therapeutic strategies based on the needs of each single patient.

The authors hope that this paper may make a contribution to the understanding of MCS, and that the suggestions for future research will provide inspiration to scientists who are interested in this widespread disease.

References

1. Lago Blanco E, Puiguriguer Ferrando J, Rodriguez Enriquez M, et al. (Multiple chemical sensitivity: Clinical evaluation of the severity and psychopathological profile). Med Clin (Barc) 2016; 146(3):108-111
2. Thomas JG. A critical analysis of multiple chemical sensitivities. Med Hypotheses 1998; 50(4):303-311
3. Bell IR. White paper: Neuropsychiatric aspects of sensitivity to low-level chemicals: a neural sensitization model. Toxicol Ind Health 1994; 10(4-5):277-312
4. Buchwald D, Garrity D. Comparison of patients with chronic fatigue syndrome, fibromyalgia, and multiple chemical sensitivities. Arch Intern Med 1994; 154(18):2049-2053
5. Orriols R, Costa R, Cuberas G, et al. Brain dysfunction in multiple chemical sensitivity. J Neurol Sci 2009; 287(1-2):72-78
6. Randolph TG. Human ecology and susceptibility to the chemical environment. Ann Allergy 1961; 19:908-929 concl
7. Katoh T. (Multiple Chemical Sensitivity (MCS): History, Epidemiology and Mechanism). Nihon Eiseigaku Zasshi 2018; 73(1):1-8
8. Korkina, L.; Scordo, M.G.; Deeva, I.; Cesareo, E.; De Luca, C. The chemical defensive system in the pathobiology of idiopathic environment-associated diseases. Curr. Drug Metab. 2009, 10, 914–931.
9. De Luca, C.; Scordo, M.G.; Cesareo, E.; Pastore, S.; Mariani, S.; Maiani, G.; Stancato, A.; Loreti, B.; Valacchi, G.; Lubrano, C.; et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. Toxicol. Appl. Pharm. 2010, 248, 285–292.
10. Micarelli A., Cormano A., Caccamo D., Alessandrini M. Olfactory-Related Quality of Life in Multiple Chemical Sensitivity: A Genetic-Acquired Factors Model. Int. J. Mol. Sci. 2020, 21(1), 156
11. Cabungcal, J.H.; Preissmann, D.; Delseth, C.; Cuenod, M.; Do, K.Q.; Schenk, F. Transitory glutathione deficit during brain development induces cognitive impairment in juvenile and adult rats: Relevance to schizophrenia. Neurobiol. Dis. 2007, 26, 634–645
12. Farooqui, T. A potential link among biogenic amines-based pesticides, learning and memory, and colony collapse disorder: A unique hypothesis. Neurochem. Int. 2013, 62, 122–136.
13. Gardiner, J.; Barton, D.; Overall, R.; Marc, J. Neurotrophic support and oxidative stress: Converging effects in the normal and diseased nervous system. Neuroscientist 2009, 15, 47–61.
14. Bell IR, Schwartz GE, Peterson JM, et al. Possible time-dependent sensitization to xenobiotics: self-reported illness from chemical odors, foods, and opiate drugs in an older adult population. Arch Environ Health 1993; 48(5):315-327
15. Cullen MR, Redlich CA. Significance of individual sensitivity to chemicals: elucidation of host susceptibility by use of biomarkers in environmental health research. Clin Chem 1995; 41(12 Pt 2):1809-1813
16. Meggs WJ. Neurogenic inflammation and sensitivity to environmental chemicals. Environ Health Perspect 1993; 101(3):234-238
17. Vojdani A, Ghoneum M, Brautbar N. Immune alteration associated with exposure to toxic chemicals. Toxicol Ind Health 1992; 8(5):239-254
18. Kipen H, Fiedler N, Maccia C, et al. Immunologic evaluation of chemically sensitive patients. Toxicol Ind Health 1992; 8(4):125-135
19. Ziem G, McTamney J. Profile of patients with chemical injury and sensitivity. Environ Health Perspect 1997; 105 Suppl 2:417-436
20. Leonard BE, Song C. Stress, depression, and the role of cytokines. Adv Exp Med Biol 1999; 461:251-265
21. Hirvonen MR, Nevalainen A, Makkonen N, et al. Induced production of nitric oxide, tumor necrosis factor, and interleukin-6 in RAW 264.7 macrophages by streptomycetes from indoor air of moldy houses. Arch Environ Health 1997; 52(6):426-432
22. Hsueh KC, Lin YJ, Lin HC, et al. Serum leptin and adiponectin levels correlate with severity of allergic rhinitis. Pediatr Allergy Immunol 2010; 21(1 Pt 2):e155-159
23. MacDougald OA, Burant CF. The rapidly expanding family of adipokines. Cell Metab 2007; 6(3):159-161
24. Lau DC, Dhillon B, Yan H, et al. Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol 2005; 288(5):H2031-2041
25. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005; 115(5):911-919; quiz 920
26. Hoover DR, Donnay A, Mitchell CS, et al. Reproducibility of immunological tests used to assess multiple chemical sensitivity syndrome. Clin Diagn Lab Immunol 2003; 10(6):1029-1036
27. Black DW, Doebbeling BN, Voelker MD, et al. Multiple chemical sensitivity syndrome: symptom prevalence and risk factors in a military population. Arch Intern Med 2000; 160(8):1169-1176
28. Kreutzer R, Neutra RR, Lashuay N. Prevalence of people reporting sensitivities to chemicals in a population-based survey. Am J Epidemiol 1999; 150(1):1-12
29. Bell IR, Miller CS, Schwartz GE.: An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. Biol Psychiatry 1992; 32(3):218-242
30. Brown RJ. Psychological mechanisms of medically unexplained symptoms: an integrative conceptual model. Psychol Bull 2004; 130(5):793-812
31. Eis D, Helm D, Muhlinghaus T, et al. The German Multicentre Study on Multiple Chemical Sensitivity (MCS). Int J Hyg Environ Health 2008; 211(5-6):658-681
32. Johnson D, Colman I. The association between multiple chemical sensitivity and mental illness: Evidence from a nationally representative sample of Canadians. J Psychosom Res 2017; 99:40-44
33. Eek F, Karlson B, Osterberg K, et al. Factors associated with prospective development of environmental annoyance. J Psychosom Res 2010; 69(1):9-15
34. Skovbjerg S, Christensen KB, Ebstrup JF, et al. Negative affect is associated with development and persistence of chemical intolerance: a prospective population-based study. J Psychosom Res 2015; 78(5):509-514
35. Bailer J, Witthoft M, Rist F. Psychological predictors of short- and medium term outcome in individuals with idiopathic environmental intolerance (IEI) and individuals with somatoform disorders. J Toxicol Environ Health A 2008; 71(11-12):766-775
36. Martini A, Iavicoli S, Corso L. Multiple chemical sensitivity and the workplace: current position and need for an occupational health surveillance protocol. Oxid Med Cell Longev 2013; 2013:351457

37. LaKind JS, Sobus JR, Goodman M, et al. A proposal for assessing study quality: Biomonitoring, Environmental Epidemiology, and Short-lived Chemicals (BEES-C) instrument. Environ Int 2014; 73:195-207
38. Rea WJ, Ross GH, Johnson AR, et al. Confirmation of chemical sensitivity by means of double-blind inhalant challenge of toxic volatile chemicals. Bol Asoc Med P R 1991; 83(9):389-393
39. Staudenmayer H, Selner JC, Buhr MP. Double-blind provocation chamber challenges in 20 patients presenting with "multiple chemical sensitivity". Regul Toxicol Pharmacol 1993; 18(1):44-53
40. Pearson DJ. Psychologic and somatic interrelationships in allergy and pseudoallergy. J Allergy Clin Immunol 1988; 81(2):351-360
41. Bass C, Gardner WN. Respiratory and psychiatric abnormalities in chronic symptomatic hyperventilation. Br Med J (Clin Res Ed) 1985; 290(6479):1387-1390
42. Rea WJ. Chemical sensitivity: (volume 4): tools of diagnosis and methods of treatment.: Lewis Publishers; 1997
43. Vojdani A. Antibodies as predictors of complex autoimmune diseases. Int J Immunopathol Pharmacol 2008; 21(2):267-278
44. Kimata H. Effect of exposure to volatile organic compounds on plasma levels of neuropeptides, nerve growth factor and histamine in patients with self-reported multiple chemical sensitivity. Int J Hyg Environ Health 2004; 207(2):159-163
45. Cabrera-Chavez F, de la Barca AM. Bovine milk intolerance in celiac disease is related to IgA reactivity to alpha- and beta-caseins. Nutrition 2009; 25(6):715-716
46. Tay SS, Clark AT, Deighton J, et al. Patterns of immunoglobulin G responses to egg and peanut allergens are distinct: ovalbumin-specific immunoglobulin responses are ubiquitous, but peanut-specific immunoglobulin responses are up-regulated in peanut allergy. Clin Exp Allergy 2007; 37(10):1512-1518.
47. Wilders-Truschnig M, Mangge H, Lieners C, et al. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. Exp Clin Endocrinol Diabetes 2008; 116(4):241-245
48. Ciprandi G, De Amici M, Tosca MA, et al. Immunoglobulin production pattern is allergen-specific in polysensitized patients. Int J Immunopathol Pharmacol 2009; 22(3):809-817
49. Fukuyama T, Ueda H, Hayashi K, et al. Detection of low-level environmental chemical allergy by a long-term sensitization method. Toxicol Lett 2008; 180(1):1-8
50. Terr AI. Sick Building Syndrome: is mould the cause? Med Mycol 2009; 47 Suppl 1:S217-222
51. Edmondson DA, Nordness ME, Zacharisen MC, et al. Allergy and "toxic mold syndrome". Ann Allergy Asthma Immunol 2005; 94(2):234-239
52. Duramad P, Tager IB, Holland NT. Cytokines and other immunological biomarkers in children's environmental health studies. Toxicol Lett 2007; 172(1-2):48-59
53. Hillert L, Musabasic V, Berglund H, et al. Odor processing in multiple chemical sensitivity. Hum Brain Mapp 2007; 28(3):172-182
54. Simon TR, Hickey DC, Fincher CE, et al. Single photon emission computed tomography of the brain in patients with chemical sensitivities. Toxicol Ind Health 1994; 10(4-5):573-577
55. Bell IR, Szarek MJ, Dicenso DR, et al. Patterns of waking EEG spectral power in chemically intolerant individuals during repeated chemical exposures. Int J Neurosci 1999: 97(1-2):41-59
56. Azuma K, Uchiyama I, Tanigawa M, 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 2015; 20(3):185-194
57. Cui X, Lu X, Hiura M,et al. Prevalence and interannual changes in multiple chemical sensitivity in Japanese workers. Environ Health Prev Med 2014; 19(3):215-219