"Italian Consensus on Multiple Chemical Sensitivity (MCS)"

Consensus document and guidelines on Multiple Chemical Sensitivity (MCS) by the Italian Workgroup on MCS

23rd May 2019

We would like to thank Francesca Romana Orlando and Donatella Stocchi, from the Italian Association on Environmental and Chronic Toxic Injury (A.M.I.C.A.), for their collaboration in the bibliographical and documentary research.

1. MULTIPLE CHEMICAL SENSITIVITY (MCS): CASE DEFINITION

The first reports about sensitization and allergies to chemical substances date back to 1956 when the US allergist Dr. Theron G. Randolph[1-3] defined as "environmental disease" a group of disorders observed in some of his patients after the exposure to various chemical compounds, not related to each other.

In 1987 Dr. MR Cullen used the definition of "Multiple Chemical Sensitivity" (MCS) to define an "acquired disorder characterized by recurrent symptoms, affecting multiple organs and systems, which arise in response to a demonstrable exposure to chemicals", even for low doses, much lower than those causing reactions in the general population.[4]

1.1 The International Consensus (1999)

In 1989 an international multidisciplinary study, conducted by 89 clinicians and researchers with different experience and points of view on MCS, was published as the International Consensus on MCS[5] in 1999 in *The Archives of Environmental Health*, Vol. 54, No. 3, 147-149, May / June 1999. The International Consensus defines MCS is based on the observation for 10 years of the clinical characteristics of Multiple Chemical Sensitivity that is defined as:

[1] a chronic condition,
[2] with recurrent symptoms,
[3] in response to low levels exposures,
[4] to multiple and unrelated chemicals,
[5] the symptoms improves or disappears when the triggering agents are removed,
[6] MCS involves a symptoms in different organs.

The 1999 Consensus on MCS establishes the clinical characteristics of patients with Multiple Chemical Sensitivity (MCS) using the Environmental Exposure and Sensitivity Inventory Questionnaire ("EESI"), [6.7] which was then modified by the Prof. C. Miller and Dr. TJ Prioda in the version "Quick Environmental Exposure and Sensitivity Inventory"[8] with the acronym "QEESI ©". It is used in the United States, Canada, Japan, [9] in Germany[10], in Austria for the diagnosis of MCS. There are several modified versions of the QEESI©, adapted and validated for the specific geographical and socio-economic area such as that of Japan[11] and Denmark.[12]

In a more recent work Dr. Michael Lacour and colleagues (2005)[13] proposed an extension of the case definition criteria, defining the MCS as:
[1] a chronic condition, lasting more than 6 months and causing a worsening of lifestyle and organic functions;

[2] the symptoms recur in a reproducibly way and they involve the nervous system, with a characteristic hypersensitivity to odors;
[3] the central nervous system is involved and at least one other apparatus;
[4] there are reproducibile response to chimica exposures even at low levels;
[5] the response is to unrelated chemicals;
[6] there is the improvement or complete resolution of the symptoms after the removal from the exposure.

1.2 Triggering of MCS

A review of studies[14] on the toxicological basis of MCS identified seven substances involved in the induction of the disease:

1. Organic solvents and related compounds;
2. Insecticides, pesticides, organophosphorus herbicides and carbamates;
3. Organochlorine insecticides;
4. Pyrethroid pesticides;
5. Sulphurous hydrogen (H2S);
6. Carbon monoxide (CO);
7. Mercury (in all its chemical forms).

Dr. William J. Rea and other authors found molds[15,16] and mycotoxins[17,18] among the risk factors.

Furthermore, Dr. William Meggs (2017) identified the following risk factors for MCS[19]:

- combustion products, such as tobacco smoke, passive and active, diesel exhausts, wood smoke, vehicle exhaust gases, domestic gas burners, fuel oil and coal;
- powders such as cement, grain and cotton powder;
- fragrances and perfumes;
- organic solvents, such as oil-based paints;
- pesticides, including insecticides, fungicides, nematocides;
- gases like sulfur dioxide, formaldehyde, ozone, chlorine, nitrogen oxides, chlorine dioxide, ammonia, chloramine, bleach (sodium hypochlorite) and their mixtures;
- xenobiotics in foods, such as sulfites and other preservatives, artificial colorings and flavoring agents, residues of agricultural pesticides;
- natural substances in foods such as psoralens.

1.3 Clinical features of the disease

According to Prof. Claudia S. Miller (1997)[20] the organs affected by the Loss of Tolerance of Chemical Agents are:
- neurological apparatus: headache, migraine, trigeminal neuralgia, convulsions, attention deficit disorder (ADHD), neurocognitive deficits, insomnia;
- otorhinolaryngological apparatus: sinusitis, polyps, NARES, tinnitus, recurrent otitis, allergic rhinitis;

- cardiovascular system: arrhythmia, tachycardia, hypotension, hypertension, Raynaud's phenomenon, lipotimia/fainting;
- respiratory system: asthma, bronchospasm, tracheitis, chronic tonsillitis, hyper-reactive airway syndrome, hypersensitivity to toluene;
- gastroenterological apparatus: irritable colon, colitis, gastroesophageal reflux (GERD), celiac disease, gluten sensitivity, food intolerances, food allergies;
- rheumatology (on connective and musculoskeletal tissue): fibromyalgia, carpal tunnel syndrome, dysfunction of the temporomandibular joint (TMJ), arthritis, connective tissue disease, lupus (LES), autoimmunity;
- integumentary system (skin): eczema, systemic dermatitis, rash, rash, urticaria / angioedema, photosensitivity, skin photosensitivity, dermographism;
- psychological disorders: anxiety, depression, manic depression, bipolar disorder, mood swings, panic attacks;
- various syndromes associated with MCS: Chronic Fatigue Syndrome (CFS), Gulf War Syndrome.

Recent studies have included MCS in the set of "Central Nervous System Sensitization Syndromes", which is also referred to fibromyalgia, and Chronic Fatigue Syndrome, conditions that occur in comorbidity with MCS, [21.22] as well as the Sick Building Syndrome.[23,24]

Once the state of sensitization to chemical substances is activated, adverse reactions can occur following exposure to multiple chemicals, including solvents, volatile organic compounds (VOCs), building products/materials, pesticides, insecticides, herbicides, fungicides, biocides and other chemical products used in agriculture (fertilizers), fragrances, perfumes, deodorants, cigarette smoke and passive smoke, preservatives, food colorings and additives, drugs, anesthetics, petrochemical derivatives, air pollution (ex. PM2.5, PM10, black carbon, nitrogen oxide, ozone).

In some cases of MCS the sensitization is not limited to chemical agents, but the reactions occur also following exposure to strong natural odors (for example wood terpenes and food sulphites), strong lights (photosensitivity) or sounds (hyperacusis)[25-27], tactile stimuli, such as intense heat or cold and electromagnetic fields, thus suggesting a common mechanism of neurological sensitization and damage to the defense mechanisms against environmental agents, probably related to an alteration of the functionality of the amygdala.[28]

It should be specified, however, that hyperosmia is not a unique trait of MCS because in the literature cases of exposure to toxic substances that have led to the decrease or loss of smell are reported.[29]

Furthermore, some studies have found that the olfactory function of MCS patients does not differ from the control population.[30,31]

Other research has found comparable levels of olfactory sensitivity, despite the stimulation producing symptoms of sensitivity.[32]

The research group of Prof. Marco Alessandrini of the University of Tor Vergata in Rome clarified this aspect, emphasizing that several studies on MCS have found an

association between mucosal irritation and the triggering of symptoms, probably through mediators of the inflammation.[33,34] This phenomenon is compatible with the hypothesis of neurogenic inflammation of MCS, and activation of an immune reaction with the release of neuropeptides, chemokines and cytokines in peripheral tissues.[35,36]

In the experience of Prof. Andrea Mazzatenta exposure to natural odors does not generate any variation in the test pattern Olfactory Real Time - Volatile Organic Compounds, which is currently being tested in relation to MCS, while sensitizing substances cause hyperosmic pathological responses.[37]

In addition to fibromyalgia and chronic fatigue syndrome, present in approximately 10% of MCS patients, the following co-morbidities were reported in association with MCS (on a sample of 226 patients): gastrointestinal disorders (27.8%) , thyroid disorders (24.9%), allergies / intolerances (22.7%), respiratory pathologies (21.6%), cardiovascular (19.6%), liver disorders (7.7%), psychiatric (7, 7%), headache (6.7%), Sjogren's syndrome (3.6%), osteoporosis (3.6%), vasculitis (1.5%), pituitary disorders (1.5%) and diabetes (1 , 5%). 13, 9% of patients had no co-morbidity.

1.4 Proposed mechanisms for MCS

In the past, various hypotheses on the etiopathogenesis of MCS were proposed[38]. mechanisms considered are:

- mechanisms concerning the limbic system[25,39-41]
- immunological mechanisms[42-45]
- biochemical mechanisms[46-48]
- neurophysiological and respiratory mechanisms[49,50]
- vascular mechanisms[51]
- psychological mechanisms[52,53]

The Italian Consensus on MCS does not deal with the hypothesis on the psychological mechanisms of the disease since the studies that hypothesize it have been the object of strong criticism both for the methodological deficiencies and for the conflict of interests of the scientists who propose this thesis.

It should also be remembered that all the research on the psychological or psychiatric pathogenesis of MCS found significant clarification from researchers at Johns Hopkins University who pointed out that it is ineffective to use personality tests such as MMP2 (i.e. Minnesota Multiphasic Personality Inventory 2) for the study of the pathogenesis of environmental diseases, such as Multiple Chemical Sensitivity (MCS)[54.55] and fibromyalgia[56], concluding that the presence of psychological-psychiatric symptoms in patients with Multiple Chemical Sensitivity (MCS) is compatible with the objective limitations imposed by the disease, rather than being the cause, and specifying that many toxic substances can act on the central nervous system simultaneously causing both sensitization to chemical agents and psychological-psychiatric symptoms.

As regards the neurological mechanisms of MCS, various studies have also been carried out on the use of the electroencephalogram (EEG),[57] for example Dr. Iris Bell has found, in particular, an increase in the "resting alpha" wave in EEG tracks.[58]

Other neuroradiological investigations include the mapping of cerebral electrical activity, PET[59,60] (positron emission tomography) and SPECT (single photon emission computed tomography), which in the literature highlight abnormalities in cerebral perfusion of MCS patients, especially in the autonomic central nervous system area, compared to controls.[61-65]

In 2001 Prof. Martin Pall proposed a pathogenesis of MCS on a toxicological basis linked to the activation by some toxic substances of a biochemical cycle with dysregulation in the brain (nitric oxide cycle otherwise known as "NO / ONOO"). This hypothesis, which has found broad consensus in the scientific community and which is compatible with previous hypotheses on the neuronal sensitization of Dr. Iris Bell and on the neurogenic inflammation of William Meggs, is also able to explain the comorbidity of Multiple Chemical Sensitivity with other pathologies related to the same mechanism, including fibromyalgia, chronic fatigue syndrome and tinnitus / tinnitus.[14,66-70] These theories are confirmed by the clinical observation of a lowering of MCS reactions after chemical exposure to inhibitors and / or antagonists of NMDA receptors (acronym of N-methyl-D-aspartic acid), but further studies are needed for confirmation.

In 2010, a group of Italian researchers[71,72] reinforced the hypothesis of biochemical mechanisms underlying the disease, detecting alterations in the biochemical molecular framework of detoxifying enzymes, particularly with a reduction in the catalase activity of glutathione-S-transferase (lacking in about 80% of patients)[71.72] and typical alterations of the composition of fatty acids that make up the cell membrane. These evidences can explain both the altered ability of the metabolism of xenobiotic substances and the neurological problems, given that the nerve cells strongly depend on the lipid component. The same work group[73] highlighted the association between the alteration of the biochemical parameters of oxidative stress and the immunological parameters through the identification of plasma profiles of pro-inflammatory cytokines.[71-73]

In the same patients subsequently the presence of polymorphisms in some genes coding for the phase I detoxification enzymes was observed, belonging to the family of cytochromes P450 (CYP), and of phase II, such as glutathione-S-transferase (GST). The frequency of such polymorphisms, often present in combination in various haplotypes in individual patients, was significantly different in the cohort of MCS patients compared to the control group, consisting of healthy subjects recruited in the general population.[69-70] This suggests that it is possible to identify within the MCS population of the subgroups of patients most susceptible to the toxic effects of xenobiotics due to the presence of variations in gene sequence, which constitute a risk factor for the onset of alterations in the detoxification mechanisms.[74,75]

The Italian studies found in MCS patients also higher level of nitrites and nitrates, involved in the oxidative/inflammatory processes, and of oxidative damage to DNA with respect to the healthy control population, even with the same genetic structure with the controls regarding the presence of polymorphisms of genes coding for endothelial nitric oxide synthase (NOS3) and inducible (NOS2), and glutathione peroxidase (GPX1). [76,77] These observations could support the pathogenetic hypothesis of a synergy between environmental exposure to substances toxic and high fragility of MCS patients. It could be

hypothesized that subjects with genetic alterations in the detoxification mechanisms at a certain stage of their life find themselves without adequate defenses because the toxic load has increased, becoming unsustainable.

The role of inflammation had previously been investigated by Dr. Hajime Kimata, who found alterations in histamine levels, nerve growth factor (NGF) and other inflammatory markers in patients with Multiple Chemical Sensitivity (MCS).[78]

Swedish researchers have discovered an increase in inflammatory factors in patients with respiratory symptoms of chemical sensitivity. Alternatively, it is possible to hypothesize that epigenetic modifications induced by the environment and lifestyle are involved in the life of some people. These same people lose the ability to adequately detoxify the body from toxic substances and become hypersensitive to chemicals, falling ill with MCS and developing oxidative stress and inflammation. To date there are still no studies available in the literature on the presence of epigenetic modifications in MCS patients.

A confirmation on the existence of high levels of histamine in MCS patients comes from a more recent study, which also indicated the existence of an activation of the immune system, with damage to the blood-brain barrier, as suggested by the increase in nitrotyrosine and protein S100B, and the production of antibodies against myelin. Furthermore, hypoperfusion of the capsulothalamic area was observed, indicating that the inflammatory process involves the limbic system and the thalamus.[82]

2.EPIDEMIOLOGY

Studies of prevalence[83-85] and incidence of MCS are conducted with different methodologies, such as telephone interviews, hospital diagnosis surveys or other methods.

The Environmental Protection Agency (EPA) in the US has reported that about one-third of people employed in a closed work environment report a particular sensitivity to one or more common chemicals.

In the United States the most extensive epidemiological study was published in a series of articles by Caress and Steinemann who found in 2005 the national prevalence of MCS diagnosed by medical personnel in 2.5% of the population and self-reported MCS in the 11.2% .[85] Slightly higher data were found on a pilot study in the Atlanta community: 12.6% of self-reported MCS and 3.1% of MCS diagnosed by medical staff.[85.86]

In the last 10 years the incidence of ascertained Multiple Chemical Sensitivity (MCS) diagnoses in the United States has tripled: according to the latest 2018 study by Anne C. Steinemann, in fact, in America there are 55 million adults suffering from chemical sensitivity and by MCS. The study also found that 71% of people with Multiple Chemical Sensitivity are also asthmatic and 86.2% of those with MCS report reactions to perfumed consumer products, such as environmental deodorants, perfumed laundry soaps , cleaning detergents, scented candles, perfumes and personal care products.[87]

An epidemiological estimate in Germany shows a prevalence of 9% of cases of self-reported Multiple Chemical Sensitivity (MCS) and 0.5% of MCS diagnosed by doctors.[88]

In 2018, an epidemiological study conducted by researcher Anne C. Steinemann showed a diagnosis prevalence of MCS in the adult population in Australia of 6.5% out of a population of 26 million inhabitants. Therefore in Australia there are about 1 million people who have been diagnosed with MCS by health personnel.[83,84]

Four scientific studies report a significant comorbidity between intolerance to intense odors, which is a prevalent symptom in MCS, and the risk of chronic cardio-respiratory diseases, [89-93] thus detecting that the impact of MCS in terms of public health can be potentially very high.

2.1 Categories at risk for MCS

From an analysis of the Literature it is clear that the categories at risk of developing Multiple Chemical Sensitivity are:

- industrial workers, subject to acute or chronic exposure to industrial chemicals;
- other professional categories; farmers, hairdressers, healthcare employees with specific risk activities (radiologists, anesthesiologists);
- people who live or work in closed environments (teachers, students, employees, workers, etc.) especially if with inadequate air exchange, potentially exposed to the inhalation of volatile substances given off by building materials, carpets, equipment or items for office, printers, tobacco smoke, etc.; [94]
- residents in communities whose air or water is contaminated by chemical products (contaminated aquifers, air pollution caused by industries, proximity to toxic waste disposal sites, aerial pesticide treatments, etc.);
- individuals who for some reason have found themselves exposed, even just for once, to toxic chemicals (pesticides, drugs, victims of industrial and chemical accidents, galvanic industry, typography, metal exposures, metal catalysts, exposure to enamels and paints, inorganic and organic acids); [94]
- veterans of the Gulf War;
- wearers of implants containing silicone (for example, breast implants);
-wearers of metal prostheses with systemic allergy to some of their components (mercury amalgam for dental fillings, orthopedic and / or dental prosthetic implants in titanium alloy, chrome-cobalt) [96.97]
- born by caesarean section.[98]

3. DIAGNOSTIC GUIDELINES

3.1 First consultation

The general practitioner can prescribe some basic blood tests for a preliminary assessment:

- Protein electrophoresis;
- Ferritin;
- Electrolytes: sodium (Na), magnesium (Mg), zinc (Zn);
- Creatine phosphokinase (CPK);
- Erica Serum cholinesterase;
- VES;
- C reactive protein;
- total IgE;
- Interleukin-2 serum receptor;
- Ale Basal Cortisol;
- Basotest on chemical known for adverse reaction.

3.2 Diagnosis by exclusion

MCS needs a differential diagnosis with other pathological disorders such as mastocytosis and porphyria which are characterized by sensitization to chemicals and sunlight. According to the 1999[5] International Consensus, "Multiple Chemical Sensitivity should be excluded only if a single other multi-organ disorder, such as mastocytosis or porphyria, can account for the entire spectrum of signals and symptoms, and of the their association with chemical exposures, excluding Chronic Fatigue Syndrome (CFS) or Fibromyalgia (FM), which are not so related ".

3.3 Rapid Diagnostic Questionnaire of Exposures and Chemical Sensitivities (QEESI©)

Patient management with suspected Multiple Chemical Sensitivity (MCS) begins with a very accurate and comprehensive clinical anamnestic examination that defines the intensity, timing and mode of onset of symptoms, with particular attention to the possible role of environmental factors and to the possible temporal correlation between exposure and onset of symptoms.

This evaluation can take place through the validated QEESI© questionnaire designed by Claudia Miller and Mitzel in 1995[94] and validated in 1999 by Miller and Prihoda.[6]

The Quick Environmental Exposure and Sensitivity Inventory (QEESI ©) is realized, in fact, in 2005 by Prof. Claudia Miller as a short version of the previous EESI questionnaire for multiple intolerances from chemical sensitivities, proposed by the 1999 International Consensus.

The questionnaire has four scales of values to establish the severity of symptoms, chemical intolerances, other intolerances and the environmental impact on the health of the subject. Each scale provides a score from 0 to 10 values and also includes the

evaluation of the masking index, or of the possible lack of awareness on the part of the interviewed subject of his intolerance and of his responses to environmental exposures.

In a study carried out on 421 subjects, including four exposure groups and a control group, the QEESI © has shown to have a sensitivity of 92% and a specificity of 95% in discriminating chemical sensitive people and the common population. [6]
The Italian translation of the QEESI© has been prepared by the authors of this Consensus, the "Italian Workgroup on MCS".

3.4 Allergology evaluation

The medical literature and international legislation, such as the Federal Protocol of the United States Department for Rehabilitation, make it clear that MCS is not an allergy and that, unlike allergic diseases that are treatable and manageable with drugs, MCS involves a form of disability and impediment to social life.

However, recent studies have shown that MCS has an association with allergies, [22.99,100] for this the doctor must instruct the patient with suspected MCS to keep a diary of the symptoms on which to take note of the environmental exposures, of the food and of the eventual associated symptoms.

It is necessary to prescribe the total Immunoglobulin E (IgE) dosage and further investigations with specific IgE for food, pollen, dust, mold and drugs. In summary, in case of clinical suspicion, perform specific or recombinant IgE assays (ISAC and ALEX test).

In patients with MCS, patch tests have not always proved to be effective and, moreover, represent a risk factor that is incompatible with the Hippocratic principle "first do no harm". For this reason the allergological evaluation in MCS patients includes the use of patch tests (epicutaneous tests) as a second choice to be made only in those cases with clinical suspicion of contact reactions. On the base of precautionary principle it is good to follow the same general and safety measures adopted for the use of epicutaneous tests (patch tests) in the state of pregnancy, also taking into account the age and clinical status of the subject with MCS. Furthermore, the allergological evaluation must take into account that the patch test on MCS patients can cause not only reactions on the skin, but also and especially unexpected non-specific symptoms of different organs and systems. The authors report, for example, cases of patients with MCS who responded to the metal patch test with an epistaxis phenomenon.

The Lymphocyte Transformation Test (LTT), although not yet accredited at the level of scientifically based guidelines as a type IV metal allergy test, is indicated by several scientific works as an effective test (and above all free of risks because it is carried out with peripheral blood sampling) for the diagnosis of metal sensitization in patients with MCS and also has medical-legal validity.[22,96] It is hoped that soon the research will establish whether the LTT test fully meets the appropriateness criteria for this type of diagnosis.

3.5 Otolaryngology evaluation

Otorhinolaryngology evaluation is fundamental to characterize both the functionality and reactivity of the upper airways tract and the sensory pathways. The following tests are recommended:

· rhinolaringofibroscopia; [26,36,59,60,101-104]

· rhinometry; [26,36,59,60,101-104]

· olfactometry with Sniffin 'Stick Tests (threshold, discrimination and odor identification); [26,36,59,60,101-104]

· otoneurological tests, for the study of the vestibulum-oculomotor reflex, of visual dependency, of acoustic pathways (audio-impedance examination, ABR and otoacoustic emissions, hyperacusis questionnaires) and postural control (posturographic examination); [60.101-104]

· eventually PET/CT-FDG with pure olfactory stimulus.[26,36,59,60,101-104]

In the clinical experience of Prof. Paolo Pigatto of the University of Milan, exposure to irritating chemicals is associated in patients with MCS to epistaxis.

3.6 Domestic and workplace environmental assessment for individuals with MCS

The living environment of the patient with MCS must be analyzed to research the possible factors that trigger the sensitization to chemical substances, but also to the reduce risk factors to prevent further sensitization, once the patient's detoxification system suffers a damage.

It is possible to carry out the following environmental assessments according to the doctor's opinion and the sources of risk that are observed:

- - research into domestic dusts of metals, molds, endocrine disruptors (phthalates, bisphenol A (BPA);
- - measurement in the air of solvents such as formaldehyde, toluene, benzene, lindane and other volatile organic compounds;
- - measurement of low and high frequency electromagnetic fields, not only to verify compliance with legal limits, but also to identify any possible sources of exposure that worsen the oxidative stress; experiments on mice show that the EMF of Wi-Fi for example reduces the blood glutathione levels (often deficient in patients with MCS).

3.7 Neurological evaluation

The neurological consultation has a primary importance in the diagnosis of Multiple Chemical Sensitivity since the chemical exposures often have effects of neurological toxicity and symptoms reported by the patients, following the exposures, have as primary target neurological functions of the autonomous central nervous system, such as loss of balance, spatial disorientation, short-term memory loss, up to tremors and, in the most serious cases, convulsions.

In addition to the basic neurological examination, which is generally normalin MCS patients, it is essential to deepen the diagnosis with specific functional tests. In literature, the following tests are used for the diagnosis of MCS: pupillography, [105] Simple and Choice Reaction Time Tests, [106] Balance tests, [107] Visual Contrast Tests, [108-111] Visual Color Test, [107,112] Tests of Perception of Vibrations, [107] EEG, [57,112] SPECT[61-65]).

The assay of the S100B protein is recommended as an index of the permeability of the blood-brain barrier (Belpomme, 2015), [82] which is a consequence of exposure to toxic substances and electromagnetic fields.[113,114]

For patients with previous or current mercury exposure, the Neuro-Specific Enolase (NSE) assay in serum is indicated for neurological damage assessment.[115,116]

3.8 Dental evaluation

Patients with MCS with dental prostheses consisting of metal alloys or misture, such as amalgam fillings, should be visited to assess the possible release of metal ions in the oral cavity. Metals can cause two types of reactions: toxicological, due to prolonged exposure to low doses, and an allergological reaction that affects the immune system. The toxicological reaction can include neurotoxic and immunotoxic effects, as well as enzymatic alterations (decrease in glutathione) and hormonal disorders (especially in the thyroid and pituitary glands).[117,118]

Dental amalgam fillings can release in the saliva metals such as mercury, silver, tin, copper and nickel. Dental bridges and metal crowns can release gold, palladium, chromium, beryllium, cobalt and titanium. Ceramics and dental porcelain can release aluminum into saliva, while dental resins can release zirconium.[119]

The so-called "chewing-gum test", for the dosing of metals in chewing-gum post-chewing saliva, not available in Italy, is an indispensable tool for assessing the release of metals from dental materials in saliva and should be introduced routinely in clinical dental practice.[22,120,121]

The toxicological investigations recognized for the assessment of the patient's exposure to dental metals, or deriving from other sources.[22,119,122-124]

Analysis of metals in the blood:
- Mercury blood
- Blood lead
- Blood and / or serum aluminum
- Blood cadmium
- Blood manganese
- Blood and / or serum nickel

Analysis of metals in urine:
- Mercury in urine
- Arsenic in urine

3.9 Endocrinological evaluation

The endocrinologist must evaluate, in addition to the correct functioning of the thyroid that represents a primary target organ for the toxicity of chemical compounds (endocrine disruptors) [125] and electromagnetic fields, [75,82] the hormonal system of the hypothalamic-pituitary-adrenal axis, through the "basal cortisol" dosage and any other diagnostic investigations in case of cortisolemia alterations.[22,123]

3.10 Cardiological evaluation

Cardiocirculatory problems have been observed in the literature in patients with MCS. In particular, tachycardia, arrhythmia, mitral valve prolapse, [126] electrocardiogram abnormalities.[58,89]

These abnormalities of the cardiovascular system, on the one hand, are consistent with the findings of dyslipidemia in the composition of fatty acids in patients with MCS compared to controls,[127] on the other hand have been explained by Dr. W. J. Rea as the direct consequence of vasculitis associated with vasoconstrictive action local toxins and dysregulation of the autonomic central nervous system.[128,129]

In the presence of other risk factors, such as obesity, hypertension and diabetes, cardiological checks should be monitored accordingly.

3.11 Rheumatological evaluation

Medical research is investigating specific alterations of the immune system in MCS patients, with particular reference to circulating antibodies and T-helper / suppressor cells.[44,130]

An association was observed between MCS and rheumatologic diseases, especially Hashimoto's Thyroiditis, Systemic Lupus erythematosus (SLE), Psoriasis and Atopic eczema. For this reason, a baseline screening for ANA and ENA.[73,126,131,132] antibodies is recommended.

Levin and Byers (1992) found, in particular, thyroid and smooth muscle antibodies in MCS patients and some patients showed more autoimmuitary pathologies.[133] Levin and Byers also found that some patients developed cancer, lupus (LES) , multiple sclerosis and adult diabetes, assuming that, on a genetic basis, these diseases were activated precisely by the same environmental exposure that had caused the MCS.[44]

Dr. Alberto Migliore of the San Pietro Fatebenefratelli Hospital in Rome found a statistically significant association between MCS and Sjogren's Syndrome.[134]

In patients with MCS associated with exposure to toxic metals, in particular, an autoimmunity screening is advised, as the action on the immune system of metals is known, with the association of Hashimoto, Lupus (LES), sclerosis multiple and neurological autoimmunity such as those of gangliosides.[73,135,136]

3.12 Genetic evaluation (II level analysis)

Considering that MCS patients may have alterations in the genes involved in the metabolism of xenobiotic substances (eg, drugs, natural and/or environmental toxins) and that in turn could cause metabolic disorders and accumulation of toxic substances with an increase in oxidative stress , in some patients the evaluation of polymorphisms is useful in the case of chemotherapy treatments, medication intake.

Screening of genetic polymorphisms associated with phase I and II detoxification enzymes should be considered as second or third level screening according to the patient.

Since patients with Multiple Chemical Sensitivity may need to perform surgical interventions, long-term drug therapies or chemotherapeutic therapies, which may cause adverse effects due to the altered metabolism capacity of xenon biotic substances or due to immunological sensitization, in order to to avoid or reduce adverse effects, in selected cases it is advisable to carry out tests of polymorphisms of genes coding for the phase I and phase II detoxification enzymes (CYPs, GST, NAT).[10,74,75,137-141]

These analyzes, called "Integrated Drug Metabolism Panel (D-MIFAR)", are available at the Advanced Molecular Diagnostic Center (DIMA) of the Sant'Andrea Hospital in Rome, which specializes in personalized medicine and was commissioned in 2013 to lead a study project for the "Application of personalized diagnostic and treatment methods to the MCS (Multiple Chemical Sensitivity) syndrome: development of a model for the National Health Service" conducted at the UOD Advanced Molecular Diagnostics of the Sant'Andrea 753 Hospital of 12/21/2012 and on the funds of the study protocol M028048 F. Hofmann.

In patients with Multiple Chemical Sensitivity, some polymorphisms of genes coding for phase I and II detoxifying and antioxidant enzymes are prevalent that are responsible for a reduced, excessively fast or excessively slow metabolization of xenobiotic substances.[10,74,139-141]

For this reason, in consideration of the already present excess of oxidative stress, in case it is necessary to prescribe drugs to patients with MCS it is useful to carry out the analysis of these polymorphisms which is available at the MIFAR center of the Hospital Sant'Andrea in Rome. The center specializes in personalized medicine and is able to offer advice to select the most suitable drug for the patient's metabolism, especially if it is necessary to prescribe prolonged therapies, anesthesia or particularly toxic pharmacological treatments, such as chemotherapy.

3.13 Metabolic evaluation (II level analysis)

The research of the Italian groups has found statistically significant alterations of some biomarkers of oxidative stress. Although at present the research is not conclusive, the investigation through these markers can offer a picture of the patient's antioxidant capacity.

Examination of the detoxification metabolism through the dosage:

- levels of erythrocyte antioxidant and detoxifying enzymatic activities: catalase, superoxide dismutase, glutathione transferase, glutathione peroxidase;
- erythrocyte levels of reduced and oxidized glutathione.

Diagnosis of the production of reactive species (free radicals) and stable markers of cellular oxidation:
- levels of derivatives of reactive metabolic oxygen species (dROMS);
- levels of nitrotirosina (indirect indicator of nitrosative stress, and therefore of the levels of reactive nitrogen species, such as peroxynitrite);
- plasma levels of malonylaldehyde (MDA) and 8-hydroxyguanosine (8- (dOH) G;
- profile of fatty acids of the erythrocyte membrane.

Diagnosis of cellular energy balance:
- levels of erythrocyte ATP (adenosine triphosphate);
- levels of ATP (adenosine triphosphate) of platelet-enriched plasma.

Diagnosis of antioxidant defenses:
- total plasma antioxidant capacity
- low molecular weight antioxidant plasma levels: lipophilic antioxidants, i.e. vitamin E (alpha-tocopherol), reduced and oxidized coenzyme Q (ubiquinol / ubiquinone), vitamin A
- antioxidants and water-soluble radical scavengers, i.e. vitamin C (ascorbate), reduced glutathione, oxidized glutathione, alpha-lipoic acid;
- 6-hydroxy-melatonin urinary sulfate (also useful for understanding sleep disorders) .[82]

Diagnosis of inflammatory status:
- cytokine dosage, pro and anti inflammatory, with MULTIPLEX fluorescence immunoenzymatic microarray technique, through which it is possible to study the evolution of the profile at individual level and monitor the evolution of the pathology and the clinical efficacy of the treatments on the individual patient.

The Italian research of the group of Prof. Andrea Mazzatenta has identified a non-invasive diagnostic test for the evaluation of the patient's antioxidant capacity in relation to chronic hypoxia. Starting from the assumption that the physiological antioxidant defenses maintain the ROS (Reactive Oxygen Species) at harmless levels preventing damage with a balance closely related to the concentration of oxygen, doctors have found that chronic exposure to pollutants, as well as aging , can lead to chronic hypoxia that causes a remodeling of the structure and function of the cardio-respiratory system, of the brain, lungs, liver and muscles, all organs involved in MCS. Through the analysis of breath it is possible to evaluate the levels of carbon monoxide which are an index of chronic hypoxia.[49,50]

4. MANAGEMENT OF PATIENTS WITH MULTIPLE CHEMICAL SENSITIVITY

4.1 "First of all, do no harm": environmental chemical avoidance

Scientific research has clarified that Multiple Chemical Sensitivity is a pathology related to the environment and, unlike allergic reactions that are treatable with corticosteroids and antihistamines, the symptoms of MCS are caused by different mechanisms ranging from the imbalance of the detoxification system of substances xenobiotics, reduced cerebral perfusion, chronic inflammation. For this reason, the US federal legislation assigns to MCS, unlike allergies, the qualification of invalidating condition that prevents the full development of work capacity and social relationship.

Although there is no scientific consensus on the therapies for MCS, the literature agrees on the need to apply the principle of Hippocrates "first not to harm" and, therefore, the first effective therapy for patients with MCS is the avoidance of the specific substances that trigger reactions and also the avoidance of xenobiotics in general in order to prevent further sensitization.[9,142,143]

The doctor, therefore, has the fundamental task of instructing MCS patients and their families on the most suitable behaviors to avoid exposure to chemical substances and irritants, through the choice of furnishings, products for personal hygiene and for the home, clothes and food as free of chemical compounds as possible.

It is also important that the Legislator supports with specific rules the need for patients with MCS to pursue chemical environmental avoidance even in their professional activity, education and relationship life in order to keep them active and productive in society. The legal protection of the right to chemical avoidance would significantly reduce for these patients the risk of psychological and emotional consequences linked to social isolation, exclusion from the world of work and even the lack of social recognition of their condition.

Numerous legislative initiatives in the United States, Canada, Australia, Japan and Germany protect the right of MCS patients to work, education, safe housing and social participation through different protocols of environmental chemical avoidance, as per example the protocol for MCS of the Department of Urban Planning and Public Building of the State of Washington, the protocol for MCS of the Department of Rehabilitation of the State of Washington or the most recent Guidelines for Disabilities of the Government of South Australia .

4.2 Therapeutic aids for subjects with disabilities for MCS

In the United States the MCS is recognized by the Americans with Disabilities Act, the law on disability that provides the right to obtain therapeutic aids necessary to reduce the limitations associated with the disease. Also in Italy there are hundreds of patients with recognition of civil disability for MCS, even with percentages of 100%, with the right to

accompaniment and to the Law 104 for serious disability. Some have also obtained the equalization of MCS to a motor disability as it prevents the ability to move, for example on foot in busy streets or in public transport.

Patients with disabilities for MCS must be guaranteed, according to their individual needs and level of disability, the following therapeutic aids:

- latex-free paper mask;
- cotton mask and filters;
- mask for protection from gas and VOCs with HEPA and activated carbon filters;
- purifier for portable household air in metal with HEPA filters, with activated carbon, with a percentage of rubber gaskets less than 3% and relative filters;
- air purifier for cars in metal with HEPA filters, with activated carbon, with a percentage of rubber gaskets less than 3% and relative filters.
- active carbon water purifier and relative filters;
- gaseous oxygen;
- glass oxygen bubbler;
- Tygon oxygen tube with ceramic mask or latex free glasses.

This type of systemic allergy is difficult to diagnose through provocation tests, tests that also put the already hypersensitive patient at risk, but ascertains through the blood test of lymphocyte transformation that is currently provided by some ASLs to patients with MCS through the regime of residual pathologies.

4.3 Reduction of risk factors

Still within the scope of the protocol for the avoidance of sensitizing and irritating factors, it is useful to identify the possible factors of oxidative or immunological risk to which the patient is subjected to later try to remove or minimize them.

In patients with dental or orthopedic prostheses, for example, it is necessary to ascertain the eventual systemic lymphocytic reaction to the materials with which the patient is in contact 24 hours a day. It has been observed, in fact, in patients with MCS (but also with other chronic diseases) and with lymphocytic reactivity to metals, an improvement in symptoms following the correct removal of fillings and / or metal prostheses and their replacement with compatible materials.[96] Other studies have identified mercury as one of the possible mechanism of toxicological action of MCS .[14,144] In particular, an association has been found between autoimmunity, the symptom of chronic fatigue and metal lymphocytic allergy, especially nickel.[97]

The removal of mercury amalgam fillings, in particular, must take place through a protected removal protocol that allows absolutely excluding the patient's exposure to mercury vapors that are normally released during amalgam removal.[22,135]

Part of the literature is critical about the safety of dental amalgam and the scientific debate has not yet ended although several countries in Europe have already banned the use of this material. Evidence suggests taking into consideration the safe removal of these fillings in case of sensitization to one of the components or toxic overload from mercury or other metals.[145-148] In particular, a review of studies on the dental amalgam of the Swedish

government concludes with the indication to check for any chronic dental amalgam poisoning whenever there are unexplained multi-organ symptoms.

Other risk factors for MCS patients are pesticides and chemical fragrances.

Pesticides, including herbicides, insecticides and agricultural chemicals, are among the substances most commonly implicated in the activation of MCS cases in the United States and among those most often indicated as a cause of reactions by patients. The University of Maryland[149] conducted a review of the pesticide use policies adopted to ensure safe access to MCS patients, concluding that depending on the severity and conditions one of these systems can be adopted:

- Prohibition of pesticide use throughout the university
- Prohibition of pesticide use in some areas frequented by the patient with MCS
- Pesticide application only in periods when nobody is present
- Preventive notice of pesticide application to allow removal of subjects with MCS.

Since the chemical composition of perfumes, environmental deodorants, many personal hygiene products, and cleaning products is subject to industrial secrecy, it is not always possible to assess the possible risk factors on a case by case basis of each product for the patient. For this reason, in patients with MCS a reduction in the use of products containing chemical fragrances is indicated, even in the absence of a specific awareness of the same.

Schools, workplaces, hospitals, GP clinics, common environments (such as entrance halls and staircases for apartment buildings) and municipalities where MCS patients live should adapt to the vital need of these patients not to expose themselves to chemical fragrances, pesticides and other dangerous chemical compounds where there are alternative, risk-free solutions for the patient himself. In the Municipality of Rome, for example, several Departments have already issued instructions to the local municipal agency for pest control not to pass insecticides and herbicides for a radius of a hundred and fifty meters around the home of a patient with MCS, based on their reporting.

4.4 Symptomatic therapy of MCS

At the current state of scientific knowledge it is not possible to determine a standard protocol of pharmacological or nutritional treatment of MCS based on a consensus of evidence, although there are positive indications of the effectiveness of some approaches. For this reason, any therapeutic attempt must be addressed on the basis of the patient's individual clinical history and symptomatology and only after having implemented all the possible precautions for a reduction in sensitizing factors, chemical and / or irritant agents.

Any pharmacological therapy must be established through the evaluation of the patient's individual tolerance, with the investigation of past reactions to drugs and possibly through the study of genetic polymorphisms, where necessary (for example in the case of a family history of drug reaction).

We need to identify drugs without substances to which the patient is sensitive and products containing as few chemical agents as possible - such as preservatives, additives and artificial colorings - in order to avoid further sensitization. Any pharmacological therapy must start with a dosage at least halved compared to the recommended doses and then gradually increase it until the necessary doses are reached, to check if the patient tolerates the product.

Warning: intravenous medications should always be administered by glass drip and not plastic.

Italian research has identified a possible treatment to alleviate the discomfort related to the olfactory disorder in MCS: the intranasal administration of hyaluronic acid, which has proved to be quite effective and well tolerated by patients.[101]

4.5 Oxygen therapy and hyperbaric chambre

Some MCS patients report poor tissue oxygenation as an effect of exposure to toxic substances, oxidative stress, [150,151] or because the neural inflammation reduces blood vessel flow.[152]

Some studies suggest that, in cases of MCS with cardiorespiratory reactions, with symptoms of asthenia and mental confusion, it is suggested the verification of oxygen saturation (oximetry) in order to establish a possible oxygen therapy.[126,153] Therapy may be given as a remedy for reactions following accidental chemical exposures or as a therapy for a few minutes a day, depending on the case.

4.6 Nutritional integration approach

A recent study shows that MCS patients often have an inadequate nutritional habit, being underweight, overweight or obese, have a low amount of muscle mass and a poor quality diet.[154]

Several therapeutic approaches for MCS are reported in the literature, mainly aimed at correcting oxidative stress and electrolyte imbalance, but the research did not reach conclusive evidence on the risks and benefits.

A study funded by the German Ministry of Health and Social Affairs showed an improvement in symptoms in MCS patients who followed an approach aimed at lowering chronic inflammation and total toxic burden through nutritional supplementation, physical exercise, the sauna. This research confirms past studies that had documented the improvement of the clinical picture of MCS patients following a similar multidisciplinary approach.[155]

Some patients, however, taking supplements, such as vitamins and glutathione, suffer serious deterioration due to the mobilization of accumulated toxins and their consequent unwanted redistribution. The primary risk is to mobilize lipophilic toxins from fat tissue and cause their unwanted redistribution to other more sensitive fatty tissues, such as the brain and peripheral nerves.

Further double-blind investigations are needed to identify the effectiveness of each individual treatment and the interaction of multiple treatments. Thanks to the possibility of biochemically determining the imbalances present at the enzymatic, vitamin, trace and lipidomic level. These studies could also compare the results that are so objectivable with those found by the patient from a symptomatic point of view.

4.7 Multidisciplinary management of the patient with Multiple Chemical Sensitivity (MCS)

Given the extreme variety of afferent problems, a multidisciplinary diagnostic approach to MCS is needed. Preliminary results of a first study of the Nova Scotia Environmental Health Center in Canada indicate that a multidisciplinary approach results in a reduction in the use of health facilities by MCS patients and, therefore, also in a reduction in management costs. [156]

5. HOSPITALS FOR MCS

In consideration of the fundamental need of the patient with MCS to minimize the chemical environmental exposures, the healthcare environments aimed at welcoming patients with MCS must meet specific characteristics of air quality and reduction of chemical and electromagnetic pollutants. Research on the construction of Controlled Environmental Units for chemically sensitive patients began in the United States in the 1980s by Dr. William J Rea and his colleagues at the Environmental Health Center in Dallas. His experience is reported in some popular books and has been replicated by various environmental clinics around the world.

Environmental position

The clinic for patients with Multiple Chemical Sensitivity (MCS) must be positioned on the ground floor with an independent entrance or on the upper floors reachable via an external staircase so as not to impose on patients the crossing of hospitalization wards and waiting rooms. The outpatient clinic must be away from areas for the collection and disposal of waste, from the laundry, from chemical laboratories, from operating theaters, from radiological and chemotherapeutic departments, from heating boilers, from electrical control units and from mobile phone repeaters or Wi-Fi -Fi.

Le aree esterne all'ambulatorio devono essere tenute libera da pesticidi, erbicidi o altri fitofarmaci chimici. Prima di scegliere i locali da adibire ad ambulatorio per MCS è opportuno effettuare delle misurazioni professionali dei campi elettromagnetici di basa e di alta frequenza per assicurarsi che siano molto al di sotto della soglia stabilita dalla legge, in quanto i limiti di legge tutelano la popolazione in generale, ma non i soggetti vulnerabili e ipersensibili, come appunto sono i malati di Sensibilità Chimica Multipla.

Interior and furniture

The interiors and the furniture must be made with non-toxic and odorless materials, preferably steel, glass, plexiglass or other rigid phthalate-free plastic. In the clinic used for dentistry or surgery, it is preferable to use unpolished natural stoneware majolica also on the walls because they do not absorb odors and are easier to clean. The room should also be equipped with a kit consisting of latex-free and phthalate-free oxygen tubes, a washable ceramic mask with suitable and reusable soaps, and vinyl or cotton gloves.

Cleaning

Cleaning should preferably be carried out with steam-driven machines that have steel pipes and boilers without plastic parts, or with water and bicarbonate or with hydrogen peroxide subsequently rinsed with hot water (if it is necessary to disinfect). All tools must be for the exclusive use of these environments.

Access policy

Access to the MCS clinic is forbidden to anyone wearing perfumes, hair sprays or traces of cigarette smoke or car or environmental perfumers. A case of angioedema triggered by the scent of a nurse is reported.[158]

The ideal solution would be to adopt a pre-entrance vestibule or a locker room next to the clinic where the medical staff can change their overall gown in the hospital and wear one "for MCS" of cotton, washed only with water and bicarbonate or water and detergent without perfumes.

A kit must be prepared containing shirts, gloves, latex-free and phthalate-free oxygen tubes (for example Tygon), a latex-free oxygen mask that can be easily re-used by washing with suitable soaps.

For the MCS patient, only powder-free vinyl or nitrile gloves and cotton gloves can be used (those in the pharmacy are not suitable because they are treated with biocides).

Lighting

Natural lighting is the best, as light bulbs are suitable for incandescent or hot LED lights. while fluorescent lamps are to be excluded, compact fluorescent ones for several reasons: first of all because they contain mercury and can irreparably contaminate environments in case of breakage, secondly because they emit electromagnetic fields that can cause reactions in subjects with Lupus (LES) and with hypersensitivity, then because light can have a flicker that causes reactions in subjects with neurological problems, such as migraine.

6. HOSPITALIZATION

Safe hospitalization for MCS patients presents a difficult but not impossible challenge. The reference protocol for hospital reception and for the emergency room for chemically sensitive patients is that of the Mercy Medical Center in New York

There are many others.

In 2018, the Madrid region implemented a patient first aid protocol for MCS addressed to all hospitals.

The Kinston General Hospital in Kinsgton, Ontario, Canada, provides smoking, fragrance and latex prohibition protocols throughout the hospital.

The health administration of the region David Thompson, in the United States, provides for the prohibition of wearing and using perfumed products in all hospitals.

The hospital in Hamburg in Germany equipped a room with a ban on perfumes for patients staying with MCS.

In 2010, the Government of South Australia issued Guidelines for hospitals in the region to help administrators and health sector personnel respond effectively to patients' treatment and hospitalization needs in order to improve their response to therapies.[159]

In the introduction, the Guidelines define MCS as "a disabling condition described by severe physical symptoms triggered by exposure to chemicals". More details on the guidelines are described in the chapter on therapies. The South Australian Region has also included the MCS in the guidelines on disability with regard to construction: "Disability Access Checklist Guide for Government Owned & Leased premises" .[160]

These guidelines are intended to clarify the requirements of the Commonwealth Disability Discrimination Act (DDA) and state policy to promote the independence of disabled people. With regard to MCS, for example, the guidelines offer indications on construction materials, on the design of entrances (possibly independent and easily accessible).

Even in Italy there are several clinical experiences and hospitalization protocols for patients with MCS. At the moment there are two outpatient reception protocols for MCS: one at the Cona hospital in Ferrara and the other at the Lecce Hospital. Both refer to the protocol for chemically sensitive patients of the Mercy Medical Center in New York, USA, which represents a milestone on accessibility in hospitals for these patients.

In Rome in the past the hospital "G.B. Grassi "of Rome is based on the same protocol to implement a protocol for MCS First Aid.

In the past, other hospitals, such as the one in Castelvetrano (TP), the San Filippo Neri in Rome, the Sant'Andrea in Rome, the Niguarda in Milan, the San Giovanni Battista hospital in Foligno (PG), the L'Aquila hospital , the Niguarda hospital and the university hospital of Padua, have exceptionally adopted outpatient and hospitalization protocols for patients with MCS, without however integrating them with the hospital routine.

The case of the Castelvetrano hospital is particularly interesting because it has created the only example of a dental surgery for MCS, suitable for the safe removal of

dental amalgam fillings and other metal prostheses in a patient with severe MCS who was not able to travel , calling from Germany a dentist expert in this type of procedure.

The experience of hospitalization and surgical treatment at the Eagle hospital was described by the study on the use of anesthetics by Prof. Alba Piroli.[161]

6.1 Basic instructions for hospital management

The protocols for MCS must be adopted for patients with a history of chemical allergy contained in perfumes, insecticides, detergents, soaps for the home, etc.

The medical, paramedical, nursing and auxiliary personnel must be trained and must receive precise instructions on the behavior and procedures to be adopted in the event of admission of a patient with sensitivity to chemicals. All personnel must be involved and motivated to create a sanitary protection cord around the patient with chemical sensitivity, with exactly the same care with which the staff is trained to contain the biological risk in case of infection.

Where possible, the National Health System should guarantee the patient with MCS the possibility of receiving home care or the provision of care in the hospital for the shortest possible time.

6.2 Hospital admission

The staff that takes care of the patient must make sure of:

· arrange the patient in a private room, marked on the outside by a sign that warns of the presence of a subject with MCS and the absolute prohibition of entering if perfumes are worn;

· ideally the hospital room should be able to look out onto an internal courtyard or onto a road with little traffic so that it can be ventilated in the event of contamination;

Ificare decontaminate the room well in advance, cleaning it with water and bicarbonate and with other products that are always free of fragrances;

· use sheets, pillowcases and 100% cotton towels or allow the patient to bring them from home;

· mark the history of the patient's allergies and reactions in the medical record;

Are mark any pharmacological treatments that the patient has adopted in the past to contain the reactions;

Are mark antibiotics, anesthetics, anti-inflammatories and other essential drugs tolerated;

· advise the drug services center of the need to find the drugs tolerated by the patient;

Are advise the canteen service center of the patient's needs or allow his relatives to bring food from home;

· provide the patient with water in a glass bottle or allow him to take it from home;

· take the "kit for MCS" from the pantry.

6.3 Access rules in the hospital room

· Patient care staff should not wear perfumed products, hair spray or perfumes, or carry their mobile phone with them.

Ospedale Hospital staff must wash their hands with fragrance-free soap or white soap and wear latex-free gloves before touching the patient.

· You should not allow plants and flowers to be kept in the patient's room.

Iente No inflatable latex balloons.

· Alcohol disinfectants should not be used on the patient. Food grade alcohol is fine.

· Remove the top of the vials before removing the drugs.

· Do not give injections through a latex window.

· The patient must wash with products that are familiar to him and that do not cause him any reaction.

· Products derived from petroleum, such as hair gel, should not be used.

S MCS patients who have to undergo surgery should notify the Anesthesia department well in advance so that the doctor can discuss which anesthetic and what antibiotic and anti-pain medications to use.

6.4 Kit for MCS

The hospital must prepare an emergency and hospitalization kit for patients with Multiple Chemical Sensitivity, associating this disease with one color. At Mercy Medical Center, for example, materials for MCS are marked with yellow signs.

The kit must include:

· latex-free surgical gloves;

Ice gloves for clinical examination free of latex and dust;

· cleaning products without perfume and hydrogen peroxide;

· hydrogen peroxide for disinfection;

Per solution for drips with 5% dextrose in 1000 cc. of water;

· porcelain oxygen mask, Tygon tube or latex free glasses;

· Travert 1000 cc electrolyte solution (in glass);

500 500 cc sodium bicarbonate solution in glass vials;

· kit for intravenous administration in glass vials;

· sheets, pillowcases, tablecloths, sterile cotton towels, washed cotton pillows with non-perfumed detergents and without softener (not dry-cleaned);

· disposable cotton tunics washed with fragrance-free detergents;

O disposable headgear, shoe covers and tunics;

· latex free paper plasters;

· intravenous butterfly valve;

Cro Velcro Tourniquet / cuff sphygmomanometer;

· odorless liquid soap for staff;

· paper masks for staff without latex;

· 0.9% normal salt solution 1000 (in glass).

6.5 Pharmacy

· Use glass bottles for intravenous solutions.

· Do not use drugs to replace others or generic drugs for MCS patients without checking with their doctor first.
· MCS patients may react to dyes, preservatives, artificial sweeteners and flavorings, cereal starch or any other excipient.
· Masterful preparations are safer than tablets for MCS patients, given their lower content of thickeners and preservatives; furthermore, the masterly preparations allow the opening of capsules to ingest only the active ingredient.
Ate Monitor the medications of patients with MCS by listing these patients under the heading "Code of High Allergy".

6.6 Use of anesthetics for patients with MCS

Anesthetic management of MCS patients represents a major challenge for anesthesiologists. In particular, there is a need to administer only "safe" drugs for the patient, which do not trigger or worsen the symptoms of the disease.
In the past G.H. Ross (1992) [155] of the Dallas Environmental Health Center indicated some drugs used in anesthesia and potentially characterized by a good tolerance profile for MCS patients:
- pentothal (rarely used today);
-fentanyl and other substances similar to morphine with a long duration of action;
- curare;
- scopolamine and similar compounds.

Inhaled anesthetics should generally be avoided, because fluorinated hydrocarbons and nitrous oxide are notoriously immunosuppressive agents. On the other hand, these anesthetics, in particular Sevoflurane, have been used without problems in patients with MCS.[161,162]

According to a recent review concerning the approaches used by anesthesiologists in patients with MCS, [163] it is strongly advised against the use of inhaled anesthetic agents in patients who manifest significant symptoms due to exposure to artificial fragrances, preferring in these cases the use of only intravenous anesthetics.

Aiji Sato et al. highlight how scarce the scientific documentation that indicates the safest anesthesia in these patients, in particular "there are only four reports concerning general anesthesia in patients with MCS in the last years.[161-165] Therefore, it is important for anesthesiologists to determine the most appropriate drugs to administer that do not cause or worsen the symptoms, especially through a thorough clinical history of patients to be subjected to anesthesia.

The best approach is to prepare the environment and protect the patient from any substance that can be considered dangerous or cause inappropriate reactions.[142,166]

The study by McD Fischer and colleagues of 2008164 collects a series of 27 patients anesthetized with different methods in various structures. The analysis of the data showed that in patients with MCS the problems did not arise both during anesthesia but rather in the post-operative period, sometimes extending over time. Although these reactions cannot be considered life-threatening, the study recognizes that their influence on

patients' well-being is negative and sometimes there is a worsening of the clinical picture of MCS.

In the conclusions of the review, in the absence of guidelines, the authors offer suggestions dictated by common sense: 1) avoid the drugs that patients report not tolerate; 2) avoid drugs or substances that give positive allergy tests; 3) take information from patients even days after surgery.

Certainly it is important to avoid administering to the patient the drugs that, due to the anamnesis, are the cause of adverse reactions; in the same way it is good practice to encourage the patient to take note of the drugs he has taken in the past without problems or, conversely, to describe the symptoms manifested after taking certain substances. Knowing the drugs used in a previous anesthesia can certainly help anesthesiologists in choosing safer anesthetics for that individual patient.

This line of behavior appears to be the most correct for the evaluation of the patient when it is possible to rely only on the anamnestic data and on the examinations that eventually the patient already has available, as happens in urgent situations; however, in interventions scheduled for election, the anesthetic strategy should be guided by an even more thorough evaluation.

If time allows, the preparation of the patient with MCS must allow the doctor to take into account all the aspects of the complex syndrome that afflicts the patient and aim at the goal of a preparation for anesthesia as personalized as possible: l The objective must be to bring the patient to the intervention in the best possible conditions for him, to submit him to the most suitable anesthesia.

For this purpose it is necessary to keep in mind some aspects of the pathophysiology of MCS, especially the neuro-immuno-toxic component. In light of the role proposed by Martin L. Pall on the NO / ONOO circle as a mechanism of action underlying MCS and of diseases characterized by sensitization of the central nervous system, in these patients it is appropriate:

1. avoid stimulation of NMDA receptors,
2. avoid possible allergic reactions caused by exposure to drugs used during anesthesia,
3. know the detoxification capacity of drugs.

The first objective can be achieved by carrying out an intra-hospital pathway devoid of volatile organic compounds (VOCs) before the induction of anesthesia. It must also be taken into consideration that the drugs of general anesthesia depress all the functions of the central nervous system; many of these drugs depress the excitatory state of NMDA receptors [167,168], this condition allows the administration without apparent damage, even of volatile anesthetics which, when awake, would not be tolerated even in traces. In reality, as already mentioned above, the problem is not the intraoperative period, but the subsequent one. In fact, after the end of their delivery, small amounts of inhalation anesthetic continue to be eliminated from the body for hours through the airways, sometimes for more than a day.

This condition is to all intents and purposes similar to a continuous exposure and, as such, can cause states of increased malaise and disorientation that can be erroneously

attributed to the trauma of the intervention. It is intuitive that in this situation postoperative stress can significantly increase. Therefore, in the absence of data to the contrary, in patients with MCS it is advisable to abstain from the use of volatile anesthetics whatever their nature.

As previously stated, in MCS patients there is often a genetic structure that expresses enzymes with decreased ability to detoxify drugs and free radicals, so it is very important to have information about the actual metabolic capacities of the patient in order to implement an approach personalized therapy. This information can be provided today by the MIFAR (Integrated Drug Metabolism) profile developed at the S. Andrea Hospital in Rome, which can be accessed through the SSN. It is an exam that must be scheduled with adequate advance, considering that the laboratory takes at least 40 days to provide the complete answer to the exams and for the MIFAR report.

With the information acquired through these investigations it is possible to prepare an anesthesiology and therapeutic plan as personalized as possible, able to minimize the possibility of adverse events.

6.7 Food service

Patients with MCS need controlled nutrition based on their individual needs. The foods must be free of dyes, preservatives, artificial flavorings such as monosodium glutamate, artificial sweeteners, genetically modified organisms (GMOs), nor must they be cooked in aluminum or copper.

Many patients are hypersensitive to certain foods, such as milk, gluten or legumes for example. It should be noted that gluten intolerance affects many more people than celiac disease, even if it involves equally debilitating symptoms.

Food and drink for MCS patients must be kept in glass, steel and never aluminum or tin containers.

Often the ideal solution may be to allow the patient, with the doctor's consent, to bring their tolerated food and their own water from home.

In case of reaction to the food provided by the canteen, mark it on the medical record to avoid reactions in the future.

7. EMERGENCY TREATMENT FOR MCS

In order to guarantee to patients with Multiple Chemical Sensitivity (MCS) a first aid service, in case of emergency, it is essential to establish two types of procedures: one for ambulance rescue and one for admission to the First Aid ward.

Each emergency unit must be equipped with an "Emergency Kit for MCS", including:

Late a latex-free kit with gloves, a mask for the personnel and oxygen glasses for the patient;

- soap free of fragrances and fragrances;
- hydrogen peroxide;

· glass drip bottles;
· aluminum roll (like the kitchen roll) to seal off any odorous parts of medical equipment (tubes, rubber gaskets, etc.) or parts of furniture and furnishings contaminated with fragrances and not removable;
· Ice gown, headgear, disposable paper shoe covers.

In ambulance:
· the use of environmental deodorants in ambulances is prohibited;
· first aid personnel must refrain from smoking during service hours and from wearing perfumed hair gel, perfumes or deodorants;
· before leaving, ambulance personnel must obtain an "MCS emergency kit", they must remove all alcohol packs and latex objects from the ambulance, take the aluminum roll to cover those non-removable parts of the ambulance that can cause reactions in the patient, especially if made of rubber;
· turn off the ambulance engine on arrival to allow the patient to get on board, then close all doors before running the engine again;
· while travelloing in the traffic keep the windows closed and the air recirculation on.

At the arrival at the emergency room:
· immediately ask the patient with MCS the contact details of their referring doctor;
Ask the patient if she/he has an information in case of emergency and, if she/he is unconscious, check if she/he carries special instructions or health warning tags with her/him;
· check for the presence of any data in the hospital's computer archives;
· do not administer drugs, intravenous treatments, do not test the patient with MCS without his prior approval or without that of his personal physician, unless there is an immediate risk to his life;
· immediately isolate the patient with MCS from all other patients and visitors, ie the patient must not wait in the waiting room, but must be closed in a separate room;
Presente where present, the patient must be taken to a First Aid Room with a "priority code", possibly removing all latex products from the room, alcohol packages and rubber materials.
· take the "kit for MCS" from the pantry.

23rd May 2019

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Reference

1. Randolph TG. Human ecology and susceptibility to the chemical environment. Springfield, Ohio: Charles C. Thomas; 1978.
2. Randolph TG. Environmental medicine: beginnings and bibliographies of clinical ecology: Clinical Ecology Pubns; 1987.
3. Moss RW, Randolph TG. An alternative approach to allergies: the new field of clinical ecology unravels the environmental causes of mental and physical ills. New York: Lippincott & Crowell; 1980.
4. Cullen MR. The worker with multiple chemical sensitivities: an overview. *Occup Med* 1987; **2**(4): 655-61.
5. Multiple chemical sensitivity: a 1999 consensus. *Arch Environ Health* 1999; **54**(3): 147-9.
6. Miller CS, Prihoda TJ. The Environmental Exposure and Sensitivity Inventory (EESI): a standardized approach for measuring chemical intolerances for research and clinical applications. *Toxicol Ind Health* 1999; **15**(3-4): 370-85.
7. Miller CS, Prihoda TJ. A controlled comparison of symptoms and chemical intolerances reported by Gulf War veterans, implant recipients and persons with multiple chemical sensitivity. *Toxicol Ind Health* 1999; **15**(3-4): 386-97.
8. Miller C. The Quick Environmental Exposure and Sensitivity Inventory (QESSI©). 01/03/2019. http://qeesi.org/.
9. Sachiko H, Hiroshi Y, Hiroaki K, et al. Use of QEESI© questionnaire for a screening study in Japan. *Toxicol Ind Health* 2005; **21**(3-4): 12.
10. Schnakenberg E, Fabig KR, Stanulla M, et al. A cross-sectional study of self-reported chemical-related sensitivity is associated with gene variants of drug-metabolizing enzymes. *Environmental health : a global access science source* 2007; **6**: 6.
11. Hojo S, Kumano H, Yoshino H, Kakuta K, Ishikawa S. Application of Quick Environment Exposure Sensitivity Inventory (QEESI) for Japanese population: study of reliability and validity of the questionnaire. *Toxicol Ind Health* 2003; **19**(2-6): 41-9.
12. Skovbjerg S, Berg ND, Elberling J, Christensen KB. Evaluation of the quick environmental exposure and sensitivity inventory in a Danish population. *J Environ Public Health* 2012; **2012**: 304314.
13. Lacour M, Zunder T, Schmidtke K, Vaith P, Scheidt C. Multiple chemical sensitivity syndrome (MCS)--suggestions for an extension of the U.S. MCS-case definition. *Int J Hyg Environ Health* 2005; **208**(3): 141-51.
14. Pall ML. Multiple Chemical Sensitivity: Toxicological Questions and Mechanisms. In: John Wiley & Sons L, ed. General, Applied and Systems Toxicology; 2011.
15. Pall ML, Anderson JH. The vanilloid receptor as a putative target of diverse chemicals in multiple chemical sensitivity. *Arch Environ Health* 2005; **59**(7): 363-75.
16. Vojdani A, Thrasher JD, Madison RA, Gray MR, Heuser G, Campbell AW. Antibodies to molds and satratoxin in individuals exposed in water-damaged buildings. *Arch Environ Health* 2004; **58**(7): 421-32.
17. Rea WJ. A Large Case-series of Successful Treatment of Patients Exposed to Mold and Mycotoxin. *Clin Ther* 2018; **40**(6): 889-93.
18. Lieberman A, Rea W, Curtis L. Adverse health effects of indoor mold exposure. *J Allergy Clin Immunol* 2006; **118**(3): 763; author reply 7-8.
19. Meggs WJ. The Role of Neurogenic Inflammation in Chemical Sensitivity. *Ecopsychology* 2017.
20. Miller CS. Toxicant-induced loss of tolerance. *Addiction* 2001; **96**(1): 115-37.

21. Yunus MB. Central sensitivity syndromes: a new paradigm and group nosology for fibromyalgia and overlapping conditions, and the related issue of disease versus illness. *Semin Arthritis Rheum* 2008; **37**(6): 339-52.
22. Pigatto PD, Minoia C, Ronchi A, et al. Allergological and toxicological aspects in a multiple chemical sensitivity cohort. *Oxid Med Cell Longev* 2013; **2013**: 356235.
23. Gibson PR, Lindberg A. Physicians' perceptions and practices regarding patient reports of multiple chemical sensitivity. *ISRN Nurs* 2011; **2011**: 838930.
24. Wiesmuller GA, Hornberg C. [Environmental medical syndromes]. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2017; **60**(6): 597-604.
25. Bell IR, Hardin EE, Baldwin CM, Schwartz GE. Increased limbic system symptomatology and sensitizability of young adults with chemical and noise sensitivities. *Environ Res* 1995; **70**(2): 84-97.
26. Viziano A, Micarelli A, Alessandrini M. Noise sensitivity and hyperacusis in patients affected by multiple chemical sensitivity. *International archives of occupational and environmental health* 2017; **90**(2): 189-96.
27. Heinonen-Guzejev M, Koskenvuo M, Mussalo-Rauhamaa H, Vuorinen HS, Heikkila K, Kaprio J. Noise sensitivity and multiple chemical sensitivity scales: properties in a population based epidemiological study. *Noise Health* 2012; **14**(60): 215-23.
28. Hillert L, Jovanovic H, Ahs F, Savic I. Women with multiple chemical sensitivity have increased harm avoidance and reduced 5-HT(1A) receptor binding potential in the anterior cingulate and amygdala. *PloS one* 2013; **8**(1): e54781.
29. Emmett EA. Parosmia and hyposmia induced by solvent exposure. *Br J Ind Med* 1976; **33**(3): 196-8.
30. Doty RL, Deems DA, Frye RE, Pelberg R, Shapiro A. Olfactory sensitivity, nasal resistance, and autonomic function in patients with multiple chemical sensitivities. *Arch Otolaryngol Head Neck Surg* 1988; **114**(12): 1422-7.
31. Fernandez M, Schwartz GE, Bell IR. Subjective ratings of odorants by women with chemical sensitivity. *Toxicol Ind Health* 1999; **15**(6): 577-81.
32. Caccappolo E, Kipen H, Kelly-McNeil K, et al. Odor perception: multiple chemical sensitivities, chronic fatigue, and asthma. *J Occup Environ Med* 2000; **42**(6): 629-38.
33. Ross PM, Whysner J, Covello VT, et al. Olfaction and symptoms in the multiple chemical sensitivities syndrome. *Prev Med* 1999; **28**(5): 467-80.
34. Dantoft TM, Elberling J, Brix S, Szecsi PB, Vesterhauge S, Skovbjerg S. An elevated pro-inflammatory cytokine profile in multiple chemical sensitivity. *Psychoneuroendocrinology* 2014; **40**: 140-50.
35. Bascom R, Meggs WJ, Frampton M, et al. Neurogenic inflammation: with additional discussion of central and perceptual integration of nonneurogenic inflammation. *Environ Health Perspect* 1997; **105 Suppl 2**: 531-7.
36. Viziano A, Micarelli A, Pasquantonio G, Della-Morte D, Alessandrini M. Perspectives on multisensory perception disruption in idiopathic environmental intolerance: a systematic review. *International archives of occupational and environmental health* 2018; **91**(8): 923-35.
37. Mazzatenta A, Pokorski M, Di Giulio C. Real time analysis of volatile organic compounds (VOCs) in centenarians. *Respir Physiol Neurobiol* 2015; **209**: 47-51.
38. Ashford N, Miller C. Sensibilità alle Sostanze Chimiche; 2003.
39. 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): 218-42.
40. Bell IR, Schwartz GE, Peterson JM, Amend D. Self-reported illness from chemical odors in young adults without clinical syndromes or occupational exposures. *Arch Environ Health* 1993; **48**(1): 6-13.

41. Bell IR, Schwartz GE, Peterson JM, Amend D, Stini WA. 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): 315-27.
42. Albright JF, Goldstein RA. Is there evidence of an immunologic basis for multiple chemical sensitivity? *Toxicol Ind Health* 1992; **8**(4): 215-9.
43. Broughton A, Thrasher JD, Gard Z. Immunological evaluation of four arc welders exposed to fumes from ignited polyurethane (isocyanate) foam: antibodies and immune profiles. *American journal of industrial medicine* 1988; **13**(4): 463-72.
44. Levin AS, Byers VS. Multiple chemical sensitivities: a practicing clinician's point of view. Clinical and immunologic research findings. *Toxicol Ind Health* 1992; **8**(4): 95-109.
45. Ziem GE, Davidoff LL. Illness from chemical "odors": is the health significance understood? *Arch Environ Health* 1992; **47**(1): 88-91.
46. Galland L. Biochemical abnormalities in patients with multiple chemical sensitivities. *Occup Med* 1987; **2**(4): 713-20.
47. Johnson A, Rea WJ. Review of 200 cases in the environmental control unit, Dallas. 7th International Symposium on Man and His Environment in Health and Disease. Dallas, TX; 1989.
48. Levine SA, Reinhardt JH. Biochemical-Pathology Initiated by Free Radicals, Oxidant Chemicals, and Therapeutic Drugs in the Etiology of Chemical Hypersensitivity Disease. *Orthomolecular Psychiatry* 1983; **12**(3): 27.
49. Mazzatenta A, Di Giulio C, Pokorski M. Pathologies currently identified by exhaled biomarkers. *Respir Physiol Neurobiol* 2013; **187**(1): 128-34.
50. Mazzatenta A, Pokorski M, Cozzutto S, Barbieri P, Veratti V, Di Giulio C. Non-invasive assessment of exhaled breath pattern in patients with multiple chemical sensibility disorder. *Adv Exp Med Biol* 2013; **756**: 179-88.
51. Fisherman EW, Cohen G. Chemical intolerance to butylated-hydroxyanisole (BHA) and butylated-hydroxytoluene (BHT) and vascular response as an indicator and monitor of drug intolerance. *Ann Allergy* 1973; **31**(3): 126-33.
52. Black DW. The relationship of mental disorders and idiopathic environmental intolerance. *Occup Med* 2000; **15**(3): 557-70.
53. Staudenmayer H, Binkley KE, Leznoff A, Phillips S. Idiopathic environmental intolerance: Part 1: A causation analysis applying Bradford Hill's criteria to the toxicogenic theory. *Toxicol Rev* 2004; **22**(4): 235-46.
54. Davidoff AL, Fogarty L. Psychogenic origins of multiple chemical sensitivities syndrome: a critical review of the research literature. *Arch Environ Health* 1994; **49**(5): 316-25.
55. Davidoff AL, Keyl PM. Symptoms and health status in individuals with multiple chemical sensitivities syndrome from four reported sensitizing exposures and a general population comparison group. *Arch Environ Health* 1996; **51**(3): 201-13.
56. Orriols R, Costa R, Cuberas G, Jacas C, Castell J, Sunyer J. Brain dysfunction in multiple chemical sensitivity. *J Neurol Sci* 2009; **287**(1-2): 72-8.
57. Schwartz GE, Bell IR, Dikman ZV, et al. EEG responses to low-level chemicals in normals and cacosmics. *Toxicol Ind Health* 1994; **10**(4-5): 633-43.
58. Bell IR, Schwartz GE, Hardin EE, Baldwin CM, Kline JP. Differential resting quantitative electroencephalographic alpha patterns in women with environmental chemical intolerance, depressives, and normals. *Biol Psychiatry* 1998; **43**(5): 376-88.
59. Alessandrini M, Micarelli A, Chiaravalloti A, et al. Involvement of Subcortical Brain Structures During Olfactory Stimulation in Multiple Chemical Sensitivity. *Brain Topogr* 2016; **29**(2): 243-52.
60. Chiaravalloti A, Pagani M, Micarelli A, et al. Cortical activity during olfactory stimulation in multiple chemical sensitivity: a (18)F-FDG PET/CT study. *Eur J Nucl Med Mol Imaging* 2015; **42**(5): 733-40.

61. Callender TJ, Morrow L, Subramanian K. Evaluation of chronic neurological sequelae after acute pesticide exposure using SPECT brain scans. *J Toxicol Environ Health* 1994; **41**(3): 275-84.
62. Callender TJ, Morrow L, Subramanian K, Duhon D, Ristovv M. Three-dimensional brain metabolic imaging in patients with toxic encephalopathy. *Environ Res* 1993; **60**(2): 295-319.
63. Heuser G, Mena I, Alamos F. NeuroSPECT findings in patients exposed to neurotoxic chemicals. *Toxicol Ind Health* 1994; **10**(4-5): 561-71.
64. Hillert L, Musabasic V, Berglund H, Ciumas C, Savic I. Odor processing in multiple chemical sensitivity. *Hum Brain Mapp* 2006; **28**(3): 172-82.
65. Ross GH, Rea WJ, Johnson AR, Hickey DC, Simon TR. Neurotoxicity in single photon emission computed tomography brain scans of patients reporting chemical sensitivities. *Toxicol Ind Health* 1999; **15**(3-4): 415-20.
66. Pall M. Explaining Unexplained Illnesses : Disease Paradigm for Chronic Fatigue Syndrome, Multiple Chemical Sensitivity, Fibromyalgia, Post-Traumatic Stress Disorder, Gulf War Syndrome and Others. 1st ed; 2007.
67. Pall ML. Common etiology of posttraumatic stress disorder, fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity via elevated nitric oxide/peroxynitrite. *Med Hypotheses* 2001; **57**(2): 139-45.
68. Pall ML. NMDA sensitization and stimulation by peroxynitrite, nitric oxide, and organic solvents as the mechanism of chemical sensitivity in multiple chemical sensitivity. *FASEB J* 2002; **16**(11): 1407-17.
69. Pall ML, Bedient SA. The NO/ONOO- cycle as the etiological mechanism of tinnitus. *Int Tinnitus J* 2008; **13**(2): 99-104.
70. Pall ML, Satterlee JD. Elevated nitric oxide/peroxynitrite mechanism for the common etiology of multiple chemical sensitivity, chronic fatigue syndrome, and posttraumatic stress disorder. *Annals of the New York Academy of Sciences* 2001; **933**: 323-9.
71. De Luca C, Scordo G, Cesareo E, Raskovic D, Genovesi G, Korkina L. Idiopathic environmental intolerances (IEI): from molecular epidemiology to molecular medicine. *Indian J Exp Biol* 2010; **48**(7): 625-35.
72. De Luca C, Scordo MG, Cesareo E, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. *Toxicol Appl Pharmacol* 2010; **248**(3): 285-92.
73. De Luca C, Raskovic D, Pacifico V, Thai JC, Korkina L. The search for reliable biomarkers of disease in multiple chemical sensitivity and other environmental intolerances. *Int J Environ Res Public Health* 2011; **8**(7): 2770-97.
74. Caccamo D, Cesareo E, Mariani S, et al. Xenobiotic sensor- and metabolism-related gene variants in environmental sensitivity-related illnesses: a survey on the Italian population. *Oxid Med Cell Longev* 2013; **2013**: 831969.
75. De Luca C, Thai JC, Raskovic D, et al. Metabolic and genetic screening of electromagnetic hypersensitive subjects as a feasible tool for diagnostics and intervention. *Mediators Inflamm* 2014; **2014**: 924184.
76. De Luca C, Gugliandolo A, Calabro C, et al. Role of polymorphisms of inducible nitric oxide synthase and endothelial nitric oxide synthase in idiopathic environmental intolerances. *Mediators Inflamm* 2015; **2015**: 245308.
77. Gugliandolo A, Gangemi C, Calabro C, et al. Assessment of glutathione peroxidase-1 polymorphisms, oxidative stress and DNA damage in sensitivity-related illnesses. *Life Sci* 2016; **145**: 27-33.
78. 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): 159-63.

79. Johansson A, Millqvist E, Nordin S, Bende M. Relationship between self-reported odor intolerance and sensitivity to inhaled capsaicin: proposed definition of airway sensory hyperreactivity and estimation of its prevalence. *Chest* 2006; **129**(6): 1623-8.
80. Ternesten-Hasseus E, Lowhagen O, Millqvist E. Quality of life and capsaicin sensitivity in patients with airway symptoms induced by chemicals and scents: a longitudinal study. *Environ Health Perspect* 2007; **115**(3): 425-9.
81. Ternesten-Hasseus E, Johansson K, Lowhagen O, Millqvist E. Inhalation method determines outcome of capsaicin inhalation in patients with chronic cough due to sensory hyperreactivity. *Pulm Pharmacol Ther* 2006; **19**(3): 172-8.
82. Belpomme D, Campagnac C, Irigaray P. Reliable disease biomarkers characterizing and identifying electrohypersensitivity and multiple chemical sensitivity as two etiopathogenic aspects of a unique pathological disorder. *Rev Environ Health* 2015; **30**(4): 251-71.
83. Pigatto PD, Guzzi G. Prevalence and Risk Factors for MCS in Australia. *Preventive Medicine Reports* 2019; **in press**.
84. Steinemann A. Prevalence and effects of multiple chemical sensitivities in Australia. *Prev Med Rep* 2018; **10**: 191-4.
85. Caress SM, Steinemann AC. A national population study of the prevalence of multiple chemical sensitivity. *Arch Environ Health* 2005; **59**(6): 300-5.
86. Caress SM, Steinemann AC. A review of a two-phase population study of multiple chemical sensitivities. *Environ Health Perspect* 2003; **111**(12): 1490-7.
87. Steinemann A. National Prevalence and Effects of Multiple Chemical Sensitivities. *J Occup Environ Med* 2018; **60**(3): e152-e6.
88. Hausteiner C, Bornschein S, Hansen J, Zilker T, Forstl H. Self-reported chemical sensitivity in Germany: a population-based survey. *Int J Hyg Environ Health* 2005; **208**(4): 271-8.
89. Baldwin CM, Bell IR. Increased cardiopulmonary disease risk in a community-based sample with chemical odor intolerance: implications for women's health and health-care utilization. *Arch Environ Health* 1998; **53**(5): 347-53.
90. Baldwin CM, Bell IR, O'Rourke MK. Odor sensitivity and respiratory complaint profiles in a community-based sample with asthma, hay fever, and chemical odor intolerance. *Toxicol Ind Health* 1999; **15**(3-4): 403-9.
91. Baldwin CM, Bell IR, O'Rourke MK, Lebowitz MD. The association of respiratory problems in a community sample with self-reported chemical intolerance. *Eur J Epidemiol* 1997; **13**(5): 547-52.
92. Bell IR, Peterson JM, Schwartz GE. Medical histories and psychological profiles of middle-aged women with and without self-reported illness from environmental chemicals. *J Clin Psychiatry* 1995; **56**(4): 151-60.
93. Caress SM, Steinemann AC. National prevalence of asthma and chemical hypersensitivity: an examination of potential overlap. *J Occup Environ Med* 2005; **47**(5): 518-22.
94. Miller CS, Mitzel HC. Chemical sensitivity attributed to pesticide exposure versus remodeling. *Arch Environ Health* 1995; **50**(2): 119-29.
95. Fiedler N, Kipen H, Natelson B, Ottenweller J. Chemical sensitivities and the Gulf War: Department of Veterans Affairs Research Center in basic and clinical science studies of environmental hazards. *Regul Toxicol Pharmacol* 1996; **24**(1 Pt 2): S129-38.
96. Stejskal VD, Danersund A, Lindvall A, et al. Metal-specific lymphocytes: biomarkers of sensitivity in man. *Neuro Endocrinol Lett* 1999; **20**(5): 289-98.
97. Sterzl I, Prochazkova J, Hrda P, Bartova J, Matucha P, Stejskal VD. Mercury and nickel allergy: risk factors in fatigue and autoimmunity. *Neuro Endocrinol Lett* 1999; **20**(3-4): 221-8.

98. Watai K, Fukutomi Y, Hayashi H, Kamide Y, Sekiya K, Taniguchi M. Epidemiological association between multiple chemical sensitivity and birth by caesarean section: a nationwide case-control study. *Environmental health : a global access science source* 2018; **17**(1): 89.
99. Pigatto PD, Guzzi G. Contact allergy to metals and multiple chemical sensitivity. *Contact Dermatitis* 2019.
100. Hojo S, Mizukoshi A, Azuma K, et al. Survey on changes in subjective symptoms, onset/trigger factors, allergic diseases, and chemical exposures in the past decade of Japanese patients with multiple chemical sensitivity. *Int J Hyg Environ Health* 2018; **221**(8): 1085-96.
101. Alessandrini M, Micarelli A, Bruno E, et al. Intranasal administration of hyaluronan as a further resource in olfactory performance in multiple chemical sensitivity syndrome. *Int J Immunopathol Pharmacol* 2013; **26**(4): 1019-25.
102. Alessandrini M, Micarelli A, Chiaravalloti A, et al. Cortico-subcortical metabolic correlates of olfactory processing in healthy resting subjects. *Sci Rep* 2014; **4**: 5146.
103. Micarelli A, Viziano A, Bruno E, Micarelli E, Alessandrini M. Vestibular impairment in Multiple Chemical Sensitivity: Component analysis findings. *J Vestib Res* 2016; **26**(5-6): 459-68.
104. Micarelli A, Viziano A, Genovesi G, Bruno E, Ottaviani F, Alessandrini M. Lack of contralateral suppression in transient-evoked otoacoustic emissions in multiple chemical sensitivity: a clinical correlation study. *Noise Health* 2016; **18**(82): 143-9.
105. Shirakawa SR, W.J., Ishikawa S, Johnson AR. Evaluation of the autonomic nervous system response by pupillographical study in the chemically sensitive patient. https://aehf.com/articles/A77.htm.
106. U.S. Congress OoTA. Neurotoxicity: Identifying and Controlling Poisons of the Nervous System. Washington, DC: U.S. Government Printing Office: OTA-BA-436; April, 1990.
107. Kilburn KH. Chemical Brain Injury (Environmental Health): Van Nostrand Reinhold; 1998.
108. Anger WK, Letz R, Chrislip DW, et al. Neurobehavioral test methods for environmental health studies of adults. *Neurotoxicol Teratol* 1994; **16**(5): 489-97.
109. Hudnell HK, Benignus VA. Carbon monoxide exposure and human visual detection thresholds. *Neurotoxicol Teratol* 1989; **11**(4): 363-71.
110. Hudnell HK, Boyes WK, Otto DA, et al. Battery of neurobehavioral tests recommended to ATSDR: solvent-induced deficits in microelectronic workers. *Toxicol Ind Health* 1996; **12**(2): 235-43.
111. Hudnell HK, Otto DA, House DE. The influence of vision on computerized neurobehavioral test scores: a proposal for improving test protocols. *Neurotoxicol Teratol* 1996; **18**(4): 391-400.
112. Seppalainen AM, Raitta C, Huuskonen MS. n-Hexane-induced changes in visual evoked potentials and electroretinograms of industrial workers. *Electroencephalogr Clin Neurophysiol* 1979; **47**(4): 492-8.
113. Salford LG, Brun A, Sturesson K, Eberhardt JL, Persson BR. Permeability of the blood-brain barrier induced by 915 MHz electromagnetic radiation, continuous wave and modulated at 8, 16, 50, and 200 Hz. *Microsc Res Tech* 1994; **27**(6): 535-42.
114. Nittby H, Brun A, Eberhardt J, Malmgren L, Persson BR, Salford LG. Increased blood-brain barrier permeability in mammalian brain 7 days after exposure to the radiation from a GSM-900 mobile phone. *Pathophysiology* 2009; **16**(2-3): 103-12.
115. Guzzi G, Ronchi A, Bolengo I, et al. NSE: Marker of the Clinical Toxicity of Mercury. *Toxicol Lett* 2015; **238**(2 Supplements): S162.
116. Pigatto P, Ronchi A, Guzzi G. NSE as a biomarker of mercury exposure. *Clin Toxicol (Phila)* 2014: [ahead of print].

117. Guzzi G, Grandi M, Cattaneo C, et al. Dental amalgam and mercury levels in autopsy tissues: food for thought. *Am J Forensic Med Pathol* 2006; **27**(1): 42-5.
118. Minoia C, Ronchi A, Pigatto P, Guzzi G. Effects of mercury on the endocrine system. *Crit Rev Toxicol* 2009; **39**(7): 627.
119. Pigatto PD, Ferrucci S, Brambilla L, Passoni M, Rossi V, Guzzi G. Toxic metals screening in MCS patients. 16th Euro-Global Summit on Toxicology and Applied Pharmacology; 2019 July 04-05; Valencia; 2019.
120. Pigatto P, Arancio L, G. G, Severi G. Metals from amalgam in saliva: association with lichenoid lesions, leukoplakia, burning mouth syndrome. *Toxicol Lett* 2005; **158S**: 169.
121. Pigatto PD, Minoia C, Ronchi A, Guzzi G. Mercury in saliva: immunotoxic and allergenic metal. *Allergy Asthma Proc* 2009; **64**(Suppl. 90): 537.
122. Guzzi G, Ronchi A, Barbaro M, et al. Multiple chemical sensitivity and toxic metals. *Toxicol Lett* 2016; **258 (Suppl)**: s113.
123. Pigatto PD, Ronchi A, Dolcetta D, et al. Exposure to metals, multiple chemical sensitivity and neurogenic inflammation. *Journal of Clinical Toxicology* 2018; **8**: 1.
124. Guzzi G, Pigatto PD, Legori A, Ferrucci S, Brambilla L. Multiple sensitization to metals in MCS. *Contact Dermatitis* 2018; **79 (Suppl.1)**: 1.
125. Wade MG, Parent S, Finnson KW, et al. Thyroid toxicity due to subchronic exposure to a complex mixture of 16 organochlorines, lead, and cadmium. *Toxicological sciences : an official journal of the Society of Toxicology* 2002; **67**(2): 207-18.
126. Ziem G, McTamney J. Profile of patients with chemical injury and sensitivity. *Environ Health Perspect* 1997; **105 Suppl 2**: 417-36.
127. De Luca C, Valacchi G. Surface lipids as multifunctional mediators of skin responses to environmental stimuli. *Mediators Inflamm* 2010; **2010**: 321494.
128. Rea WJ. Environmentally triggered thrombophlebitis. *Ann Allergy* 1976; **37**(2): 101-9.
129. Rea WJ. Environmentally triggered small vessel vasculitis. *Ann Allergy* 1977; **38**(4): 245-51.
130. Heuser G, Vojdani A. Enhancement of natural killer cell activity and T and B cell function by buffered vitamin C in patients exposed to toxic chemicals: the role of protein kinase-C. *Immunopharmacol Immunotoxicol* 1997; **19**(3): 291-312.
131. Hybenova M, Hrda P, Prochazkova J, Stejskal V, Sterzl I. The role of environmental factors in autoimmune thyroiditis. *Neuro Endocrinol Lett* 2010; **31**(3): 283-9.
132. Nogue S, Fernandez-Sola J, Rovira E, Montori E, Fernandez-Huerta JM, Munne P. [Multiple chemical sensitivity: study of 52 cases]. *Med Clin (Barc)* 2007; **129**(3): 96-8; quiz 9.
133. Heuser G. Editorial: Diagnostic Markers in Clinical Immunotoxicology and Neurotoxicology. Interntnl J Occup Med Tox; 1992: V to X.
134. Migliore A, Bizzi E, Massafra U, Capuano A, Martin Martin LS. Multiple chemical sensitivity syndrome in Sjogren's syndrome patients: casual association or related diseases? *Arch Environ Occup Health* 2007; **61**(6): 285-7.
135. Daunderer M. Handbuch der Amalgam-Vergiftung; 1992.
136. Stejskal J, Stejskal VD. The role of metals in autoimmunity and the link to neuroendocrinology. *Neuro Endocrinol Lett* 2001; **20**(6): 351-64.
137. Berg ND, Rasmussen HB, Linneberg A, et al. Genetic susceptibility factors for multiple chemical sensitivity revisited. *Int J Hyg Environ Health* 2010; **213**(2): 131-9.
138. Cui X, Lu X, Hiura M, Oda M, Miyazaki W, Katoh T. Evaluation of genetic polymorphisms in patients with multiple chemical sensitivity. *PloS one* 2013; **8**(8): e73708.

139. Dantoft TM, Skovbjerg S, Andersson L, et al. Gene expression profiling in persons with multiple chemical sensitivity before and after a controlled n-butanol exposure session. *BMJ Open* 2017; **7**(2): e013879.
140. Fujimori S, Hiura M, Yi CX, Xi L, Katoh T. Factors in genetic susceptibility in a chemical sensitive population using QEESI. *Environ Health Prev Med* 2011; **17**(5): 357-63.
141. McKeown-Eyssen G, Baines C, Cole DE, et al. Case-control study of genotypes in multiple chemical sensitivity: CYP2D6, NAT1, NAT2, PON1, PON2 and MTHFR. *Int J Epidemiol* 2004; **33**(5): 971-8.
142. Gibson PR, Elms AN, Ruding LA. Perceived treatment efficacy for conventional and alternative therapies reported by persons with multiple chemical sensitivity. *Environ Health Perspect* 2003; **111**(12): 1498-504.
143. Ziem GE. Multiple chemical sensitivity: treatment and followup with avoidance and control of chemical exposures. *Toxicol Ind Health* 1992; **8**(4): 73-86.
144. Rowat SC. Integrated defense system overlaps as a disease model: with examples for multiple chemical sensitivity. *Environ Health Perspect* 1998; **106 Suppl 1**: 85-109.
145. Harris HH, Vogt S, Eastgate H, et al. Migration of mercury from dental amalgam through human teeth. *J Synchrotron Radiat* 2008; **15**(Pt 2): 123-8.
146. Heintze U, Edwardsson S, Derand T, Birkhed D. Methylation of mercury from dental amalgam and mercuric chloride by oral streptococci in vitro. *Scand J Dent Res* 1983; **91**(2): 150-2.
147. Mitchell RJ, Osborne PB, Haubenreich JE. Dental amalgam restorations: daily mercury dose and biocompatibility. *J Long Term Eff Med Implants* 2006; **15**(6): 709-21.
148. Mutter J. Is dental amalgam safe for humans? The opinion of the scientific committee of the European Commission. *J Occup Med Toxicol* 2011; **6**(1): 2.
149. Brown AE. Developing a pesticide policy for individuals with multiple chemical sensitivity: considerations for institutions. *Toxicol Ind Health* 1999; **15**(3-4): 432-7.
150. Ewing JF, Maines MD. Glutathione depletion induces heme oxygenase-1 (HSP32) mRNA and protein in rat brain. *J Neurochem* 1993; **60**(4): 1512-9.
151. Horvath I, Loukides S, Wodehouse T, Kharitonov SA, Cole PJ, Barnes PJ. Increased levels of exhaled carbon monoxide in bronchiectasis: a new marker of oxidative stress. *Thorax* 1998; **53**(10): 867-70.
152. Gregersen P, Klausen H, Elsnab CU. Chronic toxic encephalopathy in solvent-exposed painters in Denmark 1976-1980: clinical cases and social consequences after a 5-year follow-up. *American journal of industrial medicine* 1987; **11**(4): 399-417.
153. Ziem GE. Profile of Patients with Chemical Injury and Sensitivity, Part II. *Int J Toxicol* 1999; **18**(6): 9.
154. Loria-Kohen V, Marcos-Pasero H, de la Iglesia R, et al. Multiple chemical sensitivity: Genotypic characterization, nutritional status and quality of life in 52 patients. *Med Clin (Barc)* 2017; **149**(4): 141-6.
155. Ross GH. Treatment options in multiple chemical sensitivity. *Toxicol Ind Health* 1992; **8**(4): 87-94.
156. Fox RA, Joffres MR, Sampalli T, Casey J. The impact of a multidisciplinary, holistic approach to management of patients diagnosed with multiple chemical sensitivity on health care utilization costs: an observational study. *J Altern Complement Med* 2007; **13**(2): 223-9.
157. Sampalli T, Berlasso E, Fox R, Petter M. A controlled study of the effect of a mindfulness-based stress reduction technique in women with multiple chemical sensitivity, chronic fatigue syndrome, and fibromyalgia. *Journal of multidisciplinary healthcare* 2009; **2**: 53-9.

158. Tannenbaum H. Angioedema provoked by olfactory stimuli. *Can Med Assoc J* 1982; **127**(8): 735-6.
159. Australia GoS. A review of the Multiple Chemical Sensitivity (MCS) Guidelines for South Australian Hospitals 2010. 2010. https://www.sahealth.sa.gov.au/wps/wcm/connect/ff826a004f0e15b79823fe9ea2e2f365/MCS%2Bhosp%2BGuideline%2BReview%2Breport%2B2016.FINAL.pdf?MOD=AJPERES&CACHE=NONE&CONTENTCACHE=NONE (accessed 11/03/2019.
160. Australia GoS. Disability Access Checklist Guide for Government Owned & Leased premises. 2006. http://www.sacfs.asn.au/download/SA%20Gov%20Access%20Assement%20%20guide%20version%20SBF%20final%20DTEI%202007_30_11.pdf (accessed 11/03/2019.
161. Piroli A, Ciccozzi A, Petrucci E, et al. Anaesthesia management in patients with multiple chemical sensitivity syndrome. *Int J Immunopathol Pharmacol* 2013; **26**(4): 961-4.
162. Fernandez Martin MT, Alvarez Lopez JC. Sevoflurane anaesthesia for nasal surgery in a patient with multiple chemical sensitivity. *Rev Esp Anestesiol Reanim* 2018; **65**(1): 49-52.
163. Sato A, Furuno S, Kamimura Y, et al. General anesthetic management of a patient with multiple chemical sensitivity for oral surgery: a case report. *JA Clinical Reports* 2019; **5**(1): 10.
164. Fisher MM, Rose M. Anaesthesia for patients with idiopathic environmental intolerance and chronic fatigue syndrome. *Br J Anaesth* 2008; **101**(4): 486-91.
165. Stoppe C, Cremer J, Rex S, et al. Xenon anaesthesia for laparoscopic cholecystectomy in a patient with multiple chemical sensitivity. *Br J Anaesth* 2011; **107**(4): 645-7.
166. Skovbjerg S, Brorson S, Rasmussen A, Johansen JD, Elberling J. Impact of self-reported multiple chemical sensitivity on everyday life: a qualitative study. *Scand J Public Health* 2009; **37**(6): 621-6.
167. Hollmann MW, Liu HT, Hoenemann CW, Liu WH, Durieux ME. Modulation of NMDA receptor function by ketamine and magnesium. Part II: interactions with volatile anesthetics. *Anesth Analg* 2001; **92**(5): 1182-91.
168. Petrenko AB, Yamakura T, Sakimura K, Baba H. Defining the role of NMDA receptors in anesthesia: are we there yet? *Eur J Pharmacol* 2013; **723**: 29-37.