

COMMENTARY

Multiple chemical sensitivity: pursuit of a scientific consensus, need for a public health response

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Abstract

On the international scene, Multiple Chemical Sensitivity (MCS) is defined, by several experts, as a multisystem syndrome that develops following chronic exposures to low doses of common chemical contaminants. Its general characteristics are, however, the object of conflicting opinions and a source of debate and research aimed at the appropriate nosological and therapeutic frameworks. In the face of a potentially debilitating trend, both in the occupational and in the economical and social sphere, the scientific community has not so far found an agreement. This problem leads patients and their associations to periodically claim some requests. The syndrome is also taken into consideration at a political level, especially due to the close connection with the problems related to environmental pollution and to decision making in the field of control and prevention. For these reasons we believe that an appropriate widespread surveillance network for MCS should be set up in Italy, capable of intercepting possible cases, analyzing them at a multidisciplinary level, and following their evolution.

Key words

- multiple chemical sensitivity
- idiopathic environmental intolerance
- prevention

Environmental health is the study of the environmental causes of disease in humans. There is general agreement that most environmentally-induced diseases are characterized by a multifactorial etiology, and the cases attributable to a given exposure are indistinguishable in morphologic terms from those induced by different causal agents: the only observable difference is their diverse occurrence in subpopulation groups characterized by different exposure patterns. So, etiological-epidemiological studies characterized by the adoption of sophisticated designs in terms of case definition, exposure assessment, control of confounding and adequate statistical power, are required to estimate valid risk indicators. Concurrently, another lesson learnt from environmental epidemiology is that the general population includes susceptible or vulnerable subgroups, that can experience a higher burden of environmentally-induced disease than the general population, because of characteristics like age and gender, genetic predisposition, or a higher sensitivity to well-defined, or undefined, chemical or physical agents. In this frame, Multiple Chemical Sensitivity (MCS) is described by clinical ecologists as a complex disorder with multisystemic symptoms that

occur as a result of exposure to various environmental contaminants at concentrations below the threshold limit values (TLV) that, when and if fixed, are considered safe for the general population [1]. The main categories of chemicals involved in this process are: volatile organic chemicals (VOCs), apolar solvents [2], organophosphate and carbamate pesticides with anticholinesterase activity [3] and heavy metals. According to the toxicological theory, after chronic exposures or a single acute exposure, some more sensitive individuals may experience a progressive loss of tolerance – TILT theory – [4, 5] with lowering of the threshold. This condition would cause an overreaction of the organism with particular implication of the central nervous system, limbic hyperactivity [2, 6] and other apparatuses and systems also following exposures to different classes of substances. It is under investigation if, due to particular metabolic polymorphisms in detoxification enzymes [7, 8] and/or due to subsequent epigenetic modifications, these subjects would no longer be able to adequately detoxify their organisms, with an increase in free radicals (hydroxyls and nitroso compounds) capable of causing inflammatory processes in different organs and

tissues [2, 9]. The biomarker of inflammation, oxidative stress, reduced or altered detoxification enzymes, are considered as possible early marker for MCS. The main route of exposure, especially in the workplace, appears to be inhalation. Anyway, the co-presence and co-responsibility of dermal and oral absorption both in the initial awareness-raising phase and in the subsequent steps cannot be excluded. In some studies, an increase in the incidence of side effects from taking drugs [10] as well as some foods and beverages containing alcohol, caffeine and additives [4] has been found in these sensitive people. The analysis of the genetic polymorphisms implicated in drugs metabolism, can highlight particular patterns that reduce the ability of detoxification and modify pharmacological efficacy. Hopefully, in the future, specific patterns of these polymorphism will be considered a risk factor to develop MCS and analyzed both for primary prevention and for appropriate dosage of therapies.

Various chemical provocation studies have not so far provided unequivocal results [11] both in relation to the symptomatology tested, according to the substance administered by inhalation and in relation to the dose and time of administration. Some authors, hypothesizing the absence of a dose-response curve, have lowered the controlled administration even at doses lower than 1% of the TLV or have used non-toxic substances but able to determine responses at the level of the olfactory organ and of the central nervous system.

A relatively recent review on this topic [11] reached the following conclusion:

1. the provocation and genotyping studies are still limited in number and the results are sometimes controversial also due to the different diagnostic protocols adopted;
2. diagnostic certainty is difficult to meet because of multiplicity and non-specificity of symptoms. In the early stages, the results of the analyses carried on with current diagnostic techniques are generally negative;
3. although some diagnosis and treatment guidelines have been drawn up, there is still no agreement and standardization especially with regard to the definition of "case", the relative inclusion/exclusion criteria, the questionnaires and the clinical tests to be performed;
4. in the international scientific community, the debate is still ongoing with regards to the nosological classification;
5. the Italian Ministry of Health has not yet recognized MCS as a disease and no specific disease code has so far been assigned to the syndrome in the latest version of the International Classification of Diseases (ICD).

With these premises, as further proof of the scientific interest and of the need to find answers, some Italian and foreign experts signed a consensus statement on MCS therapies and prevention strategies. This recent report, entitled "Resolution of Rome" [12] states that this syndrome requires a multidisciplinary approach and that health facilities must work together with social services to help patients obtain adequate rehabilitation and integration into an adequate environment both at

workplace and at home. An updating of the literature in the last five years (2015-2019), focused on the Italian context, highlighted that some teams of experts are directing research on specific sectors of expertise, substantially in accordance with the international scientific literature.

One of the branches of research is the analysis of genetic variability in polymorphisms implicated in the detoxification of xenobiotics, in order to assess whether there are epidemiological findings that associate the presence of certain unfavorable variants in MCS to the onset of the syndrome. In some cases the differences in the levels of oxidative and nitrous stress were also evaluated in relation to a possible increase in the levels of cytokines in inflammatory processes [13, 14]. At the same time, the Tor Vergata University team is gradually confirming the hypothesis that limbic hyperreactivity, combined with a hypoactivation of the cortical areas, is the mechanism underlying a hyper response to both odorous (hyperosmia/cacosmia) and acoustic stimuli, by using a sophisticated neuroimaging technique [15, 16]. Furthermore, the same authors also considered the audiological aspect of patients [17, 18]. Although audiometric tests have shown no functional abnormality in these patients, the suspected MCS have a greater sensitivity and intolerance to noise, correlated to an increase in anxiety, depression and stress. These results tend to confirm the hypothesis of limbic hyperreactivity without excluding the character traits due to hypervigilant personalities, as hypothesized in other studies. Two recent publications, which show positive results, must also be considered, although referring to MCS superimposed on other severe diseases. In these articles, positive responses were described in relation to the use of specific anaesthetics for thyroidectomy surgery [19] and to therapeutic treatment with citalopram and/or Deep Transcranial Magnetic Stimulation [20]. The management of MCS patients poses particular problems in the establishment of the most appropriate therapy and dosage, and this is a further focus of interest.

In October 2018, the Italian National Institute of Health (ISS), hosted a multidisciplinary workshop on the available evidences and research needs (*available online as Supplementary Material*). Altogether, these contributions corroborated the notion of MCS as a syndrome that should be actively tracked, recognized, labeled and thereafter systematically investigated through a multi-level longitudinal approach. Several Authors [21-25] have drawn up proposals for guidelines for the diagnosis and treatment of MCS that provide for an accurate medical record and implementation depending on the symptoms of multiple clinical and instrumental tests, thus also verifying the presence of other diseases.

Accurate assessment of work environments presenting chemical risks can represent a good model of analysis for the detection of MCS cases, including those who present other diseases already in treatment [22, 24]. Appropriate application of the law on safety and protection of workers should allow to intercept suspected cases when, from the initial phase of tolerance (suitability for chemical risk), the first complaints about expo-

sure-related illness arise. Environmental and biological real time monitoring should improve the assessment of the problem [11].

In this context, the possibility of highlighting a tolerance threshold valid also for the most sensitive subjects is advisable. Risk characterization and assessment are very important in the whole process of defining the syndrome because the current gaps existing in the toxicological evaluation of substances and mixtures determine difficulties in performing an adequate *a priori* risk assessment for these suspected sensitive individuals. According to us it is therefore appropriate to collect epidemiological data through procedures capable of measuring exposure and to continue investigating genetic risk factors, markers of early exposure, acute and chronic effects. A deeper analysis is deserved by the modifications of physio biological parameters during the acute episodes (systemic toxicology) that could highlight effects similar to those following toxic exposure to certain categories of substances such as solvents and pesticides [11]. For example, the process of myocardial sensitization to catecholamines, combined with a process of limbic hyperactivity, could explain some of the symptoms (tachycardia with or without arrhythmia, tremors, dizziness, etc.) complained of by MCS patients, especially in the acute phases. The only partial reversibility of the process, as well as a possible undiagnosed damage through the currently available tests and instruments, could determine an exacerbation of the symptomatology following further exposures. Management of the MCS patient is both symptomatic and by avoidance of the substances identified as possible activators. Psychological/psychiatric support therapy is also recommended. Due to the lamented disability resulting from this condition, it is important to know if a cer-

tain therapy is not only able to limit the symptom, but eventually allows the complete recovery of the ability to tolerate further re-exposure to the substances.

It should also be emphasized that the absence of a scientific agreement on this syndrome leads patients to make periodic requests to the Government. This closes the cycle, switching the decision to a scientific level by requiring clarifications in the form of Parliamentary Questions that have been sent to the ISS over the years.

It's necessary now to develop a national network of public centers able to diagnose potential cases of MCS, following a training initiative, designed by ISS together with the collaborating centers (Figure 1). This means building a national epidemiological surveillance system for potential MCS cases by creating a network of centers that use a shared protocol. The availability of a national database of ascertained and suspected MCS patients, besides improving available scientific knowledge on the patterns and natural records of the disease could also generate etiologic hypotheses, to be tested in the frame of *ad hoc* analytical epidemiologic studies. Parallel to the much-needed effort to define a consensus on diagnostic procedures, equity in health care for these patients must be provided all over the country, avoiding the unbearable practice of health-driven migration. A new deal between MCS patients, politicians and the health system, on both national and regional level, appears to be necessary as it was also highlighted in a recent Italian Bill (Senate of the Italian Republic n. 1272-XVIII Legislature).

Conflict of interest statement

No conflict of interest.

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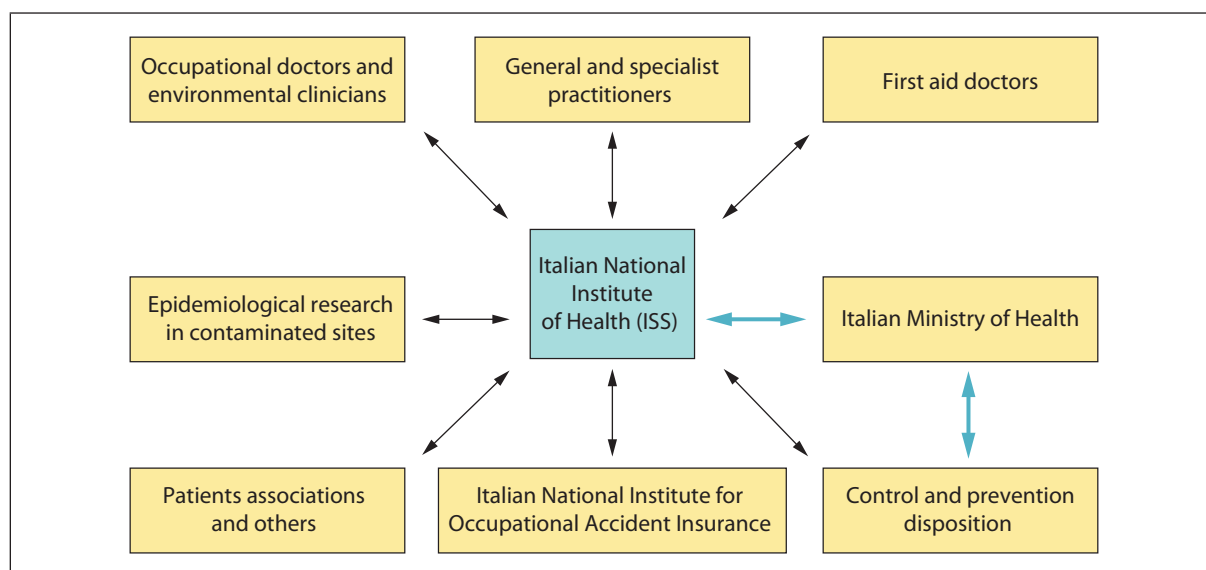


Figure 1

This is a possible information flow chart that provides for the sharing of medical records of suspected cases of mcs between the centers and the Italian National Institute of Health (ISS), in absolute respect of privacy. The aim is both performing general assessments for the verification of a single diagnostic protocol and both subsequently allow to set up a Register of Italian MCS cases, coordinated by the Institution.

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