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Sick Building Syndrome and multiple chemical sensitivity: patient-related risk factors

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Introduction

Sick Building Syndrome (SBS) and Multiple Chemical Sensitivity (MCS), together with other conditions such as fibromyalgia, chronic fatigue syndrome, and Gulf War syndrome, grouped under the more general definition of "idiopathic environmental intolerances" (IEI), are clinical entities for which there is currently no clear definition, because of the lack of proven pathogenic mechanisms, the wide array of symptoms, the absence of clear dose-dependent clinical symptoms by exposure to triggering factors, and the absence of clear-cut diagnostic criteria 1.

The attention of the scientific debate on these environmental pathologies is justified by the fact that they now represent a socio-economic problem of great magnitude, because of possible serious disability that may arise for individuals who are affected, with consequent low quality-of-life scores and partial or complete working and social disability.

Just think that several European countries have listed MCS under the ICD (International Classification of Diseases) -10 code of the World Health Organization (WHO); also Japan since 2009 gives special attention to indoor pollution, causing SBS, considered a point of attention also by Canada.

MCS is defined as a disorder attributed to exposure to extremely low levels of a wide variety of environmental chemicals 2, generally tolerated, which is manifested by an excessive awareness and intolerance of the individual to the same chemicals.

SBS is instead characterized by subjective responses to nonspecific conditions3, however associated with the use of a building, just called "sick", and due to causes resulting from the complex interaction of several factors, such as air pollutant concentrations, personal exposure level, and individual susceptibility.

While MCS is manifested as a long-lasting chronic disease, the symptoms of SBS disappear once left the building where they occurred.

Although these syndromes are usually treated as two different clinical entities, there is evidence in the literature suggesting the presence of features common to both (table 1).

In particular, SBS is often defined as a more limited form of environmental intolerance that, after further repeated exposure to pathogens, may develop into a chronic illness with chemical sensitivity4-5.

Other authors have shown rather a real overlap between the two syndromes, when referring to the classification based on the pathogenesis of the Sick House Syndrome (SHS, a concept of Japanese origin and derived from the SBS) type 1 and 2, indicating symptoms of chemical intoxication and symptoms developed possibly due to chemical exposure, respectively 6, unlike MSC type 3 and 4, respectively showing symptoms developed not because of chemical exposure but rather because of psychological or mental factors and symptoms developed due to allergies or other diseases.

To better characterize the relationship between exposure to chemicals and the occurrence of these complex syndromes, research has followed two basic approaches to identify the main risk factors, using the results of epidemiological and experimental studies on the physiopathogenic mechanisms and starting from the assumptions that underlie these environmental intolerances there is a dysfunction (molecular or genetic) of the defense network against chemicals.

Although not yet come to final results, is now commonly accepted that the interaction between environmental factors and individual factors (such as genetic characteristics and lifestyle habits) is essential for the onset of these environmental conditions.

The aim of this paper is to summarize the currently available data in the literature on MCS and SBS with regard to factors related to the individual that appear to be associated with the development of chemical sensitivity, a characteristic common to these two environmental pathologies.

Sick Building Syndrome

SBS has been defined by WHO as a reaction to the microclimate hitting about 50% of occupants of a building; it has been estimated that the 30% of the inhabitants of new or simply renovated buildings present symptoms referable to this syndrome 7.

The most common symptoms of SBS concern the visual system, the respiratory system, and the skin, and include headache, eye irritation, and fatigue 8.

SBS is then characterized by nonspecific symptoms experienced within a building; these symptoms, while common in the general population, become more prominent the longer a person stays inside a building, but they tend to disappear when he or she goes out9.

SBS, together with MCS, Gulf War syndrome, the side effects of silicone breast implants, chronic fatigue syndrome and irritable bowel syndrome, is included in the group of "functional somatic syndromes" (FSS) because of the non-specificity of symptoms, defined as "medically unexplained symptoms" (MUS).

SBS is difficult to define and many epidemiological studies have been performed, and a number of possible contributing factors have been reported, including factors related to the building as well as individual factors 10-12.

With regard to factors relating to the building (table 2), these can be physical (temperature, humidity, noise, light, electromagnetic radiation) 13-15, biological (microbiological contaminants, molds, etc...
) 16, 11, but mainly chemical (contaminants coming from the outside air or that originate in the confined environment) 15, 12, 17.

Among the most common indoor air chemical contaminants there are Volatile Organic Compounds (VOCs), defined by the US Environmental Protection Agency as substances with vapor pressure greater than 0.1 mmHg, by the Australian National Pollutant Inventory as any chemical based on carbon chains or rings with a vapor pressure > 2 mm Hg at 25 °C, and by the European Union as chemicals with a vapor pressure > 0.074 mm Hg at 20 °C. The main indoor sources of VOCs are represented by building materials, items of furniture, detergents, flavoring agents, products for dry cleaning, paints, adhesives, textile products, but can also be represented from anthropomorphic activities such as cooking and cleaning.

Among the VOCs, benzene, formaldehyde, toluene, and xylene are listed as important triggers of SBS.

The data reported by Takigawa and coll.
11 suggest that elevated levels of indoor chemicals in confined spaces may increase the risk of SBS in newly built houses.

In fact, there seems to be a close link between the increase in the presence of chemicals in the air, such as benzene, chloroform, and formaldehyde, and the onset of the SBS.

Even damages to structural components of the building due to water seepage can be factors increasing the chemical and microbial pollution load of the building 14; in relation to this, there are numerous studies, one of the first that of Meyer and coll.
16, conducted in different countries, that have shown a link between the presence of mold and the symptoms mentioned above.

On the other hand, the presence of fungal colonies, particularly Aspergillus spp and Cladosporium spp, may be associated with an increased risk of allergic sensitization11.

Another factor not to be overlooked among the factors attributable to the building is its age: it was observed that in the inhabitants of buildings erected before 1940, as well as those who live on a farm, these symptoms occurs in lesser extent than in those of new buildings.

In the study by Emenius and coll. 14, conducted on a group of 4089 children, born in predefined areas of Stockholm, and observed during their first 2 years of life, it was concluded relatively new apartment buildings, single-family homes with crawl space/concrete slab foundation, elevated indoor humidity, and reported wintertime windowpane condensation were the homes more frequently associated with recurrent wheezing in infants, representing one of the most common causes of hospitalization in early childhood.

Thus, improvements of the building quality may have potential to prevent infant wheezing.

In general, healthy indoor air should be sought both during planning and construction of new buildings as well as during their maintenance 14, and sometimes also with simple measures.

For example, the presence of houseplants can improve indoor air quality, especially in conditions of poor ventilation, and thus contribute to the revention of diseases related to confined spaces, such as SBS 15.

So little is known about the etiology of SBS, and even less on the clinical symptoms that could be useful to establish the diagnosis with certainty.

Recently, however, Israeli and Pardo 18 have proposed that SBS may also be included as a part of "Shoenfeld's syndrome".

In fact, Shoenfeld and Agmon-Levin 19 recently suggested that four conditions (siliconosis, the Gulf war syndrome (GWS), the macrophagic myofasciitis syndrome (MMF) and post-vaccination phenomena) sharing ten clinical and pathogenic (myalgias/myopathy, arthralgias/arthritis, chronic fatigue/sleep disturbances, neurological/cognitive impairments, fever, gastrointestinal, respiratory, and skin disorders, appearance of autoantibodies, diagnosis of defined autoimmune disease), may be included under a common syndrome entitled ASIA, “Autoimmune (Auto-inflammatory) Syndrome Induced by Adjuvants”.

SBS shares nine out of the ten main symptoms of ASIA; the only missing denominator in SBS is the diagnosis of defined autoimmune disease.

Multiple Chemical Sensitivity

MCS is one of the diseases of most public concern, as exemplified by new alarming definitions such as “chemical AIDS” and “twenties century disease”, as the number of subjects affected in developed countries has been growing steadily 20. It is not a coincidence in fact that in the USA it has been recognized since 1992 as a disabling illness. For example, the city of San Francisco introduced restrictions for chemically sensitive people, such as the prohibition of smoking in meeting rooms and using chemical cleaners and detergents before meetings 21. Moreover, because of the lack of a generally accepted diagnosis, the precise prevalence of this disease is difficult to assess, having to distinguish between self-reported cases and those clinically diagnosed, with a frequency in adults which varies from 9-33% to 0.9-6.3%, respectively 22. MCS is a complex syndrome, characterized by multi-organ symptoms, most frequently in the Central Nervous System, the respiratory system and the skin, which is attributed to exposure to low levels of chemicals, foods, or other environmental agents 23 present in concentrations below what is normally associated with toxicological responses 24. At present, there are at least seven case definitions for MCS; among them, the one given by the Consensus Conference held in 1999 in the USA is considered the most comprehensive and well-known case definition 2, whereby it is a chronic condition with symptoms that recur reproducibly in response to low levels of exposure (levels lower than those normally tolerated) to multiple unrelated chemicals and improve or resolve when incitants are removed 25. Among the proposals that intend to

extend the MCS Consensus Conference diagnostic criteria is that of Lacour and coll. 26, that suggest to define CNS-related symptoms as obligatory for the diagnosis of MCS. In addition, functional symptoms in at least one further organ system should occur and the syndrome should last more than six months and be associated with significant life-style or functional impairment. To date there have not been defined conventionally accepted diagnostic criteria, nor were identified specific biomarkers, such as to enable a common language that would allow a clear comparison between the clinical characteristics of patients from various countries around the world in Americas, Asia, or Europe, and useful to understand the mechanisms underlying this syndrome27-28, leaving major unresolved issues in the scientific debate.

Susceptibility to Chemical Sensitivity and risk factors related to the patient

Sex, age, and comorbidity are the risk factors related to the patient that seem to be more involved in susceptibility to chemical sensitivity (table 3), while alcohol abuse, smoking, level of employment or education were not associated with increased risk 22, 24. Both in the USA and in European countries has been revealed a high prevalence of MCS especially in women, as confirmed by some studies reporting a rate of 70-74% of female patients suffering from this syndrome 22, 27-28. Black and coll. 29 reported being over 25 years of age as a risk factor for MCS. The study by Hojo and coll. 27 reports a difference between the sexes with regard to the age of onset of the disease: in fact, the peak age for MCS in males was 30–34 years, whereas females showed a wide age distribution with three peaks, 30–34, 45–49 and 60–64 years. The same authors have also identified a number of possible triggers for the two sexes: comparing estimated onset factors between male and female patients, they revealed exposure to chemicals in the workplace to be markedly higher in males, while a variety of estimated onset factors were noted in females. Although this syndrome seems to affect mainly the adult population, chemical sensitivity manifests itself (albeit less frequently) also in teenagers with similar symptoms, primarily affecting nose, eyes, throat and lungs, such as shown by Andersson and coll. 22 in a study assessed in a teenage population of nearly 400 adolescents between 13 and 19 years. This difference in the prevalence of the disease among teenagers and adults indicate that chemical sensitivity is not an affliction that develops early, but during adolescence, a period in life associated with extensive physiological and behavioral developmental changes 22. Rarely the scientific literature reports pediatric cases of MCS, however, there are studies, like those of Inomata and coll. 23 and Woolf 30, showing that some childhood diseases can be similar or have elements in common with the MCS. In general, a diagnosis of chemical sensitivity in children is much more complex than in adults because these subjects are not able to identify and clearly explain their symptoms; in these patients a more careful evaluation of symptoms is required, taking into consideration the environment in which the patient lives, the comments made by parents, and the family history also from a socio-economic point of view 23, 30-31; moreover, the evaluation of the patient should also aim to the exclusion of other diseases such as asthma, allergies, or immune disorders. Inomata and coll. 23 suggest that an intolerance to food and drug additives containing azo dyes may in time develop into MCS, because additives themselves might play important roles as elicitors.

In general, the scientific literature of recent years have revealed interesting associations between MCS, asthma, and allergic diseases 32, 27.

In accord with several epidemiological surveys, the symptoms of pathologically increased chemical sensitivity are fairly prevalent in the general population, being more frequent and severe in the subjects with bronchial asthma 20. In addition, the onset of respiratory symptoms following exposure to fragrance products present in the air, a typical feature of MCS, has been found to be associated with bronchial hyper-reactivity to methacholine and a positive patch test for aromatic substances present in European Standard Series 33. Finally, Berg and coll. 24 reported that individuals with more severe self-reported sensitivity to chemicals in the air show increased non-allergic cutaneous reactions. It has often been suggested that psychological factors are involved in the pathophysiology of MCS and SBS. Several authors have shown, among the main patient-related risk factors for chemical sensitivity, anxiety, the presence of a history of psychiatric illness, current depression, current anxiety, panic disorder, and post-traumatic stress disease 22, 34. It should be noted that sexual abuse, and a history of familiarity and hereditary factors, may play an important role as factors of development of MCS in adulthood 29. Among the assumptions made regarding the etiology and pathophysiology of MCS, there is a defect in the ability to metabolize and detoxify chemicals (table 3). To understand how genetic differences in metabolism of xenobiotics can affect individual sensitivity to chemicals, have been taken into account several genes encoding for enzymes involved in the metabolism of endogenous or exogenous substances and that are known to present polymorphisms, to assess whether there is a correlation between polymorphisms of these genes and the onset of MCS 20, 34-35. In particular, it has been suggested a possible correlation with polymorphisms of the genes encoding for cytochrome P450 2D6 (CYP2D6), the arylamine N-acetyltransferase 2 (NAT2), and paraoxonase 1 (PON1) 35, and the gene encoding for the methylene-tetrahydofolate reductase (MTHFR), since vitamin B12 deficiency might be related to the onset of neurological symptoms, such as happens in chemical sensitivity self-reported or clinically diagnosed. Because anxiety is often associated with MCS, correlations between these syndromes and polymorphisms of the gene encoding for the holecystokinin 2 receptor were investigated 36. However, overall results reported in the literature are quite discordant, and do not confirm an association between MCS and genetic polymorphisms, suggesting that these genetic variants are of less importance in determining the development of MCS 34. Rather it may be an alteration of cytokine and redox profile to increase the possibility of an inhibition of enzymes metabolizing chemicals or pathways leading to their expression, thus leading to decreased metabolic capacity observed in patients with MCS 20.

Conclusions

Although many hypotheses have been advanced to explain MCS and SBS pathophysiology, the etiology of these syndromes remains largely unexplained.

Epidemiological studies conducted to determine the risk factors for the development of these pathological conditions have mostly suggested an association between MCS, asthma, and female sex, but often without the support of clinical objectives.

Furthermore, the data available in the literature do not confirm with certainty the possibility of identifying genotypes associated with the development of MCS, and suggest that perhaps the failure of the defense network against chemicals that underlies these diseases is based on molecular rather than genetics, being probably mediated by redox-active agents such as nitric oxide and inflammatory cytokines (e.g. IFN-gamma and IL-10).

The unpredictability of "gene-environment" interactions that could affect the metabolizer genotype, and the high genetic heterogeneity in patients with MCS may also explain the inconsistency of the results obtained so far in this field.

In light of this, studies on larger population samples still seem to be necessary.

The health effects associated with residence, working in modern non-industrial buildings, and schools, have become a growing concern for public health.

In recent decades, following the oil crisis of the '70s, houses and confined environments have changed dramatically, particularly in order to reduce energy consumption.

Through the introduction of new constructive solutions increasingly complex, together with the use of new materials with high thermal and acoustic efficiency, it was possible to make the interiors as real sealed containers 37, 14.

These changes, which affected indoor climate of buildings, often with poor ventilation, and the introduction of new items of furniture or new technology equipment, especially with regard to the areas used for work activities, have brought serious doubts on the salubrity of confined spaces.

That is why today more and more buildings are used in reference to terms such as "healthy or unhealthy" 37.

Non-specific subjective symptoms spanning various organ systems, with particular emphasis on the eyes, respiratory system, skin, and nervous system are often attributed to “environmental illness” 7.

These “environmental illness”, such as the MCS and SBS, have serious social and economic consequences, especially when they emerge in the workplace, where exposure to different pollutants, although for a number of hours per day lower than that in homes, accounts for a substantial fraction of the overall exposure 38.

In order to reduce the impact of these diseases on our society we need not solely multi-disciplinary studies, which more clearly would define the etiologic mechanisms, but also new definitions of norms, standards, tools, and methods of investigation.

In general, MCS and SBS are not life threatening 39, but the patients' quality of life and work performances are seriously affected, thus representing a socio-economic problem and a new challenge for public health.

The salubrity of indoor air environments is a fundamental right of the people who live, work, and study in them.

Since many and not completely understood are the factors that may cause syndromes such as SBS and MCS, the search for solutions to these problems must be conducted through the combined efforts of medical doctors, nurses, and architectural engineers 17, 40, even through the planning of methodological strategies to improve indoor air quality through coordinated action at the international level (WHO, International Council for Research and Innovation in Building and Construction, International Standardization Organization, etc.

), European Union level (European Parliament for new directives, and the European Committee for Standardization), and at national level, where, apart from the Institutions responsible for health protection, an important role can be played also by the professional societies (doctors, investigators, and engineers, architects, building owners and facility managers), and patients associations.

Table 1. Common symptoms in SBS and MCS

Neurological/cognitive impairments
Headaches
Fatigue
Lack of concentration
Sleep disturbances
Myalgias/myopathy
Arthralgias/arthritis
Fever
Gastrointestinal disorders
Respiratory disorders
Mucous-membrane irritation
Eye irritation/eye dryness
Throat irritation
Cough
Skin disorders
Skin inflammation
Skin itching
Chemosensory changes
Olfactory disorders
Visual disturbances

Table 2. SBS causes related to the building

Factor	Source	References
Physical factors		
Temperature over 23°C	Improper placement of thermostats, inability of the building to compensate for climate extremes, etc...	13
Humidity over 60-70%	Poor humidity control	13-14
Inadequate ventilation	Improper design or operation of ventilating, heating and air conditioning systems	14-15
Biological factors		
Microbiological contaminants, molds, fungal colonies, etc...	Breed in stagnant water accumulated in ducts, humidifiers and drain pans, or collected on ceiling tiles, carpeting, or insulation	11, 16
Chemical factors		
Chemical contaminants from indoor sources		
Volatile Organic Compounds (VOCs)	From building materials, items of furniture, detergents, flavoring agents, products for dry cleaning, paints, adhesives, textile products	15
Chemical contaminants from outdoor sources		
Pollutants from motor vehicle exhausts, plumbing vents, and building exhausts	Entering the building through open windows, ventilation system air intakes and building leaks	12, 17

Table 3. Susceptibility to MCS and investigated patient-related risk factors

Factor		References
Sex	Higher prevalence in women	22, 27-28
Age	Being over 25 years of age	29
Peak age for MCS		
Males	30-34 years	27
females	3 peaks: 30-34; 45-49; 60-64 years	
Concomitant pathologies		
Allergic diseases, including food and drug additives intolerance		23
Asthma		27, 32
Psychiatric illness (current depression, current anxiety, panic disorder, etc)		22, 34
Psychological factors		
Post-traumatic stress disease, sexual abuse, etc		22, 29
Genetic susceptibility (polymorphisms causing a defect in chemicals metabolism)		
Cytochrome P450 2D6 (CYP2D6),		35
Arylamine N-acetyltransferase 2 (NAT2)		35
Paraoxonase 1 (PON1)		35
Methylene-tetrahydofolate reductase (MTHFR)		34
Cholecystokinin 2 receptor		36

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