

Review Article

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The role of sensory and olfactory pathways in multiple chemical sensitivity

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Abstract: Multiple chemical sensitivity (MCS) is characterised by non-specific and recurring symptoms affecting multiple organs and associated with exposure to chemicals, even at low concentrations, which are, under normal circumstances, harmless to the general population. Symptoms include general discomfort, cardiovascular instability, irritation of the sensory organs, breath disorders, hypersensitivity affecting the skin and epithelial lining of the gut, throat and lungs, anxiety, and learning and memory loss. Chemical intolerance is a key distinguishing feature of MCS, limiting considerably patients' lifestyle with serious social, occupational and economic implications. Since no specific diagnostic markers are currently available for chemical intolerance, the diagnosis relies on clinical symptoms. Despite the formulation of several hypotheses regarding the pathophysiology of MCS, its mechanisms remain undefined. A person-centred care approach, based on multidisciplinary and individualised

medical plans, has shown promising results. However, more definite treatment strategies are required. We have reviewed the main experimental studies on MCS pathophysiology, focusing on the brain networks involved, the impact of environmental pollution on the olfactory system and the correlation with other pathologies such as neurodegenerative diseases. Finally, we discuss treatment strategies targeting the olfactory system.

Keywords: central nervous system; environmental intolerances; multiple chemical sensitivity; olfactory bulb; olfactory system; pollution.

Introduction

Multiple Chemical Sensitivity (MCS) is a multisystem and poly-symptomatic syndrome. MCS subjects display a complex symptomatology due to intolerance to chemical agents [1]. Haanes and coworkers [2] have defined MCS as “symptoms associated with environmental factors”. The authors claim that MCS symptoms may not be linked to pathophysiological mechanisms, further underlining the lack of consensus in the scientific community. From a diagnostic point of view, MCS is difficult to recognise clinically and patients risk marginalisation [1, 3]. MCS pathogenesis can be traced back to an exaggerated response to oxidative and nitrosative stress, chronic neurogenic and systemic inflammation [4], altered blood brain barrier (BBB) permeability, abnormal xenobiotic metabolism and insufficient detoxifying capacity [5]. The resulting hyper-activation of sensory receptors has an impact on metabolic pathways, the immune system and the central nervous system (CNS), linked to oxidative stress [6, 7], and can result in multiple pathological manifestations. In MCS, contaminants, such as pesticides, biocides, heavy metals, metabolites, mycotoxins, perfumes, detergents, volatile organic compounds, such as formaldehyde, 2-ethylhexanol and dust [7, 8], play a role in triggering the symptoms. The difficulty in identifying the specific profile of MCS symptoms is strengthened by their

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overlapping with other chronic disease manifestations, which hinder the ability of the clinician to give a definite diagnosis at early stages. Based on our clinical experience and clinical practice-based knowledge of MCS pathophysiology, we hypothesise that MCS etiology is based on exposure to neurotoxic substances that, through inhalation, can reach the cerebral circulation leading to the pathology and manifestation of symptoms. From the nasal cavities, substances continue through the lamina cribrosa of the ethmoid bone in the olfactory bulb (OB) and beyond, e.g. to the limbic system, the diencephalon and up to the cerebral cortex. With this in mind, we have reviewed the existing literature, to gather state of the art information on MCS and prompt further studies in this area, focusing on the olfactory system. We have summarised the clinical studies relevant to MCS in Table 1.

Review search criteria

We searched Pubmed/Medline using the keywords “multiple chemical sensitivity”, “environmental intolerance”, “smell”, “olfactory stimulation”, “olfactory bulb”, “intranasal therapy” alone or combined. We chose papers from 1987 to 2020 based on their content and relevance to the aim of this review.

MCS diagnostic criteria

Currently, the diagnosis of MCS is based on the Cullen's inclusion criteria related to the patient's clinical history and their score from the Quick Environmental Exposure and Sensitivity Inventory (QEESI). According to the criteria developed by Cullen in 1987 and confirmed by a multidisciplinary evaluation in 1999 [9, 10], MCS is a chronic state involving more than one organ or system and its symptoms are triggered by even low-level exposures to chemicals and environmental substances of different classes and mode of action. No single test is currently available for diagnosis of MCS. MCS diagnosis is based on the following:

- Careful anamnesis based on a questionnaire to analyse the symptoms with specific reference to environmental exposure to micro-organisms and chemical substances, especially in relation to the patient's professional life.
- Application of QEESI and Environmental Exposure and Sensitivity Inventory (EESI) evaluation tests using a scale of reference to benchmark the results against what would be expected in a physiological/healthy

state [11, 12]. QEESI, also known as the “TILT Test”, is a multistep questionnaire that determines levels of chemical sensitisation to environmental triggers, marking the type, location and severity of symptoms after exposure and the consequent impact on life quality. This test evaluates the patients' answers and the cumulative score is a good indicator of patient's life quality.

Reduced detoxification capacity in MCS

Fabig [13] showed that MCS is triggered by a reduced detoxification capacity of xenobiotic substances. This is observed in MCS patients who express genes responsible for a reduced functioning of the enzymes involved in the metabolism of chemical substances [13]. Therefore, genetic testing approaches could be valid to aid diagnosis of MCS subjects. Xenobiotics are lipophilic and lack of electrical charges at physiological pH, which facilitates their absorption, but hinders their elimination. The purpose of the metabolism of contaminants is therefore to convert lipophilic substances into hydrophilic and facilitate excretion through two phases. During phase I, xenobiotics undergo hydrolysis, oxidation, reduction and methylation. During phase II, conjugation occurs by adding a polar compound to a functional group, thus facilitating the excretion of the final metabolite from the cell [14]. Catalytic enzymes regulate the pathway and speed of reactions. The catalysts of the first phase are P450 enzymes, e.g. CYP2D6 [15, 16]. The second phase relies on enzymes such as glutathione-S-transferase (GST) [17]. Relying on the compromised detoxification system, studies on chemically hypersensitive populations have been focused mainly on the genetic panel of these patients. The allelic variants of cytochrome P450 isoforms (CYP2C9, CYP2C19, CYP2D6, and CYP3A5), glutathione S-transferases (GSTP1, GSTM1 and GSTT1), and antioxidants [catalase, superoxide dismutase (SOD)] were studied in MCS subjects compared to healthy controls (HC) [17] and catalase and GST enzyme activities were found to be lower in MCS [6, 17]. GST polymorphisms may reduce glutathione conjugation, a key protective mechanism against oxidative damage. Reactive oxygen species generated as by-products of phase I reactions are rapidly reduced to non-toxic “physiological” levels by antioxidant enzymes such as SOD, catalase, glutathione peroxidase and by low-molecular-weight antioxidants, such as glutathione. Therefore, complex symptoms can arise when levels of reduced and oxidised glutathione decrease [17].

Table 1: Multiple chemical sensitivity clinical studies. Abbreviations listed: analysis of variance (ANOVA), single photon emission computed tomography (SPECT).

Disease	Numbers of subjects	Controls	Statistical analysis	Aim	Reference
Multiple chemical sensitivity syndrome	6 patients and 6 controls	Gender- and age-matched healthy subjects	T-tests to analyse brain activity and Mann-Whitney U test for the analysis of olfactory stimulation results	To evaluate olfactory stimulation	Azuma et al., 2015
Multiple chemical sensitivity syndrome	12 patients and 7 controls	Gender- and age-matched healthy subjects	T-tests to analyse brain activity and Mann-Whitney U test for the analysis of olfactory stimulation results	To evaluate olfactory stimulation	Azuma et al., 2016
Multiple chemical sensitivity syndrome	26 patients and 11 controls	Gender- and age-matched healthy subjects	Statistical differences were calculated by means of a 'between-groups' and 'within-subjects' ANOVA	To evaluate sub-cortical metabolic changes during a neutral and pure olfactory stimulation by using positron emission tomography	Alessandrini et al., 2016
Multiple chemical sensitivity syndrome	29 treated and 30 controls	Vehicle-treated subjects	Paired t-test with Spearman's rank correlation	To investigate the effect of a nasal spray containing hyaluronic acid in patients with multiple chemical sensitivity	Alessandrini et al., 2013
Multiple chemical sensitivity syndrome	18 patients and 18 controls	Gender- and age-matched healthy subjects	Independent t-test	To investigate hyper-reactivity in multiple chemical sensitivity during whole-body exposure to low concentrations of n-butanol	Andersson et al., 2016
Multiple chemical sensitivity syndrome	18 patients and 19 controls	Gender- and age-matched healthy subjects	Repeated-measures ANOVA	To characterise the consequences of low levels of acrolein in various plasma molecules	Claeson et al., 2017
Multiple chemical sensitivity syndrome	133 patients and 218 controls	Gender- and age-matched healthy subjects	Chi-square test and Mann-Whitney U test	To determine genetic, immunological, and metabolic makers for multiple chemical sensitivity syndrome	De Luca et al., 2010
Multiple chemical sensitivity syndrome	131 patients and 498 controls	Gender- and age-matched healthy subjects	Mann-Whitney U test	To investigate the reliability and validity of the quick environment exposure sensitivity inventory (Japanese Version)	Hojo et al., 2003
Multiple chemical sensitivity syndrome	203 patients and 162 controls	Gender- and age-matched healthy subjects	Chi-square test	To determine if multiple chemical sensitivity cases differed from controls for genetic polymorphisms in drug-metabolising enzymes	McKeown-Eyssen et al., 2004
Multiple chemical sensitivity syndrome	186 patients, 72 gulf war veterans and 76 controls	Gender- and age-matched healthy subjects	Cronbach's alpha for each scale	To measure salient aspects of chemical sensitivity that permit cross-comparisons	Miller et al., 1999
Multiple chemical sensitivity syndrome	8 patients and 8 controls	Gender- and age-matched healthy subjects	Wilcoxon test for analysis of basal brain activity and post-exposure differences. Mann-Whitney U test for analysis of psychometric scales data	To determine whether multiple chemical sensitivity patients present brain SPECT and Psychometric scale changes after chemical challenge	Orriols et al., 2009

Sensory mechanisms in MCS

The sense of smell can be defined as perception of a stimulus by the CNS, which activates the olfactory receptors (ORs) [18]. The neurons of the olfactory system are exposed to the external environment. Therefore, the olfactory

epithelium (OE) is particularly vulnerable to environmental neurotoxicants. The olfactory nerve can also act as a vector for neurotoxic agents to be transported into the CNS, bypassing the BBB [19]. Smell is controlled by specialised sensory cells localised in the main OE within the nasal cavity [20]. Olfactory sensory neurons (OSNs) or

olfactory receptor neurons are sensory neurons within the olfactory system. The main role of OSNs is to detect environmental information such as odorants and to transmit this information to the OB. In fact, each OSN expresses an OR gene and all OSNs send their axons to targets expressed in the OB, which are called glomeruli. The OSNs regenerate approximately every month [20]. Olfactory signal transduction begins with the activation of an OR in the ciliary membrane. This leads to an increase in cyclic AMP (cAMP) synthesis through the activation of the adenylyl cyclase type III (ACIII) enzyme via a G protein-coupled cascade [21]. The increase in cAMP concentration causes the cyclic nucleotide-gated ion channels to open, leading to an increase in intracellular Ca^{2+} concentration and depolarisation of the cell membrane by the Ca^{2+} -activated Cl^- channel. The ORs, olfactory marker protein, G_{olf} protein α -subunit, and ACIII are specific to the olfactory pathways and therefore could represent suitable therapeutic targets for MCS [21]. Chemosensory perception and autonomous responses during chemical exposure have been reported in MCS patients [22]. For instance, the aim of a study by Andersson and co-workers [22] was to investigate hyper-reactivity in MCS during whole-body exposure to low n-butanol concentrations. Participants with MCS and HC were exposed to the odorant n-butanol at increasing concentrations, using an exposure chamber. The MCS group displayed greater intensity in the perception of odours, higher heart rate and increased symptoms over time compared to controls. No differences were found in the two groups in regards to respiratory rate and tonic electrodermal activity responses. Therefore, MCS patients differ from HC in terms of autonomous responses and chemosensory perception during chemical exposure [22].

Brain networks involved in MCS

Genetic, infectious, and neurological factors have been implicated in MCS [23]. From a neurological perspective, the trigger may be a neurological reflex mechanism, a stimulus to emotional memory, or a conditioned response to olfactory stimuli [24]. Physiologically, the pathway that joins the olfactory region to the orbito-frontal cortex through the thalamus is a control area for olfactory stimuli [24]. Furthermore, the olfactory region is also connected to the limbic system, which is responsible for vegetative responses and smell-related emotions [24]. Alterations to this pathway could give rise to symptoms that confuse the observer, such as those presented by MCS patients after odour exposure. Several studies have investigated the

activation and involvement of cerebral networks in MCS to dissect the underlying mechanisms. For example, Azuma and co-workers observed significant activation of the prefrontal cortex (PFC) during olfactory stimulation in MCS patients [25]. In this study, the recovery process of regional cerebral blood flow (rCBF) was examined after olfactory stimulation in MCS patients and HC using near infrared spectroscopy imaging. This study showed that olfactory stimulation induced significant activations in the left and right PFC and even more evident activations in the orbitofrontal cortex (OFC) in MCS patients compared to controls [25]. The OFC is associated with response to stimuli, emotions and preferences in the decision-making processes. These results suggest that a strong exposure to irritating chemicals activates the PFC during olfactory stimulation in MCS patients, and the OFC remains activated even after stimulation [25]. In a further study, Azuma and co-workers [26] investigated the association of odour thresholds and changes in rCBF during olfactory stimulation at odour threshold levels in MCS. Two different odorants were used for olfactory stimulation, sweet and faecal, and were employed at three different concentrations (zero, odour recognition threshold, and normal level of perceived odour) in patients with MCS and controls. MCS patients displayed stronger brain responses at the recognition threshold (faecal odour) and normal perceived levels (sweet and faecal odours) compared to controls. These responses may involve cognitive and memory processing systems during past exposure to chemicals prompting further research in this area [26]. Several neuroimaging studies showed a correlation between odours and cortical activation in MCS. For instance Alessandrini and co-workers [27] investigated the subcortical metabolic changes during neutral (NC) and pure (OC) olfactory stimulation using F-2-fluoro-2-deoxy-D-glucose (FDG) with a tomography procedure in MCS patients and HC. This study showed a higher metabolism in the bilateral olfactory cortex during NC in MCS patients compared to HC. In addition, the odour pleasantness scale positively correlated with the MCS subjects' bilateral putamen FDG uptake in OC. This study also described a metabolic index of behavioural and neurological aspects of MCS complaints [27]. Another study carried out by Andersson [28] aimed to investigate whether brain responses in presence of low levels of olfactory and trigeminal stimuli differ in individuals with and without idiopathic environmental illness (IEI), and how they occur. The authors suggest that sensitised responses in the limbic system are crucial to symptom manifestation. Thus, brain responses to isoamyl acetate and carbon dioxide administered intranasally were evaluated in IEI patients and HC using functional magnetic

resonance imaging. The IEI group had a higher blood oxygenated level signal (BOLD) compared to the controls in the thalamus and in the parietal areas and a lower BOLD signal in the superior frontal gyrus. In conclusion, the above results point towards a limbic hyper-reactivity and an inability to inhibit salient external stimuli in IEI subjects. IEI responses were not characterised by hyper-reactivity in sensory areas [28].

A fundamental element in the theoretical explanations behind chemical intolerance (CI) is that olfactory sensitisation implies greater reactivity to odour stimulation, however, empirical evidence is scarce. In another study reported by Andersson [29], it is stated that olfactory sensitisation involves brain networks relevant to pain processing. Subjects who are sensitive to olfactory stimulation, express a higher BOLD in regions relevant to pain processing, as well as primary and secondary olfactory projection areas [29]. It has been speculated that CNS limbic pathways involved in anxiety are altered in MCS individuals due to the nature of MCS symptomatology. As limbic structures are most susceptible to kindling-induced seizures (kindling is defined as “a model of synaptic plasticity whereby repeated low-level electrical stimulation to a number of brain sites leads to permanent increases in seizure susceptibility”), it is possible that MCS may occur via a kindling-like mechanism [30].

Environmental pollution and MCS

MCS has been linked to environmental and construction pollution [31]. For instance, in the Västerbotten and Österbotten study [31], two questionnaires focusing on factors such as lifestyle, general health, symptom frequency and the emotional and behavioural impact of the building-related intolerance were administered to ~5,000 participants. The participants were mostly women who reported avoidance behaviour and required medical assistance. Building-related intolerance with broad-spectrum symptoms has been associated with somatic and psychiatric diseases and functional somatic syndromes. Similar multi-morbidity has been reported for environmental intolerance (EI), regardless of the type of exposure under investigation, and for CI, electromagnetic hypersensitivity and sound intolerance. In particular, in MCS, psychiatric comorbidity is commonly reported, however, somatic comorbidity and concurrent functional somatic syndromes have also been observed [31]. Cleason and co-workers designed a study to determine the chemical and physical sources in the environment that can trigger symptoms among individuals with

different EIs [32]. Participants in the Västerbotten environmental health study answered 40 specific questions regarding the environment and exposure to chemicals, buildings, electromagnetic fields and sounds [32]. The EI groups reported more symptoms from the different sources than the group with building-related intolerance. In addition, individuals with chemical and sound intolerance reported symptoms from building-related trigger factors, and individuals with electromagnetic hypersensitivity reported symptoms from chemical triggers [32]. In a subsequent study, Cleason and co-workers [33] studied the impact of heptane and a mixture of heptane and acrolein on the plasma levels of oxylipins, endocannabinoids and related lipids in healthy individuals and individuals affected by CI. No relevant variation in bloodstream oxylipins or endocannabinoids was observed in CI subjects, suggesting a limited role in CI-related inflammation [33].

Hyperosmia and MCS

The majority of MCS patients suffer from hyperosmia, an increased olfactory acuity consisting in heightened sense of smell, usually caused by a lower threshold for odour perception. This perceptual disorder arises from an altered signal between the ORs and the olfactory cortex. Prolonged olfactory stimulation on the olfactory nerve and the olfactory cerebral areas is the key cause of this symptom. Haehner and co-workers showed that mutations in the sodium channel Nav1.7, encoded by the SCN9A gene, causes high olfactory sensitivity [34]. Through various tests performed on a 50-year-old woman with this mutation, it was found that she displayed high olfactory acuity and intranasal sensitivity, very low thresholds for thermal, tactile and pain detection in the trigeminal area and hyperalgesia to the lower legs [34]. This case report illustrates gain of function in olfactory and pain sensation associated with a Nav1.7 channel mutation. Nevertheless, the genetic basis of olfactory variations in human olfactory thresholds, and in particular in hyperosmia, remains largely unknown. OR segregating pseudogenes are useful candidates to study odorant-specific variations in human olfactory thresholds [35]. To explore this hypothesis, Menashe and co-workers [35] investigated the association among olfactory detection threshold phenotypes of four odorants and segregating pseudogene genotypes of 43 ORs genome-wide. They found a strong association between the variants of the single nucleotide polymorphism in

OR11H7P and sensitivity to isovaleric acid. These findings suggest a functional role of OR11H7P in isovaleric acid sensitivity [35].

Potential treatments targeting the olfactory system in MCS

MCS is currently orphan of treatment, however, several approaches have been proposed based on antioxidant therapy and intranasal substance administration.

Intranasal pathways offer an efficient alternative for the administration of drugs to the CNS. The anatomical structures involved in the transport of drugs administered intranasally include the trigeminal nerve, the olfactory nerve and the rostral migratory stream [36]. To test the efficiency of therapy administration through the intranasal route, a study evaluated the role of the rostral migratory stream following intranasal administration [36]. In this study, intranasal administration of fluorescent tracers and iodinated peptides in mice showed distribution throughout the OB, hippocampus, cortex and cerebellum, suggesting that this system is suitable for efficient drug transport within these CNS structures without affecting peripheral tissues such as lungs and blood [36]. In a further study, intranasal administration of hyaluronic acid (HA) was used to improve the olfactory performance in MCS [37]. The effect of HA dosed intranasally, on the odour threshold and the quality of life in MCS patients were investigated on two groups of MCS patients treated with an HA or a saline nasal spray. Both groups were analysed using the Sniffin Battery Stick Test (SST), the questionnaire on olfactory disorder (QOD) and the Zung Anxiety Scale (SAS) before and 30 days after treatment. The authors showed a reduction in odour threshold and improvement in QOD and SAS after one month in the HA group. Therefore, intranasal administration of HA may represent a valid treatment option to alleviate olfactory symptoms in MCS [37].

Furthermore, intranasal administration of reduced glutathione, the most abundant endogenous antioxidant and a key regulator of oxidative stress and immune function, may also represent a valid therapeutic option in MCS patients. Glutathione depletion has been reported in several pathological states such as MCS and Parkinson's disease [38–40]. In addition, glutathione deficiency perpetuates oxidative stress, mitochondrial dysfunction and cell death [38]. Glutathione can be administered as an intranasal spray to reach CNS tissues [38–40] and has been investigated in Parkinson's disease and MCS [38–40]. For instance, intranasal reduced

glutathione resulted in increased brain glutathione levels, which persisted for at least 1 h, as observed in 15 subjects with mid-stage Parkinson's disease and determined by magnetic resonance spectroscopy [38]. In addition, a second study showed safety of intranasal reduced glutathione (maximum dose administered was 6000 mg/day) in PD patients [39].

A further study assessed patient-reported outcomes (tolerability, adverse events and health benefits) after intranasal reduced glutathione administration using a survey administered to 70 patients [41]. Reported indications for reduced glutathione prescriptions were MCS, allergies/sinusitis, Parkinson's disease, Lyme disease and fatigue. In this study, 80% of patients considered reduced glutathione to be effective without significant adverse effects [41]. In conclusion, intranasal administration of glutathione may need further evaluation as a treatment for respiratory and CNS diseases where oxidative stress is a contributor to disease pathophysiology [41]. Carnosine (β -alanyl-L-histidine) is synthesised in the olfactory system and has been identified as a potential therapy for oxidative stress-related olfactory dysfunction due to its antioxidant and neuroprotective properties. For instance, the neuroprotective effect of carnosine was investigated in a mouse model of vanadium inhalation [42]. Vanadium generates olfactory dysfunction and increases malondialdehyde (MDA) levels, loss of dendritic spines and necrotic neuronal death in granule cells, which can be modulated by carnosine, which improves olfactory function, increasing dendritic spines and decreasing neuronal death and MDA levels. Further evidence shows that carnosine can modulate zinc and copper, which could represent one of the mechanisms underlying its neuroprotective and neuromodulatory action [43]. Therefore, carnosine warrants further studies in MCS since it inhibits the production of free radicals and reactive aldehydes suppressing protein glycation, and has already shown potential benefits in other CNS disorders [44].

Conclusions

The pathogenesis of MCS is still unknown although several hypotheses have been formulated in regards to the role played by alterations in several CNS regions. MCS diagnosis is challenging because current protocols are purely based on the patient's clinical history and assessment of exposure to chemicals and their biological and physiological effects, which can be misleading. Monitoring and control of environmental and chemical hazards are at the

basis of health and safety practices in the workplace. Thus, validated and harmonised guidelines, clarifying the maximum average chemical concentration to which workers can be exposed in a specific time-period, need to be implemented and enforced. We support an approach based on the stratification of subjects based on clinical symptoms to identify high-risk individuals and design a personalised therapeutic strategy tailored to the patient's need and clinical symptomatology. In our review, we have highlighted that pesticides, metals and pollution play an important role in MCS, particularly in regards to their effect on the olfactory system. For this reason, beyond an approach based on prevention of the environmental exposure, locally treating the olfactory mucosa with antioxidants or other active substances such as carnosine, reduced glutathione and HA, may be a valid treatment strategy although further studies to analyse their mechanism of action in this system may be required. These treatments, alone or combined, may support the restoration of the neurotransmitter balance in the olfactory area, which may affect the subcortical and cortical areas connected via the olfactory system.

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