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An elevated pro-inflammatory cytokine profile in multiple chemical sensitivity

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Cytokines;
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Summary
Background: Multiple chemical sensitivity (MCS) is a medically unexplained condition characterized by reports of recurrent unspecific symptoms attributed to exposure to low levels of common volatile chemicals. The etiology of MCS is poorly understood, but dysregulation of the immune system has been proposed as part of the pathophysiology.
Objective: To compare plasma levels of cytokines in Danish MCS individuals with a healthy, sex- and age-matched control group.
Method: Blood samples were obtained from 150 un-exposed MCS individuals and from 148 age- and sex-matched healthy controls. Plasma concentrations of 14 cytokines, chemokines and growth and allergen-specific IgE were measured. All participants completed a questionnaire including questions on MCS, psychological distress, morbidities and medication use at the time of the study.
Results: Plasma levels of interleukin-1β, -2, -4, and -6 were significantly ($P < 0.001$) increased in the MCS group compared with controls, tumor necrosis factor-α was borderline significantly ($P = 0.05$) increased and interleukin-13 was significantly decreased ($P < 0.001$).
Conclusion: MCS individuals displayed a distinct systemic immune mediator profile with increased levels of pro-inflammatory cytokines and interleukin-2 and inverse regulation of Th2 associated cytokines interleukin-4 and interleukin-13 suggestive of low-grade systemic inflammation, along with a deviating Th2-associated cytokine response not involving IgE-mediated mechanisms.

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1. Introduction

Multiple chemical sensitivity (MCS) is a non-allergic chronic disorder characterized by reports of unspecific symptoms attributed to exposure to common volatile chemicals, such as fragranced consumer products, tobacco smoke, freshly printed papers or magazines (Graveling et al., 1999). Symptoms from the central nervous system (CNS) conveyed by headaches, dizziness, extreme fatigue, and concentration difficulties are common, symptoms from other organ systems, such as the airways and gastro-intestinal tract, are also frequently reported (Hausteiner et al., 2005; Lacour et al., 2005). Avoiding exposure to potential symptom-eliciting chemicals is a characteristic coping response in affected individuals, which includes avoiding public places and transportation, restricting social activities, and occupational considerations (Gibson et al., 2003). The prevalence of self-reported chemical sensitivity symptoms in population-based studies ranges from 9% to 33% (Hausteiner et al., 2005; Johansson et al., 2005; Berg et al., 2008), whereas physician-diagnosed MCS or reports of disabling consequences in the form of social and occupational disruptions are much lower, ranging from 0.5% to 6.3% (Berg et al., 2008; Kreutzer et al., 1999; Caress and Steinemann, 2003). There are currently no internationally accepted consensus criteria for MCS (Graveling et al., 1999; Das-Munshi et al., 2007); consequently, the diversity of applied case definitions in the scientific literature is high. Other labels have been ascribed to the condition, but MCS is widely used and will be used here without reference to any assumptions about the underlying etiology.

MCS is currently categorized as an unexplained disorder. The heterogeneity of the reported symptoms overlapping with other disorders, e.g. fibromyalgia (FMS) and chronic fatigue syndrome (CFS), has raised the question as to whether MCS constitutes a single disease entity with a specific etiology and pathogenesis. Several theories on the pathophysiology and risk factors involved in MCS have been suggested (Miller, 1997; Graveling et al., 1999; Yunus, 2008; Winder, 2002), but considering the clinical data available, no single theory alone has satisfactorily explained the presentations or multiple symptoms and no definitive conclusions can thus be drawn at this point (Das-Munshi et al., 2007; Graveling et al., 1999). However, evidence suggests that the symptoms are more likely to be caused by individual susceptibility factors than by an actual toxicological response (Bell et al., 2001; Das-Munshi et al., 2007) as MCS individuals do not show a typical dose—response relationship following exposure to symptom-triggering agents.

Dysregulation of the immune system has frequently been proposed as a pathophysiological mechanism likely to play a role in the etiology (De Luca et al., 2010; Meggs, 1993; Das-Munshi et al., 2007), and common MCS symptom-triggering compounds, such as formaldehyde, hydrocarbons and organochlorines, have been shown to suppress immune system functioning in humans (Vojdani et al., 1992). More supportive findings have been reported from unrelated studies, but the conclusions are inconsistent. To date, taken as a whole, immunological testing has failed to reveal any consistent pattern of reactivity or abnormalities indicative of common immunological deficiency in MCS (Kipen et al., 1992; Ziem and McTamney, 1997; Mitchell et al., 2000). One study by De Luca et al. (2010) reported increased levels of six immune-modulating cytokines in MCS individuals compared with healthy controls and abnormal serum levels of several biomarkers related to redox balance and metabolic functioning, which could suggest an impaired chemical defensive system and dysfunctional immune regulation (De Luca et al., 2010). Altered cytokine levels have also been studied in other medically unexplained disorders, such as FMS (Bazzichi et al., 2007; Kadetoff et al., 2012), CFS (Fletcher et al., 2009; Broderick et al., 2010; Maes et al., 2012) and gulf war syndrome (GWS) (Whistler et al., 2009; Skowera et al., 2004). Although results from these studies are inconclusive, several studies have reported findings of abnormal blood levels of pro-inflammatory cytokines in particular. Considering the complexities of MCS, it is unlikely that unaccompanied findings of abnormal serum levels of immunological mediators, such as cytokines alone, can be used to explain the pathophysiology of MCS. Nevertheless, they can provide useful information and serve as valuable pieces of the puzzle. Overall, the findings supporting an immunological component of MCS deserve further investigation.

The purpose of this study was to compare plasma levels of cytokines in un-exposed Danish MCS individuals with a healthy, sex- and age-matched control group. Target cytokines for the study were selected based on reported abnormalities found in similar studies and included several pro- and anti-inflammatory cytokines. Additional measurements of plasma allergen-specific immunoglobulin E (IgE) levels toward common inhalant allergens were included to account for possible differences in frequency of respiratory allergies between the two study groups.

2. Materials and methods

2.1. Study population

The study comprised 150 MCS individuals and 148 age- and sex-matched healthy controls aged 18—65 years. Participants with MCS were recruited among individuals who were registered in a research database at the Danish Research Centre for Chemical Sensitivities, Department of Dermato-allergology, Copenhagen University Hospital Gentofte, and through advertisements in patient organizations' newsletters and on the Danish Research Center's website. Age- and sex-matched healthy controls were recruited among staff members at Copenhagen University Hospital Gentofte, Denmark and staff members at Fredericia Hospital, Denmark and through flyers and posters at Copenhagen University Hospital Gentofte, Denmark as well as in the vicinity of the hospital.

2.1.1. Inclusion criteria for MCS individuals

All MCS individuals were screened for eligibility using the US Consensus Criteria for MCS and the revisions suggested by Lacour et al. (Lacour et al., 2005; 1999 Consensus on Multiple Chemical Sensitivity, 1999), which were operationalized as follows: (1) symptoms for at least 6 months; (2) symptoms occur in response to exposure to at least two of 11 common volatile chemicals; (3) presence of at least one symptom from the CNS and one symptom from another organ system; (4) symptoms causing significant lifestyle changes, (5) symptoms occur when exposed and lessen or resolve when the symptom-triggering agent is removed; (6) symptoms