Safety and Health at Work 11 (2020) 173–177

Contents lists available at ScienceDirect

Safety and Health at Work

journal homepage: www.e-shaw.net

Original Article

Moist and Mold Exposure is Associated With High Prevalence of Neurological Symptoms and MCS in a Finnish Hospital Workers Cohort

Saija Hyvönen [1,*], Jouni Lohi [2,3], Tamara Tuuminen [4]

[1] Työterveys Meditare, Finland
[2] Lapland Central Hospital, Department of Pathology, Finland
[3] University of Oulu, Finland
[4] Medical Center Kruunuhaka Oy, Finland

ARTICLE INFO

Article history:
Received 22 September 2019
Received in revised form
17 January 2020
Accepted 20 January 2020
Available online 29 January 2020

Keywords:
Dampness and mold hypersensitivity syndrome
Moisture damaged buildings
Multiple chemical sensitivity
Mycotoxins
Neuroinflammation

ABSTRACT

Background: Indoor air dampness microbiota (DM) is a big health hazard. Sufficient evidence exists that exposure to DM causes new asthma or exacerbation, dyspnea, infections of upper airways and allergic alveolitis. Less convincing evidence has yet been published for extrapulmonary manifestations of dampness and mold hypersensitivity syndrome).
Methods: We investigated the prevalence of extrapulmonary in addition to respiratory symptoms with a questionnaire in a cohort of nurses and midwives (n = 90) exposed to DM in a Helsinki Obstetric Hospital. The corresponding prevalence was compared with an unexposed cohort (n = 45). Particular interest was put on neurological symptoms and multiple chemical sensitivity.
Results: The results show that respiratory symptoms were more common among participants of the study vs. control cohort, that is, 80 vs 29%, respectively (risk ratio [RR]: 2.56, $p < 0.001$). Symptoms of the central or peripheral nervous system were also more common in study vs. control cohort: 81 vs 11% (RR: 6.63, $p < 0.001$). Fatigue was reported in 77 vs. 24%, (RR: 3.05, $p < 0.001$) and multiple chemical sensitivity in 40 vs. 9%, (RR: 3.44, $p = 0.01$), the so-called "brain fog", was prevalent in 62 vs 11% (RR: 4.94, $p < 0.001$), arrhythmias were reported in 57 vs. 2.4% (RR: 19.75, $p < 0.001$) and musculoskeletal pain in 51 vs 22% (RR: 2.02, $p = 0.02$) among participants of the study vs. control cohort, respectively.
Conclusion: The results indicate that the exposure to DM is associated with a plethora of extrapulmonary symptoms. Presented data corroborate our recent reports on the health effects of moist and mold exposure in a workplace.

1. Introduction

Dampness and mold hypersensitivity syndrome (DMHS) is a newly introduced terminology [1–3] for the "old" clinical paradigm called e.g. mold-related illness, biotoxin-related illness, chronic inflammatory response syndrome owing to water-damaged buildings, and so on. It comprises a plethora of symptoms seemingly nonrelated that however when studied thoroughly, are all related to the prolonged or cumulative exposure to dampness microbiota (DM). The clinical criteria of DMHS have been laid [1]. DMHS is a multiorgan syndrome caused by insidious chronic inflammation that can be named channelopathy or ionopathy owing to the damage to the cell membranes carried out by biotoxins emitted from DM [2–4]. Oxidative and nitrosative stress reactions are the cornerstone underlying mechanisms involved in the pathology of DMHS [5].

There is sufficient evidence that DM causes new asthma and asthma exacerbation, dyspnoea, and infections of upper airways, as well allergic rhinitis, bronchitis, alveolitis, and organic dust toxic syndrome [6–8]. However, it is not yet unanimously acknowledged that the exposure to mold microparticles, aerosolized mycotoxins or bacterial toxins of the DM community might exert even greater risk on the central nervous system (CNS) and autonomous nervous system. Although increasing body of literature describing

* Corresponding author. Työterveys Meditare, Finland.
E-mail address: saija.hyvonen@fimnet.fi (S. Hyvönen).

2093-7911/$ – see front matter
https://doi.org/10.1016/j.shaw.2020.01.003

neurologic sequelae after the exposure to DM has been published in recent years [9–12], yet this evidence has not achieved the same level of recognition, as e.g. asthma, and therefore these symptoms are often overlooked. For example, the association between the exposure to *Stachybotrys chartarum,* "the toxic mold" and neurotoxicity have been described [9]. Neurologic problems in equine stachybotrytoxicosis were first reported from the Union of Soviet Socialist Republics (USSR). Areflexia, hyperesthesia, hyperirritability, blindness, and stupor were diagnosed in all affected animals [9]. In another review, the involvement of the CNS after the exposure to indoor air DM was reported as follows: significant fatigue, weakness (70-100% of cases), neurocognitive dysfunction such as memory loss, irritability, anxiety, and depression in more than 40% of cases [10]. Numbness, tingling, and tremor were also reported as signs of neurotoxicity. Yet, in another extensive document, neurological abnormalities in DM-exposed persons were reviewed [11]. The exposure to toxic molds associates with seizures, hypotension, and myelosuppression and can cause optic demyelinating neuritis and multifocal choroiditis [11]. The authors suggested that mycotoxins being relatively nonpolar and hydrophobic pass through the blood–brain barrier and thereby may perturb the function of synapses [11].

Effects of mycotoxins and neurotoxins on neuropsychiatric symptoms and immunity have been recently summarized in an extensive review [13]. The authors selected 16 peer-reviewed articles that comprise the data on nearly 1580 patients with neurological, neuropsychiatric, and neurobehavioral disorders caused by biotoxins emitted in water-damaged buildings. The review underlines that genera such as *Trichoderma, Fusarium, and Stachybotrys* are occasional mycotoxin producers. These mycotoxins may be inhaled or may penetrate the body through mucosa and skin. Not even respiratory tract involvement but also musculoskeletal and neurologic symptoms have been reported. The authors described several mechanisms of action such as activation of the immune system leading to the production of proinflammatory cytokines; direct cytotoxic effects and the change of redox potential in affected tissues [13].

Although multiple chemical sensitivity (MCS) has been described already in 1952 [14], it has not yet been extensively studied in the context with DMHS. MCS is a condition, where a person experiences a complex array of recurrent nonspecific symptoms when exposed to low doses of chemicals that are well tolerated by most people. The person may react to perfumes, deodorants, detergents, tobacco or other smoke, fresh printed matters, paints, varnishes, glues, hairdresser's products, dust, formaldehyde, or some other known chemicals and spices. CNS symptoms are central to the pathology of MCS [15]. Although the disease has been known for decades [14–18], only a few studies from Finland reported the association of MCS with chronic exposure to DM [1,19]. For example, in a study on children exposed to DM, we observed that the development of MCS was associated with the exposure to DM in a dose-response manner [20]. However, large epidemiological studies linking MCS to DMHS are still missing.

The aim of this study was to estimate in addition to respiratory symptoms the risks for neurological symptoms and MCS in the two cohorts of adults. One cohort was exposed to DM in their workplace and the control cohort had no known moist and mold exposure.

2. Materials and methods

2.1. The cohorts

The study cohort included 90 nurses and midwives who were working during a variable period of time in a water-damaged Obstetric Hospital in Helsinki until 2017, when the building was shut down owing to raising public concern. All participants were females. We were able to enroll into the study 90 employees who were symptomatic. The control group was selected from office workers with no known exposure to bad indoor air. Forty five of 150 employees volunteered to participate in the study.

The distribution of the participants in the study cohort in the age categories of <30, 30-44 and ≥ 45 years was as follows: 8%, 63%, and 29%, respectively. In the control cohort, the corresponding age distribution was 16%, 57%, and 27%. However, the control cohort was represented equally by both genders.

Six of 90 (6.7%) and two of 45 (4.4%) in the study and the control cohorts were smokers, respectively. We considered self-reported symptoms and diseases diagnosed by a medical doctor. Data from both cohorts were collected by the same questionnaire.

2.2. Water damage in the hospital and DM

The hospital was constructed in 1960, and there had been several water leakages from the water pipes and the sewer system. The damage evaluation was carried out in April 2017, and 46 microbiological samples were collected and analyzed by an accredited environmental microbiology laboratory. Extensive microbial growth was demonstrated in 24 of 46 (52%) samples taken from various floors and wings of the building. The following species and genera were recovered: *Penicillium spp, Actinomyces, Aspergillus spp, Paecilomyces variotti, Cladosporium sp, Aspergillus niger, Aspergillus sydowii, and Exophiala spp*.

2.3. Diagnoses and symptoms

We used the questionnaire (Appendix 1) to collect the symptoms. We were interested to study the prevalence of the so-called "brain fog" and other CNS manifestations such as vertigo, problems with concentration and memory, speech difficulties, body balance, and finding words without any special neurological diagnose. The symptoms mediated by the autonomous nervous system such as numbness in the limbs, face or tongue, tetanus or muscle weakness, and arrhythmia, were also recorded. We collected data on MCS, musculoskeletal pain, doctors' diagnosed asthma, allergic rhinitis, atopic skin lesions, urticaria, rheumatic disease, fibromyalgia (FM), hypothyroidism, inflammatory bowel disease, cardiac diseases, migraine, diabetes, multiple sclerosis, epilepsy, cancer, anxiety, depression, sleep disorder, chronic fatigue, hematologic diseases, elevated blood pressure, or other illnesses described by participants.

2.4. Data analysis

Asthma, self-reported respiratory, cardiac, neurologic, musculoskeletal symptoms, and MCS were defined as primary variables (Table 1). The cohorts were not matched with respect to gender: 100% were female in the exposed cohort vs. 55% in the nonexposed cohort. In addition, the overall morbidity was higher in the exposed cohort. In that cohort, two doctor's diagnosed diseases were reported in 69%, whereas in the nonexposed cohort, the corresponding morbidity was in 27%. The Mantel-Haenszel method was used to estimate confounding effects of the overall morbidity. Therefore, the participants were divided into two strata of the confounding factors (0-1 diagnoses and ≥ 2 diagnoses). The odds ratios (OR) were calculated for both strata to compare the cohorts with respect to primary variables. The Breslow-Day test was used to test the homogeneity of the ORs, and the Mantel-Haenszel method was used to get the weighted average of the ORs across the strata. The prevalence of symptoms was high, which led to extreme OR

Table 1
The prevalence of disease manifestations in a cohort of midwives and nurses exposed to DM (n = 90) compared with an unexposed cohort (n = 45)

Disease or a symptom	Study cohort (exposed)		Control cohort (nonexposed)		Exposed vs. nonexposed	
					RR	95% CI *p* value
CNS symptoms	56/90	62%	5/44	11%	4.94	2.72–6.91 <0.001
Dysfunction of peripheral nervous system	45/90	50%	4/44	9%	4.36	1.90–7.41 0.001
Asthma	51/90	57%	9/45	20%	1.86	0.86–3.13 0.11
MCS	36/90	40%	4/43	9%	3.44	1.39–6.44 0.01
Fatigue	69/90	77%	10/42	24%	3.05	2.19–3.64 <0.001
Muscle or joint pain	46/90	51%	9/41	22%	2.02	1.11–3.02 0.02
Respiratory symptoms	72/90	80%	12/42	29%	2.56	1.84–3.04 <0.001
Cardiac arrhythmia	51/90	57%	1/41	2.4%	19.75	4.47–36.30 <0.001

DM, dampness microbiota; MCS, multiple chemical sensitivity; CNS, central nervous system; RR, risk ratio; CI, confidence interval.

estimates. The formula of Zhang-Yu was used to convert the overall morbidity-adjusted ORs to risk ratios (RRs). The results are given as overall morbidity-adjusted RRs with 95% confidence intervals (CIs).

Possible confounding effect of gender could not be estimated in the same way because all participants were female in the exposed cohort. Instead, subgroup analyses including only female participants were conducted. Risk ratios without adjustment were calculated to compare the exposed female participants to the nonexposed female participants . The chi-squared test was used for secondary diagnoses and symptoms. All statistical tests were two-tailed, and *p*-values <0.05 were considered statistically significant. Analyses were performed using IBM SPSS Statistics for Windows (version, 25.0, Armonk, NY, USA, IBM Corp.).

3. Ethical consideration

This retrospective cohort study required no ethical approval.

4. Results

The results are presented in Table 1. The logistic regression analysis shows a significant difference between the cohorts in the prevalence of CNS symptoms RR: 4.94 (95% CI: 2.72-6.91, $p < 0.001$), autonomous nervous system, i.e. numbness of limbs, tongue or face, tetanus or weakness of muscles RR: 4.36 ($p < 0.001$), arrhythmia RR: 19.75 ($p < 0.001$), fatigue RR: 3.05 ($p < 0.001$), and MCS RR: 3.44 ($p = 0.01$). The risk for any neurological symptom was RR: 6.63 ($p < 0.001$). Neurological symptoms were divided into central and peripheral categories to recognize possible psychiatric reasons for the symptoms. CNS symptoms as concentration and memory problems are more commonly related to depression, anxiety and sleep disorders, which were more common in the study group although with no significant differences between the groups.

The prevalence of overlapping neurologic symptoms in the exposed cohort was very high. Forty of 90 (44%) of the exposed cohort experienced four or more neurologic symptoms simultaneously, whereas only one of the 45 (2.2%) of the nonexposed individuals had four or more neurologic symptoms.

The risk of respiratory symptoms was also higher in the exposed cohort, RR: 2.56 ($p < 0.001$). Asthma was diagnosed in 57 vs. 20% in the exposed vs. nonexposed cohort and the risk of asthma (RR: 1.86, $p = 0.11$) did not reach statistical significance.

The average duration of working in the damaged building for those reporting MCS was 7.8 years (min two months - max 25 years), but for those who did not report MCS, it was 4.9 years (min less than a week - max 40 years).

No association between the exposure to DM and infertility, cancer, multiple sclerosis, hypothyroidism, epilepsy, hematologic or embolic diseases was found. Rheumatoid arthritis was reported in 11 vs. 0%, cardiac diseases in 17 vs. 2.2%, migraine 22 vs. 6.7%, anxiety 14 vs. 2.2%, depression 21 vs. 4.4%, sleep disorder 23 vs. 6.7%, but the difference in the prevalence was not statistically significant owing to the small numbers of reported cases.

5. Discussion

This study confirms that toxic indoor air at workplace is a great health hazard [21]. We confirmed also that prevalence of MCS was drastically different between the cohorts being 40 vs. 9.3% ($p = 0.01$) in the exposed vs. nonexposed participants, respectively. In this study, MCS development was associated with the duration of the exposure to DM. The individuals reporting MCS had on the average longer working history in the building, 7.8 years, whereas those who did not report MCS had worked for 4.9 years. The results corroborated earlier reports from Finland that MCS develops after prolonged or cumulative exposure to DM [1,19,20].

MCS is a syndrome involving multiple organs, the CNS at the first place. As demonstrated here, CNS symptoms were very prevalent in DM exposed vs. nonexposed individuals, 62 vs 11% ($p < 0.001$).The US case definition for MCS was published in 1999 [17], and after careful systematic literature review, Lacour et al. [15] extended the definition in 2005. The authors reviewed more than 1400 publications during the years 1997-2003 and came to the conclusion that patients report nonspecific complaints of CNS as the main characteristics. Functional disturbances in other organ systems as optional complaints were also reported. Pathophysiological mechanisms of MCS have been reviewed recently [22]. In this context, it is worth to mention a few: the hyperactivation of the sensory receptors e.g. on the C-fibers of trigeminal nerve; hyperactivation of transient receptor potential vanilloid-1 and transient receptor potential acrolein-1 receptors [23,24]. Many mycotoxins and metabolites secreted by molds may disrupt or translocate

through the blood–brain barrier [25] and cause neuroinflammation [26].

As a matter of fact, comorbidity with MCS, chronic fatigue syndrome (CFS) and FM has been earlier reported. In the questionnaire, we collected the data on the prevalence of CFS and FM that appeared to be 5 of 90 and 0 of 90, respectively among the exposed workers. However, we were unable to estimate whether the responders might have had undiagnosed CFS which requires the assessment in accordance with the international criteria [27]. We were unable to do medical examination of the participants of this study because neither of us were a treating physician to the nurses and midwives. In Finland, CFS is not diagnosed as a routine clinical practice. Profound fatigue is pathognomonic for DMHS. As a compromise, we collected data on chronic fatigue without setting clinical diagnosis of CFS (ICD-10 code G93.3). Fatigue can be caused by several independent mechanisms: (*a*) recurrent infections [1]; (*b*) dysregulation of immune and neuroendocrine systems [2–4], especially of thyroid–hypophysis–hypothalamus and hypophysis–pituitary–adrenal axes, and untreated nonthyroid illness [28]; (*c*) mitochondrial damage owing to inhaled toxins [2–4]; (*d*) neuroinflammation [2–4]; (*e*) dysregulation of autonomous nervous system with a decreased activation of the sympathetic nervous system [2–4].

As shown in the study by Tuuminen et al. [20], we observed a high rate of overlapping symptoms. Of the exposed individuals, 44% reported four or more different neurologic symptoms of the eleven listed in the questionnaire, whereas only one (2.2%) of control cohort participant reported four simultaneous symptoms. Importantly, neurological symptoms such as “brain fog” and dysautonomia presented as paroxysmal tachycardia were as frequent as symptoms of the respiratory tract.

The theoretical basis for the clinical data reported here is no more obscure. Recently, a report on the *in vivo* investigation into neurotropism of bacterial toxins has been published [25]. The experimental model used piglets. These *in vivo* studies are fundamental to our understanding why the exposure to DM may cause neuropsychiatric and neurobehavioral abnormalities. To estimate toxins translocation from the gut to other organs and especially to the brain the piglets were fed with isotope-marked neurotoxins, and their concentrations were measured in different tissues after the animals were succumbed. The measurement method was isotope dilution and assay mass spectrometry. In our view, the extrapolation of the piglet study to the human pathophysiology is justified: the piglets anatomically and immunologically are close to humans. In this context, it is important to emphasize that valinomycin and cereulide, being the target of the piglet study [25] are produced by Gram positive bacteria. They can be present in the bad indoor air because DM is an ecological niche both for molds, as well as toxin-producing bacteria such as *Bacillus spp* and *Actinomycetes*. The dosages used in the piglet experiment were well comparable with those present on the air droplets in the moldy environment. Thus, the *in vivo* research on piglets is fully relevant to the pathogenesis of neurological and neurobehavioral sequelae in DMHS.

There are several limitations of our study. First, the study cohort comprised only females. Females are more prone to the effects of toxins because many mycotoxins are fat soluble [2,4], and female body contains more adipose tissue compared with males. In addition, the cohorts were small in numbers. Unfortunately, we were unable to contact all the employees of the infested building; we succeeded in contacting only 90 of approximately 700 (13%). Volunteer participation of individuals from the control group was suboptimal; therefore, the study cohort might represent underestimated morbidity. Yet, another limitation of our study is the collection of the symptoms through the questionnaire without personal clinical examination of the participants. Psychiatric disorders were reported as depression 21%, anxiety 14% and sleep disorder 23%, compared with 4.4%, 2.2%, and 6.7% in the control cohort. Importantly, the work of midwives is more stressful with night shifts compared with the work of office workers. These factors may have had an adverse impact on experienced health problems. Although we have information on the damage done to the workplace by DM, we do not have sufficient information on the exposure of every participant. The real caveat of this investigation is the absence of validated biomarkers to prove the individual's exposure. In the future, the detection of biotoxins in patient's urine would be of a great clinical value. Yet, another limitation of this study is that we were unable to present environmental analysis from the control building, but in most cases the buildings are studied only upon suspicion of problems with indoor air quality.

In this study, we demonstrate that the exposure to DM indeed is associated with MCS and neurologic, cardiac, musculoskeletal, and respiratory symptoms. Here, the risk for asthma did not reach the level of statistical significance. This hurdle can be explained by the fact that our control cohort reported asthma twice the prevalence of the general population [29]. In other words, the control cohort was not representative. It might have been possible that those who have had symptoms or a disease in the control cohort were more eager to participate in the questionnaire. On the other hand, persons in the study cohort experiencing severe symptoms might have changed the employer and therefore were dropped out from our register. Although calculated prevalence and risks are inaccurate, they represent a trend or even “a top of the iceberg”. Because mold infestation in public buildings (schools, day care centers) is a very common problem in Finland, it is tempting to speculate that persons from the control cohort might not have been completely intact in terms of previous exposure. We should keep in mind that DMHS is a syndrome that develops at discrete intermittent and cumulative exposures [1,3].

The strength of our study is the following. Here, we present both data on the morbidity of the study cohort and the evidence of microbiological infestation of the building leading to the conclusion of the possible causality of neurologic symptoms owing to DM exposure.

Presented data have an important message that neurological symptoms should be neither neglected nor downplayed nor overlooked. Our results question the Finnish current practice of occupational disease assessment when the person is exposed to DM. In Finland, only occupational asthma is being acknowledged for legal compensation. We do not know whether the reported neurological symptoms will finally resolve in an exposed cohort because we do not have longitudinal observation. However, based on our clinical experience and from the literature survey, we know that MCS is a chronic disease that may turn less symptomatic only at complete avoidance of biotoxins and chemicals, which is very problematic in our modern environment.

6. Conclusions

On the basis of presented results, we propose that there is causality between the exposure to DM and high prevalence of MCS with a plethora of neurological symptoms. CNS symptoms, dysautonomia, MCS, and fatigue in persons exposed to DM in the buildings by no means are neither medically unexplained syndromes nor functional disorders.

Conflicts of interest

The authors have no conflicts of interest.

Acknowledgments

The authors thank MSc Tuija Poussa for her professional statistical work and Professors Ville Valtonen and Mirja Salkinoja-Salonen for their invaluable comments during the study design and the preparation of this manuscript. We also want to thank all the participants of the present study.

Author contribution

S.H. conceived the study design, T.T. and S.H. wrote the first draft, J.L. reviewed the literature. All authors wrote the final manuscript and approved it.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.shaw.2020.01.003.

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