Dampness and Mold Hypersensitivity Syndrome is a Biotoxicosis that should be Diagnosed Promptly

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Abstract

Long-lasting or cumulative exposure to indoor dampness microbiota (DM) emitting fungal and bacterial toxins is a serious health hazard. Dampness microbiota (DM) comprises molds, yeasts, gram positive and gram negative bacteria species. The following genera and species are often found: *Aspergillus, Penicillium, Fusarium, Stachybotrys chartarum*, etc. Gram positive bacteria may include *Actinomycetes, Nocardia, Mycobacteria* and *Bacilli*. Many genera are toxin producers. The ecological community of DM may vary over time depending on the microbial unrestricted competition for the availability of nutrition factors.

Keywords: Dampness Microbiota; Asthma; Allergic Alveolitis; Dampness; Mold Hypersensitivity Syndrome; Inflammation; Mycotoxins; Biotxin; Clinical Toxicology

Introduction

Environmental exposure to toxic products in addition to the exposure to nanoparticles or fragments of mold spores that are about 2-10 μm, and decay products from construction materials, volatile organic compounds (VOCs) together with biocides used for cleaning will eventually cause severe morbidity starting with the irritation of the mucosa and ending with chronic inflammation, stimulation or inhibition of different compartments of the innate and/or adaptive immunity, loss of tolerance in different forms of hypersensitivity to alimentary products, fragrances and products of petrochemical industry. Immunologic processes, hyper activation of sensory receptors, neurogenic inflammation and central sensitization may lead to the development of invalidating Multiple Chemical Sensitivity (MCS) [1]. Exposure to myco-/bio toxins is a risk factor for the development of autoimmunity and even cancer, although these casual associations are difficult to prove because they require very long observation periods and extremely good feed-back and honest registration.

DMHS may affect practically every body organ whereas respiratory problems being the best studied [2]. Exposure to DM toxins creates susceptibility to infections, may cause Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and increases the risks of a malfunction of (neuro)endocrine and autonomic nervous systems that may result in Post-orthostatic tachycardia (POTS) [3]. The symptoms caused by the exposure to myco-/bio toxins are non-specific. However, the diagnosis of the exposure to DM should be done promptly, before the development of devastating sequaeae. Many mold species are mycotoxin producers. Mycotoxins are small molecules of secondary metabolism that can cause adverse health effects on animals and humans at very low concentrations. Many mycotoxins are lipophilic and are stored in adipocytes and in the brain, which is composed of various neurolipids. When the...
body's capacity to acquire lipophilic toxins is saturated, it starts to react to hydrophilic substances. Molds also secrete exotoxins that split organic molecules, such as starch, cellulose and lignin. Exotoxins are strong allergens.

The effects of mycotoxins are highly variable (reviewed in details in [4,5]. The same toxins can be produced across different species and genera of molds and bacteria. Bad indoor air may contain a mixture of toxins that might potentiate the effects of each other. Some mycotoxins can up- or downregulate several genes, can inhibit DNA, RNA and protein synthesis, and can cause oxidative stress. Some mycotoxins are vasoactive, some have cardiovascular effects, and many affect the immunological and (neuro)endocrine system. Mycotoxins may activate NLRP3 inflammasome and their effects on the cellular levels are comparable to the effects of ricin, tobacco and asbestos and therefore they are regarded as biological weapons. Some mycotoxins are carcinogenic. For example, aflatoxins (AFB1) and its metabolite AFM1 produced by *Aspergillus flavus*, *A. parasiticus Aversicolor* and other *Aspergillus* species are established carcinogens by IARC. They are genotoxic, enhance malignant cell proliferation and invasion. Myco- /biotoxins may work synergically and can potentiate the effects of each other.

Trichothecenes and gliotoxin are probably the strongest known toxins. Toxic effects occur at a lower concentration when inhaled compared to oral administration. Trichothecenes T-2 and deoxynivalenol (vomitoxin) impair the immune response to respiratory infections. T-2 toxin, patulin, penicillinic acid, aflatoxin, satratoxins have been shown to affect macrophage function and are cytotoxic. Trichothecenes cause immunosuppression of lymphocytes and stimulate macrophages to produce IL-1β, they inhibit protein synthesis in ribosomes, impair mitochondrial function, activate MAP kinase (MAPK) and induce apoptosis (programmed cell death). Mycotoxins may affect the expression of calcium trafficking and MAPK signal transduction, neutrophil influx, the production of TNFα cytokines, and immunosuppression. Some mycotoxins can cause novel ion channels in the cell and promote K+ efflux from the cell. Bleaching used in remediation, e.g. chlorine-containing biocides makes DM more toxic and mutagenic because mycotoxins become better soluble in fat and therefore better penetrate the skin and stored in the adipose tissue and in the brain. Many toxins are cytotoxic and may interfere with the opsonization of xenobiotics and inhibit phagocytosis by macrophages. For example, *Aspergillus fumigatus* inhibits the action of dendritic cells.

A lot of research on DM biotoxins has been published from Finland by a research group led by emerita professor Mirja Salkinou-Salonen who should be given a tribute for her pioneer work. In Finland, the problem of bad indoor air achieved the status of a national catastrophe. Novel toxins and their mechanisms of action have been described. For example, *Acremonium* species isolated from a water damaged building may produce acrebols that inhibited the respiration chain and ATP production in the boar spermatozooids; *Aspergillus westerdijkiae* isolated from the dust of a kindergarten grew in the presence of borate and polyguanides, may produce avrainvillamide and stephacidin B (which is a dimer of the above) that were shown to inhibit the motility of boar spermatozooids and destroyed boar epithelium cells by damaging the membrane potential, and caused apoptosis. These toxins are 100 times more toxic to boar cells than stephacidin A, ochratoxin A, sterigmatocycin, and citrine; Gram positive bacteria *Bacillus cereus* may produce cereulide that caused visible damage of mitochondria in the boar spermatozooids at concentration 2 ng/mL. *Bacillus amyloliquefaciens*, gram positive bacteria isolated from a water damaged building, may produce amilocin that was shown to form new channels in the cell membranes, was immunotoxic for the human macrophages, activated NLRP3 inflammasome, caused the production of pro-inflammatory cytokines, caused in a dose-dependent manner K+ efflux in monocytes, keratinocytes and spermatozooids at concentration 1-2μM; *Paenibacillus polymyxa*, gram positive bacteria isolated from symptoms causing building, may produce A and B fusarids that are cyclic lipopeptides and are novel ion forming toxins; *Streptomyces griseus*, gram positive bacteria isolated from the dust of a kindergarten may be a valinomycin producer that caused motility inhibition of the boar spermatozooids (EC50 10-63 ng/mL), oedema of the mitochondria, disruption of cellular membranes, and inhibited ATP production. *Stachybotrys chartarum*, the so called “Toxic black mold” is often isolated from water damaged buildings may produce Satratoxin G belonging to trichotecenes, T-2 toxin, zearalenone (a non-steroid estrogen, mycoestogen) and altogether approximately 60 different metabolites that may be inhibitors of protein synthesis by interfering with initiation, elongation and termination steps; The products from *S. chartarum* may also active NLRP3 inflammasome. The following species and genera were recovered from water damaged buildings: *Streptomyces*, *Nocardiosis*, *Bacillus simplex*,  

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Bacillus pumilus, Trichoderma harzianum Rifai, the extract of which caused mitochondrial oedema and damaged the membrane potential of the boar spermatozoa. The list of the biotoxins derived from water damaged microbiota presented here is only a “scratch of the surface”.

Over the past three years, convincing research evidence has been published that toxicogenic indoor microbes e.g. Stachybotrys, emit toxins as liquid vesicles (microvesicles, exoms) in which the concentrations of toxins are more than 1000-fold higher compared to the same microbial particle emissions (spores, hyphae fragments). Biotoxins, collectively called peptaibols, were emitted from water damaged surfaces in guttation droplets in a building with indoor-isolated Trichoderma sp [6,7]. The concentrations measured from the dust particles approximately more than 1000 times underestimate the amount of toxins released by indoor water vapor. Many of the toxins are rather large, fat-soluble molecules (300 to 1000 Da) that adhere to the indoor micro cavities and surfaces at low indoor air humidity. This is especially the case in cold seasons at schools when the indoor air humidity during e.g. nights, weekends, etc., is low, 6-20%. This humidity is not enough for aerosolization of toxins. When the environment is crowded with people who exhale 100% water vapor, humidity rises to 60%, especially in school classes, day care centers and others with high human density. So, to detect toxins, sampling should be done by wiping with a cloth dampened with alcohol, or with a cup of sticks directly from the interior surface, instead of vacuuming or sweeping dust. Another option is to collect air humidity with a dehumidifier (peltier) (Prof Mirjja Salkinoja- Salonen’s communication).

Generally speaking, in clinical laboratory medicine, e.g. in clinical microbiology, the adequacy of sample collection for bacteriologic or virologic work-up has been emphasized through continuous medical education. Proper collection technique ensures a reliable clinical diagnosis. The same principle should be applied also to environmental toxicology. The sample should be taken adequately to facilitate the most informative result, and there should be no compromise on this point. Although health hazards of indoor air myco-/biotoxins are very well documented, there is still an enormous gap between scientific knowledge and clinical reality. Resistance from construction industry, environmental control authorities and mainly from insurance companies restricts adoption of adequate sampling techniques and legal consequences because that means responsibility and monetary compensation.

From the point of view of a treating physician the road map for further development is proposed as the following:

1. Clinical toxicology and principles of environmental medicine should be included into the curriculum of medical education worldwide.
2. The techniques of sampling in the water damaged buildings should be adequate according to the best practice (see above).
3. The use of the so-called “health-based accepted cut-off levels” for myco-/biotoxins should be abandoned the soonest the best because in environmental toxicology there are no “acceptable levels”. As said, different toxins work synergically, and even a small amount of myco-/biotoxin might have a detrimental health effect, especially in a vulnerable persons or when the person is exposed simultaneously to alimentary toxins, heavy metals, eg through the amalgam filling, etc.
4. International scientific collaboration should be enhanced to promote clinical and environmental toxicology that should go hand-in-hand to timely prevent devastating morbidity such as DMHS.

Conflict of interests

Tamara Tuuminen and Jouni Lohi declare no conflict of interests.

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