EDITORIAL

Molds, Mycotoxins, the Brain, the Gut and Misconceptions

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MOLDS

Molds are present in homes and other indoor places that are water damaged and they produce mycotoxins. One mold species can produce several different mycotoxins and one mycotoxin can come from several different molds. Even small amounts of mold growth in an air conditioner or in ducts will result in the occupants being chronically exposed, constantly breathing mold spores and mycotoxins, causing illness.

Diseases caused by fungi (molds) are called mycosis and, fortunately, they are not a communicable disease. Mycoses can be aggravating, as in athlete's foot, or critical, as in Invasive Aspergillosis. Mycoses have increased over the last four decades as a result of the AIDS pandemic, the advent of chemotherapy, transplantation, immunosuppression with medications including corticosteroids, access to the vascular system, as well as climate change with more floods, hurricanes, and storms affecting homes, schools, public buildings, and workplaces.[1]

In patients who are adversely affected by molds and mycotoxins, it is important that the patient no longer be exposed to these prior to beginning treatment. Therefore, testing of the indoor spaces and subsequent remediation are crucial. The purpose for this is to follow the first rule of toxicology: remove the patient from the toxin or remove the toxin from the patient. The testing and remediation of molds are not standardized in the United States. Testing for airborne mold spores in an indoor space only reveals what is present at the time of testing, not 24/7, and can vary hour to hour depending on the activity in the room. It does not reveal any hidden molds, such as those in attics, insulation, ventilation ducts, basements, crawl spaces, wall cavities and others. The Environmental Protection Agency (EPA) cautions that 50% of fungal growth can be hidden, meaning hidden from sight. Therefore, after testing and remediation, there may still be some hidden mold left.[1,2] The ERMI test (Environmental Relative Moldiness Index developed by the EPA), a misunderstood and misapplied test as it does not give the following information:

1. Variability of molds within a home or building.
2. Whether or not a home or building has a water problem.
3. The extent of the water problem.
4. Where the problem is in the home or building.
5. Whether or not there are unusual fungi present.
6. Exposure if air samples are not used.

Specifically, the EPA states: "We substantiated the allegation that firms were using the mold index tool although the EPA had not validated the tool for public use. The EPA readily acknowledged that it had not validated or peer reviewed MSQPCR or ERMI for public use."[3]

This is a problem for both patients and clinicians, as with continued exposure to molds and mycotoxins, patients do not improve, and as stated above, it can be difficult to find to proceed with remediation.

MYCOTOXINS

Mycotoxins are secondary metabolites of fungi, and most that affect the health of humans come from the genera Aspergillus, Fusarium, and Penicillium.[3] Each of these genera can produce a number of different mycotoxins. It is important to note the size of mycotoxins: hair is 100 microns thick, mold spores 2-3 microns, and mycotoxins 0.1 microns, about the size of a virus. The size of mold spores allows them to reach the deepest recesses of the nasal sinuses and of the lungs, where they can colonize with their mycotoxins. Field studies of water-damaged home have shown concentrations at nano-particles in indoor dust that are at least 1000 times or greater than the indoor air mold spore counts. These particulates are mycotoxins.[2] Therefore, when an indoor report gives the spore count, the mycotoxin count can be 1000 times higher.

Mycotoxins are odorless, invisible, and tasteless. They are diverse and differ in their molecular structure, which

leads to differences in their toxicological and biological properties. Mycotoxins can cause a variety of adverse health effects and pose a serious health threat to humans, ranging from acute toxicity to long-term effects such as autoimmune diseases, neurological disorders, and cancer.

Toxicity of mycotoxins is via several mechanisms, including inhibition of ribosomal protein synthesis, DNA and RNA biosynthesis, and mitochondrial function. These effects at the cellular level lead to oxidative stress, cell cycle arrest, apoptosis, and cell membrane dysfunction.[4] The alteration of immune responses due to chronic mycotoxin exposure may also adversely affect the ability of the immune system to respond to environmental challenges. This may explain why patients complain of increased susceptibility to chemical irritants and report more sensitivity to many chemicals, odors, etc. The immunosuppressive effects of mycotoxins include inhibition of superoxide release, microbiocidal activity, cytokine release by leukocytes, and T-lymphocyte-mediated cytotoxicity. Mycotoxins do not inhibit the immune system from forming antibodies in responding to antigens.[4-6]

A common misconception is that mycotoxins are stored in fat cells. Because mycotoxins affect mitochondrial function causing cell death, they destroy cells and are not stored in them. Fat cells store persistent organic compounds (POPs) that are toxic, but not mycotoxins.

Mast cells are immune cells that are present in most tissues that surround blood vessels and nerves, and are found in the skin, lung mucosa, and digestive tract, as well as in the oral cavity, nose, and conjunctiva. Exposure to mycotoxins have been linked to activation of mast cells, and IgE antibodies to mycotoxins stimulate mast cells to release heparin, histamine, pro-inflammatory cytokines, and prostaglandin GD2. Signs of this release include neurological symptoms such as brain fog, headaches, nausea, fatigue, and irritation of the respiratory tract. Recent publications show that this stimulation by IgE antibodies to mycotoxins in serum can lead to Mast Cell Activation Syndrome (MCAS), a frequently undiagnosed disorder.[7-9]

THE BRAIN

It has been well established in the peer-reviewed medical literature that the first area mycotoxins affect in humans is the central nervous system, the brain, and nerve tissues. Mycotoxins can cross the blood-brain barrier (BBB). A recent study demonstrated that T-2 toxin can cross the BBB and accumulate in the brain leading to neurotoxicity.[10] A study by Patel et al and another study showed that the mycotoxin deoxynivalenol (DON) reduced the BBB integrity and caused cytotoxic effects at very low concentrations.[6,10] In vivo and in vitro studies have demonstrated that cellular oxidative stress is the direct mechanism of cytotoxicity caused by mycotoxins. Brain cells are vulnerable to oxidative stress injury caused by DON, Ochratoxin-A, and T-2 toxins from the environment.[11,12]

Mycotoxins have significant toxic effects on the brain as well as the peripheral nervous systems.[13] Studies have demonstrated that mycotoxins can cause loss of myelin, leading to multiple sclerosis-like symptoms, chronic inflammatory demyelinating polyneuropathy (CIDP), and other demyelinating disorders. In the peripheral nervous system, the loss of myelin can be of sensory nerves, motor nerves, or both. A study of 119 patients exposed to molds and mycotoxins in which all tested positive for mycotoxin antibodies in blood serum demonstrated demyelination of nerves. One conclusion of the study was that all participants showed blood serum antibodies to neural tissue, including myelin basic protein antibodies, myelin associated glycoprotein antibodies, and others, and had significant neurological effects on the patients.[14] Another study showed patients can develop demyelinating optic neuritis from exposure to mycotoxins leading to blurred vision, reduced visual fields, and diminished pupillary response. Patients suffering from this disorder were successfully treated with oral itraconazole and intravenous gamma globulin.[15]

Rutgers Medical School published a study in 2010 that stated: "We propose here that fungal toxins are the underlying cause of multiple sclerosis and thus may offer an avenue towards an effective cure."[16] A study in the Journal of Neurological Sciences demonstrated both in vivo and in vitro that the mycotoxin gliotoxin causes demyelination leading to multiple sclerosis.[16,17] Brasel et al demonstrated that antibodies to trichothecene mycotoxins from Stachybotrys chartarum can be measured in the blood serum of patients exposed in mold-infested indoor environments.[18] In a study of 500 patients affected by molds and 500 controls, Vojdani et al showed that IgG serum antibodies to the mycotoxin satratoxin were significantly greater ($P < .001$) in the patients than in the controls.[19]

Autism Spectrum (ASD) disorder can be triggered by mycotoxins. A study of 172 children with ASD with 61 controls; the authors showed significant differences in comparing antibodies to mycotoxins between the two groups, with the ASD group showing elevated serum antibodies to mycotoxins.[20] Tufts University School of Medicine studies have found evidence implicating mycotoxins as causing ASD. In one of their conclusions, the authors wrote: "…exposure to mold and mycotoxins can affect the nervous system, directly or through immune cell activation, thus contributing to neurodevelopmental disorders such as ASD."[21] A follow up study the following year from this same institution confirmed these finding.[22,23] Neurophysiological testing in children showed that the evoked potentials of brainstem, visual, and somatosensory were abnormal after long-term exposure to mycotoxins.[24,25]

In the medical textbook *Environmental Contaminants and Neurological Disorders* published in 2021, Chauhdary et al discuss the mechanisms by which mycotoxins affect the brain. Trichothecenes and T-2 toxins induce neuronal apoptosis and neuroinflammation. Satratoxin, deoxynivalenol (DON), T-2 toxin inhibit ceramide synthesis and cause neurodegeneration in the cerebral cortex. Ochratoxin A causes dopaminergic neuronal loss and apaptosis in striatum,

substantia nigra, and hippocampus, which can also be found in patients with Parkinson's disease. Satratoxin elicits olfactory sensory neuronal apaptosis and bilateral atrophy of olfactory nerve layer of the olfactory bulb in the brain and can lead to anosmia.26 The inflammation provoked by mycotoxins induce inflammatory markers such as NF-kappa B and TNF-alpha to have access to the olfactory bulb and frontal cortex, causing the deposition of amyloid beta plaques, a pathological hallmark of Alzheimer's disease and other neurodegenerative disorders.

Motor neuron diseases such as amyotrophic lateral sclerosis (ALS) are fatal neurodegenerative conditions that affect the brain and spinal cord motor neurons leading to muscle weakness. Increased weakness of the muscles used for breathing eventually leads to death. Neuroinflammation is commonly seen with ALS. Familial ALS affects 5-10% of all cases, and the rest, 90-95%, are sporadic.[27] One of the hallmarks of ALS is the excessive secretion of glutamate from neurons. The mycotoxins verrucarin and verrucarol increase the release of glutamate by 1300%.[28,29] This important evidence demonstrates the effects of mycotoxins on excessive activation of glutamate in the role of the development of ALS.[30]

THE GUT

Certain foods may contain mycotoxins. Mycotoxins most commonly occur in foods with poor storage after harvest, mainly in some areas of Africa and rural China. The National Institutes for Occupational Safety and Health (NIOSH), a part of the Centers for Disease Control and Prevention (CDC), has reported that very low levels of mycotoxins can be found in some foods. These amounts are in parts per billion, too minuscule to cause any serious adverse health effects in humans. The amounts of mycotoxins tested in foods have been shown in many studies to be below the Tolerable Daily Intake (TDI) set by the Food and Drug Administration (FDA), the European Food Safety Authority (EFSA) and the U.N. Food and Agricultural Organization/ World Health Organization Joint Expert Committee on Food Additives. One example is a recent study from July 2021 by Frey et al that showed one to four mycotoxins were found in both pasteurized and unpasteurized milk from cows: 91% of all the milk tested had one mycotoxin, and 30% had two to four mycotoxins. However, all the mycotoxin levels were well below TDI, and easily excreted in urine, as are most mycotoxins found in beverages and foods. This is why testing for mycotoxins in urine is not helpful in assessing mycotoxins from any indoor space. In addition, the microbiome can detoxify mycotoxins as discussed below.[31]

Several studies have established the effects of the gut microbiome on mycotoxin toxicity. The gut microbiome consists of all the microorganisms in the gastrointestinal tract, which include bacteria, viruses, fungi, and protozoa. The main phyla are Firmicutes, Bacteroides, Actinobacteria, and Proteobacteria. The function of the microbiome includes the synthesis of vitamins, enzymes, and amino acids; the absorption of minerals and nutrients; the breakdown of macromolecules; and producing short-chain fatty acids. Studies have also shown the microbiota-to-host relationship in immunity, autoimmunity, metabolic diseases, and neuroendocrine response.[32]

There are four histological and anatomical layers in the gut: the mucosa, the submucosa, the muscularis propria, and the muscular mucosea. The epithelial layer in the gut is made up of epithelial cells, the goblet cells in the villi, and the Paneth cells in the crypts. The epithelial cells are connected by desmosomes, adherens junctions, and tight junctions, and these form a mechanical bond of adjacent cells to produce a physical barrier. This barrier blocks entry of large particles and pathogens, and is permeable to water, electrolytes, and to dietary nutrients. Next is a chemical barrier made up of mucus, antimicrobial peptides, and cytokines secreted by the epithelial cells. The third barrier is the immunological one, consisting of the lamina propria, which contains capillary and gut-associated lymphoid tissue (GALT) that are made by immune cells: macrophages, dendritic cells, and lymphoid cells. In addition, secreted immunoglobulin A and cytokines are produced by the immune system to complete this protective barrier. Therefore, the gut barrier is the totality of three interlaced systems: the first is the microbiota, the second is the physical and chemical barrier made up of epithelial cells and their secretions, and the third is the immune barrier. All three work synergistically.[33]

The microbiome has the ability to transform the toxicity of mycotoxins by several different mechanisms, most of which change and modify the toxocokinetics of mycotoxins and thereby diminish their toxicity.[34-38] There are two basic mechanisms involved; one is the change to the structure of mycotoxins via biotransformation, and the other by changing the absorption of mycotoxins.[39] The most common mechanism is the chemical transformation by enzymes present in microbe cells and those excreted by microbe cells into the gut. These reactions of hydrolysis of mycotoxins reduce their toxicity.[40] Another effect by the gut microbiota on mycotoxins is the ability of components of microbes, mainly cell walls, to form adducts and bind to mycotoxins, reducing their absorption.[41] Bacterial and protozoal fractions are able to degrade trichothecene mycotoxins, such as satratoxin, T-2 toxin, and others.[42] A study showed that Provotella copri and Butyrivibrio fibrosolvens very effectively acetylated T-2 toxins, and fecal microbiota hydrolyzed deoxynivalenol (DON).[43]

CONCLUSION

The symptoms of patients exposed to molds and mycotoxins may very well be due to the effect of mycotoxins on the central and peripheral nervous systems rather than from the gut and/or liver. As explained above, the amounts of mycotoxins in foods and beverages are below TDI, too minuscule to cause health effects in humans, and is usually excreted in urine. Therefore, treatment is best directed first at the central and peripheral nervous system.

According to Dr. A Vojdani, PhD, MSc, CLS, who has over 200 publications and many on molds and mycotoxins, the

following points should be considered before deciding to use urine level of mycotoxins as an indication of exposure to mold in a water-damaged building:

1. What is the source of the mycotoxins detected in the urine?
2. Why is the detection of mycotoxins in the urine not an indication of neo-antigen formation between mycotoxins and human tissue antigens that play a role in pathophysiology of autoimmune and neuroimmune diseases?
3. This is because most of the mycotoxins detected in urine originates from food, and this is why the detection of mycotoxins in urine is not an indication of body burden of mycotoxins and should not be used as biomarkers of exposure to mycotoxins in water-damaged buildings.

Testing patients for mycotoxins by serum antibodies is the most advanced and precise method and has been well established by numerous published studies. Antibodies to mycotoxins also gives the body burden to these mycotoxins. It is crucial to understand that antibodies to mycotoxins can form adducts and attach to human tissue, triggering autoimmunity. Just as important is to treat the mycotoxicosis, and the autoimmune reaction may fade away, rather than the reverse which is treating the autoimmunity first. As these are toxins and not living organisms with a cell membrane, an immunoglobulin G (IgG) antibody to mycotoxins indicates current exposure and/or colonization in contrast to the 4 pathogens in microbiology which are viruses, bacteria, parasites, and pathogenic fungi, in which an IgG antibody would represent a past exposure. Immunoglobulin E (IgE) antibodies to mycotoxins indicate mast cell stimulation and can lead to Mast Cell Activation Syndrome (MCAS).[44,45] Therefore, to get the full picture of the effects of mycotoxins in a patient, including the body burden and autoimmunity, and the crossing of the BBB, serum antibodies to mycotoxins is the most accurate method as confirmed by numerous studies published in peer-reviewed medical journals.

Effective and safe treatment has been shown to be the prescribing of azoles.[15,46] A publication in the journal Microorganisms from October 2021 demonstrated that azoles are safe even in patients with acute-on-chronic liver failure and continuous renal replacement therapy.[47] A currently popular treatment method that lacks medical evidence is the use of binders. Animal studies in pigs, rabbits, sheep, broiler chickens, ducks, turkeys, rats, and mice have shown that specified binders may remove mycotoxins under certain precise laboratory conditions in these animals. However, there are no medical or scientific published studies to support their use in humans. Just as any medication or vaccine that has no human trials should not be used in humans, the same principle applies to binders.

It will take some time to wean some health care practitioners from testing for mycotoxins in urine and treating patients with binders as this is all they have learned. However, there is no evidence in medical science that urine testing for mycotoxins as currently being performed is valid for measurement of indoor exposure and that treatment with binders for humans suffering from the effects of mycotoxins is in any way effective.

AUTHOR DISCLOSURE STATEMENT

Andrew Campbell, MD, is medical advisor to Mymycolab LLC.

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