Effects of Mycotoxins on Neuropsychiatric Symptoms and Immune Processes

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ABSTRACT

Purpose: The effects of air pollutants have been receiving increased attention both clinically and in the media. One such pollutant is mold, fungal growth in the form of multicellular filaments known as *hyphae*. The growth of molds is omnipresent not only in outdoor settings but also in indoor environments containing excessive amounts of moisture.

Methods: PubMed was searched for relevant articles using terms such as *mold, mycotoxins, fungi, immunity, inflammation, neurodevelopment, cognition, Alzheimer's,* and *autism*.

Findings: Exposure to molds is most commonly associated with allergies and asthma. However, it is now thought to be associated with many complex health problems, since some molds, especially *Trichoderma, Fusarium* and *Stachybotrys* spp, produce mycotoxins that are absorbed from the skin, airways, and intestinal lining. People exposed to molds and mycotoxins present with symptoms affecting multiple organs, including the lungs, musculoskeletal system, as well as the central and peripheral nervous systems. Furthermore, evidence has recently implicated exposure to mycotoxins in the pathogenesis of autism spectrum disorder. The effects of mycotoxins can be mediated via different pathways that include the secretion of pro-inflammatory cytokines, especially from mast cells.

Implications: The information reviewed indicates that exposure to mold and mycotoxins can affect the nervous system, directly or through immune cell activation, thus contributing to neurodevelopmental disorders such as autism spectrum disorder.

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Key words: autism, brain, cognition, fungus, inflammation, mast cells, mold, mycotoxins.

INTRODUCTION

Mold is a type of fungus grown in multicellular filaments on moist food and other surfaces. While generally thought to be an outdoor problem, mold contamination in buildings is quite common.[1–8] One study from Harvard University (Cambridge, Massachusetts), in 13,369 white children aged 8 to 12 years from 24 communities across North America, reported that the prevalence of indoor mold growth was between 22% to 57%, affecting >50% of households in 5 communities. The reported prevalence of asthma symptoms ranged from about 3% to 11% of the children.[9] Another study in 5951 children from 9 cities in Russia reported positive associations between water damage or the presence of molds in the home and asthma, wheezing, dry cough, bronchitis, and respiratory allergy.[10]

Many studies describe the adverse health consequences of mold-contaminated indoor environments, and especially mycotoxins,[11,12] on the skin and respiratory systems.[13] Some indoor molds, including *Trichoderma, Fusarium,* and *Stachybotrys* spp, produce mycotoxins,[1–8,14] exposure

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to which occurs through dermal contact, inhalation, and ingestion.[11] Inhabitants of affected dwellings typically report headaches and respiratory and musculoskeletal symptoms.[9,15–17] Some studies have also reported that mold-exposed groups had altered neurologic functioning, including changes in body balance, blink-reflex latency, visual fields, reaction time, and color discrimination, compared with controls.[18–21] The exposed groups also demonstrated depression.[22]

Increasing evidence has implicated the pathogenic potential of nanoparticulate fragments of fungi, and more specifically mycotoxins.[23–26] Moreover, while a single mycotoxin may not produce any effect, a combination of mycotoxins could induce toxicity at very low levels.[27] The major classes of mycotoxins include ochratoxin (A, B, and C), produced by *Penicillium* and *Aspergillus* spp, as well as the trichothecenes (T2).[14] Ochratoxin A is the most common mycotoxin found in foods and water-damaged buildings, and has been associated with serious health problems,[28] including severe neurologic issues, in humans.[29,30]

The trichothecene mycotoxins are subclassified as nonmacrocyclic, produced mostly by *Fusarium* spp, and macrocyclic, produced mostly by *Myrothecium*, *Stachybotrys,* and *Trichothecium* spp. Trichothecene mycotoxins can be released at ~300-fold the concentration of spores.[24] These are commonly detected in the air of contaminated buildings, and exposed persons have significantly more T2 mycotoxins in their sera as compared to controls.[25,31–33] These toxins can cause multisystemic effects, including gastrointestinal, cardiovascular, and neuropsychiatric complications.[23] One study reported neurotoxic effects on human cells exposed to satratoxin A at levels found in water-damaged buildings.[34] Trichothecene mycotoxins released by *Stachylobotrys* spp, such as satratoxins G and H, have been shown to produce neurotoxicity in humans.[35,36] The nonmacrocyclic T2 fumonisin B1 has also been associated with neurotoxicity.[37]

Here we review the risk factors, signs and symptoms, diagnoses, and mechanisms of action of mycotoxins, especially as they relate to neuropsychiatric effects.

MATERIALS AND METHODS

PubMed was searched for relevant articles using terms such as *mold, mycotoxins, fungi, immunity, inflammation, neurodevelopment, cognition, Alzheimer's,* and *autism*. The reference lists of identified articles were searched manually for additional papers eligible for inclusion. Data from articles that were prior to 1990 and those in languages other than English were excluded from the review.

RESULTS

A total of 150 articles were identified from the database search. Data from articles that were published prior to 1990 and those in languages other than English were excluded. Data from 16 articles (N = 1580 patients) were included in the present review. The Table summarizes most of the key studies reviewed.

Neuropsychiatric Effects From Mold Exposure

Findings in Adults

Individuals exposed to mold report an extensive range of symptoms, including malaise, fatigue, and cognitive impairment, which appear to be related to the duration of exposure.[18–21] In one study, patients who had been exposed to mold were impaired on a variety of cognitive measures, including verbal learning, visuospatial learning and memory, psychomotor speed, and emotional functioning.[20] Mold-exposed patients in other studies also displayed similar symptoms of neurologic dysfunction as compared to controls, including an inability to stand on one's toes, inability to walk in a straight line with eyes closed, short-term memory loss, altered blink-reflex latency, verbal recall impairments, as well as issues with color discrimination and reaction time.[38,40]

Another group of researchers assessed the psychological, neuropsychological, and electrocortical effects of exposure to mixed colonies of toxigenic molds in 182 patients with a confirmed mold-exposure history.[19] The patients reported moderate to severe levels of cognitive, physical, and emotional symptoms, mostly depression, while quantitative electroencephalography results showed hypoactivation in the frontal cortex, which could potentially be due to brain stem involvement and insufficient excitatory input from the reticular-activating system.[19] Neuropsychological testing also indicated impairments similar to those seen in mild traumatic brain injury, in which there were findings of impaired functioning on multiple cognitive tasks when compared to premorbid estimates of intelligence.[19] This picture is consistent with that from another study, in which neuropsychological data from and symptoms in 31

Table. Summary of important studies reviewed.

Environmental Exposure	Species	Subjects	Controls	Results	Findings	Conclusions	Study
Mold in home and workplace	Humans	10	10	Compared to normative data, mold-exposed patients were impaired on a number of cognitive measures.	The most consistent deficits were found in visuospatial learning/memory, verbal learning, and psychomotor speed.	Mold/mycotoxin exposure leads to neuropsychological detriments.	Baldo et al[20]
Mold	Humans	65 Patients	202 Community subjects	The mold-exposed group exhibited decreased function for balance, reaction time, blink-reflex latency, color discrimination, visual fields, and grip, as compared to referents.	Most functions tested were abnormal.	Indoor mold exposure is associated with neurobehavioral deficits.	Kilburn[38]
Mixed mold mycotoxicosis; water-damaged buildings	Humans	209 Patients	N/A	Many of the exposed individuals had increased lymphocyte phenotypes and numerous other immune abnormalities.	Exposure to mixed molds and their associated mycotoxins in water-damaged buildings leads to multiple health problems involving the CNS.	Mold-exposed patients reported a greater frequency and intensity of neurological and inflammatory symptoms.	Gray et al[39]

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Environmental Exposure	Species	Subjects	Controls	Results	Findings	Conclusions	Study
Mixed molds	Humans	182 Mold-exposed normal	N/A	Hypoactivation of the frontal cortex and insufficient excitatory input from the reticular activating system. Neuropsychological testing also revealed impairments similar to mild TBI.	A dose–response relationship between measures of mold exposure and abnormal neuropsychological test results suggested that toxic mold causes significant problems in exposed individuals.	Mold exposure leads to neuropsychological detriments.	Crago et al[19]
Mold/mycotoxins in home	Humans	100 Patients	N/A	Immune abnormalities were found in > 80% of the patients and symptoms of neurological dysfunction in 70% of all patients. Objective abnormal autonomic nervous system tests were positive in all 100 patients tested.	Objective neuropsychological evaluations of 46 of the patients who exhibited symptoms of neurological impairment showed typical abnormalities in short-term memory, executive function/ judgment, concentration, and hand/eye coordination.	Mold/mycotoxin exposure leads to neuropsychological detriments.	Rea et al[40]

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Environmental Exposure	Species	Subjects	Controls	Results	Findings	Conclusions	Study
Mold	Humans	6 Patients	N/A	Reports data on six patients claiming harm from mold.	Only 2 patients who were also depressed showed credible evidence of neuropsychological dysfunction.	No credible evidence of harm due solely to mold exposure.	Stone et al[41]
Toxic mold	Humans	53 Patients	N/A	No concomitant cognitive deficits or a significant reduction in intellectual functioning.	Lack of significant evidence for cognitive dysfunction	Mold exposure does not lead to cognitive deficits.	Reinhard et al[42]
Mold and terbutaline	Humans	8 ASD boys in non-chemical community; 6 ASD mold-exposed children	145 Non-ASD in nonchemical community; 29 non-ASD mold-exposed children	The 6 mold-exposed ASD kids had most.	Neuropsychological abnormalities were more frequent in mold-exposed children.	Mold exposure increased neuropsychological abnormalities in ASD children.	Kilburn et al[43]
Toxic mold	Humans	15 Normal adults	N/A	Mold-exposed subjects show statistically significant decreases in attention span and significant increases in reaction time to stimuli compared to controls.	After 10 sessions of HBOT, a statistically significant improvement was seen in both measures.	HBOT a possible treatment method for mold-exposed patients.	Ezra et al[44]

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Environmental Exposure	Species	Subjects	Controls	Results	Findings	Conclusions	Study
Mold-contaminated homes in early postnatal period	Humans	277 Normal babies	N/A	Long exposures to indoor molds (>2 y) tripled the risk for low IQ scoring compared with controls.	Early postnatal exposure to indoor molds reduced children's cognitive development.	Mold exposure negatively affected children's IQ.	Jedrychowski et al[45]
No exposure	Humans	57 Patients with mastocytosis	N/A	Patients with mastocytosis presented high levels of cognitive impairment (memory and/or attention).	Memory and attention impairment in mastocytosis is frequent, even in young individuals.	Mast cells emotionality affect in cognition.	Moura et al[46]
Home dampness, pets and farm animal contact; microbial compounds (bacterial endotoxin and fungal extracellular polysaccharides)	Humans	482 Children	N/A	Persistent home dampness in the child's bedroom during early life significantly decreased the general score on MSCA by 4.9 points and it decreased the CPSCS by 6.5 points. None of the measured microbial compounds were related with the psychometric test scores.	Damp room in early life can have adverse effects on neuropsychological development at 4 years old.	Damp housing in early life adversely affects neuropsychological development.	Casas et al[47]

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Table. (continued).

Environmental Exposure	Species	Subjects	Controls	Results	Findings	Conclusions	Study
Mold	Humans	31	65 Patients with traumatic TBI & 26 with moderate TBI	Most participants were found to have reduced cognitive function in multiple domains, with memory and executive functions the most commonly affected areas.	Mold-exposed participants reported significantly more symptoms.	Mycotoxins/mold exposure contributed to cognitive dysfunction.	Gordon et al[48]
Ochratoxin A	N/A	N/A	N/A	Ochratoxin A exerted a male-specific neurotoxicity, probably via microRNA modulation of the neuroligin 4X gene.	Proposed gene-environment interaction.	Possible explanation for the male prevalence of ASD.	Mezzelani et al[49]
Mycotoxins	Humans	25 Patients with ASD	29non-ASD	Screened for 87 urinary mycotoxins, but only 9 of 54 children had detectable mycotoxins in their urine.	No urine mycotoxins were associated with ASD-diagnosed children.	No association between urine mycotoxin exposure and autism.	Duringer et al[50]
No exposure	Humans	54 Patients with mastocytosis	Healthy, age-matched controls	Patients displayed significantly lower levels of TRP and 5-HT.	High perceived stress and high depression scores were associated with low TRP.	TRP metabolism was altered in mastocytosis and correlates with perceived stress and depression.	Georgin-Lavialle et al[51]

5-HT = serotonin; ASD = autism spectrum disorder; CPSCS = California Preschool Social Competence Scale; HBOT = hyperbaric oxygen treatment; MSCA= McCarthy Scales of Child Abilities; TBI = traumatic brain injury; TRP = tryptophan.

individuals exposed to toxic mold showed that most participants had decreased cognitive functioning in multiple domains, with memory and executive functions being the most commonly affected areas.[48] These symptoms were similar to those in matched groups of 65 individuals with mild traumatic brain injury and 26 persons with moderate traumatic brain injury.[48]

One study conducted in patients with confirmed exposure to mixed-mold infestation in water-damaged buildings found that exposure to mycotoxins was associated with multisystem issues involving the nervous and immune systems.[40]

Other studies used both objective and subjective measures and showed that the presence of mold and dampness was associated with the prevalence of depression and emotional distress.[52–54] This conclusion was subsequently confirmed using multivariate analyses.[55]

There are also some contradictory reports. Unlike the cognitive impairments suggested in other studies, the results from a study by Reinhard et al[42] (N = 50) did not reveal a significant reduction in intellectual functioning, nor did they show a dose effect of self-reported duration of exposure on cognitive outcome. Another study did not find any association between exposure to mold and neuropsychiatric symptoms.[56] It is also possible that symptoms of cognitive impairment are not unique to mold and mycotoxin exposure. For instance, researchers examining neurobehavioral and pulmonary impairment in 105 adults with indoor exposure to molds, as compared to controls and 100 chemical-exposed adults, found that the increased neurobehavioral impairments associated with mold exposure were comparable to those of chemical exposures.[57]

It is also unclear whether neuropsychological problems are due to the adverse effects of mycotoxins or the emotional and financial stress of keeping a house clean in the face of recurrent mold.[52] Investigators have also hypothesized that housing is intimately linked to an individual's perception of control, so those experiencing high demands from a moldy home, yet a low sense of control, may have an elevated risk for anxiety and depression.[58–60] Nonetheless, the association between mold or dampness in the home and depressive symptoms was diminished, but not eliminated, when perception of control over one's home or a physical health index was included in the model.[22] Furthermore, since living in a moldy home is associated with poor physical health outcomes, such as respiratory and gastrointestinal tract issues, poor physical health is another likely contributor to depressive tendencies.[52,54,61–63]

There is also a concern that some neuropsychiatric symptoms may be associated with socioeconomic factors present in individuals living in moldy dwellings. The Health Public Housing Initiative in Boston, Massachusetts tried to identify and correct such associations.[64,65] One study showed increased exposure to mold in a workplace, especially fumonisins B1 and B2, due to contaminated onions.[66] Workers at a waste-management company in Portugal were exposed to increased levels of aflatoxin B1.[67] In an analysis in breast-feeding mothers in Lebanon, the presence of aflatoxin B1 in breast milk was correlated with low socioeconomic status.[68] A strong association between poverty and exposure to aflatoxin was also reported in a cross-sectional study from Kenya.[69]

Findings in Children

Exposure to molds that produce potent toxins has been associated with acute pulmonary hemorrhage and hemosiderosis among infants.[70] One study showed a correlation between exposure to excessive moisture or mold in a home or school environment and the occurrence of respiratory issues, including infections, repeated wheezing, and prolonged cough.[10,61,64,71–77]

Some studies in children have focused on cognitive-development deficits resulting from exposure to air pollutants both prenatally and during childhood.[78,79] In children with long-term exposure to molds, there were significant neurologic findings on clinical neurologic and neurobehavioral questionnaires, as well as abnormalities on a series of neurophysiological tests, including electroencephalography, brain stem evoked potential, visual evoked potential, and somatosensory evoked potential.[80]

A 6-year follow-up study conducted in Poland explored cognitive functioning in 277 infants born at term and exposed to mold in contaminated homes in the early postnatal period. The presence of visible mold patches on indoor walls was checked at consistent time intervals over gestation and after birth, up to the age of 5 years. Longer (>2 years) exposure to indoor molds was associated with deficits in intelligence quotient compared to that in controls.[45] In a population-based birth-cohort study from Spain, 482

children underwent psychometric testing at 4 years of age; information on home dampness, pet ownership, and farm-animal contact was regularly monitored and reported by parents through questionnaires, while bacterial endotoxins and fungal extracellular polysaccharides were measured in living-room sofa dust collected when the children were 3 months of age.[47] The results revealed that persistent home dampness in a child's bedroom during early life was associated with a significant decrease in the general cognitive score on both the McCarthy Scales of Child Abilities and the California Preschool Social Competence Scale.[47]

Recent epidemiologic studies have reported a significant association between exposure to mycotoxins and autism spectrum disorder (ASD), which now affects an estimated 1 in 59 children[81] and remains without a clear pathogenesis despite advances in identifying multiple mutations.[82,83] Two studies have provided strong evidence of an association between exposure to mycotoxins and ASD. In the first, data from 52 children with ASD were compared to those from healthy children (31 siblings and 27 unrelated subjects), with a significant association between levels of ochratoxin A in urine and serum found in children with ASD.[84] In a subsequent cross-sectional study, levels of different mycotoxins (aflatoxin M1, ochratoxin A, and fumonisin B1) were shown to be significantly higher in serum and urine from 172 children with ASD as compared to 61 healthy controls.[85] Another study compared neurobehavioral and pulmonary functioning between mold-exposed boys with ASD, non–mold-exposed boys with ASD, terbutaline-exposed children, and unaffected children from a community with no known chemical exposures.[43] After comparisons were adjusted for confounding variables and variances, the results showed that the mold-exposed boys with ASD averaged significantly more abnormalities than did the other groups, especially in balance, vision, and blink-reflex latency.[43] Additionally, other studies have shown that mold-exposed children experienced cognitive deficits compared to controls, but that the effects were not specific to mold or related to psychometric test scores.[47,48]

One pilot case–control study, conducted in school-aged children, showed that, of 87 urinary mycotoxins measured via LC-MS/MS, no singular mycotoxin or group of mycotoxins was associated with ASD diagnosis in children.[50] However, serum IgE or IgG levels in those exposed to mycotoxins may be a more reliable index of long-term exposure, and detoxification may be required to release mycotoxins from fat or other depots into the urine so that they may be detected.

Immune Pathways of Mycotoxin Toxicity

Unlike bacterial toxins, which are proteins, mycotoxins have diverse structures.[86] Mycotoxins have different mechanisms through which they exert their effects,[87,88] depending on whether studies are performed *in vitro* or *in vivo*.[89] Mycotoxins may produce their detrimental effects not only by affecting transcription and translation, but also through inflammatory responses mediated by cytokines.[88] Mycotoxins could also affect the neuroimmune axis[90] via activation of a number of kinases, including mitogen-activated protein kinase (MAPK).[88,91–97] Macrocyclic trichothecenes are potent activators of MAPKs.[98] Exposure to satratoxin H leads to the activation of MAPKs, the development of oxidative stress, and the depletion of reduced glutathione.[35] In addition, zearalenone, a mycotoxin produced by a number of *Fusarium* spp, has been shown to affect immune mediators, MAPK signaling, and gene expression.[99]

Ochratoxin A exposure reduces mitochondrial function and could lead to apoptosis in neurons,[100–102] as well as dysfunctional responses in cultured murine microglia and astrocytes.[103,104] In studies in mice, satratoxin G was shown to produce apoptosis in sensory neurons in the olfactory bulb,[105] as well as encephalitis associated with persistently high levels of pro-inflammatory cytokines in the frontal brain region.[106]

Many pro-inflammatory cytokines are secreted from mast cells,[107–109] which are found perivascularly in all tissues, including the brain.[110–114] Recent studies have shown strong associations between the prevalence of mast cells and an increased risk for ASD.[115,116] A case of particular interest is mastocytosis, characterized by the abnormal accumulation of mast cells in one or multiple organs,[108] and mast cell–activation syndrome, characterized by unregulated mast cell activation.[117] We had reported that the prevalence of ASD is 10-fold higher in children with mastocytosis than in the general population.[116] Moreover, one third of patients with mastocytosis

display various neuropsychological symptoms, including fatigue,[118] cognitive impairment,[46] and depression.[51] It is of interest that mycotoxins can stimulate mast cells[119–121] and microglia[85] because mast cell–microglia interactions have been implicated in neuropsychiatric disorders, especially "brain fog."[122–125]

Increasing evidence suggests the presence of localized inflammation in the brain in patients with ASD.[115] Environmental triggers, such as mycotoxins, have been associated with ASD.[126–129] Such triggers could increase the permeability of the gut–blood and blood–brain barriers through mast cell mediators,[130–132] especially cytokines,[133] allowing circulating and environmental toxins to pass into the brain, trigger microglia proliferation, and disrupt neuronal connectivity.[115,134] For instance, it has been reported that propionic acid and ammonia released by *Candida albicans* in the gastrointestinal tract[135] leads to the generation of β-alanine, which could cross the blood–brain barrier and act as a partial antagonist to γ-aminobutyric acid receptors.[135]

Ochratoxin A is one of the major food-contaminating mycotoxins, and it may exert a male-specific neurotoxicity of a specific target gene through microRNA modulation both *in vitro* and *in vivo* with respect to ASD. Researchers have focused on the neuroligin 4X–encoding gene (*NLGN*), which is expressed on the X chromosome and carries a few single-nucleotide polymorphisms that have been linked to ASD.[49] Some of these point mutations may prevent phosphorylation of the protein encoded by *NLGN*, disrupting proper synaptic functioning.[136]

Most recently, mycotoxins were shown to bind to proteins involved in neuronal plasticity.[137] Exposure to satratoxin H was shown to increase susceptibility to other neurotoxic mycotoxins.[34,138]

CONCLUSIONS

Exposure to mold and their mycotoxins continues to be a major health problem worldwide. Recent studies have greatly expanded our understanding of the systemic impact of mold toxicity on the human body, including the brain. Exposure to mycotoxins has demonstrated positive associations with asthma, wheezing, and bronchitis, as well as fatigue, musculoskeletal pain, headaches, anxiety, mood, cognitive impairments, and depression. A better understanding of the molecular pathways that underlie the link between mycotoxin exposure and cognitive impairment, as well as the impact of mold and mycotoxins on the immune and nervous systems, is urgently needed.

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