# Mycotoxins and Human Disease

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## Abbreviations

| | |
|---|---|
| AFB1 | Aflatoxins B1 |
| IARC | International Agency for Research on Cancer |
| HBV | Hepatitis B |
| AFM1 | Aflatoxin M1 |
| DON | Deoxynivalenol |
| OTA | Ochratoxin A |
| BEN | Balkan endemic nephropathy |
| GI | Gastrointestinal |
| WDB | Water-damaged buildings |
| NAC | *N*-Acetylcysteine |

## 14.1 History

Mycotoxins are secondary fungal metabolites that can be produced in crops and other food commodities. When ingested, mycotoxins may cause a mycotoxicosis, the term first used by Forgacs and Carll [1], which can result in an acute or chronic disease episode [2]. The oldest recognized mycotoxicosis of humans is ergotism caused by the plant parasitic fungus, *Claviceps purpurea*. After periodic outbreaks in central Europe, the disease became epidemic in the Middle Ages, where it was known as St. Anthony's fire [3, 4]. Gangrenous symptoms were described in medieval episodes of ergotism in humans, where early symptoms were hallucinations and swollen limbs with burning sensations, with subsequent necrosis leading to loss of appendages [4].

Today, the word *mycotoxin* simply means a toxin produced by a fungus. Modern mycotoxicology began with the discovery of the aflatoxins in the early 1960s [3]. Since that time, numerous other mycotoxins have been discovered [5].

## 14.2 Introduction

Mycotoxins are a relatively large, diverse group of naturally occurring, fungal toxins, many of which have been strongly implicated as chemical agents of toxic disease in humans and animals. The history and use of mycotoxins are very long and go back to antiquity, e.g., the philosopher Socrates was executed by drinking of a mixture containing poison hemlock. Today, there are potentially 20,000 to 300,000 known mycotoxins of micro- and macrofungi. Microfungi are the surrogate for the fungus itself that produces mycotoxins on the cellular level. Macrofungi refer to the fruiting bodies (mushrooms) that are appreciated deli food but may be poisonous and deadly. The diversity of toxic mechanisms will be equally as great. The number of mycotoxins actually known to be involved in disease is considerably less, but even this number is difficult to

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assess due to the diversity of effects of these unique compounds on humans [6–9].

The usual route of mycotoxin exposure is ingestion as food or feed contaminants. However, dermal and inhalation also may be important routes of exposure. Direct effects of mycotoxins range from acute disease where severe conditions of altered health may exist prior to death as a result of exposure to the toxin. These conditions are more likely following exposure to high levels of a mycotoxin. Other, more insidious or occult conditions (e.g., growth retardation, impaired immunity, decreased disease resistance) or more chronic disease manifestations (e.g., tumor formation) may result from prolonged exposure to small quantities of toxin [7, 10, 11]. Awareness is growing regarding the hazards of mycotoxins as contaminants of food and feed.

## 14.3 Microfungi

### 14.3.1 Classes of Mycotoxins

The mycotoxins that pose the greatest potential risk to human and animal health as food and feed contaminants are aflatoxins, trichothecenes, fumonisins, zearalenone, ochratoxin A (OTA), and ergot alkaloids. However, other mycotoxins should be included because of their frequency of occurrence in commodities, their products, or their co-occurrence with other important mycotoxins. This expanded list includes cyclopiazonic acid, sterigmatocystin, gliotoxin, citrinin, penitrems (perhaps other tremorogenic mycotoxins), patulin, and miscellaneous mycotoxins such as fusarin C, fusaric acid, penicillic acid, mycophenolic acid, roquefortine, Penicillium roqueforti (PR) toxin, and isofumigaclavines A and B [7, 9–11].

#### 14.3.1.1 Major Classes of Mycotoxins

*Aflatoxins* are naturally occurring mycotoxins that are produced by various species of *Aspergillus*. The major aflatoxins commonly isolated from foods and feeds are aflatoxins B1 (AFB1), B2, G1, and G2 [12]. Aflatoxin is considered as hepatotoxic, carcinogenic, immunosuppressive, and antinutritional contaminant of many staple food commodities. Mutation of the P53 gene is considered as a key event in aflatoxin-induced carcinogenesis [10, 13, 14]. The endo-epoxide primarily binds to cellular proteins and is associated with direct cytotoxicity and the impairment of liver function. AFB1 is classified as a group 1 carcinogen by the International Agency for Research on Cancer (IARC) (Table 14.1) [15]. Epidemiological evidence suggest a synergistic effect of AFB1 and chronic hepatitis B (HBV) infections in the prevalence of liver cancer in humans [11, 13, 16]. Animal studies show that AFB1 also interferes with vitamins A, D, B12, iron, selenium, and zinc nutrition [10, 13, 17].

**Table 14.1** Classification of food mycotoxins as potential human carcinogens

| Group | Classification of food mycotoxins |
|---|---|
| 1 | Aflatoxin B1, B2, G1, G2 |
| 2A | – |
| 2B | Aflatoxin M1, ochratoxin A, sterigmatocystin |
| 3 | Citrinin, patulin, luteoskyrin, cyclochlorotine, deoxynivalenol |
| 4 | – |

Group 1, carcinogenic to humans; Group 2A, probably carcinogenic to humans; Group 2B, possibly carcinogenic to humans; Group 3, not classifiable as to its carcinogenicity to humans; Group 4, probably not carcinogenic to humans (classified by the International Agency for Research on Cancer)

Another important hepatic metabolite is aflatoxin M1 (AFM1), which is excreted into milk both in animals and in humans. This results in an undesirable exposure of infants. AFM1 is less biologically active than AFB1 but can also be converted into epoxide forms that lead to hepatotoxicity and hepatocarcinogenicity [9, 12, 13]. IARC has classified AFM1 as a group 2B carcinogen (possibly carcinogenic to humans) (Table 14.1) [15].

*Trichothecenes* are a family of nearly 150 structurally related compounds produced by several fungal genera: *Fusarium*, *Cephalosporium*, *Myrothecium*, *Stachybotrys*, *Trichoderma*, and others [18]. The most common trichothecene mycotoxin is deoxynivalenol (DON, sometimes referred to as vomitoxin), which is common contaminant of corn and wheat in Europe [18, 19].

*Fumonisins* are mycotoxins produced by *Fusarium verticillioides* [19–21]. There is evidence linking *F. verticillioides* infected corn to the high incidence of human esophageal cancer in South Africa and China [19, 21–23]. *F. verticillioides* is an almost universal inhabitant of corn [19, 21, 22, 24].

*Ochratoxins* are a group of structurally similar metabolites commonly produced by *Aspergillus ochraceus* and *Penicillium verrucosum*. The major mycotoxin in this group is OTA. OTA has been suggested as the etiological factor of the Balkan endemic nephropathy (BEN) [18].

*Ergot alkaloids* are produced by several species of *Claviceps* that infect grains or grain products. These mycotoxins are involved in either nervous or gangrenous syndromes in humans. Ergotism is one of the oldest mycotoxicoses known, although occurrence of the disease has declined over time [2–4].

#### 14.3.1.2 Minor Classes of Mycotoxins

*Cyclopiazonic acid* is mycotoxin isolated from molds commonly found on agricultural commodities or used in fermented food production (*Aspergillus flavus*, *Aspergillus versicolor*, *Aspergillus tamarii*, and several *Penicillium* species used in the production of fermented sausages in Europe). This includes *Penicillium camemberti*, used in the production of Camembert cheese, and *Aspergillus oryzae*, used in the production of soy sauce in the Far East. This mycotoxin has been shown to occur naturally in corn, cheese, peanuts, and sunflower seeds [2, 7].

*Sterigmatocystin* is produced by several species of *Aspergillus* and *Bipolaris* and by *Penicillium luteum*. Sterigmatocystin has been detected at low concentrations in green coffee, moldy wheat, and in the rind of hard cheese [2, 7].

*Citrinin* is a yellow mycotoxin produced by several *Penicillium* and *Aspergillus* species, including *Penicillium verrucosum* strains that produce OTA. Like OTA, citrinin causes kidney damage in laboratory animals [2, 7].

*Patulin* is produced primarily by species of *Penicillium* and *Aspergillus*, and its limited toxic properties are of major concern because it occurs in apples and, subsequently, applesauce and juice [2, 7].

*Citreoviridin* originally was isolated from molds obtained from rice associated with a disease called "cardiac beriberi" that has occurred for three centuries in Japan (2). This mycotoxin also occurs in corn and other foods and feeds infected by some species of *Penicillium* and *Aspergillus* [2, 7].

*Fusaproliferin* has been detected in corn samples infected by *Fusarium proliferatum*, and *Fusarium subglutinans* that have been tested are capable of fusaproliferin production in culture [19, 21]. Although the significance of this compound in animal and human health remains to be determined, its acute toxicity to brine shrimp exceeds that of more familiar compounds such as the fumonisins.

### 14.3.2 Mycotoxin-Producing Fungi

Mycotoxins are produced by a wide array of diverse fungal species that generally are not aggressive pathogens. Most of the mycotoxins that are considered to be important are produced primarily by three genera of fungi: *Aspergillus*, *Penicillium*, and *Fusarium*. *Claviceps* and *Stachybotrys* also are important producers of mycotoxins [7, 10, 12, 22, 24].

Within the genus *Aspergillus*, the major class of mycotoxins is the aflatoxins. The crops most usually affected are corn, cotton, peanuts, and certain tree nuts. Although not conclusive in all crops, high temperatures seem to play a role in aflatoxin contamination [10, 14].

Within the genus *Fusarium*, there are a number of important mycotoxin-producing species. The major causative agents are *Fusarium graminearum*, *F. verticillioides*, *F. proliferatum*, and *F. subglutinans*. These latter agents may produce fumonisins during the pathogenic state in corn. *Fusarium graminearum* is a significant pathogen on wheat, barley, corn, and oats and is a major producer of DON in these grains [19, 21, 24].

*Penicillium* spp. are more typically associated with storage of crops and the production of

**Table 14.2** Human diseases in which analytic and/or epidemiologic data suggest or implicate mycotoxin involvement

| Disease | Substrate | Etiologic agent (spp.) | Ref. |
|---|---|---|---|
| Akakabio-byo | Wheat, barley, oats, rice | *Fusarium* | [8] |
| Alimentary toxic aleukia (septic angina) | Cereal grains (toxic bread) | *Fusarium* | [19] |
| Balkan endemic nephropathy | Cereal grains | *Penicillium* | [41] |
| Cardiac beriberi | Rice | *Aspergillus*, *Penicillium* | |
| Dendrodochiotoxicosis | Fodder (skin, inhalation) | *Dendrodochium toxicum* | |
| Ergotism | Rye, cereal grains | *Claviceps purpurea* | [4] |
| Esophageal tumors | Corn | *Fusarium moniliforme* | [20] |
| Hepatocarcinoma (acute aflatoxicosis) | Cereal grains, peanuts | *Aspergillus flavus*, *A. parasiticus* | [37–39] |
| Kashin-Beck disease, "Urov disease" | Cereal grains | *Fusarium* spp. | [8] |
| Kwashiorkor | Cereal grains | *Aspergillus flavus*, *A. parasiticus* | [32] |
| Onyalai | Millet | *Phoma sorghina* | [7] |
| Reye's syndrome | Cereal grains | *Aspergillus* spp. | [60] |
| Stachybotryotoxicosis | Hay, cereal grains, fodder (skin contact, inhalation) | *Stachybotrys atra* | [25] |

mycotoxins such as OTA. OTA usually is formed in storage or during drying of certain commodities for processing [22, 23].

A number of fungi are capable of producing toxic alkaloids, and *Claviceps* spp. are the most notable in this regard. Toxic alkaloids also are produced by the genera *Epichloe* and *Neotyphodium*, both of which can be endophytic in certain plant species such as fescue and ryegrass [2].

*Stachybotrys* is a cellulolytic saprophyte that can be found in a variety of commodities, and the trichothecene metabolites of this organism can produce disease similar to some of those produced by *Fusarium* spp. Recently, this organism seemed to be involved in human disease where building materials were contaminated with the organism and possibly its toxic metabolites [25].

### 14.3.3 Impact of Mycotoxins on Human Diseases

Mycotoxicosis, the disease resulting from exposure to a mycotoxin, may be manifested as acute to chronic and ranges from rapid death to tumor formation [6, 9]. More occult disease may occur when the mycotoxin interferes with immune processes, rendering the patient more susceptible to infectious diseases. Humans likely are exposed to mycotoxins through several routes such as ingestion by contaminated food (the most prominent means of exposure), contact, and inhalation [2, 6, 9]. There are many diseases that have been described in humans for which either analytic or epidemiologic evidence implicates a mycotoxin etiology (Table 14.2) [9–11, 14]. The aflatoxins are known causes of acute aflatoxicosis in humans, as well as potential cofactor of hepatic carcinoma, together with HBV [11, 16]. OTA has been conjecturally associated with the Balkan endemic nephropathy (BEN). The rural populations in the Balkans have a high incidence of chronic kidney problems and tumors of the excretory organ system [18, 42–44]. The most likely toxic products of the *Fusarium* spp., the trichothecenes, are conjecturally associated with the most prominent disease described alimentary toxic aleukia. The trichothecene, DON, is capable of producing a disease in mice that is similar in histological descriptions to human glomerulonephropathy [18, 22, 23]. Stachybotryotoxicosis is a disease that occurs in humans and is suspected to be caused by toxins of the organism *Stachybotrys chartarum* [25]. The fumonisins have been associated with esophageal cancer in

certain human populations [22]. Of interest to many investigators is that a number of mycotoxins are immunosuppressive and likely could be involved in human disease. Today, there is an apparent growing concern within the medical community regarding mycotoxin involvement in human diseases [6, 9]. The following section discusses mycotoxicoses for which there is considerable evidence for involvement of a specific mycotoxin(s). These and other human diseases where mycotoxin involvement is likely are presented in Table 14.2.

#### 14.3.3.1 Acute Illness and Death

The symptoms of severe mycotoxicosis include hemorrhagic necrosis of the liver, bile duct proliferation, edema, and lethargy. Adult humans usually have a high tolerance of aflatoxin, and, in the reported acute poisonings, the children are those who die [26]. Acute poisonings, about 25% of which result in death, occur as a result of high levels of exposure [26, 27]. Reports of death and serious illness usually originate from developing countries within the zone of risk [28, 29].

#### 14.3.3.2 Chronic Effects of Mycotoxins in Human Populations

In many regions of the world, dietary staples, especially cereal grains, contain low levels of mycotoxins. The impact of regular low-level intake of mycotoxins on human health is likely to be significant with a number of possible consequences including impaired growth and development, immune dysfunction, and the disease consequences of alterations in DNA metabolism [19].

#### 14.3.3.3 Growth and Development

Numerous animal studies have shown that one of the first effects of mycotoxin ingestion is reduced feed intake and growth [22, 30]. There are facts revealing a very strong association between exposure to aflatoxin in the children and both stunting and being underweight. Both conditions reflect significant malnutrition and exposure of the children to aflatoxin in utero and subsequently after birth [30]. In West Africa, the aflatoxin exposure of children between 9 months and 5 years of age examined their growth, development, and height [30]. The children were also co-exposed to a number of infectious diseases, and it is likely that the exposure to disease and aflatoxin would significantly compromise growth and development through reduced food intake and also the repartitioning of nutrients to maintain an upregulated immune system and away from growth and development [31, 32].

#### 14.3.3.4 Immunosuppression

Immunosuppression is a likely major economic effect of mycotoxins. Mycotoxins known to have this effect are aflatoxins, certain trichothecenes, OTA, and gliotoxin. These mycotoxins can be immunotoxic and exert effects on cellular responses, humoral factors, and cytokine mediators of the immune system and can cause a variety of immune-related changes, including thymic aplasia and inhibition of phagocytosis by macrophages, delayed cutaneous hypersensitivity, lymphocyte proliferation, and leukocyte migration [23, 33, 34]. The effects on immunity and resistance are often difficult to recognize in the field because signs of disease are associated with the infection rather than the toxin that predisposed the individual to infection through decreased resistance and/or reduced vaccine or drug efficacy. There are evidences who reveal strong association between aflatoxin exposure and reduced immunocompetence in children [35] and adults [36], suggesting that aflatoxin ingestion decreases resistance to infection in human populations. DON can both stimulate and suppress the immune system, with dysregulation of IgA and the development of kidney disease in animal models that closely resembles human glomerulonephritis IgA nephropathy [33, 34].

#### 14.3.3.5 Carcinogenicity, Mutagenicity, and Teratogenicity

Several food-contaminating mycotoxins have been defined as harmful carcinogens by the IARC (Table 14.1), that is, DON/nivalenol, zearalenone, ochratoxin, fumonisins, and aflatoxins [2, 15]. There is significant body of evidence demonstrating human exposure in utero to a number of

mycotoxins, but the relevance of this exposure to birth defects or impaired embryonic development has received relatively little attention [19]. Recent epidemiological investigations of human populations in Texas, China, Guatemala, and Southern Africa that rely on foods prepared from maize, which is often contaminated with fumonisins, found a significantly higher incidence of neural tube defects in babies [19].

#### 14.3.3.6 Hepatocellular Cancer and Mycotoxins

Two major factors, aflatoxin and HBV, which commonly occur in the same populations, influence the risk of liver cancer. Independently, each factor significantly increases the relative risk of cancer, and most studies report them, together, to be synergistic [37, 38]. The suggested mechanism for this synergy is that aflatoxin suppresses DNA repair mechanisms that help limit the development of hepatocellular cancer from HBV, and HBV prevents detoxification, but it is also possible that the immunotoxicity of aflatoxin interferes with the suppression of cancer. AFB1 is the most well-known bioaccumulative toxin with strong mutagenic effect, involved in the development of hepatocellular cancer [37–39]. When individuals are exposed to AFB1 for a long time, monooxygenases produce reactive epoxide in the liver, leading to formation of toxic derivatives with nucleic acids and proteins [39, 40].

#### 14.3.3.7 Mycotoxins and Balkan Endemic Nephropathy

There are convincing evidence that chronic poisoning with OTA is possible causative agents of BEN [41–44]. OTA, produced primarily by *Aspergillus ochraceous* or *Penicillium verrucosum*, occurs on several commodities prevalent in human diets, including barley and green coffee beans [42, 44]. OTA-mediated nephropathy is endemic, and outbreaks have been associated with weather conditions [43, 44]. This mycotoxin is considered a possibly carcinogenic to humans particular in the role of developing BEN-associated cancer (Table 14.1). However, the mechanism of OTA-derived tumor formation is unknown, and conflicting results regarding the potential of OTA to react with DNA to form covalent DNA adducts have been reported [45, 46].

#### 14.3.3.8 Mycotoxins and Gastrointestinal Infections

The gastrointestinal (GI) tract, as the primary targeting organ, is exposed directly to mycotoxins with a higher concentration than other tissues and organs, which can affect the regeneration, proliferation, differentiation, and repair of intestinal epithelial cells. Some mycotoxins, such as AFB1, OTA, and DON, could reduce the expression of zonula occludens protein and increase intestinal mucosal permeability, thus damaging the barrier functions of intestinal epithelial cells and inducing bacterial translocation [21, 47]. Moreover, mycotoxins can influence the immune system of the GI tract [21, 48]. Mycotoxins could trigger mucosal immunoregulatory mechanisms such as the secretion of mucus, antimicrobial peptides, and immunoglobulins and directly induce inflammation by inducing intestinal epithelial cells to secrete chemotactic factors and pro-inflammatory cytokines [49]. Mycotoxins may be associated with chronic inflammation of the intestine in genetically susceptible patients with inflammatory bowel disease or coeliac disease [5, 47]. The long-term exposure of trichothecene toxins can increase intestinal colonization by aerobes [48]. The definite disturbance of human GI fungal and bacterial microbiota induced by mycotoxins still remains largely unknown.

#### 14.3.3.9 Mycotoxins and Airway Diseases

Inhalation of mycotoxins is especially hazardous to those living inside damp, wet, and moldy buildings [50]. These toxins, mostly produced by fungi *Stachybotrys*, elicit recruitment of alveolar macrophages and neutrophils, pulmonary hemorrhage, and cytokine production and could trigger chronic obstructive pulmonary disease, while inhalation of a toxic dose of mycotoxin

leads to systemic effects exclusive of lung injury [51, 52]. The most frequently recovered mycotoxins in nasal washings of individuals with respiratory diseases living in water-damaged buildings (WDB) are macrocyclic trichothecenes, found in 44% of the nasal washing specimens, whereas aflatoxin is present in 17% of these cases. On the other hand, mycotoxins were not found in nasal washings of a healthy control population. Other positive findings for the presence of mycotoxins in various tissues include trichothecenes in sera, breast milk, placenta, umbilical cord, and tissues (sinus) of individuals exposed in WDB [53, 54]. Clinical symptoms expressed by individuals living in WDB contaminated by *Stachybotrys*, mostly *S. atra* and *S. chartarum*, are pulmonary irritation and headaches, fatigue, malaise, diarrhea, inflammation of the nose, chest pain, or leukopenia [54, 55]. Strategy for prevention of this mycotoxicosis is using of polycarbonate membrane filters that could retain airborne particles of trichothecenes contaminated materials [50].

#### 14.3.3.10 Mycotoxins and Deficiency of Vitamin B12

There are several pieces of evidence to show that mycotoxins affect cellular activities of the brain for which vitamin B12 plays a major role. Vitamin B12 possibly interacts with mycotoxins to effect some of the biochemical and neurological changes [56, 57]. It is believed that the biochemical consequences of fumonisin disruption of sphingolipid metabolism are increased free sphingoid bases and their 1-phosphates, alterations in complex sphingolipids, and decreased ceramide biosynthesis [24]. It is not yet clear whether vitamin B12 deficiency precludes fungal infection or vice versa. However, the factors commonly believed to predispose to recurrent chronic fungal infections included deficiency in whole blood folate, iron, and vitamin B complex [57]. These diseases occur as result of metabolic disorders and are due to inactivity of enzymes that are characteristic of vitamin B complex deficiencies (Table 14.3) [58].

**Table 14.3** Signs, symptoms, and clinical neurologic indications of vitamin B12 deficiency

| Signs and symptoms | Clinical neurological indications |
|---|---|
| Headache, fatigue, loss of appetite | Nerve damage and demyelination |
| Pinky-red sore or smooth tongue | Degeneration of perip heral nervous system leading to paralysis |
| Growth failure in children | Progressive peripheral neuropathy |
| Psychosis, confusion | Spinal degeneration and macrocytic cells |
| Depression, memory loss | Alzheimer's disease, allergies, asthma |
| Anxiety, insomnia | Crohn's disease, multiple sclerosis, insomnia, sciatic neuritis, trigeminal neuralgia, osteoarthritis |

## 14.4 Macrofungi

### 14.4.1 Overview

Macrofungi, well known as mushrooms, are diverse group of the visible fruit of fungi, with known toxic effect on human [59, 61–63]. Approximately 100 of the known species of mushrooms are poisonous to humans, with new toxic species continually being identified [65, 66]. The geographical distribution of toxic mushrooms as well as toxicity of different mushrooms within the same genus may vary greatly (Table 14.4). Some mushrooms initially classified as edible have recently been reclassified as toxic [59]. Mushroom poisoning, termed mycetism or mycetismus, most commonly ensues after mushrooms are foraged, misidentified, and then consumed [64–66]. Worldwide, hundreds of mushroom poisonings are fatal each year [59, 65–67]. Most fatalities are secondary to *Amanita phalloides* ingestions [63, 65–67].

Some toxic mushroom ingestions will produce self-limited toxicity. Others will prove fatal. Generally, most toxic mushrooms produce some GI distress, and commonly GI symptoms are the first symptoms reported [59, 65]. A latency of <6 h to development of GI symptoms was utilized

to predict that a mushroom ingestion should produce limited toxicity. This practice has limitations, and these limitations have become more apparent as new toxic mushrooms are recognized and more cases are reported. A study from Turkey reported 317 cases of mycetism, without delineating which mushrooms produced toxicity, and found that common symptoms include nausea (86.6%), vomiting (79.8%), and diarrhea (21.1%). More than 20% of patients who eventually developed hepatic failure had a latent phase of <6 h [62–65]. Similarly, there are reports about severe mushroom-induced hepatitis, 33% with initial symptoms within <6 h of ingestion [59, 63]. Not all patients presenting with symptoms within 6 h of ingestion have a benign course [59, 62, 63, 65]. Interestingly, if *A. phalloides* ingestion is known, or strongly suspected, to have occurred and diarrhea develops in <8 h, the prognosis is poorer [63–65]. Conversely, GI symptoms occurring >6 h after ingestion remain concerning for a possible serious clinical course and possible fatality [59, 62, 64–67].

### 14.4.2 Neurotoxins

Neurotoxic mushrooms may produce cholinergic, epileptogenic, inebriating, encephalopathic, or hallucinogenic syndromes [59, 63]. Many of these syndromes have associated visual disturbances. Some contain toxins that affect vasculature and are classified under neurovascular toxins (Table 14.4).

#### 14.4.2.1 Cholinergic Syndromes

Some mushrooms contain muscarine that stimulates peripheral muscarinic receptors. Muscarine acts like acetylcholine, but is not degraded by cholinesterase, and therefore has a longer duration of action [63]. The amount of muscarine in *Amanita muscaria* is very low, and muscarinic symptoms are rarely seen after its consumption [59, 65]. *Inocybe*, *Clitocybe*, *Boletus*, and *Rubinoboletus* species can contain sufficient muscarine to produce muscarinic toxicity. Onset of toxicity is 15 min to 5 h after ingestion. Flushing, vasodilation, diaphoresis, lacrimation,

**Table 14.4** Geographical distribution of recently described toxic mushroom

| Primary system affected by toxins (effects) | Geographical location of mushroom harvest[a] | Mushrooms |
|---|---|---|
| Neurological (encephalopathy) | Germany | *Hapalopilus rutilans* (purple dye polypore) |
| Neurological (convulsive encephalopathy) | Japan | *Pleurocybella porrigens* (angel's wing) |
| Neurovascular (red, swollen, painful extremities) | Japan, South Korea | *Clitocybe acromelalgia* |
| Neurovascular (red, swollen, painful extremities) | France, Italy, Morocco | *Clitocybe amoenolens* (poison dwarf bamboo or burn mushroom) |
| Cardiac (sudden death) | Yunnan Province, China | *Trogia venenata* (little white) |
| Cardiac (sudden death) | Jiangxi Province, China | *Amanita franchetii*, *Ramaria rufescens* |
| Renal | Canada (South-West), USA (Pacific Coast to North-West) | *Amanita smithiana* (toxic lepidella or North American lepidella) |
| Renal | France (South), Spain, Italy | *Amanita proxima* (Mediterranean Amidella) |
| Renal | Japan | *Amanita pseudoporphyria Hongo* |
| Muscular (rhabdomyolysis, myocarditis) | France, Poland | *Tricholoma equestre* (yellow trich or yellow knight or man on horseback) |
| Muscular (rhabdomyolysis, myocarditis) | Taiwan, Japan, Korea, China, Nepal | *Russula subnigricans* (blackening russula) |
| Immune/heme (hemolysis, hepatorenal failure) | Northern Hemisphere | *Paxillus involutus* (poison pax or brown roll rim) |
| Immune/heme (pancytopenia) | Northeastern Asia | *Ganoderma neojaponicum Imazeki*[b] |
| Immune/heme (pancytopenia) | Japan, China, Korea, Java | *Podostroma cornu-damae* |

[a]Copyright: J. Med. Toxicol. (2014) 10;173-189; Reference: [59]
[b]Newly reported and association not as well established as other causes of mycetism

miosis, blurred vision, hypersalivation, bronchorrhea, bronchospasm, vomiting, diarrhea, abdominal pain, tremor, restlessness, and bladder contraction can follow ingestion. Hallucinations, bradycardia or tachycardia, hypotension or hypertension, syncope, shock, and confusion are common [66, 67]. Treatment is supportive: fluid and electrolyte replacement, vasopressors, and atropine in case of bronchorrhea and bradycardia. Toxicity generally resolves within 12 h of ingestion [59, 63].

#### 14.4.2.2 Epileptogenic Syndromes

The classic epileptogenic mushroom is *Gyromitra esculenta* (false morel), which may be confused with *Morchella* sp. (true morel, which is deemed edible but which can produce neurological symptoms if poorly cooked) or *Verpa bohemica* (early morel) [68]. Symptoms begin 4–12 h after ingestion. Clinical progression is vomiting and diarrhea followed by neurological symptoms (vertigo, ataxia, nystagmus, tremor, convulsions, and coma), sometimes followed by hepatic necrosis, jaundice, methemoglobinemia, hemolysis, and rhabdomyolysis [66–69]. Approximately 10% of poisoned patients die [70]. Treatment is supportive, while pyridoxine is recommended for neurologic symptoms including seizures with dosing regimen of 70 mg/kg up to 5 g, intravenously [66–69, 71]. Seizures may be resistant to benzodiazepines and barbiturates prior to GABA repletion aided by pyridoxine treatment [69]. In Japan, 2004, convulsive encephalopathy occurred epidemically, with latency of 1–31 days, when patients with hemodialysis-dependent renal failure ingested *Pleurocybella porrigens* (also called *Nothopanus porrigens*, Sugihiratake, and angel's wing). Patients exhibited convulsions (78%), myoclonus (47%), dysarthria (31%), ataxia (25%), and paresis or paralysis (22%) [72]. Intractable status epilepticus has also been reported [73–76]. Magnetic resonance imaging may reveal intracranial lesions involving the subcortical white matter of the insular cortex, claustrum, external capsule, putamen, and globus pallidus [76]. The mortality rate is approximately 30% [72, 73].

#### 14.4.2.3 Encephalopathic Syndromes

In Germany, encephalopathy and hepatorenal insufficiency associated with purple urine have been reported following ingestion of *Hapalopilus rutilans* (Purple Dye Polypore) [59, 63, 65, 74]. The syndrome begins with nausea, vomiting, and abdominal pain approximately 12 h after ingestion. Hepatorenal laboratory abnormalities and neurological symptoms, such as vertigo, ataxia, drowsiness, hypotonia, and visual complaints, follow [66, 74]. *P. porrigens*, *Grifola frondosa*, and *Pleurotus eryngii* poisonings may be also presented with encephalopathy. Any mushroom that produces fulminant hepatic failure (e.g., *A. phalloides*) or that is epileptogenic (e.g., *G. esculenta*) may be associated with encephalopathy [63, 69].

#### 14.4.2.4 Hallucinogenic Syndromes

Hallucinogenic mushrooms generally contain psilocybin and include *Psilocybe* spp., *Panaeolus* spp., and *Stropharia aeruginosa* [64]. Psilocybin-containing species may turn bluish (bruise) upon handling especially the stalks; however, this is nonspecific, as some other species that do not contain psilocybin bruise similarly [64]. Symptoms reflected in altered time-space perceptions, auditory, and visual hallucinations begin 15–30 min after ingestion and generally last up to 6 h and rarely last 12 h [66]. Mydriasis, hypertension, tachycardia, dysrhythmias, and myocardial infarction have also been reported [59, 63, 75]. Seizures and hyperthermia have been reported in children [75]. Treatment is supportive. Benzodiazepine and barbiturates have been used to control agitation and seizures [69, 75].

#### 14.4.2.5 Neurovascular Toxins

*Clitocybe amoenolens* (burn mushroom) and *Clitocybe acromelalga* are associated with erythromelalgia. Erythromelalgia involves erythema, swelling, and pain of the distal extremities. Ingestion of only a few mushrooms can produce toxicity. In humans, symptoms appear 24 h after ingestion, and patients present with paresthesia of the digits followed by paroxysmal burning pain [63, 74]. Paroxysmal dilation

of the blood vessels of the skin occurs, what is associated with tactile and burning pain and red, swollen hands and feet. Heat and a position decline induced paroxysmal crisis, which generally occurs nocturnally. Cyanosis or erythema may worsen during pain paroxysms. More severe cases are associated with local diaphoresis and trophic changes of the digits. The pain can be incapacitating. Dipping the extremities in cold water often provides relief, while traditional analgesics may be ineffective. The syndrome can last for weeks to months [59, 63, 69, 74].

#### 14.4.2.6 Cardiotoxins and Sudden Death

A seasonal illness, called "Yunnan" sudden unexplained death, has been epidemiologically traced to *Trogia venenata* (little white) consumption. The exact toxin responsible for the syndrome is not yet known [77, 78]. Patients report nausea, vomiting, diarrhea, abdominal pain, and fatigue, while recurrent syncope and sudden unexpected death may occur. Many patients report palpitations, chest discomfort, dizziness, syncope, seizures, ventricular tachycardia, fibrillation, and elevated plasma enzymes in the hours preceding death [77, 78]. Postmortem examination revealed focal lymphocytic myocarditis, with breakage of the muscle fibers, lymphocytic infiltration of the liver, pulmonary alveolar edema, acute kidney necrosis, hepatocyte necrosis, and congestion of the liver, lung, or spleen [78].

#### 14.4.2.7 Hepatotoxins

Amatoxins and gyromitrin are protoplasmic poisons that produce hepatotoxicity [77]. Many *Amanita* spp. contain amatoxin, in the first place *A. phalloides* (death cap), as well as some *Galerina* and *Lepiota* (e.g., *L. brunneoincarnata* and *L. helveola*). As little as 0.1 mg amatoxin/kg body weight may be lethal in adults [67, 77, 79].

In general, supportive care is the mainstay for mycetism [59, 79]. If a patient is actively vomiting, activated charcoal may not contribute to decontamination. Antiemetics may limit natural decontamination. Determining what mushrooms are likely to have been ingested, and therefore what treatments are most appropriate, will likely be based on the geographic location of mushroom harvesting (see Table 14.5) [63]. If a hepatotoxic mushroom, such as *A. phalloides*, has been ingested or is suspected, prompt treatment with an antidote seems prudent (Table 14.5) [67, 79].

**Table 14.5** Antidotes for amatoxin in poisoning (recommended doses based on previously published reports)

| Antidote | Mechanism of action[a] | Dose |
|---|---|---|
| Silibinin[b] | Competes with amatoxins for transmembrane transport; inhibits penetration of amanitin into hepatocytes; scavenges free radicals; produces anti-inflammatory effects; increases ribosomal RNA synthesis, increases protein synthesis | 5 mg/kg IV over 1 h; then 20 mg/kg/24 h continuous infusion (diluted in 5% glucose to a concentration of 2 mg silibinin/ml) for 3 days (alternatively, 20 mg/kg/24 h can be divided into 6 doses) |
| *N*-acetylcysteine (NAC) | Promotes glutathione regeneration; scavenges free radicals | Follow dosing for APAP treatment: 150 mg/kg IV over 1 h, followed by 12.5 mg/kg/h for 4 h, followed by 6.25 mg/kg/h until hepatic failure resolution |

[a]Retrieved from: J. Med. Toxicol. (2014) 10;173-189; Reference: [59]
[b]Silibinin is not approved as a therapeutic treatment for hepatic disease by the Food and Drug Administration in the USA; it is approved and available in Europe and Australia

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