Review paper

The role of fungi in allergic diseases

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Postep Derm Alergol 2013; XXX, 1: 42-45
DOI: 10.5114/pdia.2013.33377

Abstract

Allergic diseases such as allergic rhinitis, pharyngitis, laryngitis, asthma, airborne dermatitis, or allergic conjunctivitis, can be caused or aggravated by components of bioaerosol from natural environment or from indoor environment in enclosed spaces, workplaces and homes. The main components of bioaerosol are fungi and their metabolites, which are common in the environment.

Key words: fungi, allergy.

The major part of bioaerosol is fungi, especially filamentous fungi that belong to common aeroallergens [1-4]. Commonly known as molds they belong mainly to three phyla: *Zygomycota*, *Ascomycota* and *Deuteromycota*. Molds are made of hyphae which form the mycelium. The structure of the mycelium can vary depending on the species, growing conditions and the presence of nutrients in the medium. Phyla of these fungi differ mainly by the way they reproduce. Ascomycetes have a mycelium barrier (septa) and reproduce sexually, producing spore bags. Fungi belonging to *Zygomycota* have multinucleated mycelium with no barriers, and have the ability to multiply vegetatively or by spores. Fungi of the cluster *Deuteromycota* reproduce only vegetatively by conidia, which arise directly from the mycelium or on special hyphae, conidiophores [5, 6].

Mold spores and conidia are resistant to the lack of water, they can survive in a dry state even for many years. These fungi produce a huge amount of spores that in the polluted air and dust can be transported over thousands of kilometers [7]. Fungi masterfully adapt to the environment and can use a number of different sources of energy by strict regulation of their metabolism and the expression of proteins needed only in certain environments and under certain conditions, and the enzyme-rich metabolism enables the use of environment very poor in nutrients such as plastics [8]. They also have the ability to synthesize a number of stress proteins that protect them against extreme environmental conditions [9].

The incidence of fungal spores is seasonal and high concentrations are achieved in the summer due to the presence of nutrients in the soil, favorable temperature and humidity [10]. Therefore, in the temperate zone, as in Poland, peak concentration of mold spores mostly occurs in the air in the late summer and early autumn, when rainy days are followed by sunny, dry and windy days. The spores are common in very large quantities, not only in the external environment, but also indoors. Fungal spores present in the environment enter the room with air or are carried by humans and animals. The high concentration of spores indoor applies especially to states of increased humidity, poor ventilation or air conditioning systems [11, 12].

In external environment allergenic fungi include the genera *Cladosporium*, *Alternaria*, *Botrytis*, *Epicoccum*, *Fusarium*, *Aspergillus* and *Penicillium*. The soil is most intensively inhabited, where fungi use the remains of plants and animals. Many species are specialized pathogens of various crops, ornamental plants, fruit and vegetables. Some of them cause diseases of economically important plants, and others are only endemic [13]. They thrive best at the temperature of 6-35°C, and high humidity (over 70%) promotes the growth [14].

Contemporary authors emphasize that all building works create perfect conditions for settlement, growth and reproduction of many microorganisms, and the air of houses and spaces, properly operated and maintained hygienically, is not much different from the clean outdoor air [15]. Fungi of the genera: *Mucor*, *Penicillium*, *Aspergillus*, *Rhi-*

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Received: 25.10.2012, **accepted:** 14.01.2013.

zopus, *Alternaria* and *Cladosporium* dominate the fungi isolated from dust mites and they are indoor fungi [16, 17]. Allergens of indoor fungi are present in the air space throughout the year. The number of spores in the air in some homes may exceed 250 000 per cubic meter. Their development is aggravated by poor access of light, windproof environment, limited ventilation and high humidity. These conditions occur mainly in basements, laundry rooms, bathrooms and kitchens, and farm areas in the country, as well as in wooden cabins and summer houses. Regular users of pools and saunas are also exposed to allergens. Outbreaks of mold growth is often found in rooms with wet wallpaper or in the grout between tiles. A characteristic musty smell, caused by volatile metabolites of fungi released to the air, is the evidence of significant invasion [18]. Potential sources of indoor pollution also include household chores such as cooking, smoking, vacuuming or sweeping. Fungal spores of genera *Alternaria*, *Aspergillus*, *Botrytis*, *Cladosporium*, *Scopulariopsis* and *Penicillium* forming a part of bioaerosol, may be released from groceries, flowers, dust, carpets, wooden material and furniture. The presence of plants in the home may also increase the concentration of fungi in the air, as for example *Aspergillus* spores are often in the soil of pot plants [19]. A fungal colony is sometimes seen as greenish, brown and black spots, which may indicate an invasion of fungi of the genus *Penicillium*, *Aspergillus* or other. These fungi, and particularly their toxins, form the so-called image of a "sick building" (sick building syndrome – SBS) and it is one of increasing medical problems in developed countries [20, 21]. According to the WHO guidelines, sick buildings include mold-infected premises in which more than 30% of the population has symptoms like headaches, sore throats, chronic fatigue, flu-like symptoms, skin changes. These problems may be the cause of numerous diagnostic and therapeutic mistakes. But it is not clear what level of fungus causes health effects, but it is assumed hypothetically at 1000 cfu/m^3 [22].

Molds are encountered not only in dwellings. Some professions are exposed to high levels of mold spores and mycotoxins in the workplace. Occupational exposure to molds takes place among the employees of the food industry (e.g. bakers, millers, workers in the food industry). Professional groups exposed to contact with molds include also farmers, gardeners, workers processing wastes and sawmill workers [23-26].

Many modern studies have reported that exposure to mold can cause an allergic reaction. Hippocrates (460-377 BC) has indicated that the air is a factor contributing to the development of various diseases and the cause of the development of certain infectious diseases [27]. Bronchospasm and aphonia after inhaling the spores of *Penicillium* was described by Charles Blackley. In 1873, he described for the first time hay fever, using a still currently used diagnostic method, i.e. a skin test, which involves sensitization of the skin by rubbing the pollen, thus demonstrating the relationship between disease symptoms and the pollen of flowering grasses, as a causative factor. In addition to skin allergies and respiratory diseases, food allergies are equally problematic. They represent a significant diagnostic and therapeutic problem when after eating foods that contain fungi allergens, a strong reaction of the body is observed. Products that may have allergenic effects include: molding fruit and vegetables, blue cheese, beer, champagne, homemade wine, ketchup, soya sauce, grapes, and fruits and vegetables stored for a long time in refrigerators [28].

Mold spores can also cause lung disease especially attacking people with a weakened immune system (cancer or AIDS patients). Milder symptoms after exposure to mold include malaise, headache, nausea and other psychosomatic symptoms [29].

It is estimated that approximately 2-6% of the general population in developed countries is allergic to fungi. Mostly sensitivity is detected to genera of *Alternaria*, *Cladosporium*, *Aspergillus*, *Penicillium* and *Fusarium*. Allergy to fungi often appears as type I immediate, IgE-mediated hypersensitivity. In the case of atopic sensitization, it can manifest itself as asthma, rhinitis or conjunctivitis, urticaria, or atopic dermatitis. Occasionally it can be called a type II hypersensitivity reaction as is the case in response to the mannan – polysaccharide of the cell wall of *Candida* and *Aspergillus*. An example of the type III hypersensitivity is allergic alveolitis and bronchopulmonary aspergillosis (ABPA) [28, 30]. Aalveolitis and bronchopulmonary aspergillosis is a pulmonary disease, hypersensitivity Th2 response to *Aspergillus fumigatus* that affects asthma and cystic fibrosis (CF) patients. Allergy to *A. fumigatus* is common in atopic asthma as well as in patients with cystic fibrosis. Bronchopulmonary aspergillosis is characterized by wheezing and pulmonary infiltrates, which can lead to pulmonary fibrosis and/or bronchitis [31].

In a large part of the population, allergies occur in the form of rhinitis, also accompanied by ocular signs. The small size of fungal spores, usually not exceeding 10 µm (e.g. *Aspergillus fumigatus* 3.5-5.0 µm, *Aspergillus niger* 3.0-4.5 µm, *Penicillium brevicompactum* 7-17 µm, *Cladosporium macrocarpum* 5-8 µm, *Epicoccum nigrum* 15.0-25 µm, or *Trichoderma harizanum* 2.8-3.2 µm) enable deep penetration of the bronchi, which in turn often leads to allergic reactions of the lower respiratory tract, such as asthma and allergic alveolitis. *Alternaria* and *Aspergillus* fungi are the most common allergens responsible for severe allergic rhinitis and asthma, as well as severe and difficult asthma, which constitutes 5-10% of asthma cases. Fungi of the genus *Alternaria* are the most common mold causing asthma and increase the severity of the disease and mortality. They mostly cause allergy in adults prone to respiratory infections [32, 33].

Asthma is an allergic reaction of an early type, in which IgE antibodies are involved. The characteristic symptoms of asthma include bronchoconstriction and asthmatic attack, occurring most often at rest. The increase in the inci-

dence of asthma is the reason why many researchers are looking for the causes of its formation, both genetic and environmental. It is known that many allergens can work together to intensify an allergic reaction. Recently it has been found that chitin, which is a component of the fungal cell wall, evokes a strong immune response leading to allergy and allergic asthma [34, 35].

Symptoms of the respiratory system caused by response to a fungal allergen is stronger as compared to other allergens commonly found in the environment. The reason probably is that the fungi except proteins have additional capacity to multiply and infect the skin and colonize the respiratory tract [27].

Another allergic disease caused by fungi is allergic alveolitis – *alveolitis allergica*. It is an occupational disease including different subunits, of which the "farmer's lung" is the most famous. The main symptoms of *alveolitis allergica*, which usually occur 4-8 h after contact with organic dust include: fever, chills, combined with attacks of dyspnea, headache, muscle pain, stinging in the chest and a feeling of total breakdown. The radiographic changes are visible as micronodular sclerosis, which can turn into extensive fibrosis. It is not a rare disease, but rather rarely diagnosed by a physician, because some of the first symptoms resemble the flu or cold symptoms. It is important to determine whether the patient was in an environment contaminated with organic dust. In *alveolitis allergica*, it is characteristic that this disease occurs mainly among older farmers over 50 years of age [29].

Pathogenic fungi responsible for skin infections are dermatophytes including *Aspergillus niger*. Dermatophytes have affinity for keratin, a protein found in the epidermis. They use keratin as food, and the mycelium develops and destroys the anatomical structures. It causes inflammation of the skin, which is a response to fungal antigens [36]. Another aspect is cross autoimmune reactions caused by high homology to fungal antigens of some human proteins, which occur especially in patients with chronic asthma. Taking into account all of these mechanisms, it was hypothesized that the damaging effects of fungi in the respiratory tract are associated with a parallel induction of inflammation and damage to the respiratory epithelial cells by the action of non-allergenic proteins and toxins [37].

Molds produce mycotoxins, which have carcinogenic, teratogenic and neurotoxic properties [38]. A single mold can produce 40 or more proteins that can cause allergy. In addition, there is significant cross-reactivity between mold allergens [39]. In addition to these secondary metabolites, such as toxins and enzymes, non-protein components of the cell wall such as glucan or chitin may also have allergy effects [40, 41].

In the last two decades, there has been a significant increase in the number of allergy cases caused by exposure to molds. Allergies and infections related to fungi mainly concern immunocompromised patients. However, fungi are a significant threat to the health of all people exposed to them. Although in recent years, a large number of mold allergens have been characterized, which proved to be very useful in the diagnosis, the actual role of these microorganisms and various mechanisms of pathogenesis remains unknown.

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