EDITOR'S PICK

My Editor's Pick for this edition of *EMJ Allergy and Immunology* is the article provided by E. Uzunoglu, which offers a fascinating overview of the microbiological hazards that are connected with occupational allergies. Uzunoglu accurately highlights the importance of a multidisciplinary response to occupational disease, making this a captivating read that provides topical recommendations.

Prof Dr Jacques Bouchard

MICROBIOLOGICAL BIOHAZARDS ASSOCIATED WITH OCCUPATIONAL ALLERGIES

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ABSTRACT

Microbiological occupational allergens usually originate from a part or products of bacteria, fungi, or arthropods. They may be harmful on their own or their impact may come from cross-reactions of their substance. It is mostly the respiratory system, conjunctiva, and skin that are affected. This short review clarifies the microbiological biohazards associated with occupational allergies.

Keywords: Occupational hazards, bioaerosols, mycotoxins, endotoxins, fungi, arthropods.

INTRODUCTION

Occupational allergies are a group of immunologic disorders that are caused by workplace allergens. They are socioeconomically important diseases that may cause workforce loss, morbidity, and mortality. Therefore, early diagnosis and detection of allergens are important.[1] Allergies resulting from these biological agents mostly affect the respiratory tract, conjunctiva, and/or skin. They usually cause allergic rhinitis, allergic asthma, toxic or hypersensitivity pneumonia, allergic alveolitis, farmer's lung, conjunctivitis, and dermatitis.[2,3] There are several biological hazards that cause occupational allergies, such as toxins, body fluids, virulence factors, or whole cells of bacteria, fungi, plants, and animals, including arthropods.[2,4,5] The majority of the allergen biohazards are mostly in bioaerosol and/or droplet form. Bioaerosols are organic dusts originating from toxins or the main components of bacteria or fungi, faeces, the bodies of mites and insects, pollens, and different proteins from mammals. In recent years, researchers have focussed on this subject due to a great deal of workers being exposed to these dusts. Bioaerosols are the major allergic risk factors in agriculture and the agricultural industry, waste recycling, food processing, the detergent industry, laboratories, libraries, and medicine. Although there is great awareness about bioaerosols, the pathogenesis and dose-dependent effects are still unclear.[2,3] There is no specific classification for allergen biohazards. According to the Haz-Map database,[6] infectious occupational biohazards are classified into six categories: contact with infected living animals; contact with contaminated animal products; tick, flea, or mite bite; contact with human or animal waste; contact with an infected patient or blood; and raising dust containing pathogens. However, this classification does not exactly fit to the

microbiological biohazards associated with occupational allergies. In this paper, a short review will be given of different microbiological biohazards in workplaces that cause occupational allergies.

BIOHAZARDS ORIGINATING FROM BACTERIA

Endotoxin

The major allergen originating from bacteria in workplaces is endotoxin, which is a lipopolysaccharide (LPS) gram negative molecule. The outer cell membrane of gram negative bacteria is made up of a high molecular weight, heteropolymeric substance. Its main components are O-antigen, core polysaccharide, and lipid A molecules. It is a highly conserved layer among different gram-negative species and its immunological effects are attributed to Lipid A moiety. The destructive effects of the LPS molecule was first shown in 'Monday asthma' of cotton workers in the 1960s.[7] To date, a long list of occupations have been reported, such as herb processing, grain and vegetable agriculture, wood processing, waste collection and sorting, cucumber and tomato nurseries, swine farms, sewage, and so on.[2,3] A possible explanation for the pathophysiological mechanism is the adjuvant-like effect of endotoxins on airway inflammation after contamination with water, food, and other products.[7]

In the USA, a national survey about endotoxin has shown that LPS is an allergen which exacerbates asthma symptoms.[8] Eisenbarth et al.[9] reported that low concentrations of LPS were enough for development of airway hypersensitivity in mice. Moreover, Strohmeier et al.[10] found that allergised mice without a LPS receptor did not develop airway hyper-responsiveness. However, there is a paradox in the literature about the immunological benefits and harmful effects of LPS. According to the 'hygiene hypothesis', it is considered that a lack of microbial exposure might be a risk factor for allergic diseases. In this theory, LPS exposure protects the individuals against Type 1 hypersensitivities, by switching T helper Type 2 (Th2) cells into Th1 cells. Briefly, innate immune cells recognise LPS and produce cytokines that influence development of adaptive immunity. Among these cytokines, interleukin (IL)-12 stimulates T cells to switch to effector T cells that primarily secrete interferon (IFN)-γ. There is a positive feedback between innate and adaptive immunity cells and this IFN-γ augments IL-12 response by stimulating antigen-presenting cells of innate immunity. Both IL-12 and IFN-γ inhibit Th2 cytokine production (e.g. IL-4, IL-5, and IL-13) and help to develop Th1-type immune response instead of the Th2-type that protects against atopic diseases.[7]

Although the hygiene hypothesis considers LPS as a protective factor against allergy development, studies are still unclear. LPS of bacteria may have pro-inflammatory properties that induce respiratory symptoms. In addition, depending on the duration of exposure, dosage, and environmental and genetic factors, the responses of the workers may vary.[7] Therefore, more systematic studies defining both genetic and environmental factors are needed.

Peptidoglycan

Peptidoglycan (PGN) is a cell wall component of almost all bacteria, but predominantly gram-positives. It is a polymeric substance, made up of (1,4) linked N-acetylglucosamine and N-acetylmuramic acid. Bacterial PGN is one of the main components of bioaerosols and there is evidence suggesting that PGN causes bioaerosol-induced inflammation especially in humans working in livestock farm houses. In a clinical study, it was shown that swine dust containing PGN caused acute inflammatory reactions by increasing fever and blood granulocyte concentration in swine farmers.[11] Both *in vivo* and *in vitro* studies showed that PGN is a mast cell stimulator via toll-like receptor (TLR) dependent mechanisms.[12] Inhalation of this substance may trigger TLR-2, increase the influx of mast cells into the alveolar compartment and/or gastrointestinal tract, and cause production of different pro-inflammatory cytokines and chemokines such as TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1, and IL-5.[13] On the other hand, there are also studies supporting the hygiene hypothesis and demonstrating that PGN can decrease both mast cells development and the number of mature mast cells by apoptosis, like LPS. It is estimated that the environmental exposure to PGN also protects from both asthmatic symptoms and bacterial infections like the endotoxin component of bacteria.[11]

Other Virulence Factors

Several molecules like toxins or peptides of bacteria also augment inflammatory reactions in sensitised individuals. Among these, *Staphylococcus aureus* has the leading role with its numerous virulence factors.[5] Methicillin-resistant *S. aureus* (MRSA) is a causative agent of severe health problems in

healthcare workers and animal farmers. They are at risk of both nasal and skin infection with MRSA strains.[14,15] In the Netherlands, there is a high MRSA colonisation rate (29.0%) among pig farmers compared to the general population (0.1%).[15] *S. aureus* infection increases the severity of the atopic skin diseases due to its virulence factors, such as superantigens, Panton-Valentine Leukocidin, protein A, lipoteichoic acid, and many others. These virulence factors cause T cell, mast cell, and macrophage activation, and cytokine release.[16] Therefore, physicians have had a tendency to add antibiotics to their prescriptions in patients with atopic skin disorders. In a study from Germany, 13.5% of the nurses who were suffering from occupational skin disorders were also infected with MRSA. Hand eczema was significantly more frequent and severe in MRSA carriers than in non-carriers. According to the results of the dermatology studies, it seems that the best treatment method for the occupational allergic skin disorders is taking precautions against MRSA infection among healthcare workers.[17]

BIOHAZARDS ORIGINATING FROM FUNGI

A single fungal cell can produce >40 proteins that can cause allergy.[18] Both the molecules they produce and the allergic fragments they carry in their structures can cross-react with each other.[18] To date, 112 genera of fungi are thought to be a source of allergens. Potential allergens are from three major classes: Ascomycota, Zygomycota, and Basidiomycota. Ascomycota is the largest group and includes the most common allergic genera *Alternaria*, *Cladosporium*, *Penicillium*, and *Aspergillus*. Yeasts have been also reported as the cause of allergic diseases. Ascomycetes and Basidiomycetes also have yeast forms. *Candida albicans*, *Malessezia furfur*, and *Saccharomyces cereviseae* are the most common species that cause allergic diseases.[19]

Any fungus found in the environment may be an opportunistic pathogen in an immunocompromised patient. Clinical manifestations of fungi may vary from infection in allergic bronchopulmonary disease to active infection.[20] Allergy to fungi generally occur as immunoglobulin (Ig)E-mediated, Type I hypersensitivity. This atopic condition can manifest as asthma, rhinitis, conjunctivitis, urticaria, or atopic dermatitis. Fungi also cause Type II hypersensitivity that arises secondary to mannan, a polysaccharide which is present in *Candida* and *Aspergillus* cell walls and Type III hypersensitivity reactions such as allergic alveolitis and bronchopulmonary aspergillosis.[19]

Fungal Fragments

An important component of bioaerosols is the aero allergic filamentous fungi and their metabolites. Among the filamentous fungi, *Cladosporium*, *Alternaria*, *Botrytis*, *Epicoccum*, *Fusarium*, *Aspergillus*, and *Penicillium* genera are generally found outdoors.[18] Among these genera, *Penicillium*, *Aspergillus*, *Alternaria*, and *Cladosporium* are aeroallergens that can be transported in enclosed areas via air, humans, or animals. Indoor areas also include species such as *Mucor* and *Rhizopus*.[21] Spores are the reproductive cells of moulds, which when germinated transform into micelles. Micelles are branched as hyphae. Gorny et al.[22] showed that fragments or intact spores of the fungi and hyphae are also potential allergens. The spores increase in number in the open air especially at the end of summer and the first months of autumn, and can be transported thousands of kilometres away via organic dusts.[18] In enclosed spaces that are not well ventilated and humid, the number can reach ≤250,000 per cubic metre and the spores remain in the environment all year round.[23] In particular, food, waste, wood industry, laboratory, agricultural, and museum workers are at risk of allergic diseases due to fungi.[24-26]

β-1, 3-glucan is an immunologically active glucose polymer present in the cell wall of fungi. It plays a role in the pathogenesis of bioaerosol-mediated inflammatory and allergic respiratory diseases by stimulating both Th1 and Th2 cells. Animal experiments have shown that the synergistic effect of β-1, 3-glucan with bacterial endotoxin causes airway inflammation and, moreover, β-1, 3-glucan alone can increase IgE levels.[27,28] In another study about the pro-inflammatory properties of β-1, 3-glucan, garbage men showed a significant inflammatory response in their nasal mucosa following β-1, 3-glucan exposure, but a significant increase could only be observed in *in vitro* experiments with high concentrations.[29]

Secondary Metabolites

Mycotoxins are allergenic, carcinogenic, teratogenic, and neurotoxic products of fungal metabolism. Mycotoxins are considered to be occupational risk factors for agricultural workers. They contaminate many nutrients and seeds, such as hazelnut, peanut,

corn, oat, wheat, milk, coffee, pistachio, almond, bean, and rice. Drought, high temperature, insect infestation, and high humidity increase fungus reproduction and mycotoxin production. Primer and secondary amines, hydroxyl and phenolic groups, lactams, carboxylic acids, and amides have been identified in many mycotoxins.[30] In a study on corn silos, 10 different fungal genera (especially *Penicillium* and *Paecilomyces*) and 6 different mycotoxins (zearalenone, T-2 toxin, aflatoxins, fumonisins, ochratoxins, and deoxynivalenol) produced by these fungi were detected.[31] Supronienе et al.[32] found five *Fusarium* species and three mycotoxins (zearalenone, T-2 toxin, and deoxynivalenol) at low concentration in cereals produced by organic agriculture. These mycotoxins that are found in foods are harmful not only for the workers but also for the consumers. This remains a serious problem for developing countries not paying attention to contamination during food production and storage.[30]

Apart from mycotoxins, fungi also produce chemicals that have low molecular weight and high volatility, such as mixtures of alcohols, aldehydes, acids, ethers, esters, ketones, terpenes, thiols, and their derivatives. These chemicals are the volatile compounds (VOC) produced by fungi. Very little is known about the biosynthetic origins or molecular structures of these molecules. About 300 fungal VOC have been defined up to now. In places with fungus reproduction, the heavy smell that people easily perceive is caused by these chemicals.[33] It is said that the VOC may be the cause of the syndrome known as 'sick building syndrome', which is seen in individuals working in closed areas for long hours and is accompanied by symptoms, such as headache, nasal discharge, sore throat, and chronic fatigue. According to data from the World Health Organization (WHO), 30% of the individuals with these complaints are living in such buildings with mould and poor ventilation.[18] Although there is insufficient information about the effects on humans, fungal VOC showed neurodegenerative effects on *Drosophila melanogaster*.[34] Therefore, further studies are urgently needed.

BIOHAZARDS ORIGINATING FROM PARASITES

Arthropods

Allergy to arthropods arises from inhaled body particles, accidental contact, sting, or bite and venom injection of bees, ants, and wasps.[35] Although these types of allergies are observed in atopic individuals, non-sensitised workers are also affected. Outdoor workers, construction personnel, farmers, foresters, wildlife workers, food processors, beekeepers, laboratory and field biologists, and silk producers are especially at risk. The first line of defence should be avoidance or exclusion of the offending agent. However, the majority of the medically important arthropods are unknown and misdiagnosed, as many workers never report minor contacts and the lesions are very similar.[36] Recently Uzunoğlu et al.[4] observed a blister dermatitis due to contact with *Paederus* type insects among nut farm workers. Although many different *Paederus* species have been identified during entomology studies in various European countries, no clinical case report has been reported from the European countries, except Italy.[37] *Paederus* dermatitis is an acute irritant contact dermatitis caused by pederin, a haemolymph fluid released when *Paederus* beetles are crushed against the skin.[38,39] Pederin is a caustic and toxic amide that contains two tetrahvdropyran/furan rings.[40] It causes inflammation, vesicles, and pustules. This dermatitis can heal itself in a week or can lead to various complications. These complications are post-inflammatory hyperpigmentation, secondary infections, extensive peeling of the skin, and ulcerous dermatitis requiring hospitalisation.[41] Fever, arthralgia, nausea, vomiting, and neuralgia can be seen in severe cases.[42] It can be confused with viral and bacterial skin diseases such as bullous impetigo, herpes simplex, and herpes zoster. Other diseases that must be considered in the differential diagnosis are bullous or allergic contact dermatitis, liquid burns, and phytodermatitis.[43] General medicine, ophthalmology, dermatology, or entomology books do not include enough information about this clinical phenomenon.[44] Questioning the patient's occupation or whether they have undertaken a farmland visit and carrying out a physical examination of the patient has paramount importance in diagnosis.[45]

Although some allergen exposures are a result of direct contact with arthropods, the majority of the cases are because of inhalation of bioaerosols. Cockroach, mite, and silkworm moth allergies are the best studied of all the arthropod induced sensitivities.[35] During silk production, potent allergens of silkworm moth (*Bombyx mori*) such as sericin, fibroin, pupal fragments, and also *Anthrenus* beetle larvae that feed on silk waste cause asthma, allergic rhinitis, conjunctivitis, and

dermatitis in workers.[45] Cockroach infestations are a great challenge for seagoing ships and their crew.[46] Steroid therapy dependence and IgE levels are higher in cockroach asthmatics than the other asthmatics.[47] Kang et al.[48] analysed the allergens of crude whole body extract of American, German, and Oriental cockroaches. They compared the results with the sera of 16 cockroach-allergic patients with asthma. Up to 12 allergenic bands were identified from 13 of 16 individual sera. Another arthropod group that is well documented is mites. Mites are microscopic organisms that cause inflammatory reactions in those who are atopic and exposed to a high concentration of mites in the early stages of their life.[49] The secretion and faecal matter of the mites have a strong antigenic character.[50] They can induce both clinically unimportant and life threatening allergic reactions. It is known that the mites in cereal storage are the reasons for occupational disease in the employees, including farmers, and they can cause dermatitis, allergic rhinitis, asthma, and conjunctivitis.[51] Storage from the families *Acaridae* and *Glycyphagidae* are usually predominant. They are in a wide range of food including grain, fishmeal, hay, and substances containing sugars like dried fruit and cereals.[52] In 1997, Armentia et al.[53] examined the sensitivity of various mite species on 4,000 people living near cereal facilities. The prevalence of mite sensitisation among 50 grain workers was nearly 19%. The six highest prevalences of sensitisation were to the four Pyroglyphid dust mites: *Dermatophagoides pteronyssinus* (Trouessart) (58%) and *Dermatophagoides farinae* (Hughes) (48%), *Tenebrio molitor L*. (50%) and cockroach *Blatta orientalis L*. (36%), and to two of the storage mites, *Lepidoglyphus destructor* (Schrank) and *Tyrophagus putrescentiae* (Schrank) (both 38%). Additionally, 11 grain workers who were sensitised to storage mites gave negative Radio Allergosorbent Test (RAST) results with the dust mites.[53] Numerous mites (including *Pyemotes ventricosus*) causing occupational dermatitis were observed due to exposure to infested foods since the 1980s. Symptoms vary from skin eruption to chills, fever, malaise, diarrhoea, and anorexia. Although clinical diagnosis is often simple and based only on the patient's history, the identification of these causative mites is still troublesome.[54]

Inhalent allergies to the other arthropods such as insects, spiders, and beetles are also possible. Liebers et al.[55] determined occupational asthma against an insect allergen (*Chit*I) in a fish food factory workforce. A new respiratory allergy to cellar spider body parts due to arginine kinase was presented by Bobolea et al.[56] Increased frequency of beetle allergies are a huge problem, especially in endemic areas. Albright et al.[57] presented a case series about the multicoloured Asian lady beetle, which is a biological control agent against crop-destroying aphids in the USA. A great deal of arthropods like honeybees, flies, or even a nematode (*Anisakis simplex*), are also determined to be aerosol allergens.[58-60] It seems that the list will continue to grow due to climate change and/or poor working conditions.

CONCLUSION AND RECOMMENDATIONS

The main goals of occupational health programmes are to protect workers from occupational disease, provide safe environments, generate physically and mentally healthy employees, and enhance nations socially and economically. The prevention and treatment of occupational disease requires a multidisciplinary approach. National ministries of health, education, environment, industry, social security, and agriculture should be well-informed about occupational health practice.

Early diagnosis and prevention are the cornerstones for prevention of mortality and morbidity. Workers with inflammatory complaints usually tend to consult occupational health specialists, chest disease specialists, or dermatologists, as their main symptoms are related to the respiratory system or the skin. However, medical professionals from all disciplines should be aware of these issues. The co-operation of medical microbiologists, entomologists, epidemiologists, biomedical engineers, and immunologists is important, especially for the microbial allergens. Finally, well-organised surveillance programmes for warning of outbreaks and identification of exposure breakpoints are urgently required.

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