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OCCUPATIONAL ALLERGIES (JA POOLE, SECTION EDITOR)

Occupational Asthma: An Overview

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Abstract Occupational asthma is a form of asthma that is often under-diagnosed and under-reported. Unrecognized occupational asthma can lead to progression of disease and increased morbidity. The medical history is a critical element for establishing a diagnosis of OA. The history should include a detailed assessment of the workplace environment, the work process, changes in symptoms in and away from the workplace, and a review of relevant material safety data sheets that may provide clues regarding exposure(s) and the potential cause(s). Objective testing including spirometry pre- and post-bronchodilators, peak expiratory flow rate monitoring in and out of the workplace, provocation testing (i.e., methacholine challenge) to assess for airway hyperresponsiveness, and, if feasible, specific provocation by experienced personnel in a controlled setting to a suspected inciting agent are necessary for confirming a diagnosis. Skin or serologic testing for specific IgE to aeroallergens to assess the worker's atopic status is useful especially when considering certain forms of OA where atopy is a risk factor. Specialized laboratory testing may be useful for specific OA causes. It is important to correctly make the diagnosis of OA as the impact on the worker's future employment and earning power can be significantly affected.

Keywords Occupational · Asthma · IgE · High molecular weight · Low molecular weight · Diagnosis · Spirometry · Material safety data sheets · Surveillance · Prevalence

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Introduction

Hippocrates (460–370 BC) first described the association between asthma and occupation in reference to a number of occupations including metal workers, fishermen, farmhands, horsemen, and tailors. Over the ensuing centuries, a variety of sensitizing and irritating agents have been identified to cause occupational asthma (OA). Confirmation of OA is usually made by connecting exposure at work to a known inciting agent and documenting the objective presence of asthma that was not present prior to working in their current environment. In centers that have established challenge chambers, documenting airway hyperresponsiveness in response to the suspected agent (i.e., isocyanate) is considered the gold standard for confirming the cause [1]. Accurate diagnosis is crucial to minimize health impairment, loss of employment and decline of socioeconomic status. Removal of exposure to sensitizing and irritant agents is paramount to preventing the progression of disease. In workplaces which use high or low molecular weight agents known to induce OA, immunosurveillance programs designed to prevent worker exposure have been found to be successful in preventing new occurrences [2].

Definition/Classification

Work-related asthma (WRA) encompasses work-exacerbated asthma (bronchospasm aggravated by work exposures in patients with concurrent or pre-existing asthma) and occupational asthma (asthma caused by exposures to sensitizers or allergens at work). Occupational asthma (OA) is defined as "a disease characterized by variable airflow limitation and/or hyperresponsiveness and/or inflammation due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace" [1].

Occupational asthma can be further divided based on the presence or absence of a latency period after exposure to the inciting agent. The latter condition is referred to reactive airways dysfunction syndrome (RADS) or irritant induced asthma [1].

The presence of a latency period is associated with high molecular weight agents (plant or animal proteins >1.000 Kd in size) and some low molecular weight agents (chemicals <1.000 Kd in size). Examples of high molecular weight (HMW) agents include enzymes, laboratory animal allergens. and natural rubber latex. Low molecular weight (LMW) agents, including isocyanates, acid anhydrides. and metallic acids, which are haptens. as they can only elicit an immunologic response by conjugating with an endogenous carrier protein such as albumin [3•].

Irritant-induced asthma, also referred to as Reactive Airways Dysfunction Syndrome (RADS) is characterized by the absence of a latency period after a single, high-level exposure to an irritating material resulting in airway hyperresponsiveness and asthma within 24 h [1], This diagnosis is usually made retrospectively, based on history and demonstrating the presence of airway hyperresponsiveness by non-specific provocation, as patients often do not present to a facility with expertise in the diagnosis of this variant form of OA. There is also evidence supporting chronic low level exposure to irritants in the workplace can lead to irritant induced OA [4•],

Epidemiology of OA

The incidence and prevalence of OA are not well defined, and the rates of OA vary based on occupation. Up to 15 % of all new asthma diagnoses are estimated to start in the workplace [4•, 5•]. The prevalence of new asthma diagnoses within an occupation depends on the environmental conditions, exposure levels, and duration, and the effectiveness of preventive measures. Studies have shown that the prevalence of OA in enzyme-exposed workers is up to 60 %, platinum-exposed workers 20–50 %, isocyanate-induced workers 5–21 %, laboratory animal workers 20 %, baker's asthma 7–9 %, and western cedar induced OA approximately 5 % [4•, 6–8]. The prevalence of OA may be underrepresented by cross-sectional studies because symptomatic workers tend to leave the workforce which is termed the "healthy worker effect" [9].

Due to differing methodologies, the reported incidence of OA and the reported employment in various jobs ranges widely among countries [4•]. In the 1980s, several U.S. states developed the Sentinal Event Notification System for Occupational Risks (SENSOR) for the reporting of OA cases by physicians. The purpose of SENSOR was to put physicians in contact with public health agencies responsible for investigating high-risk workplaces. While this program encouraged the increase in physician awareness about OA, many cases still remain underreported [10]. Other countries have developed similar registries with varying success.

The United Kingdom has established the SWORD (Surveillance of Work-Related and Occupational Respiratory Disease) program for the voluntary reporting of occupational illnesses. The most frequently reported occupational respiratory illness is OA, most commonly caused by diisocyanates [11]. The Finnish program has also been successful in gathering data to estimate the yearly incidence of OA [12].

Causative Agents of Occupational Asthma

Traditionally, sensitizers to occupational asthma have been divided into high molecular weight compounds (HMW) and low molecular weight compounds (LMW) [3•]. The most relevant causes of high molecular weight agents include flour dusts, enzymes (plant and animal derived), gums, foods and tobacco, rubber–derived proteins, animal- and insect-derived allergens, and fish/seafood derived allergens. The most relevant LMW agents include western red cedar, polyisocyanates and their polymers, acid anhydrides, metals, and a spectrum of chemical substances. Table 1 summarizes causes of OA reported in different professions over the past year.

Mechanisms for OA

TH2 pro-inflammatory cytokines characteristic of IgE-mediated asthma have been implicated in the development of many causes of occupational asthma induced by HMW and LMW compounds [13•], However, both IgE- and non-IgE mediated mechanisms have been implicated depending on the inciting agent. Type II cytotoxic, type III immune-complex, and Type IV cell-mediated responses have all been linked to specific causes of OA. The mechanism of irritant-induced asthma presently remains undetermined.

Table 1 Reported cases of occupational asthma in the past year [25–34]

Occupation	Sensitizing agent
Baker	Wheat
Not-specified	Papain
Farmer	*Limonium tactaricum*
Dish washing	Savinase
Seafood worker	Squid (*Loligo vulgaris*)
Hair Dresser	Perfulate salts
Dry-cure ham transporter	*Tyrophagus putrescentiae*
Detergent industry	Thermostable endo-alpha-amylase Termamyl® and protease Savinase
Guitar maker	Western red cedar
Wallpaper factory worker	Polyvinylchloride and nickel

Based on the molecular weight, allergens may act as a complete allergen or they might require structural modification to act as a complete antigen. High molecular weight allergens (i.e., protein from animal dander, insect scales, food products, and enzymes used in the food manufacturing and pharmaceutical industries) do not require structural modification to elicit an immune response. Therefore, in vivo testing and in vitro immunoassays have been successfully used to identify sensitization to specific allergens. Most low molecular weight allergens require modification to elicit an immune response (exceptions are platinum salts and sulfonechloramide). These allergens must be coupled to a carrier protein such as albumin to form a new antigenic determinant to induce an IgE mediated response [2]. The most common LMW haptens that induce a specific IgE response are trimellitic anhydride (TMA) and hexamethylene isocyanate (HDI).

Genetics of OA

Genetic associations have been reported in workers with OA. Workers with acid anhydride OA express class II HLA molecule DQB1*501, which may be protective against isocyanate or plicatic acid induced OA [14]. Laboratory animal handlers sensitized to lipocalin allergens were found to more frequently express an HLADRB1*07 phenotype [15]. Glutathione-S transferase polymorphisms have been reported to protect isocyanate-exposed workers from developing asthma [16]. Workers with slow N-acetyltransferase genotypes have an increased risk of developing isocyanate-induced OA. IL-4Rá S478P and IL-4–589 gene polymorphisms have been found to be associated with isocyanate-induced OA and more recently linkages with IL4RA, CD14, and IL-13 have been reported [14, 17•, 18•].

Patients with diisocyanate-induced asthma have been found to have a higher frequency of DQB1*0503 and an allelic combination of DQB1*0201/0301. In contrast, healthy controls who had isocyanate exposure were found to have increased frequency of the allele DQB1*0501 and the DQA1*0101-DQB1*0501-DR1 haplotype. The products of these genes have been hypothesized to regulate immune responsiveness to chemical antigens [18•]. In a recent study, subjects with diisocyanate asthma were found to have elevated levels of IFN-γ promoter methylation compared with those who did not have diisocyanate asthma. However, the role of increased methylation in diisocyanate asthma remains unclear at this time [19].

Diagnostic Criteria for Occupational Asthma

In the American College of Chest Physicians consensus statement on OA, the proposed criteria for the diagnosis of OA includes the presence of asthma, onset of symptoms after entering the workplace, association between the symptoms and work exposure, and one or more of the following: (1) workplace exposure to an agent or process known to give rise to OA, (2) significant work-related changes to FEV1 or peak expiratory flow rates, (3) significant work-related changes in nonspecific airway responsiveness, (4) positive responses to specific inhalation challenge tests with an agent to which the patient is exposed at work, or (5) onset of asthma with a clear association with a symptomatic exposure to an irritant agent in the work place [2].

Assessment of OA

Obtaining a thorough workplace history and relating exposures with asthma symptoms is a key part of the diagnosis of OA; an incomplete history can delay the diagnosis. An algorithmic approach has been suggested by the American College of Chest Physicians [2, 20]. The history should include both an employment and medical history. The employment history should include description of the work process, the dates of job initiation, interruptions at work secondary to symptoms, and, if pertinent, termination, substances to which the worker has been exposed, review of material safety data sheets for suspected inciting agents, duration of symptoms after leaving the workplace, improvement of symptoms while away from the workplace, associated dermatologic or upper respiratory symptoms, and other risk factors for occupational asthma. Due to the need for a comprehensive history, a structured questionnaire accompanied by a physician-directed history is recommended (Table 2) [2]. It is essential that the physician be familiar with the known causative HMW and LMW agents of OA and the methodologies used for diagnosis.

A worker with OA classically presents with symptoms that are initiated at work (within several hours of starting a shift) and resolve or improve shortly after leaving the workplace or when away from work on days off, weekends or vacation. IgE-mediated sensitization to HMW agents are characterized by upper airway symptoms: rhinorrhea, ocular pruritus, or nasal congestion, preceding asthma symptoms. Workers who develop chronic airway inflammation, after persistent exposure for months or years to the inciting agent, may not improve after being away from the workplace. Workers with irritant-induced asthma have variable improvement after leaving the workplace. Some may have persistent airway hyperresponsiveness several years after leaving the workplace. Occupational asthma should still be suspected despite an apparent lack of correlation with symptoms and workplace exposure. For example, some workers with diisocyanate-induced OA may exhibit a late phase airway response

Obtaining material safety data sheets (MSDSs) is essential for determining if the worker is exposed to potentially sensitizing agents. These sheets provide the generic chemical

Table 2 Key elements of the occupational history in the evaluation of occupational asthma [20, 35]

I. Demographic information
   A. Identification and address.
   B. Personal data including sex, race and age.
   C. Educational background with quantitation of the number of school years completed.
II. Employment history
   A. Current department and job description including dates begun, interrupted and ended.
   B. List all other work processes and substances used in the employee's work environment. A schematic diagram of the workplace is helpful to identify indirect exposure to substances emanating from adjacent work stations.
   C. List prior jobs at current workplace with description of job, duration and identification of material used.
   D. Work history describing employment preceding current workplace. Job descriptions and exposure history must be included.
III. Symptoms
   A. Categories:
      1. Chest tightness, wheezing, cough, shortness of breath.
      2. Nasal rhinorrhea, sneezing, lacrimation, ocular itching.
      3. Systemic symptoms such as fever, arthralgias and myalgias.
   B. Duration should be quantitated.
   C. Duration of employment at current job prior to onset of symptoms.
   D. Identify temporal pattern of symptoms in relationship to work.
      1. Immediate onset beginning at work with resolution soon after coming home.
      2. Delayed onset beginning 4–12 h after starting work or after coming home.
      3. Immediate onset followed by recovery with symptoms recurring 4–12 h after initial exposure to suspect agent at work.
   E. Improvement away from work.
IV. Identify potential risk factors.
   A. Obtain a smoking history along with current smoking status and quantitate number of pack years.
   B. Asthmatic symptoms preceding current work exposure.
   C. Atopic status
      1. Identify consistent history of seasonal nasal or ocular symptoms.
      2. Family history of atopic disease.
      3. Confirmation by epicutaneous testing to a panel of common aeroallergens.
   D. History of accidental exposures to substances such as heated fumes or chemical spills.

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names, standardized threshold limit values (TLV), standardized permissible exposure levels(PEL), and, many times, the constituents of the materials to which the patient is exposed in the workplace [14]. Sometimes, this information is not listed if it is considered proprietary, and it is then necessary to contact the safety officer from the company to obtain this information. If available, safety officers or industrial hygienists, who are usually very familiar with the workplace environment and work process, can provide valuable assistance when trying to determine the relationship between the workers symptoms and workplace exposure(s).

Objective confirmation is necessary when a patient presents with a history suspicious for OA. Initial testing involves confirmation of a diagnosis of asthma which frequently requires determination of airway hyperreactivity by demonstrating nonspecific bronchial hyperresponsiveness using non-specific agonists such as methacholine, mannitol, adenosine, or histamine. However, demonstrating the presence of non-specific hyperresponsiveness is not diagnostic of OA. Specific provocation to the inciting agent is considered the gold standard for diagnosis. Regardless of whether specific provocation involves a high or low molecular weight agent, this type of testing should only be performed in a center with considerable expertise in this procedure. Although sometimes logistically challenging to accomplish, monitoring lung function using a peak expiratory flow meter in and out of the workplace or measuring cross-shift FEV1 may be useful. Using this approach, it is sometimes possible to establish a relationship between objective changes in lung function and symptoms in the workplace. If peak expiratory flow rates are used to measure variability of lung function in and out of the workplace, paper-free electronic devices that time and date stamp each reading in addition to quantifying effort are recommended, as this will improve worker adherence and reliability of the data collected. Readings should be recorded every 2 h in the workplace and every 3–4 h at home while awake for at least 2 weeks. If possible, PEFRs should be performed for 2 weeks while the worker is out of the workplace. Peak expiratory flow rates lower at work and higher out of the workplace with variability 20 % or greater is consistent with airway hyperresponsiveness suggestive of workplace exposure(s). If cross-shift FEV1s are used, workers should undergo spirometry before and after the workshift. Typically a reduction in FEV1 by 15–20 % or greater is suggestive of workplace exposure, but there are no available data validating the use of cross-shift FEV1 to confirm a diagnosis of OA.

Skin testing or in vitro testing may have a role in the assessment of sensitization to the causative agent(s) of occupational asthma. Reagents used for skin testing or in vitro tests should be characterized and standardized by identification of the allergen source, extraction procedure and biochemical composition [2, 20]. A worker's sensitization to common aeroallergens should also be identified as some forms of high molecular weight OA such as egg-induced or enzyme-induced OA are more commonly seen in atopic individuals.

Differential Diagnosis for Occupational Asthma

Occupational asthma must be differentiated from pre-existing asthma or allergic asthma due to non-work place allergens. In the latter situations, aggravating factors may include an irritant exposure, physical factors, or common indoor allergens found in and out of the workplace. However, individuals can still have worsening of asthma symptoms due to a new workplace environment allergen or irritant exposure. Furthermore, pre-existing asthma does not preclude a diagnosis of OA. Other diseases that should be excluded when considering a diagnosis of OA include chronic obstructive lung disease, bronchiolitis obliterans, vocal cord dysfunction, endotoxin-induced asthma-like syndromes (e.g., grain fever or byssinosis), and pneumoconiosis. These diseases can be differentiated by radiographic imaging of the chest, lung volumes with diffusion capacity (DLCO), and sometimes require open lung biopsy for histology. Patients with OA typically have normal chest x-rays, an obstructive pattern on pulmonary function testing, and a normal DLCO [2].

Management of OA

The treatment of choice for OA is removal of the worker from further exposure [20]. The duration of exposure and symptoms prior to diagnosis of occupational asthma has been directly correlated to the persistence of asthma after removal from the workplace. Having an early diagnosis, well-preserved lung function, and less airway hyperreactivity has been associated with a better prognosis than workers with persistent symptoms, longer exposure periods in the work place, and greater deterioration in lung function. Occupational asthma is, otherwise, treated similar to non-OA with inhaled corticosteroids, long-acting β2-agonists, leukotriene modifying agents, xanthine oxidase inhibitors, and oral corticosteroids [21].

In situations where workers are exposed to known causes of OA (i.e., enzymes, isocyanates, or acid anhydrides), use of respirators, and personal protective equipment should be enforced. However, the use of respirators and personal protective equipment after confirming the diagnosis of OA does not reduce or prevent exposure, nor prevent the deterioration of asthma symptoms. Therefore, respirators and personal protective equipment are not considered adequate substitutes for absolute avoidance measures in workers with a confirmed diagnosis of OA [21, 22].

Occupational asthma has been associated with increased long-term work disability, which can result in significant economic hardship [23]. Therefore, when making the diagnosis of OA, it is important that providers recognize the broad implications of reduced or loss of employment, which may lead to increased financial difficulties for the worker [24•]. Industries that manufacture or work with potential sensitizing agents should be vigilant about preventing exposure and potential new cases of OA by wearing personal protective equipment and enforcing safety protocols in the workplace.

Prevention

Diagnosis of OA has a significant impact on the workers' employment and future socioeconomic status. Ideally, interventions that can prevent new cases of OA should be implemented in the workplace. An example of an effective primary prevention is the significant reduction in incident cases of OA in health-care workers when powdered natural rubber latex (NRL) gloves were replaced with non-powdered NRL gloves. Workers who develop occupational rhinitis in response to a specific allergen in the workplace should be monitored more closely as they may be an increased risk for developing OA. Early detection of lower respiratory symptoms may prompt the employer to remove the worker from the workplace environment thereby preventing progression of disease [4•]. Immunosurveillance programs have been established by companies working with high risk material in the work process such as enzymes and trimellitic anhydride. These programs have been very successful at screening workers for sensitization to the inciting agent and removing them to a different job location where they would be no longer exposed.

Conclusions

The diagnosis of OA has a significant impact on the future employment, health, and socioeconomics of the worker. Therefore, a careful history is needed to guide the appropriate evaluation and to prevent the erroneous association of workplace exposures to symptoms. Objective testing is essential for establishing a diagnosis of asthma and more specific testing when available should be performed to home in on the inciting agent(s). Ultimately, once a diagnosis of OA is confirmed, avoidance of further exposure is essential to prevent the progression of disease. Immunosurveillance programs should be employed in industries where chemicals or high molecular weight agents known to induce OA are used. These programs have been demonstrated to reduce the number of new cases of OA in the workplace.

Compliance with Ethics Guidelines

Conflict of Interest Jonathan A. Bernstein is the medical director for Flint Hills Resource's TMA immunosurveillance program.

Jessica Tan and Jonathan A. Bernstein declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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