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REVIEW

Occupational asthmagens

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Summary Occupational asthma is caused by exposure to a workplace irritant. It is one of the few subtypes of asthma where a cure can be achieved by removing the cause, or the individual, from the workplace. The agent implicated is frequently obvious to the investigating clinician, although at times it may remain elusive. This review will discuss the definition of occupational asthma and asthmagens, the working environments under which they are commonly found, and what should be done on discovery of an occupational asthmagen.

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What is asthma?

Asthma is a heterogeneous common chronic condition characterised by endobronchial inflammation with consequent bronchial hyperresponsiveness [1]. This leads to variable airflow obstruction and typical symptoms such as cough, breathlessness, chest tightness, wheeze and reduced exercise tolerance. The precise aetiology of asthma remains uncertain, but genetic and environmental factors such as viruses, allergen exposure, early use of antibiotics, and numbers of siblings have all been implicated in its inception and development [2]. Once symptoms have developed, treatment is usually indicated and can vary from intermittent use of short acting β_2-agonists to combinations of oral and inhaled medications [3].

Differentiating asthma (especially in smokers) from other airways diseases, notably chronic obstructive airways disease (COPD), can be difficult. However, a determined attempt must be made because of treatment and prognostic implications [4], and this is of considerable importance in the occupational setting. It can be argued that particular disease-labelling may delay action in terms of removing an individual with work-related symptoms from exposure to a causal agent. Similarly, individuals with COPD may not necessarily require relocation from a particular occupational environment. At present, the law states that a diagnosis of occupational asthma is required if compensation is to be successful. Thus, despite demonstrating temporally-associated work-related symptoms and variable airflow obstruction, without a documented diagnosis of occupational asthma it is unlikely that a compensation claim would succeed.

What is occupational asthma?

Occupational asthma may account for as much as 10% of new cases of adult onset asthma, and a clear association with the work environment is generally a prerequisite to its diagnosis. Symptoms are often less pronounced during holidays or weekends, although patients with persistent disease may not exhibit such clear-cut patterns. Classical occupational asthma is caused by a sensitising reaction in the airways in response to exposure to a specific asthmagen—for example, high molecular weight agents such as proteins in rat urine (in laboratory workers), or low molecular weight agents such as isocyanates (in paint sprayers).

A second form of occupational asthma is termed reactive airways dysfunction syndrome (RADS). This generally occurs as a consequence of a large single exposure to gas, vapour or fume [5]. Individuals tend not to have had previous respiratory symptoms and some authorities suggest that atopy should not be present [6]. Symptoms classically develop within 24 hours of exposure and non-specific bronchial hyperresponsiveness persists for at least three months [7]. Recently, there has been increasing discussion about whether more persistent, lower dose exposure to chemicals (which would otherwise be regarded as irritants) could lead to the development of asthma; in such instances the term ''irritant-induced asthma'' has been introduced [8]. This would therefore embrace individuals with classic RADS but the validity of this approach remains uncertain and is not universally agreed.

A third type of occupational airways disease, falling under the general heading of occupational asthma, is the so-called ''asthma-like syndrome''. This is most frequently found in agricultural sector workers. Symptoms are not necessarily classically asthmatic, but tend to be ''asthma-like''. Diagnosis can be difficult since both symptoms and investigations do not fulfil an accepted definition of asthma. It tends to be associated with exposure to one or more allergens, sometimes broadly referred to as organic dusts.

What is an asthmagen?

Asthmagens can be divided into two separate types, namely inducers and inciters. Inducers are

Table 1 Common agents known to cause asthma in the workplace and associated occupations.

Agent	Occupation
Isocyanates	Paint sprayers
Dyes	Textile workers
Latex	Health care workers
Wooddust	Timber workers
Seafoods	Seafood workers
Antibiotics	Pharmaceutical industry
Flour	Bakers
Metals	Welders
Enzymes	Pharmaceutical workers
Persulphate	Hairdressers

substances which, on single or repeated exposure, cause a previously well individual to develop asthma. In contrast, inciters (or triggers) are substances which can cause symptoms in an individual with pre-existing abnormal airway responsiveness. In the workplace these can result in a diagnosis of work-aggravated asthma which is distinct from occupational asthma.

There are a substantial number of substances which can act as inducers, and an even wider range potentially acting as inciters. Common inciters include physical factors (such as cold air), tobacco smoke, viruses and bacteria. It is important to note that inducers can also act as triggers. This review will concentrate on asthmagens which act as inducers rather than inciters.

What are the most common occupational asthmagens?

Occupational asthmagens can generally be classified by molecular weight. Low molecular weight (<5000 daltons) asthmagens largely consist of chemicals such as isocyanates, aldehydes, metals, drugs and wood dusts. High molecular weight (≥5000 daltons) asthmagens are nearly all proteins; common examples include flour and grain dust, animal proteins (such as those found in rat urine), latex, and enzymes used in the pharmaceutical industry. Currently there are over 400 recognised occupational asthmagens; Table 1 highlights those most commonly implicated in the United Kingdom (UK).

Identifying an asthmagen

In a typical work setting, identifying an occupational asthmagen tends to be relatively straightforward. The particular agent may be well recognised, and implementing control measures which reduce exposure and prevent further sensitisation of more members of the workforce may be all that is required. However, occupational asthma can sometimes appear to be a problem in a specific workplace but the asthmagen may be difficult to determine with certainty. This should prompt investigation of the workplace. Indeed, most asthmagens can usually be identified from cross-sectional studies, either of specific industrial processes (e.g. bakeries) or of specific workforces (e.g. paint sprayers within a car manufacturing plant). Theoretically, cross-sectional studies are not ideal in identifying a causal association between an exposure and disease. However, when followed by intervention and subsequent improvement in the incidence of occupational asthma, a true causal association can be inferred. The most effective method in the identification of an asthmagen in the workplace is by cohort or case reference studies. These tend to be expensive and time-consuming as they involve monitoring workforces exposed to specific agents over a given period.

Realising that there may be a cluster of cases, and different causes of occupational asthma in a particular workplace is not always simple, since individuals may have been referred to different physicians with apparent work-related symptoms. Moreover, some workers may not appreciate that their symptoms are of sufficient concern to merit medical attention. Surveillance schemes are able to overcome this problem by identifying clusters of occupations in a specific workplace. For example, the SHIELD reporting system developed in the West Midlands permits the identification of particular workers with symptoms [9]. Other surveillance systems, such as the SWORD scheme are useful, although less detailed information is documented [10]—for example, data are collected by means of identification of clusters by postcode rather than by workplace, which limits its ability to identify new causes. However, there is little doubt that increased levels of awareness and reporting of occupational asthma associated with a specific exposure can result in identification of new occupational asthmagens.

Occupational asthmagens

The most common occupational asthmagens are found characteristically in a limited number of workforces. In the UK, occupational asthma is most commonly found in paint sprayers, bakers, pastry makers, nurses, chemical workers, animal handlers, welders, food processing workers and timber

workers (see Table 1). There is thus a link between identifying asthmagenic stimuli through a specific agent or through the specific workforce in its own right. Difficulty does arise at times concerning the nature of a putative offending asthmagen. For instance, it is not entirely clear what the causal agent is in welders with occupational asthma, while in the food processing industry identifying the asthmagen will obviously depend upon the food involved.

Low molecular weight asthmagens

Isocyanates are usually found in industries where paint-spraying is undertaken [10]. Currently, larger car manufacturers have good exposure control systems and sensitisation is relatively uncommon. Less well-regulated and small enterprise paint-spraying facilities are occasionally unable to provide adequate worker protection; it is in these particular situations that airway sensitisation is more likely to occur. Isocyanates are also found in varnishes and a variety of other paints. The commonest form is toluene diisocyanate (TDI) but a number of others (such as hexamethylene diisocyanate (HDI)) are also capable of sensitising individuals.

Aldehydes are most frequently represented in reported causes of occupational asthma as gluteraldehyde. The vast majority of cases of gluteraldehyde-induced asthma occurs in the National Health Service (NHS), for example in nurses working in endoscopy suites [10]. However, the frequency of recorded new cases has declined remarkably since totally enclosed sterilising systems have been progressively installed throughout UK hospitals.

Colophony is found in the fluxes of some forms of solder [11]. Despite the fact that colophony-containing solder is used much less nowadays, cases are still occasionally encountered. The causative agent is resin acid found within the solder flux which has been derived from pine resin. Indeed, some patients who are sensitised to colophony are unable to walk through a pine forest without developing symptoms of asthma.

High molecular weight asthmagens

After isocyanates, flour and enzymes used in bakeries constitute the second most common cause of occupational asthma in the UK and in many other countries [12]. Despite a greater awareness of occupational asthma, exposure to flour in bakeries remains of concern in the UK and other European countries.

Animal protein exposures are largely identified in animal-handling laboratories [13,14]. There can be a significant fall in peak expiratory flow in these workers on days when exposure to rodents has occurred [13]. This in turn highlights the need for the control of aeroallergens in the work environment using personal protective equipment such as air filtering systems.

Latex is a major cause of sensitisation, mostly within the NHS or scientific community where latex gloves and equipment such as catheters are frequently used [15]. Apart from causing troublesome asthma, dermatological sequelae can frequently be encountered. Since the introduction of powder-free gloves to most hospitals, the incidence of latex asthma has dramatically declined. Indeed, some individuals have been able to return to work as a result of an ability to avoid latex exposure. Wood dust remains a problem in wood yards, and for forestry workers and joiners [16] particularly because of hardwoods (e.g. iroko, mahogany, western red cedar) which produce finer dusts and can cause a higher dose to be delivered to the lungs during exposure.

In general, over the last decade there has been relatively little change in the proportion of individuals with sensitisation due to specific agents, with the exception of a fall in gluteraldehyde and latex-induced asthma.

How do asthmagens ''work''?

Low molecular weight asthmagens do not directly result in production of antibodies [17]. They work by acting as haptens binding on to human proteins and are typically highly reactive compounds. There are certain molecular ''structure alerts'' which are much more likely to do this. Typical examples include the isocyanate moiety (–N=C=O), primary and secondary amines, diacarboxylic acid anhydrides and dialdehydes. These agents may be implicated in paint sprayers, solderers and cleaners, epoxy resin workers and hospital staff, respectively.

High molecular weight asthmagens usually cause the formation of immunoglobulin (Ig) E antibodies, although some generate IgG4 antibodies. The majority tend to be proteins or glycoproteins of animal or vegetable origin. Exposure to the specific agent causes the degranulation of airway inflammatory cells and the release of preformed mediators such as histamine, cysteinyl leukotrienes, prostaglandins, cytokines and interleukins, which in

turn leads to bronchoconstriction. This is important in the early asthmatic response. In some situations the asthmagen itself possesses intrinsic enzymatic activity — for example, detergents containing alcalase — and as a result of their own enzymatic activity, they may potentiate allergenicity of the molecule itself by disrupting tight junctions between cells. It is of interest that the house dust mite allergen is, in fact, a digestive enzyme from the digestive tract of the house dust mite, and in itself possesses the same enzymatic activity.

Susceptibility

Understanding what factors are associated with the development of occupational asthma in one specific individual as compared to another remains difficult, but the degree of exposure is a factor [18]. The duration of exposure and the time required before sensitisation can occur is variable, although the majority of cases of occupational asthma occur within two years of initial exposure [19]. Indeed, the duration of exposure tends to be less important in the development of occupational asthma [20]. A solitary high exposure can lead to RADS, but agents such as toluene diisocyanate may also induce classic occupational asthma in addition to RADS [21]. There is also evidence that co-exposure to allergens, for instance with gases such as nitrogen dioxide and ozone, can enhance sensitisation or exacerbate existing asthma.

While it is highly likely that genetic factors confer a degree of susceptibility, these are poorly understood at present. Smoking and atopy are clearly risk factors for some forms of occupational asthma [19]. Smoking increases the chance of developing occupational asthma to low molecular weight chemicals (particularly platinum [22]) and, along with atopy, in response to agents which cause IgE production. Smoking is also an independent risk factor in the development of occupational asthma caused by prawns [23], green coffee and caster beans [24], isocyanates [25], salmon [26] and snow crab [27].

Irritant-induced asthma

This is a much more contentious area since exposures are frequently multiple and at present the list of potential agents which could cause either RADS or irritant-induced asthma is wide. Whilst it is accepted that volatile organic compounds can induce specific IgE production in animals, the exact mechanism in humans is far from clear. There is currently considerable debate concerning the exact relationship between this condition and classical occupational asthma, and also concerning its optimum treatment.

Control

In the work setting, the aim of the occupational physician is to identify responsible asthmagens and remove the worker from exposure. In some cases this will depend upon reducing exposure to a level at which sensitisation or the development of asthma is unlikely to occur. It is important to be aware that, in only a very few cases is there sufficient evidence to support a clear threshold level below which sensitisation will not occur. Consequently, the best approach is to remove the exposure completely and find a substitute material to work with. Where this is not possible, personal protective equipment should be provided, such as is needed in animal and pharmaceutical workers. Dealing with exposures can be very effective in individual work places and has proven to be very successful in reducing the incidence of gluteraldehyde and latex-induced asthma.

The pharmacological armamentarium used in conventional asthma should be used in the same way for asthma caused by occupational exposure [3]. There should be a stepwise management regime incorporating the use of intermittent short acting β_2-agonists and regular inhaled corticosteroids with the possible addition of long acting β_2-agonists.

Conclusions

Occupational asthma, which is both preventable and treatable, is an important cause of respiratory morbidity in the working environment. It is an important diagnosis to make, in terms of preventing affected individuals becoming chronically exposed to asthmagens, and in deciding upon those who may qualify for compensation. With the persistent introduction of new chemicals and potential sensitising agents it is likely that both the incidence and prevalence of occupational asthma will continue to rise. This suggests that clinicians should maintain a high degree of vigilance when encountering all new cases of adult asthma and should record a full and detailed employment history during initial and subsequent assessment.

Conflicts of interest

None declared.

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