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Asthma on the job: work-related factors in new-onset asthma and in exacerbations of pre-existing asthma

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Occupational asthma (OA) can be defined as variable airways narrowing causally related to exposure in the working environment to airborne dusts, gases, vapours or fumes. There are many agents in the work-place that can induce asthma or cause substantial deterioration in pre-existing asthma. It has been estimated that 5–15% of adult-onset asthma can be attributed to occupational exposures. Hence adult patients, especially those with new-onset asthma, must be investigated with regard to occupational risk factors for disease. The prognosis for OA is improved if the causal exposure is controlled either by controlling the exposure at the workplace or by moving the patient out of the workplace.

Key words: epidemiology; occupation; welding; prevention and control.

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Introduction

In the past, interest in occupational lung diseases has largely focused on conditions that affect the lung parenchyma, but in recent years there has been a growing interest in the occupational causes of airways disease. This recognizes the shifting epidemiology of occupational lung disease. In the industrialized world, occupational asthma (OA) is now probably the most frequent occupational respiratory disorder, and this pattern is likely to spread worldwide.

No generally accepted definition of OA has been established. A commonly cited clinical definition, however, is 'variable airways narrowing causally related to exposure in the working environment to airborne dust, gases, vapo-;urs or fumes' (1). This is an intentionally broad definition, including both persons with new-onset asthma caused by the working environment and persons in whom pre-existing asthma has become more manifest due to aggravation caused by occupational factors. It is also important to note that OA can be, to a considerable extent, a medico-legal diagnosis. In that context, diagnostic criteria are often adjusted to national legislation (2). For example, specific inhalation challenge in the diagnosis of OA has been used predominately in jurisdictions where insurance authorities require such testing in order to accept the diagnosis of OA. A definition of OA that can be used in clinical practice or for certain epidemiological purposes is presented in Table 1. It is partly based on a U.S. definition used in a surveillance program for OA (3). It also includes work-related asthma, i.e. pre-existing asthma that is substantially aggravated by occupational exposure.

Exposure assessment is of great importance in diagnosing OA. In some work-places, occupational exposures may be very complex requiring detailed assessment with an industrial hygiene consultant, but simple questioning may elicit the suspect agent in many work practices. For example, trimellitic acid anhydride should be suspected as a potential exposure whenever epoxy glues are reported to be used. In cases where a single high level irritant exposure has triggered new-onset asthma, the so called reactive airways dysfunction syndrome (RADS), an exposure history should be clear cut (4). For occupational asthma, suspected work-practices often include use of two-part chemical systems that must be mixed just prior to use; dusty activities, especially including exotic woods; foodstuffs; animal handling; working with powdered latex gloves; or exposure to any chemical whose warning label identifies sensitization as a potential hazard.

A prerequisite for a causal relationship between exposure and asthma is that the exposure has occurred before the start or before the substantial aggravation of the condition.

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TABLE 1. Working definition of occupational asthma. This definition would include both new occupational asthma secondary to sensitization or irritant exposure and work-related exacerbations of a pre-existing disease. Modified from Matte *et al.* (3)

1. Definite asthma
   and
2. Temporally related occupational exposure to an agent, process or environment known to cause asthma or to substantially aggravate an existent asthma
   or
3. An association between asthma and work, meaning at least one of following:
   - 3.1 Temporal relation between symptoms of asthma and work
     or
   - 3.2 Significant work-related changes of FEV_1 or PEF
     or
   - 3.3 Significant work-related changes in airways responsesiveness as measured by non-specific inhalation challenge
     or
   - 3.4 Positive response to inhalation provocation testing with an agent to which the patient is exposed at work
     or
   - 3.5 Onset of asthma, or substantial aggravation of asthma, following shortly after a high exposure to airway irritants

Asthma occurring on first exposure is usually indicative of pre-existent disease whereas asthma occurring after a symptom-free 'latent' interval is more consistent with an occupational activity. Nevertheless, asthma induction can either occur quite rapidly or over a period of several years. It is important to ask the patient carefully about the timing of the first signs of asthma symptoms. For instance, asthmatic symptoms can occur following a change of job, after introduction of new materials into the work-place, or after a new process is employed. It is important to note that nasal symptoms may occur as a harbinger of illness, preceding respiratory symptoms by many months or years (5).

Other indicators of OA are that asthma symptoms occur in the evening or at night following working days, and may be lessened during weekends or holidays. These distinctions may be blurred, however, with increasing length of exposure. Moreover, ongoing asthma may continue after removal from exposure, especially if the condition is advanced (6).

Serial measurements of FEV_1 have been proposed, but exposure-related changes over a working day may be difficult to distinguish because of the normal diurnal variation of FEV_1. Serial recordings of peak expiratory flow (PEF) over a period of several weeks, when the patient is working and off work, have been found to be useful in demonstrating that a work-place exposure is associated with asthma (7). Occupational exposure may induce a gradual fall in the PEF, and withdrawal from the exposure may lead to gradual improvement in the PEF-values. Measuring PEF is very dependent on the cooperation of the patient, but this problem may be overcome by using computerized peak flow meters (8–9).

Serial measurement of non-specific bronchial hyperresponsiveness (NSBH) at work and away from work has also been recommended in evaluation of potential OA (10). NSBH should be evaluated on a working day after a minimum period of 2 weeks at work, and compared to NSBH after a period off work of longer than 2 weeks. A change of at least two dose-steps is usually required for a change in NSBH to be considered clinically significant. The NSBH may be normal if the worker not has been recently exposed (11).

Specific inhalation challenge testing has been proposed as the 'gold standard' in the diagnosis of OA related to specific sensitization (12–13). However, an important disadvantage in its use in routine clinical diagnosis is that specific laboratory inhalation challenge tests may have low sensitivity, i.e. cases with true OA have negative tests. The most likely reason for false-negative tests is that the wrong agent or too low a dose has been used. This is particularly relevant when complex processes or transient intermediates are the causative agents. A negative test may also occur if the subject has been away from work for a long period. Specific inhalation challenge is not relevant when the work-place exposure is a non-specific irritant, for example sulfur dioxide or acid aerosols. Finally, specific challenges may be dangerous if a powerful response is induced.

Epidemiology

From the available literature it can be estimated that 5–15% of adult asthma may be caused by occupational exposures (14–17). The frequency of occupational asthma depends upon many factors, including susceptibility to respiratory sensitization, the character of the industries in any given area, the number of people who are at risk, and the exposure conditions in the workplaces involved. Our limited knowledge about the occurrence of OA in the general population is based on surveillance schemes, on official statistics for occupational diseases and a few population-based epidemiological studies.

A system for the surveillance of work-related and occupational respiratory disease (SWORD) has existed in Great Britain since 1989. From that system, in 1992, an overall incidence of 37 cases of OA per million of the working population was reported (18). During the period

1989–1991 the more intensive surveillance program (SHIELD) in the West Midlands area of Great Britain estimated a rate of 43 cases of OA per million workers (19). Based on information from the Finnish Registry of Occupational Diseases, the overall incidence of OA in 1992 was 153 cases per million workers (18). The highest incidences in that registry were found among bakers, spray painters and electronic assemblers. In a Swedish Registry of self-reported occupational diseases, the annual reporting rate of OA for 1990–1992 was 80 cases per million, with the highest rates among male bakers, male welders and female chemical and plastic production workers (20). The rather large differences between the Finnish and Swedish registers compared to the British ones are probably due to under-reporting in the British systems, rather than different work conditions. The British systems are based on voluntary reporting by certain physicians, whilst in Finland it is mandatory for all physicians to report all occupational diseases, and the Swedish system is based on reporting by the subject himself. These differences underscore the caution with which frequency data for work-related asthma must be interpreted.

Occupational exposures causing asthma

About 250–300 factors (some specific and others less well-defined) encountered at work have been reported to cause OA (21). This number will continue to increase as new processes are continuously introduced into industry. In one commonly used classification scheme, the causes of OA can be divided into three major categories (Table 2) (21). Most high-molecular weight agents (HMW) ($\geq$5 kDa) induce asthma through an IgE-mediated mechanism. The high-molecular weight agents are mainly proteins that can act as complete antigens, and hence induce IgE synthesis. When these antigens are inhaled, they bind to specific IgE on the surface of mast cells or basophils. This binding induces an inflammatory reaction mediated by a variety of cytokines and other pro-inflammatory mediators (22). Among patients with HMW induced OA, IgE antibodies can be detected either by analysing circulating IgE, e.g. RAST, or by skin-prick testing if a suitable preparation of allergen is available. However, many occupational allergens are not standardized, and information on the sensitivity and specificity of skin prick tests or intra-dermal tests is often not available (10).

Many, but not all, low-molecular weight agents ($<$5 kDa) (LMW) appear to induce asthma through immunological mechanisms that are still poorly characterized, but which appear to be independent of IgE. Some low-molecular weight agents, such as acid anhydrides, persulphates and isocyanates, may act as haptens and induce asthma through an IgE-dependent mechanism. It is also important to note that although LMW allergens are often synthetic chemicals, naturally occuring LMW chemicals are also agents that can cause asthma. For example, the components in Western Red Cedar, pine rosin and green tea, all of which can cause OA, are LMW chemicals.

Exposures that can induce OA through irritant mechanisms are mainly gases or vapours that cause a toxic effect on the airways. Water solubility, and the concentration, are the key factors for determining the site of deposition in the respiratory tract and the clinical response to irritant exposures. As well as asthma, toxic oedemas, brochiolitis and rhinitis have been described after such exposures (23). There are a substantial number of case reports establishing that very high single exposures to irritant agents cause asthma, also called RADS (4). A pre-requisite for an association is that the asthma symptoms must start within 24 h of the exposure and that non-specific bronchial

TABLE 2. Selected examples of exposures causing occupational asthma

Type of exposure*	Mechanism	Exposure	Occupation
HMW	IgE-dependent	Flour dust	Bakers
		Grain dust	Millers
		Latex	Dentists, surgeons, nurses
		Enzymes	Bakers, pharmaceutical industry
		Animals	Biomedical research, animal handlers
LMW	IgE-dependent	Acid	
		Anhydrides	Plastic and epoxy resin workers
		Reactive dyes	Textile dyers
		Persulphate	Hairdressers
	Non IgE-dependent	Isocyanates	Painters
			Polyurethane workers
		Acrylates	Dental technicians, assemblers, plastic workers
Irritants	Toxic effect	Chlorine	Bleachery workers, household cleaners
		SO^2	Pulp mill workers

*HMW: high molecular weight agents; LMW: low molecular weight agents.

hyperresponsiveness is present. Some authors have additionally argued that recurrent exposures to lower concentrations of irritants can also induce OA (24,25). Although the association may be biologically plausible, controlled studies are lacking.

Atopy and cigarette smoking

Atopy, defined as positive skin prick test to common aeroallergens, is associated with increased risk for OA due to HMW agents. For instance, atopic subjects which work with laboratory animals are more likely than non-atopics to develop OA (26–27). Pre-existing atopy appears to be of little relevance to the development of OA as a result of exposure to low molecular weight agents such as isocyanates (28) and some organic acid anhydrides (29).

In some studies, tobacco smokers have demonstrated an increased risk of sensitization and also of OA caused by IgE-mediated mechanisms (2). Although the association between smoking and sensitization is not a uniform observation, it has been recommended to advise workers in industries in which such a risk has been demonstrated to refrain from smoking (2). Exposure to environmental tobacco smoke (ETS) has been linked to asthma onset in children (30), but there is no general acceptance of a causal link between ETS and adult-onset asthma (31–32). However, two large epidemiological studies have found that an increased risk of asthma was observed after exposure to ETS at home or in the work-place (33–34). In the U.S. study, for example, 10 years work in smoky work-places was associated with a relative risk of 1·4 for asthma (34).

Specific selected exposures

WELDING

Welding refers to any process of joining pieces of metal at joint faces that have been made soft or liquid by heat. In soldering, metal surfaces are joined by flowing a heated substance between them without bringing the pieces themselves to the melting point. Hence welding is performed at a higher temperature than soldering. Exposure to welding fumes implies exposure to respiratory irritants and fumes from different metals such as hexavalent chromium, zinc and aluminium (21). If the steel is painted, this further implies exposure to combustion products from burnt paint. Asthma has been described after welding in stainless steel (35–36), and an increased risk of asthma amongst welders generally has been observed in some epidemiological studies (17,37–39) supporting a relationship between welding in stainless steel and OA. In a review in 1991, however, the evidence was not considered strong enough to support a causal relationship between plain steel welding and asthma-onset (40). Nevertheless, recent epidemiological data suggest that plain steel welding may indeed be a potential cause of occupational asthma (17,39).

REACTIVE POLYMERS (ISOCYANATES AND ACRYLATES)

Isocyanates are characterized by the N=C=O group which contains two double-bonds, making them very reactive and capable of forming plastics, adhesives or elastomers in flexible or rigid form. The most relevant isocyanate products are toluene diisocyante (TDI), hexamethylene diisocyanate (HDI) and methylene diphenyldiisocyanate (MDI). In recent years, isocyanates have been recognized as one of the main causes of OA induced by LMW agents (21). The risk is considered to be higher for those diisocyanates which are more volatile at room temperature (TDI and HDI) than for MDI or polyisocyanates. It is worth noting that processes generating aerosols of MDI can provoke sensitization. If the polymerized isocyanates are heated, the monomers can be liberated thus exposing workers to free isocyanates. This may occur during welding in painted steel or in plastic material containing isocyanates. Rapid glues are used in both industry and in health care. Most of them are based on acrylates, cyanoacrylates and methylmethacrylates. Case reports about asthma among workers exposed to cyanoacrylates was first published in the mid 1980s (41–42), followed by a number of similar case reports.

LATEX

Natural rubber latex is obtained from the rubber tree *Hevea brasiliensis* and contains a polymer of polyisoprene and different proteins. In recent years, IgE mediated sensitization to latex has been recognized as a major occupational health problem amongst healthcare workers, as well as other workers who wear latex gloves (43). In a Canadian study from a rubber-processing factory, the prevalence of positive skin-prick tests to latex was 11%, and the prevalence of OA was 6%. The powder that is used on the gloves facilitates the spread of the latex allergen in air, and this has been recognized as a problem in medical centres.

ENZYMES

Enzymes are applied today in a variety of industrial processes. Bakers constitute the largest exposure group (45–46), but enzymes are also handled in pulp mills, breweries, dairies and in the textile industry. Enzymes induce asthma through an IgE mediated mechanism. The most well-known example is the epidemic sensitization to detergent enzymes in a British detergent powder factory in 1967 (46).

Exacerbations

This classification subsumes two different clinical scenarios. Exposure at the work-place may cause further impairment of a currently symptomatic asthma, or may trigger a relapse of a pre-existing asthma in a subject without current

symptomatic disease. This issue is of great clinical relevance but the literature addressing this topic is scanty.

British researchers reported that 31% of patients with non-occupational asthma reported impairment of asthma symptoms during weekdays as compared to 42% of patients with occupational asthma (48), thus indicating that workplace exposure may impair pre-existing asthma. In a community sample of adults with asthma, the prevalence of respiratory symptoms at work was about 20% (49). In the same study, it was reported that the prevalence of work-associated respiratory symptoms, which later woke the subjects at night, was about 10%. These studies indicate that workplace exposure may cause impairment in pre-existing asthma. However, neither bronchial hyperresponsiveness nor lung function were affected when 12 subjects with current asthma were exposed to high levels of wood dust (50).

In case studies of patients with suspected work-related asthma, subjects with pre-existing asthma seem to be at least twice as common as in the general population (25,51–52). The studies indicate that, in particular, irritants trigger pre-existing asthma.

Prevention and prognosis

The most important intervention for OA is prevention. The long-term strategy should be primary prevention which means the reduction or elimination of harmful exposures. This should mainly be done by changing industrial processes, for example, substitution of non-powdered for powdered latex gloves.

As noted previously, atopy is associated with an increased risk for HMW-induced OA. Hence pre-employment screening of applicants to work involving laboratory animal handling has been suggested (53). This kind of primary prevention is quite ineffective, as illustrated by the following example. Work with laboratory animals is associated with an increased risk for OA. In a British study (54), it was shown that after 2 years employment 20% of the atopics had been sensitized compared with 4% of the non-atopics. If we assume that 200 workers will be employed and 25% ($n = 50$) of them are atopics, then 20% of the 50, i.e. 10 of the 50 atopics, will be sensitized. Six of the 150 non-atopics (4% of the 150) will be sensitized. If 200 non-atopics had been employed instead, eight workers (4% of the 200) would have been sensitized. This means that only 50% (8/16) of the sensitizations would have been prevented if the atopics had been denied employment. In other words, even if the atopic 25% of the potential work-force had been excluded, the number of cases of occupational allergy would only be halved.

The indicators for an unfavourable prognosis are long duration of the exposure before asthma onset, long duration of symptoms, the degree of airways obstruction at the time of diagnosis and the persistence of markers of airways inflammation in bronchioalveolar fluid or in bronchial biopsies (55). Therefore it is extremely important to identify subjects with OA as early as possible, and subsequently to remove them from exposure. Prompt action will reduce the risk of ongoing symptoms, but most patients will require drug therapy for a prolonged period. For all practical purposes, the pharmacological treatment of OA does not differ from the therapy of other patients with asthma.

Conclusions

- OA is now the most common occupational lung disease in the industrialized world.
- The diagnosis of OA includes diagnosis of both the disease (asthma) and the causal exposure.
- Early diagnosis and removal from exposure are the most important factors for improving the long-term prognosis.
- Good industrial hygiene and modification of unsafe working practices are the keys to prevention.

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